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Clinical activity of enzalutamide in docetaxel-naïve and docetaxel-pretreated patients with metastatic castration-resistant prostate cancer

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Abstract

Background—Two randomized clinical trials have demonstrated a survival advantage with enzalutamide over placebo in both docetaxel (D)-pretreated and D-naïve metastatic castration-resistant prostate cancer (mCRPC) patients. Cross-resistance between androgen receptor-directed therapies and taxanes has been suggested, possibly leading to lower efficacy of enzalutamide in the post-D setting.

Material and Methods—We aimed to examine the impact of prior D treatment on the clinical activity of enzalutamide in patients with mCRPC. We retrospectively reviewed an institutional database to identify men with mCRPC treated with standard-of-care enzalutamide. Patients were classified as D-naïve or D-pretreated. The efficacy end points were prostate-specific antigen (PSA) response rates ($\geq 50\%$ PSA decline), time to PSA progression (TTPP) and clinical/radiographic progression-free survival (PFS) in response to enzalutamide. Differences between

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groups (D-naïve and D-pretreated) were assessed by univariate and multivariable analyses using logistic and Cox regression models.

Results—One-hundred-seven (107) consecutive patients were included: 60 were D-pretreated and 47 were D-naïve. PSA responses were 43.2% in D-naïve patients and 25.4% in D-pretreated patients ($P=0.089$). Median TTPP was 7.2 months (95% CI=4.5–17.2) in the D-naïve group *versus* 2.6 mo (95% CI=1.9–3.5) in the D-pretreated group ($P<0.0001$). Median PFS was not reached for D-naïve men and was 3.3 mo (95% CI=2.5–4.8) for D-pretreated men ($P<0.0001$). After adjusting for potential confounders including prior abiraterone use, differences remained statistically significant for TTPP (HR=2.32; 95% CI=1.19–4.50; $P=0.013$) and marginally significant for PFS (HR=1.90; 95% CI=0.94–3.84; $P=0.073$) in multivariable analyses. Among patients who achieved a PSA response to enzalutamide ($n=34$), results suggested a trend towards shorter duration of response in D-pretreated patients.

Conclusions—The clinical activity of enzalutamide appears to be blunted in patients who have previously received docetaxel chemotherapy. These results support the concept of cross-resistance between these two agents.

Keywords

prostate cancer; enzalutamide; docetaxel; cross-resistance; clinical activity

Introduction

Understanding that the androgen receptor (AR) remains an important driver of CRPC was a milestone in the development of new therapies directed against the AR signaling pathway, such as enzalutamide and abiraterone [1]. Enzalutamide is an AR antagonist that inhibits androgens from binding to the AR and prevents nuclear translocation and co-activator recruitment of the ligand-receptor complex [2]. This agent, specifically developed to target tumors harboring an amplified AR [2], was first approved by the Food and Drug Administration (FDA) in 2012 for use in the post-docetaxel setting based on an improvement in survival observed in the AFFIRM trial [3]. Mimicking the history of abiraterone (an androgen biosynthesis inhibitor) [4, 5], a clinical benefit with enzalutamide was also observed in chemotherapy-naïve CRPC patients as reported in the PREVAIL study [6]. The favorable safety profile of enzalutamide, as well as the lack of requirement for corticosteroids, have made its use in the pre-chemotherapy setting attractive, even preceding its approval by the FDA and EMA in this treatment setting.

Taxanes remain the only form of cytotoxic chemotherapy that prolongs survival in patients with metastatic CRPC. In 2004, docetaxel was established as the standard-of-care for first-line treatment of these patients [7, 8]. Although it is widely accepted that taxanes exert an antineoplastic effect through their anti-mitotic effects [9], recent preclinical studies in prostate cancer have uncovered an alternative mechanism of action attributed to the perturbation of microtubule-dependent trafficking of the AR into the nucleus (Figure 1) [10–12]. Additional evidence that taxanes may interfere with AR signaling was reported by Darshan *et al* [13], showing that the cytoplasmic sequestration of AR in circulating tumor cells of mCRPC patients was associated with favorable clinical responses to docetaxel.

