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Clinical activity of enzalutamide *versus* docetaxel in men with castration-resistant prostate cancer progressing after abiraterone

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Abstract

Background—The optimal sequence of the multiple active agents now available for metastatic castration-resistant prostate cancer (mCRPC) is unclear. Prior reports have suggested diminished responses to sequential lines of androgen receptor (AR)-targeted therapies, but it is unknown whether subsequent taxane-based chemotherapy may be more effective than sequential AR-targeting treatment. We sought to evaluate the clinical activity of enzalutamide *versus* docetaxel in men with mCRPC who progressed on abiraterone.

Methods—We performed a single-institution retrospective analysis of consecutive mCRPC patients who had progressed on abiraterone therapy and subsequently received either enzalutamide (n=30) or docetaxel (n = 31). We evaluated clinical outcomes including prostate-specific antigen decline of >30% (PSA_{30}) or >50% (PSA_{50}), PSA-progression-free survival (PSA-PFS), and clinical/radiographic PFS. We performed multivariable modeling to control for baseline and on-treatment differences between groups.

Results—Compared to subjects who received enzalutamide post-abiraterone, subjects who received docetaxel post-abiraterone had more bone metastases, more visceral metastases, higher baseline PSA, and had more frequent PSA tests while on-treatment. There were no significant differences in PSA_{30} (41% for enzalutamide *vs* 53% docetaxel) or PSA_{50} (34% vs 40%) response rates between the two groups; there remained no difference after stratifying by presence/absence of prior response to abiraterone. Median PSA-PFS was 4.1 *vs* 4.1 months for the enzalutamide and docetaxel cohorts, respectively (HR 1.35, 95% CI, 0.53-3.66, *P*=0.502). Median PFS was 4.7 *vs* 4.4 months, respectively (HR 1.44, 95% CI, 0.77-2.71, *P*=0.257). PSA-PFS and PFS did not differ after stratifying by prior response to abiraterone. In multivariable analyses, there were no significant differences in PSA-PFS or PFS between the two groups.

Conclusions—Treatment with either enzalutamide or docetaxel produced modest PSA responses and PFS intervals in this abiraterone-pretreated mCRPC population. In this retrospective study with small sample size, no significant differences in outcomes were observed between groups. Therefore, either enzalutamide or docetaxel may be a reasonable option in men who have progressed on abiraterone.

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1. Introduction

Prostate cancer (PCa) is an androgen-responsive disease. However, although nearly all men with metastatic PCa will initially respond to androgen-deprivation therapy (ADT), resistance to ADT eventually develops despite 'castrate' testosterone levels, a state known as castration-resistant prostate cancer (CRPC). The taxane agent, docetaxel, remained the only modality that improved overall survival in CRPC patients for several years, after initial FDA-approval in 2004.[1] However, more recently several agents have demonstrated increased overall survival in this setting, including two modulators of the androgen pathway, abiraterone acetate and enzalutamide. Abiraterone is an inhibitor of adrenal and intratumoral androgen synthesis through blockade of CYP17 enzymatic activity. When combined with LHRH agonists, abiraterone further decreases circulating testosterone often to undetectable levels. In the COU-AA-301 and COU-AA-302 registration trials, abiraterone demonstrated overall survival benefits in the post-docetaxel and pre-docetaxel settings, although it did not meet its pre-specified boundary for significance for OS in the chemotherapy-naïve setting.[2, 3] Enzalutamide is a second-generation anti-androgen which additionally prevents androgen receptor (AR) translocation to the nucleus and interaction with DNA androgen response elements. In the AFFIRM and PREVAIL studies, enzalutamide also improved overall survival in both the docetaxel-naïve and docetaxel-pretreated mCRPC populations.[4, 5]

