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The Influence of Prednisone on the Efficacy of Docetaxel in Men with Metastatic Castration-Resistant Prostate Cancer

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Abstract

BACKGROUND—Prednisone and other corticosteroids can provide palliation and tumor responses in patients with prostate cancer. The combination of docetaxel and prednisone was the first treatment shown to prolong survival in men with metastatic castration-resistant prostate cancer (mCRPC). Since the approval of docetaxel in 2004, additional treatments are available, including abiraterone, which is also administered with prednisone. Therefore, patients are increasingly likely to have prednisone therapy several times throughout their disease course, and the contribution of prednisone to the efficacy of docetaxel is unknown.

METHODS—We conducted a retrospective study of patients with mCPRC treated with docetaxel at our institution between 2004–2014. Patients were divided into 2 cohorts based upon whether prednisone was co-administered with docetaxel. Cohorts were further stratified based upon prior prednisone (with abiraterone) or hydrocortisone (with ketoconazole) use. The primary endpoint was clinical/radiographic progression-free survival (PFS). The secondary endpoints were >50% PSA response rate and PSA progression-free survival (PSA-PFS). A multivariable cox regression model was constructed to determine if prednisone use was independently predictive of PFS.

RESULTS—We identified 200 consecutive patients for inclusion in the study: 131 men received docetaxel with prednisone and 69 received docetaxel alone. The docetaxel-prednisone cohort had superior PFS compared to the docetaxel-alone cohort (median PFS: 7.8 vs 6.2 months, HR 0.68 [95% CI 0.48–0.97], p=0.03). Prednisone was associated with a reduced risk of progression on docetaxel in the propensity score-weighted multivariable Cox model (p=0.002). Among abiraterone- or ketoconazole-pretreated patients, no difference in PFS was observed between prednisone-containing and non-prednisone containing cohorts (median PFS: 7.1 vs 6.3 months, HR 0.96 [95% CI 0.59–1.57], p=0.87).

CONCLUSIONS—The incorporation of prednisone potentially augments the efficacy of docetaxel in patients with mCRPC. We hypothesize that this advantage is limited to patients who have not previously received corticosteroids. Prospective confirmation is needed.

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Conflict of interest:

The authors declare no conflicts of interest.

Keywords

prednisone; docetaxel; taxane; chemotherapy; metastatic prostate cancer

Introduction

Prednisone and other corticosteroids are used frequently in the treatment of advanced prostate cancer. Corticosteroids are sometimes prescribed to alleviate pain from bone metastases,[1] for management of cancer-related fatigue,[2] or to potentially reduce chemotherapy-related toxicity.[3] Beyond these palliative uses, corticosteroids have also been associated with favorable antitumor responses.[4] In addition, a number of randomized trials in advanced prostate cancer have used corticosteroids (namely prednisone) as the backbone or the control arm of these studies. This includes the study of Tannock *et al.* comparing mitoxantrone plus prednisone vs. prednisone alone which led to FDA approval of the combination for palliation of symptomatic castration-resistant prostate cancer (CRPC).[5] Thus, data on efficacy of many drugs in prostate cancer is interpreted in the context of concurrent corticosteroid use.

Docetaxel was the first chemotherapy agent shown to prolong survival in men with metastatic CRPC. In the pivotal TAX327 study, 75mg/m^2 of docetaxel given intravenously every 3 weeks was compared to mitoxantrone given every 3 weeks. Since the control group in this study consisted of mitoxantrone and prednisone, patients on the docetaxel arm also received the same dose of 5mg of prednisone administered orally twice daily.[6] The arm receiving every-3-week docetaxel (plus prednisone) demonstrated superior survival, resulting in FDA approval of docetaxel plus prednisone in 2004 for metastatic CRPC,[7] and quickly replacing the prior standard-of-care consisting of mitoxantrone plus prednisone. Notably, a non-prednisone containing regimen of docetaxel plus estramustine was also shown to be superior to mitoxantrone plus prednisone,[8] but this regimen has fallen out of favor due to the significant toxicities of estramustine and the questionable added benefit.[9]