Preclinical data have suggested at least partial cross-resistance between taxanes and AR-directed agents in prostate cancer cell lines models [14]. For example, it has been demonstrated that dynamic AR translocation to the nucleus (evaluated by time-lapse confocal microscopy) appeared to be inhibited by both taxanes and AR-directed therapies [14]. In addition, results from three retrospective clinical studies in mCRPC patients treated with both abiraterone and enzalutamide have also revealed limited activity of enzalutamide in this setting [15–17]. Other reports have shown modest activity of abiraterone in patients progressing after enzalutamide and docetaxel, respectively [18, 19]. Finally, the sequential administration of abiraterone followed by docetaxel has also been studied, suggesting a negative influence of abiraterone pretreatment on the subsequent efficacy of docetaxel [20].

The optimal sequencing of enzalutamide and chemotherapy remains an unresolved question. This will become increasingly important as more and more patients will receive enzalutamide prior to docetaxel chemotherapy. The objective of the current study was to retrospectively examine the clinical activity of enzalutamide in docetaxel (D)-naïve and D-pretreated patients, using a contemporary cohort of sequentially-treated men. We hypothesized that the clinical activity of enzalutamide will be blunted by prior exposure to docetaxel.

Material and Methods

Patient identification

We retrospectively reviewed the electronic database of the Johns Hopkins Hospital from March 2012 (when standard-of care enzalutamide was first prescribed at our center) through February 2014, under an institutional review board-approved protocol. Medical records of consecutive patients with mCRPC were reviewed to identify all patients who had ever received enzalutamide during this period. For this analysis, patients were divided into 2 groups: those who had received prior chemotherapy with docetaxel followed by subsequent enzalutamide (D-pretreated cohort), and those who received enzalutamide without prior exposure to docetaxel (D-naïve cohort).

Electronic medical records were reviewed for the following characteristics: patient age, race, Gleason score, TNM stage, neoadjuvant/adjuvant treatments, prior antiandrogen therapies (including first-generation AR inhibitors and ketoconazole), abiraterone, and chemotherapy regimens administered. Eastern Cooperative Oncology Group (ECOG) performance status, baseline hemoglobin, alkaline phosphate, albumin, PSA levels, presence of visceral metastases, extent of the disease (<5 vs ≥5 metastasis sites) and the presence of pain-related symptoms were documented at the time of enzalutamide initiation.

Patients were generally followed with clinical and PSA evaluations every 1–3 months. Imaging studies were ordered at the discretion of the treating physician, based on increasing PSA values and/or new clinical signs or symptoms. All patients received ongoing androgen deprivation therapy or had undergone prior bilateral orchiectomy. Because our database captured information from different treating physicians, follow-up protocols were not always uniform.

Statistical analyses

This was a retrospective analysis conducted to examine the impact of prior D treatment on the clinical activity of enzalutamide in patients with mCRPC. Clinical outcomes of interest included PSA response rates, time to PSA progression (TTPP), and clinical/radiographic progression-free survival (PFS). These outcomes were largely defined according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria. PSA response was defined as a reduction in the PSA level from baseline by 50%. In most instances (but not always), this was confirmed by an additional PSA evaluation performed 3 weeks later. TTPP was defined as the time interval from initiation of enzalutamide to first documented PSA progression (defined as a 25% increase in PSA from baseline or nadir). Deaths without PSA progression were censored at the time of death. Those who remained alive without PSA progression were censored at the time of last PSA assessment. PFS was defined as the interval from enzalutamide initiation to investigator-assessed clinical or radiographic progression or death from any cause (whichever occurred first). Soft tissue progression was evaluated per Response Evaluation Criteria in Solid Tumors criteria (RECIST, version 1.1) [21] and bone scan progression was assessed per PCWG2 criteria [22]. Patients with insufficient imaging data available for evaluation of PFS were still evaluated for PSA response and TTPP. Overall survival (OS) was also measured, and was defined as the interval from enzalutamide initiation to death from any cause. These survival probabilities were conditioned on patients having survived to receive enzalutamide after initial treatment.

Baseline patient demographic and treatment characteristics were compared between groups using the Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. PSA responses were compared between groups using logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI) reported. Median TTPP, PFS and OS were estimated using the Kaplan-Meier method, and survival distributions were compared using the log-rank test. Hazard ratios (HR) and 95% CI were estimated using the Cox proportional hazards model, in which whether or not a patient received prior docetaxel was considered as a baseline covariate of primary interest. In order to control for potential confounding factors, multivariable modeling was used to adjust for variables that had a significant association with outcomes in the univariate analysis. Variables that were not significantly associated with outcomes but that changed the odds ratio or hazard ratio by 10% or more when removed from the analysis were also retained in the final model[23]. Subgroup analyses were not adjusted for multiplicity.