Given the improved tolerability of hormonal manipulations using abiraterone and enzalutamide relative to docetaxel chemotherapy, there has been increased use of these agents in the chemotherapy-naïve setting. However, many patients will progress after second-line therapies and beyond and the optimal sequence of these AR-targeting agents and taxane chemotherapy agents remains unclear. Data are lacking regarding responses to sequential AR-targeting agents in the chemotherapy-naïve setting. However, cross-resistance does appear to occur in the post-docetaxel setting. Small case series have demonstrated infrequent responses to either abiraterone or enzalutamide following progression on the alternative agent or docetaxel chemotherapy; median times to progression were short, approximating 3-4 months (Table 1).[6-9] Additionally, docetaxel may exert its efficacy partly through AR-targeted disruption of the microtubule network that is necessary for translocation of AR into the nucleus.[10, 11] To this end, treatment with docetaxel following abiraterone has produced significantly shorter progression-free survival intervals than in the abiraterone-naive setting, suggesting cross-resistance between these two agents. [12]

Currently, abiraterone is FDA-approved to treat mCRPC in the chemotherapy-naïve setting; however it is unclear whether patients who progress on abiraterone should be subsequently treated with enzalutamide or docetaxel. To assess and compare the clinical activity of these agents in the post-abiraterone setting, we performed a retrospective review of consecutive mCRPC patients from a single high-volume academic center who had received previously abiraterone and were subsequently treated with either enzalutamide or docetaxel.

2. Patients and methods

2.1 Patients

This was a retrospective, single-institution analysis that included all consecutive mCRPC patients treated with either enzalutamide or docetaxel following abiraterone therapy immediately prior. CRPC was defined on the basis of evidence of disease progression (clinical, radiographic, or PSA elevation) in spite of 'castrate' serum testosterone levels (<50 ng/dL) and continuous LHRH agonist/antagonist therapy. Follow-up data (PSA measurements, radiographic studies, clinical symptom evaluations) were collected through March 2014.

Subjects with mCRPC who had progressed on abiraterone and who were subsequently treated immediately thereafter with either enzalutamide or docetaxel were identified via a query of the Johns Hopkins Hospital electronic medical record system. Additional clinical data were derived through paper chart review and included age, Gleason score, prior treatment with hormonal therapy (anti-androgens [bicalutamide, flutamide, nilutamide] or ketoconazole), baseline PSA, number and type of bone, lymph node, and visceral metastases, ECOG performance status, and prior PSA response to abiraterone. The number of PSA labs and bone/CT scans/MRIs performed in the 6 months after treatment initiation were also collected to identify differences in on-treatment practice patterns. Subjects in whom we were unable to reliably confirm the course of therapy or follow-up were excluded. Institutional review board (IRB) approval was obtained prior to data collection and analysis.

2.2 Statistical analysis

The primary objective was to determine the clinical efficacy of enzalutamide *versus* docetaxel following progression on abiraterone with respect to PSA responses (>30% and >50% decline from baseline, denoted as PSA_{30} and PSA_{50}), clinical/radiographic progression-free survival (PFS), and PSA-progression-free survival (PSA-PFS), as defined under Prostate Cancer Clinical Trials Working Group (PCWG2) criteria.[13] PSA progression was defined as a rising PSA level while on therapy that was >25% and >2 ng/mL above the baseline or nadir value. In most instances, this was confirmed at a subsequent date; however, confirmation was not consistently performed on all patients. PFS was defined as the time interval from therapy initiation until radiographic or clinical progression (or death), whichever came first. Confirmatory scans were not generally performed since patients were treated per regular clinical practice. PSA elevations alone were not considered in the definition of PFS. Subjects were censored upon initiating a new therapy subsequent to enzalutamide or docetaxel if they did not display evidence of clinical or radiographic progression by that time.