Since 2004, docetaxel has been a cornerstone of treatment for men with advanced prostate cancer. In modern clinical practice, however, prednisone is not always co-administered with docetaxel, for a number of reasons.[10] First, some oncologists have concerns about the sequelae of chronic prednisone use, such as glucose intolerance, osteopenia, fluid retention and peptic ulcers, among other risks.[11] Furthermore, there is a theoretical risk of activating the androgen receptor (AR) with prednisone, leading to growth of prostate cancer.[12] Patients experiencing progression on antiandrogen therapy occasionally have responses to antiandrogen withdrawal;[13] one basis for this observation is changes in AR signaling leading to paradoxical AR agonism with antiandrogens.[14] Similarly, other AR mutations may allow activation by glucocorticoids. For example, although the wild-type AR does not engage glucocorticoids, the T878A and L702H mutations in AR allow glucocorticoid binding to the ligand-binding domain,[15] leading to glucocorticoid-mediated activation of downstream androgen-response elements causing growth of cancer cells.[16]

Although docetaxel is frequently given in combination with prednisone based on the results of the TAX327 study, there is no compelling biological evidence for synergy between

glucocorticoids and taxanes. Thus, whether prednisone contributes to the efficacy of docetaxel or is merely a vestige of docetaxel's approval process remains unclear.[17] Two recently presented studies that tested docetaxel in metastatic castration-sensitive disease employed different strategies regarding prednisone. In STAMPEDE, docetaxel and prednisolone were added to androgen deprivation therapy (ADT) and compared to ADT alone. The patients receiving up to 6 cycles of chemotherapy had significantly improved survival (77mo vs 67mo, HR 0.76 [95%CI 0.63–0.91]).[18] In CHAARTED, patients who received up to 6 cycles of docetaxel plus ADT—without prednisone—also demonstrated significantly improved survival compared to patients receiving ADT alone (52.7mo vs 42.3mo, HR= 0.63 [95%CI 0.48–0.82]).[19] The efficacy of both CHAARTED and STAMPEDE protocols casts some doubt to prednisone's added value in this setting.

This begs the question of whether prednisone is required for patients receiving docetaxel for metastatic CRPC. Since there are no prospective trials comparing docetaxel/prednisone with docetaxel-alone, we conducted a retrospective analysis to investigate the independent contribution of prednisone on the clinical efficacy of docetaxel. This study was enabled by the fact that not all clinicians using docetaxel to treat prostate cancer at our institution routinely prescribed it with prednisone. We also examined whether prior use of abiraterone (which is also given with prednisone) or ketoconazole (which is given with hydrocortisone) influenced the effect of prednisone on docetaxel. We hypothesized that prednisone would augment the efficacy of docetaxel, but only in men who had not received prior corticosteroids in combination with either abiraterone or ketoconazole.

Patients and Methods

We conducted an IRB-approved retrospective study involving consecutive patients treated with first-line docetaxel chemotherapy for metastatic CRPC at our institution between 2004 and 2014. Only patients who received every-3-weekly docetaxel (at a planned dose of 75mg/m2) were included; those receiving weekly docetaxel were not studied. Patients who received additional concurrent therapies (*e.g.* abiraterone, enzalutamide, radium-223), those who had small cell/neuroendocrine histologies, and those without follow-up information were excluded.

Patients were divided into two cohorts: those who received docetaxel with concurrent prednisone, and those who received docetaxel alone. These two groups emerged due to variations in physician practice with respect to routinely prescribing prednisone with docetaxel. We also gathered further clinical data on age, year of docetaxel initiation, Gleason score, number and types prior hormonal therapies received (with particular attention to prior abiraterone or enzalutamide use), presence of visceral metastases, ECOG performance status, presence of pain, baseline hemoglobin, creatinine, alkaline phosphatase, and prostate-specific antigen (PSA) value. The number of cycles of docetaxel administered, date of PSA progression, and date of clinical/radiographic progression were recorded. We defined PSA progression as an increase from nadir of 25% (and at least 2ng/mL), without requiring a confirmatory PSA measurement. Clinical/radiographic progression was defined as the first of soft tissue progression, bone scan progression, or clinical progression. In patients with measureable disease, radiographic progression was determined by applying RECIST criteria

(i.e. >20% increase in the sum of target lesions). Progression on the basis of bone scan was defined as the development of 2 new osseous lesions that were not related to a flare phenomenon, similar to Prostate Cancer Working Group 2 (PCWG2) criteria;[20] however, confirmatory imaging was not required. Progression on clinical grounds was defined as an escalation of bone pain, a referral for palliative radiation to bone, a referral for surgical stabilization of bone, or any other cancer-related complication (e.g. obstructive uropathy, myelophthisic bone marrow failure). Data was censored at the time of initiation of further therapy if that date occurred prior to PSA or clinical/radiographic progression.