All tests were 2-sided and considered statistically significant at $P < 0.05$. Statistical analyses were performed using SAS (version 9.3, SAS Institute, Cary, NC) and R statistical software (version 2.15.2).

Results

Patient characteristics

A total of 107 enzalutamide-treated patients with mCRPC were identified at our institution. Median follow-up time was 8.5 months (range, 0.7–41.2). Of these, 60 (56%) had previously received docetaxel, while 47 (44%) had not received prior docetaxel. The majority of

patients also had prior exposure to CYP17 inhibitors: 84 (79%) had received previous abiraterone and 34 (32%) had received ketoconazole. The median duration of enzalutamide treatment was 4.9 months (range, 0.8–14.6) among D-naïve patients and 3.2 months (range, 0.4–19.4) in D-pretreated men ($P=0.014$).

Baseline patient characteristics, stratified by prior docetaxel use, are shown in Table 1. Although treatment assignment was not determined prospectively or by means of randomization, the arms were well balanced with respect to ECOG status, bone pain, Gleason score and TNM stage, prior neoadjuvant/adjuvant treatment, and number of prior antiandrogen therapies. At baseline, median PSA was significantly higher (94.4 ng/dL *versus* 22.8 ng/dL) and patients had more extensive disease (>5 metastasis: 91.7% *versus* 55.3%) and visceral metastases (18.3% *versus* 2.1%) in the D-pretreated group compared to D-naïve group, respectively. The proportion of patients who had prior exposure to abiraterone was significantly higher in the D-pretreated group as well (88.3% *versus* 66.0%). These differences likely reflect historical trends, as the majority of patients with more advanced disease received D before enzalutamide at our institution.

PSA-related outcomes

A total of 103 patients were evaluable for PSA-dependent outcomes. PSA responses were observed in 43.2% (19/44) of D-naïve patients and 25.4% (15/59) of D-pretreated men ($P=0.089$; Fisher's exact test). Waterfall plots depicting PSA changes with enzalutamide in D-naïve and D-pretreated populations are presented in Figure 2. Univariate Cox regression analysis suggested a trend towards higher PSA responses in D-naïve patients compared to D-pretreated men (HR 2.23; 95% CI=0.97–5.14; $P=0.060$). Multivariable analysis showed no significant difference in PSA response rates between groups after adjusting for potential confounders.

The median TTPP was 7.2 months (95% CI=4.5–17.2) for the D-naïve group and 2.6 months (95% CI=1.9–3.5) for the D-pretreated group ($P<0.0001$) (Figure 3). Univariate Cox regression analysis suggested that D-pretreated patients experienced significantly shorter TTPP than D-naïve patients (HR=3.17, 95% CI=1.91–5.28; $P<0.0001$). TTPP remained significantly shorter in D-pretreated patients in multivariable analysis (adjusted HR 2.32; 95% CI=1.19–4.50; $P=0.013$), after controlling for baseline PSA, baseline alkaline phosphatase, visceral metastases, extent of disease, and prior abiraterone use.

In patients who did achieve a PSA response with enzalutamide, we examined the durability of this response by determining the TTPP (in each of the two patient cohorts). In this analysis, 34 patients were evaluable (19 D-naïve and 15 D-pretreated). In these patients, median TTPP was 17.2 months (95% CI=5.7–17.2) among D-naïve men and 6.1 months (95% CI=3.0–8.3) among D-pretreated men (Log-rank $P=0.0007$). Univariate Cox regression analysis indicated that D-pretreated patients had significantly shorter TTPP compared to D-naïve patients (HR 5.83; 95% CI=1.85–18.4; $P=0.003$). This difference was marginally significant in the multivariable analysis (HR 5.89, 95% CI=0.99–35.0; $P=0.051$) after adjusting for baseline PSA, baseline alkaline phosphatase, visceral metastases, extent of disease, and prior abiraterone use.

Progression-free survival

Median PFS was 3.3 months (95% CI=2.5–4.8) in D-pretreated patients while it was not reached for D-naïve patients ($P<0.0001$; Log-rank test) (Figure 4, *top*). Univariate Cox regression analysis suggested that D-pretreated patients experienced significantly shorter PFS than D-naïve patients (HR 2.83; 95% CI=1.64–4.88; $P=0.0002$). The multivariable analysis indicated a persistent trend towards a negative prognostic effect of prior D treatment after adjusting for baseline PSA, baseline alkaline phosphatase, ECOG performance, bone pain, visceral metastasis, extent of disease, and prior abiraterone use (adjusted HR 1.90; 95% CI=0.94–3.84; $P=0.073$).