Descriptive statistics were used to summarize the patient characteristics of the two groups. Differences between cohorts were compared using Wilcoxon-Mann Whitney test for continuous variables or Fisher's exact test for categorical variables. PSA-PFS and PFS were summarized using the Kaplan-Meier method, and differences between groups were determined via the log-rank test. Univariable Cox proportional hazards models, multivariable models, and propensity score-weighted multivariable models were constructed

to evaluate the effect of confounding variables on PSA-PFS and PFS. Covariates that were significant in the univariable analysis that were included in the multivariable model were treatment group, number of PSA values available within 6 months after initiation of therapy, baseline PSA level, and presence of visceral metastases. The propensity score-weighted multivariable model was further adjusted for bone metastases, lymph node metastases, lung metastases, liver metastases, and PSA response to abiraterone. All tests were two-sided and considered significant at $P<0.05$. Statistical analyses were conducted using R version 2.15.1.

3. Results

3.1 Patients

A total of 61 consecutive patients were identified who had previously progressed on abiraterone and who were subsequently treated with either enzalutamide (n = 30) or docetaxel (n = 31). Patient and tumor-specific characteristics are summarized in Table 2. Patients who received docetaxel following abiraterone had significantly more bone metastases, a higher likelihood of having visceral metastases, higher baseline PSA values, and more PSA measurements collected while on treatment, compared to those receiving enzalutamide. There were no significant differences noted in age, Gleason score, number of bone/CT scans/MRIs, ECOG performance status, prior hormonal therapies, or primary refractoriness to abiraterone (defined as failure to achieve a PSA_{30} response at any time during therapy).

3.2 Enzalutamide *versus* docetaxel after abiraterone

No differences were noted between the enzalutamide and docetaxel groups with respect to PSA_{30} and PSA_{50} rates, PSA-PFS, or PFS. After progression on abiraterone, 12 enzalutamide-treated patients (41%) achieved a PSA_{30} response and 10 (34%) experienced a PSA_{50} response. Of the docetaxel-treated patients, 16 (53%) and 12 (40%) experienced a PSA_{30} and PSA $_{50}$, respectively. There were no significant differences between the groups in PSA_{30} or PSA_{50} responses. Waterfall plots depicting changes in PSA after enzalutamide or docetaxel treatment are shown in Figure 1. A multivariable logistic model was constructed to control for baseline PSA and primary refractoriness to prior abiraterone therapy; there remained no difference in either PSA_{30} (OR for docetaxel = 2.17, 95% CI, 0.68-7.30, P=0.20) or PSA_{50} (OR 1.68, 95% CI, 0.51-5.66, p=0.40) between the two groups.

The median PSA-PFS was 4.1 months (95% CI, 2.8-7.4 months) for the enzalutamide group and 4.1 months (95% CI, 2.5-5.7 months) for the docetaxel group (log rank p=0.327), with a hazard ratio of 1.35 (95% CI, 0.53-3.656, P=0.502). Similarly, PFS was 4.7 months (95% CI, 3.4-NA months) and 4.4 months (95% CI, 2.9-6.7 months)in the enzalutamide and docetaxel groups, respectively (HR 1.44, 95% CI, 0.77-2.71, p=0.257) (Figure 2). Neither the PSA-PFS nor the PFS were significantly different after stratifying for subjects with primary abiraterone resistance (median PSA-PFS 4.9 *vs* 4.1 months for enzalutamide *vs* docetaxel, p=0.51; median PFS 6.0 *vs* 4.7 months for enzalutamide vs docetaxel, p = 0.27) or prior PSA response to abiraterone (median PSA-PFS 3.0 *vs* 3.2 months for enzalutamide *vs* docetaxel, p=0.58; median PFS 3.4 vs 3.3 months for enzalutamide vs docetaxel, p = 0.74) (Figure 3).

Multivariable and propensity score-weighted models were constructed to account for baseline differences between the enzalutamide and docetaxel cohorts. After controlling for the number of PSAs collected in the 6 months after initiation of therapy, baseline PSA level, and presence of visceral metastases, the docetaxel group demonstrated a HR of 1.39 (95% CI, 0.53-3.66, p=0.50) for PFS in a multivariate Cox model and a HR of 1.76 (95% CI, 0.76-4.06, p=0.18) in a propensity score-weighted model. Results were similar for PFS with an HR of 1.44 (95% CI, 0.53, 3.92, p=0.47) in the multivariate Cox model and an HR of 1.81 (95% CI, 0.79-4.12, p=0.16) in the propensity score-weighted model (Table 3).