The primary endpoint was clinical/radiographic progression-free survival (PFS). We chose PFS as the endpoint instead of overall survival because most patients received multiple subsequent therapies that may have confounded survival estimates. Secondary endpoints included >50% PSA response rates and PSA progression-free survival (PSA-PFS); PSA response rates correlate with overall survival in meta-analyses of docetaxel-based trials.[21] We also performed subgroup analyses investigating the effect of prednisone on docetaxel's efficacy in 2 substrata: men who had previously received abiraterone or ketoconazole and men who had not received abiraterone or ketoconazole before.

Statistical considerations: A comparison of baseline characteristics between the docetaxel/prednisone group and the docetaxel-alone group was performed using Fisher's exact test for categorical variables and Wilcoxon-Mann Whitney test for continuous variables. Best PSA responses were depicted using standard waterfall plots; PSA response rates were compared using Fisher's exact test. PFS and PSA-PFS were displayed using Kaplan-Meier curves, and differences between groups were sought with the log-rank test. To adjust for baseline clinical characteristics, univariate and propensity score-weighted multivariable regression models were constructed to determine if prednisone use was independently predictive of clinical outcomes. To estimate whether the influence of prednisone on docetaxel efficacy differed according to prior abiraterone or ketoconazole use, multivariable Cox regression analyses were performed with the interaction terms of 'prednisone' and 'abiraterone'/'ketoconazole', and simultaneously adjusted for the other clinical variables.

Results

We identified 200 consecutive patients for inclusion in the study: 131 men received docetaxel with prednisone, and 69 received docetaxel alone, reflecting different practice patterns at our institution. Summary statistics for each cohort are listed in Table 1. Groups were generally balanced with respect to baseline characteristics. More patients had missing performance status data in the docetaxel-alone group. Prior abiraterone use was significantly more common in the docetaxel/prednisone cohort. Enzalutamide treatment prior to chemotherapy[22] was uncommon in both groups during this time. Notably, all patients who received prior enzalutamide also received abiraterone.

Clinical/radiographic PFS for the entire docetaxel-treated population (depicted in Figure 1) was the primary endpoint. In an unadjusted analysis, PFS was superior in the docetaxel/prednisone group compared to the docetaxel-alone group (median PFS: 7.8 vs 6.2 months, HR 0.68 [95% CI 0.48–0.97], p=0.03). The clinical/radiographic PFS advantage for the

docetaxel/prednisone cohort was supported by the difference in the number of chemotherapy cycles received. On average, the docetaxel/prednisone cohort received 7.3 cycles of docetaxel compared to 5.7 cycles for the docetaxel alone cohort. These numbers corresponded to a median of 7 cycles (range 1 – 19) versus 6 cycles (range (1 – 13) for docetaxel/prednisone and docetaxel alone cohorts, respectively.

We next constructed a propensity score-weighted multivariable Cox model to determine factors independently associated with PFS (Table 2). In this model, prednisone use was significantly associated with a reduced risk of clinical/radiographic progression on docetaxel, after adjusting for other factors (HR 0.53 [95% CI 0.35–0.80], p=0.002). Performance status 0 (vs 1-2) was also associated with reduced risk for clinical/radiographic progression. Gleason score 7 or 8-10 appeared to be more favorable than Gleason score 6, an unexpected finding, although only 6% of patients had Gleason 6 disease. Prior data has shown that the incremental benefit for high-grade tumors is greater with docetaxel compared to lower-grade tumors, but patients with lower-grade tumors have longer survival.[23] Prior abiraterone or ketoconazole use was not significantly associated with inferior PFS in this model; however, the interaction test between treatment with prednisone and prior abiraterone or ketoconazole use was significant.