In patients who did achieve a PSA response to enzalutamide ($n=34$), we examined the durability of this response by evaluating PFS in each of the two cohorts. Median PFS was not reached in D-naïve men and was 7.5 months (95% CI=3.4–19.4) in D-pretreated men ($P=0.112$; Log-rank test). The multivariable analysis suggested a trend towards inferior PFS in D-pretreated patients compared to D-naïve patients (HR 8.21, 95% CI=0.71–94.7; $P=0.091$), after adjusting for baseline PSA, alkaline phosphatase, ECOG status, bone pain, visceral metastases, extent of disease, and prior abiraterone use.

Overall survival

After a median follow-up of 8.5 months (range, 0.7–41.2) for all enzalutamide-treated patients (9.3 months for D-naïve patients and 8.4 months for D-pretreated patients), 35 deaths had occurred. Median overall survival (OS) was 16.2 months (95% CI=11.5–not estimable) for D-naïve patients and 11.6 months (95% CI=8.7–15.2) for D-pretreated patients ($P=0.003$; Log-rank test) (Figure 4, *bottom*). After controlling for baseline PSA, alkaline phosphatase, ECOG status, visceral metastases, extent of disease, and prior abiraterone use, the multivariable analysis did not reveal a statistical difference in OS depending on prior D exposure (HR 1.68; 95% CI=0.55–5.07; $P=0.361$), although OS was numerically inferior in D-pretreated patients. The variables remained statistically significant included baseline alkaline phosphatase, ECOG performance status, and presence of visceral metastases.

Effect of prior docetaxel duration

Among the enzalutamide-treated patients who had previously received docetaxel ($n=60$), the median number of D cycles administered was 6 (range, 2–12 cycles). Twenty evaluable patients received <6 cycles and 38 evaluable patients received ≥6 cycles of docetaxel. PSA responses to enzalutamide were observed in 25% (5/20) of men who received <6 cycles of D, and in 26% (10/38) of those who received ≥6 cycles of D ($P>0.999$; Fisher's exact test). When considering the number of chemotherapy cycles as a continuous variable, there was no significant difference between patients who had a PSA response to enzalutamide *versus* those who did not ($P=0.956$; Wilcoxon rank sum test). Among patients receiving docetaxel prior to enzalutamide, 56 were evaluable for their PSA response to docetaxel. To this end, PSA response to docetaxel failed to predict subsequent PSA response to enzalutamide (OR 1.10; 95% CI=0.33–3.73; $P=0.877$).

Discussion

This retrospective study is one of the first to examine the influence of prior docetaxel exposure on the subsequent clinical efficacy of enzalutamide, using contemporaneous cohorts of D-naïve and D-pretreated patients. The majority of the benefit from enzalutamide appeared to be confined primarily to patients without prior docetaxel therapy, although a proportion of D-pretreated patients (25%) did achieve a PSA response to enzalutamide. Interestingly, in men experiencing a PSA response to enzalutamide, TTPP and PFS both tended to be longer in D-naïve (compared to D-pretreated) patients, although this observation was not statistically significant given this small subset of patients. We also observed numerically superior OS in D-naïve patients, although this improvement did not reach statistical significance after adjusting for potential confounders; this could potentially be explained by the small numbers of events included in this study resulting in an underpowered analysis.

Not surprisingly, the longer TTPP and PFS in D-naïve patients did not translate to a significant difference in OS among our unselected cohort of patients. Part of the reasons could be underpowered due to small number of events (i.e., 35 deaths). Further, multivariate analysis adjusting for the prognostic factors of ECOG performance status, baseline alkaline phosphatase levels, and presence of visceral metastases seemed to suggest that these factors were more important drivers in the OS difference than the prior docetaxel use. This finding could possibly be explained by the fact that some patients with the triumvirate are less likely to receive docetaxel-based therapy and as such the overall ability to get docetaxel may be a reflection of the presence of these unfavourable markers or more aggressive disease. In addition, differences in the distribution of subsequent life-prolonging treatments (e.g. sipuleucel-T, radium-223, cabazitaxel) were not accounted for in this analysis and may have affected OS.