4. Discussion

In this retrospective study, we analyzed clinical outcomes in men with metastatic CRPC who received either enzalutamide or docetaxel following progression on abiraterone. We found that the two groups demonstrated similar PSA responses as well as PSA-PFS and PFS intervals. These two groups clearly differed with respect to their baseline characteristics, with the docetaxel-treated patients generally having more advanced disease with increased baseline PSA and a greater likelihood of visceral metastases than the enzalutamide-treated patients. This likely reflects historical practice of treating rapidly-progressing or symptomatic patients with chemotherapy. Additionally, there was a difference in practice patterns between the two groups, with significantly more PSA values obtained for the docetaxel group, likely reflecting the desire to minimize the risk of continuing treatment with docetaxel, a considerably more toxic agent than enzalutamide, in the face of emerging resistance. Importantly, after controlling for these factors, there remained no significant difference with respect to responses or progression, although the power to assess differences was limited by the small sample size.

With five agents approved for the treatment of metastatic CRPC in the last four years, there is currently little guidance as to the most effective sequencing of these agents, particularly as abiraterone and enzalutamide have each demonstrated efficacy in both the chemotherapy-naïve and post-docetaxel populations.[2, 4, 5] Given the relatively benign toxicity profile of abiraterone and enzalutamide relative to chemotherapy, these agents are increasingly being prescribed in the front-line setting (although use of enzalutamide in the pre-chemotherapy space is currently considered off-label use). Our findings are reassuring in that following progression on abiraterone, either enzalutamide or docetaxel remain reasonable agents with modest activity.

Prior reports of second AR-targeted agents following treatment with a prior AR-targeted agent or chemotherapy have demonstrated modest response rates and only transitory benefits.[6-9] Multiple mechanisms of resistance in CRPC cells include AR gene amplification, enhanced AR sensitivity and promsicuity, ligand-independent AR signaling such as through the AR-V7 splice variant, or bypass pathways.[14] In the case of abiraterone, resistance may also result from up-regulation of steroidogenic gene expression.[15]

In the present analysis, stratification based on prior abiraterone response showed that men who were refractory to abiraterone (*i.e.* failed to achieve a PSA_{30} response) did not demonstrate inferior responses to enzalutamide compared to docetaxel. Although these

subsets were small, the similarly poor responses to either enzalutamide or docetaxel in the primary abiraterone refractory men potentially suggest overlapping mechanisms of resistance. There is emerging evidence that one mechanism of action of docetaxel may be related to blockade of AR nuclear trafficking via microtubule inhibition.[10, 11, 16, 17] Further, the presence of AR splice variants, such as AR-V7, appears to predict lack of response to docetaxel *in vitro*. Clinically, a recent analysis found that men who were pretreated with abiraterone and subsequently received docetaxel demonstrated significantly decreased responses and PFS intervals with docetaxel compared with abiraterone-naïve men that received docetaxel.[12] The present study thus further supports the hypothesis of cross-resistance to AR-targeting as a possible mechanism of resistance for docetaxel.

Limitations of this study include its relatively small sample size and retrospective nature as well as incomplete information with regards to all covariates. Significant differences between the two groups existed in terms of baseline characteristics, and practice patterns also differed in the two groups especially with respect to PSA testing intervals. Furthermore, PSA and radiographic studies were not uniformly obtained even within the context of each therapy. Although multivariable and propensity score weighting were used to control for these differences, there may be other unknown covariates that could have influenced our results. Nevertheless, this represents a first attempt to evaluate the comparative efficacy of docetaxel and enzalutamide in abiraterone-pretreated patients, although this would clearly be accomplished better in the setting of a prospective randomized trial. In the chemotherapy-naïve setting, one trial will randomize men to either the sequence of first-line abiraterone and second-line enzalutamide or the converse sequence (NCT02125357). A trial currently in development will randomize men who have progressed on first-line abiraterone or enzalutamide to either cabazitaxel versus the alternative hormonal agent. Lastly, a trial currently in development plans to randomize men who have progressed on abiraterone to either docetaxel or enzalutamide. The outcomes of these studies will inform future decisions about the optimal sequence of therapies in CRPC.