Although the notion that CRPC is an AR-addicted tumor has been embraced by the field, mechanisms of cross-resistance between AR-directed therapies and taxanes (which may significantly influence patient outcomes) are more poorly understood. These resistance mechanisms are particularly centered on the AR, and include disruption of AR trafficking along microtubules as well as induction of AR splice variants [14, 24]. This can be illustrated clinically by the reduced activity of enzalutamide in D-pretreated men (compared to D-naïve men) in the present study, supporting the hypothesis that prior therapy with docetaxel might negatively influence the clinical activity of the subsequent enzalutamide treatment. During the analysis of the D-pretreated subgroup, the question of whether the duration of the prior D exposure had an impact on subsequent enzalutamide activity was raised. To this end, both patient cohorts (PSA responders *versus* PSA non-responders) were well balanced in terms of dose-intensity of prior docetaxel, suggesting a relatively rapid acquisition of the resistance mechanism to subsequent enzalutamide rather than a dose-dependent effect on the efficacy of the subsequent enzalutamide. Moreover, lack of a PSA response to docetaxel did not preclude a subsequent PSA response to enzalutamide, which has also been observed previously [17]. Although this finding seems counterintuitive, it could be speculated that only partial cross-resistance between these two agents should be expected since the mechanism of action of enzalutamide (a multi-level AR pathway

inhibitor) and the proposed mechanism of D-mediated resistance (AR trafficking impairment) do not completely overlap. Furthermore, docetaxel likely exerts some cytotoxic effect independent of any inhibitory effect on AR signaling. We also cannot rule out that other potential mechanisms of resistance to enzalutamide may be induced by prior docetaxel treatment (such as activation of nuclear factor-kappa B2/p52 [25, 26]) rendering tumors more refractory to enzalutamide and leading to a shorter duration of clinical benefit regardless of an initial PSA response.

Our results demonstrated inferior clinical outcomes than those reported in the AFFIRM (post-docetaxel) and PREVAIL (pre-docetaxel) trials, respectively. While in the AFFIRM study, 54% of enzalutamide-treated patients achieved a PSA response (with a TTPP of 8.3 months and a PFS of 8.3 months), our cohort of D-pretreated patients fared significantly worse (PSA response rate 25%, TTPP 2.6 months, PFS 3.3 months). The PREVAIL study also revealed superior clinical outcomes in enzalutamide-treated patients when compared to our D-naïve population in terms of both PSA responses and TTPP (PSA responses: 78% *versus* 43%; median TTPP: 11.2 *versus* 7.2 months). These seemingly inferior outcomes in the present study are likely driven (at least in part) by the high proportion of our patients treated with prior CYP17 inhibitors (abiraterone and/or ketoconazole) and due to the presence of more advanced disease including visceral metastases. However, to our knowledge, our study represents the only comparative analysis with a contemporaneous control group evaluating the influence of docetaxel use on the subsequent efficacy of enzalutamide, and as such reflects the current real-world practice.

Our data must be interpreted with caution, particularly given the inherent biases of retrospective studies. Importantly, the decision of whether to administer enzalutamide in D-naïve or D-pretreated patients was made at the discretion of the treating physician and based on patients' preferences and was not random. Although adoption of enzalutamide in the pre-docetaxel setting was influenced by emerging trends in patient care over the time period of our analysis, there were likely individual patient characteristics (*e.g.* disease extent, presence of visceral disease, or pain) that also influenced the treatment decision and could have confounded the outcome. Furthermore, given the availability of multiple treatments in the mCRPC setting and the lack of proper sequencing data, patient preferences and their perception of tolerability may at least in some cases have also influenced physician decision to opt for one or another drug. To correct for this bias, we attempted to minimize confounding by controlling for the most influential clinical factors in the multivariable analysis with the intention to identify factors that are independently associated with TTPP, PFS and OS, although we could not adjust for unmeasured variables. Variables that were not significantly associated with outcomes but that changed the OR or the HR by 10% or more when removed from the analysis were also retained in the final model. Despite these shortcomings, we believe that our data are clinically relevant and may help to shed light on some of the mechanisms of cross-resistance between taxanes and AR-directed agents.

Conclusion

Our data suggest that prior use of docetaxel blunts the activity of subsequent enzalutamide among patients with mCRPC. Moreover, even in patients who did achieve a PSA response

to enzalutamide, TTPP and PFS were inferior in those who had previously received docetaxel. Although cross-resistance between enzalutamide and docetaxel is clinically suggested by the results presented here, there are yet no biomarker predictors of response/resistance to these agents to help clinicians decide which one to use first. To this end, it might also be expected that the activity of docetaxel would be blunted by prior exposure to enzalutamide. Therefore, larger prospective clinical trials are needed to evaluate sequential strategies in further detail (*i.e.* enzalutamide followed by docetaxel *versus* docetaxel followed by enzalutamide), ideally using a biomarker-enrichment design.

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Figure 1.
Overlapping mechanisms of action for enzalutamide and docetaxel

A. Docetaxel-pretreated group **B. Docetaxel-naïve group**

Figure 2.
Maximal PSA change during Enzalutamide
+ Bars are truncated due to > 100% PSA increase

No. at risk										
w/o prior D	47	40	26	17	14	8	6	4	1	0
w/ prior D	60	37	16	10	5	0	0	0	0	0

Figure 3.
 PSA: prostate-specific antigen, mon: months
 w/o prior D: without prior docetaxel
 w/prior D: with prior docetaxel

Figure 4.
mon: months
w/o prior D: without prior docetaxel
w/prior D: with prior docetaxel

Table 1

Baseline Patients Characteristics by docetaxel treatment

	Docetaxel-naïve (n=47)	Docetaxel-pretreated* (n=60)	P value
Race, no (%)			
Non-AA	42 (89.4)	51 (85.0)	0.574
AA	5 (10.6)	9 (15.0)	
Gleason score, no (%)			
7	23 (48.9)	19 (31.7)	0.071
8	22 (46.8)	39 (65.0)	
Unknown	2 (4.3)	2 (3.3)	
T stage, no (%)			
T1/T2	14 (29.8)	17 (28.3)	0.82
T3/T4	25 (53.2)	36 (60.0)	
Tx	8 (17.0)	7 (11.7)	
N stage, no (%)			
N0	24 (51.1)	39 (65.0)	0.46
N1	11 (53.2)	12 (12)	
Nx	12 (25.5)	9 (15)	
M stage, no (%)			
M0	33 (70.2)	43 (71.7)	0.82
M1	13 (27.7)	15 (25.0)	
Mx	1 (2.1)	2 (3.3)	
Neo-/Adjuvant treatment, no (%)			
No	36 (76.6)	40 (66.7)	0.29
Yes	11 (23.4)	20 (33.3)	
Prior antiandrogen therapy**, median no (%)	2 (1 – 4)	2 (1 – 5)	0.76
Prior abiraterone therapy, no(%)			
No	16 (34)	7 (11)	0.008
Yes	31 (66)	53 (88.3)	
ECOG performance status, no (%)[#]			
0	26 (55.3)	29 (48.3)	0.56
1	21 (44.7)	31 (51.7)	
Bone pain, no (%)			
No	27 (57.5)	27 (45.0)	0.24
Yes	20 (42.5)	33 (55.0)	
Extent of disease, no (%)			
0–5 metastatic sites	21 (44.7)	5 (8.3)	

	Docetaxel-naïve (n=47)	Docetaxel-pretreated* (n=60)	P value
> 5 metastatic sites	26 (55.3)	55 (91.7)	<0.0001
Visceral metastases, no (%)			
No	46(97.9)	49(81.7)	
Yes	1 (2.1)	11 (18.3)	0.011
Hemoglobin level, g/dl, mean (SD)	12.1 (±2.0)	11.3 (±1.8)	0.007
Albumin level, g/dL, mean (SD)	4.3 (±1.0)	4.0 (±0.4)	0.042
Alkaline phosphatase level, IU/l, mean (SD)	158.4 (±210.8)	167.1 (±170.3)	0.019
Baseline PSA level, ng/ml, median (SD)	22.8 (0.3–393.0)	94.4 (1–3204)	0.0005

AA: African-American, ECOG: Eastern Cooperative Group, SD: standard deviation, PSA: prostate-specific antigen

* Patients treated with docetaxel before enzalutamide

** Antiandrogen therapy refers to a first-generation androgen-receptor antagonist (*i.e.* flutamide, bicalutamide, nilutamide) or ketoconazole

There were no patients with ECOG performance status 4. Only 2 patients in the Docetaxel-pretreated group and 1 patient in the Docetaxel naïve group had a PS of 3