5. Conclusion

This study is the first to evaluate abiraterone-pretreated mCRPC patients who subsequently received either enzalutamide or docetaxel as their next systemic therapy. No differences were observed in PSA response rates or PFS intervals between the two groups, after controlling for baseline and on-treatment differences. Additionally, there were no differences in efficacy noted between the two agents when comparing abiraterone-responsive or abiraterone-refractory men. While this study suggests that either agent may be reasonably effective in the post-abiraterone setting, prospective trials are needed to fully define the optimal sequencing of AR-targeting and chemotherapy agents.

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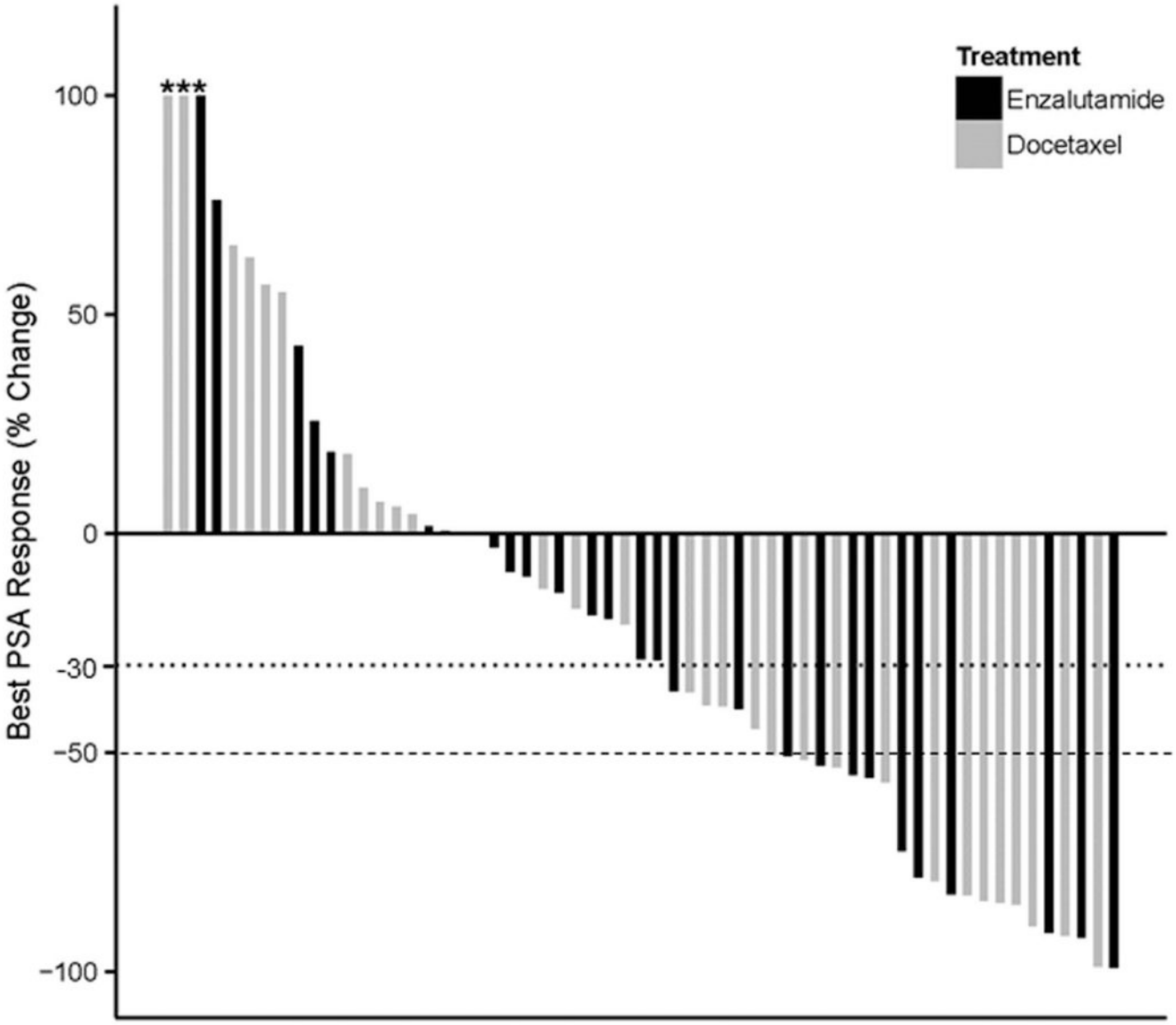

Figure 1.

Waterfall plot depicting the maximal prostate-specific antigen (PSA) decline (or minimum increase for those without a PSA decline) after initiation of enzalutamide or docetaxel. Dashed lines indicated PSA_{30} and PSA_{50} responses. *Bar is truncated due to >100% PSA increase.

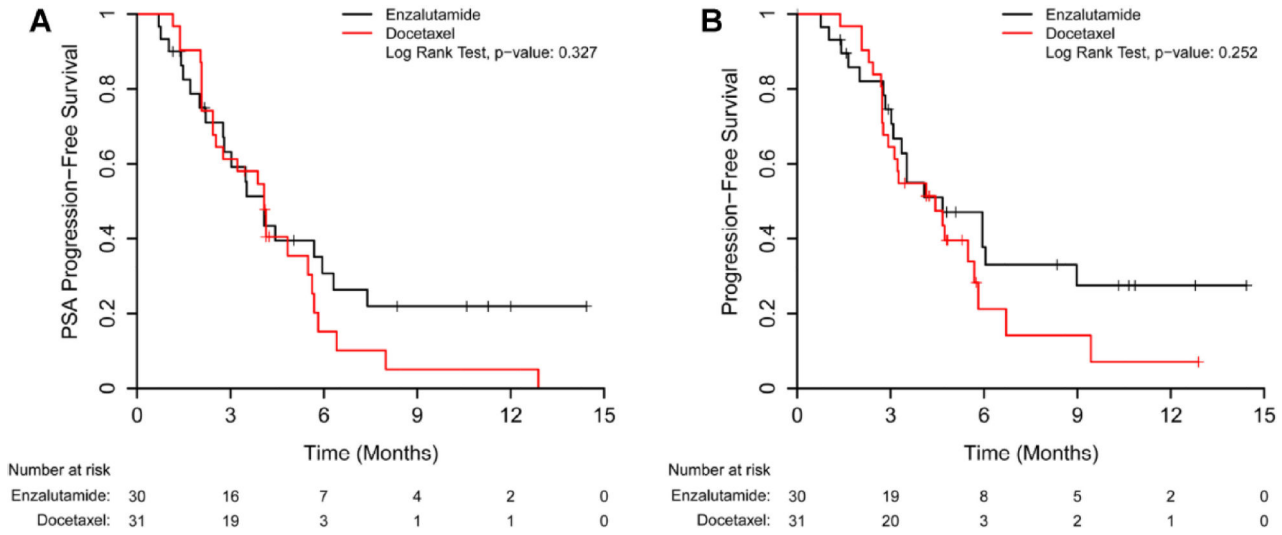

Figure 2.

Kaplan-Meier curves for (A) PSA-progression-free survival (PSA-PFS) and (B) clinical/radiographic progression-free survival (PFS) during treatment with either enzalutamide or docetaxel.

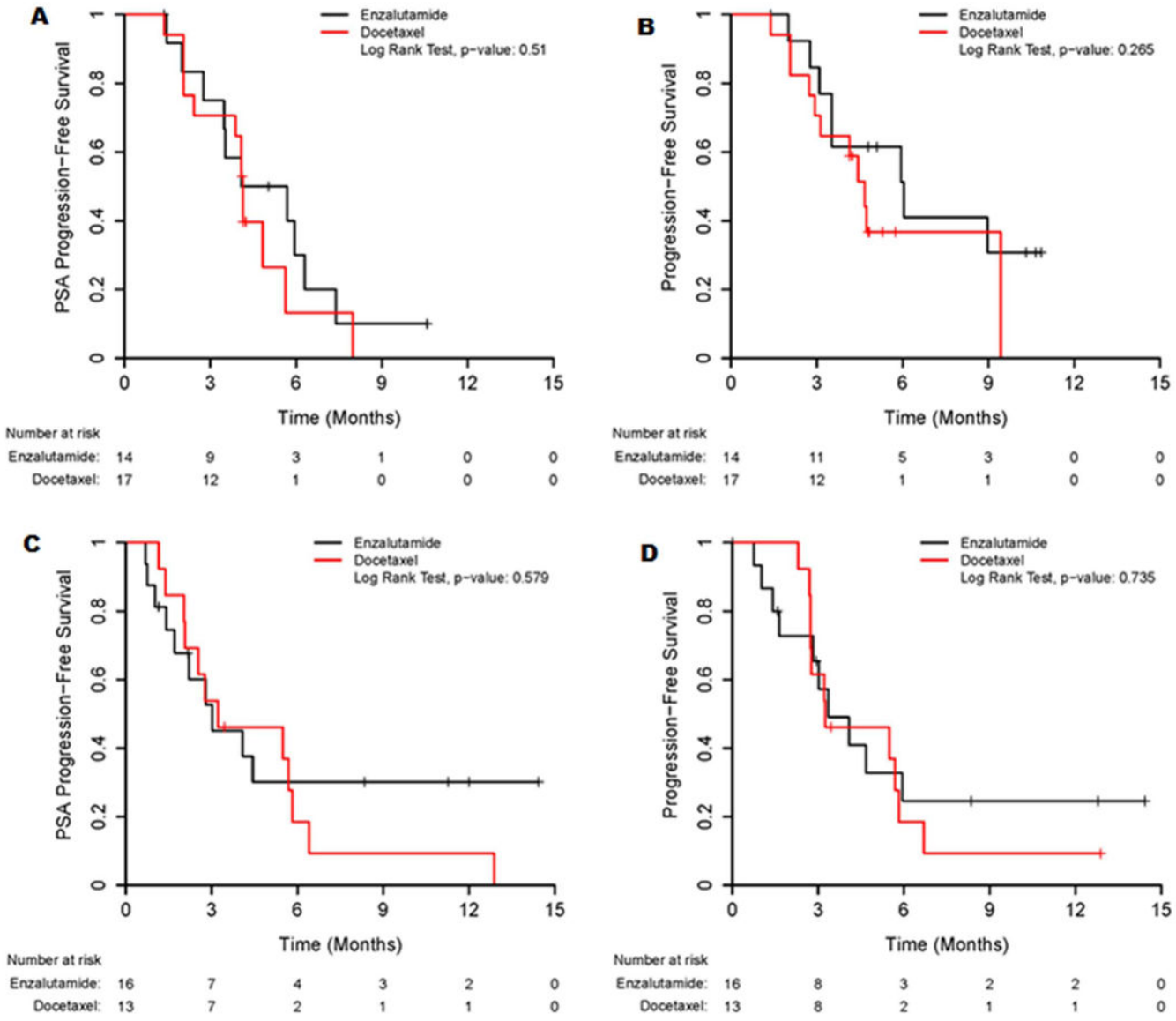

Figure 3.

Kaplan-Meier curves for (A) PSA-PFS and (B) PFS in patients refractory to prior abiraterone (*i.e.* failure to achieve PSA_{30}); and (C) PSA-PFS and (D) PFS in patients with prior response to abiraterone (>30% PSA decline).

Table 1

Clinical response to 3rd line hormonal agents in prior case-series. ORR = overall response rate by RECIST 1.1 criteria.

	Active therapy	Prior therapies	PSA_{50} rate	ORR	Time to progression
Noonan *et al.* [8]	Abiraterone	Enzalutamide and docetaxel	4%	0%	3.9 mo
Loriot *et al.* [6]	Abiraterone	Enzalutamide and docetaxel	8%	8%	2.7 mo
Schrader *et al.* [7]	Enzalutamide	Abiraterone and docetaxel	28.6%	2.9%	Not assessed
Badrising *et al.* [9]	Enzalutamide	Abiraterone and docetaxel	21%	Not assessed	3.0 mo

Table 2
Baseline demographic and on-treatment characteristics

	Enzalutamide (n = 30)	Docetaxel (n = 31)	p-value
Age, yr, mean (SD)	70.6 (9.0)	68.3 (8.3)	0.214
Gleason Score, no. (%)			
6	3 (10)	1 (3)	0.102
7	12 (41)	6 (21)	
8-10	14 (48)	22 (76)	
Missing	1	2	
Bone metastases, no. (%)			
0	5 (17)	1 (4)	<0.001
1-3	25 (83)	7 (25)	
4-10	0 (0)	5 (18)	
>10	0 (0)	15 (54)	
Missing	0	3	
Any visceral metastases, no. (%)	17 (30)	13(48)	0.008
Missing	0	4	
Anti-androgen pre-treatment, no. (%)	28 (93)	28 (93)	>0.99
Missing	0	1	
Ketoconazole pre-treatment, no. (%)	19 (63)	22 (73)	0.58
Missing	0	1	
Baseline PSA , median (IQR)	26 (13-296.8)	192 (70.5-456.9)	<0.001
Missing	1	2	
PSA_{30} response to abiraterone, no. (%)	16 (53)	13 (43)	0.606
Missing	0	1	
ECOG PS, no. (%)			
0-1	29 (97)	21 (95)	>0.99
2-4	1 (3)	1 (5)	
Missing	0	9	
Number of PSAs in 6 months after initiation of therapy, mean (SD)	3.61 (2.18)	5.94 (2.25)	<0.001
Missing	2	0	

Table 3

Multivariable Cox and Propensity score-weighted multivariable Cox model s for prostate-specific antigen progression-free survival (PSA-PFS) and clinical/radiographic progression-free survival (PFS).

Multivariable Cox Model						
		PSA-PFS			PFS	
	HR	95% CI	*p* value	HR	95% CI	*p* value
Enzalutamide (vs docetaxel)	1.39	0.53-3.66	0.50	1.44	0.53-3.92	0.47
Number of PSAs in 6 months after treatment initiation	0.95	0.80-1.14	0.61	0.96	0.80-1.15	0.63
Baseline PSA	1.00	1.00-1.00	0.49	1.00	1.0-1.0	0.09
Presence of visceral metastases	0.88	0.45-1.74	0.72	0.85	0.42-1.74	0.66
Propensity Score-Weighted Multivariable Cox Model						
		PSA-PFS			PSA	
	HR	95% CI	*p* value	HR	95% CI	*p* value
Enzalutamide (vs docetaxel)	1.76	0.76-4.06	0.18	1.81	0.79-4.12	0.16
Number of PSAs in 6 months after treatment initiation	0.89	0.77-1.04	0.14	0.91	0.79-1.05	0.21
Baseline PSA	1.00	1.00-1.00	0.24	1.00	1.00-1.00	0.01
Presence of visceral metastases	0.78	0.45-1.35	0.37	0.77	0.43-1.36	0.37