In a prespecified analysis, we examined clinical/radiographic PFS stratified by prior abiraterone or ketoconazole use (abiraterone is prescribed with 10mg of prednisone daily and ketoconazole is prescribed with 30mg of hydrocortisone daily, so patients with prior abiraterone or ketoconazole exposure also had prior corticosteroid exposure). Among corticosteroid-naïve patients (i.e. no prior abiraterone or ketoconazole), docetaxel/prednisone was superior to docetaxel alone (Figure 2A; median PFS: 8.9 vs 5.9 months, HR 0.49 [95% CI 0.29–0.84], p=0.009). For abiraterone- or ketoconazole-pretreated patients, a difference in PFS was not seen between docetaxel/prednisone and docetaxel-alone arms (Figure 2B; median PFS: 7.1 vs 6.3 months, HR 0.96 [95% CI 0.59–1.57], p=0.87).

PSA responses were also analyzed in the 2 patient cohorts. Best PSA responses are illustrated in the waterfall plots in Figure 3; >50%PSA responses were numerically higher in the docetaxel-prednisone cohort. Table 3 shows >50% PSA response rates stratified by prior abiraterone or ketoconazole use; superior PSA responses in the docetaxel/prednisone group were only observed in those who had not previously received abiraterone or ketoconazole. In a propensity score-weighted multivariable logistic regression model, poor performance status and liver metastases were independently associated with a poor PSA response.

We also compared PSA progression-free survival (PSA PFS) between cohorts. Median PSA PFS was similar in the docetaxel/prednisone and docetaxel-alone cohorts in an unadjusted analysis (5.5 vs 5.0 months, HR 0.80 [95% CI 0.57–1.13], p=0.20). For the subgroup of patients without prior abiraterone or ketoconazole use, prednisone use was significantly associated with a reduced risk for PSA progression (HR 0.59 [95% CI 0.36–0.99], p=0.04). For abiraterone- or ketoconazole-treated patients, however, the differences were non-significant (HR 1.09]95% CI 0.68–1.75], p=0.71). In the propensity score-weighted multivariable Cox model, concurrent prednisone use was associated with a decreased risk of

PSA progression (HR 0.53 [95% CI 0.35–0.79], p=0.002), and the interaction test between prednisone use and prior abiraterone or ketoconazole use was significant (p=0.04).

Discussion

Both prednisone and docetaxel are active agents in the treatment of advanced prostate cancer. In our study, we postulated that docetaxel plus prednisone would be more effective than docetaxel alone. Indeed, patients in the docetaxel/prednisone cohort had superior outcomes (longer PFS, longer PSA PFS, higher PSA repose rates) than those receiving docetaxel alone. One possible explanation for this result is that patients received additive benefit from two drugs that are each known to be effective in prostate cancer through different mechanisms.

The activity of prednisone as a single agent has been well characterized. For example, in a randomized phase III trial of mitoxantrone/prednisone versus prednisone-alone, patients receiving 10mg of prednisone daily had >50% PSA response rates of 24% and a PFS of 4.1 months.[24] Comparable responses were reported in the control arm of the pre-chemotherapy COU-AA-302 study of abiraterone/prednisone versus prednisone-alone.[25] In that study, 24% of patients receiving prednisone 10mg daily achieved a >50% PSA response rate, with a PFS of 8.1 months. The mechanism by which prednisone exerts its activity in prostate cancer is at least partially understood. Corticosteroids can suppress adrenal androgens leading to a more complete androgen blockade. They can also inhibit growth of prostate cancer cells through action on various cellular signals, including upregulation of TGF-beta and downregulation of IL-6.[26]

Docetaxel, a taxane chemotherapeutic, acts through its stabilization of microtubules, preventing mitosis. When used for prostate cancer, docetaxel is also believed to interfere with androgen receptor trafficking.[27] Docetaxel's efficacy has been observed to be reduced when used after multiple hormonal agents, including abiraterone.[28] Because of the proposed cross-resistance between abiraterone and docetaxel, we performed a prespecified subgroup analysis based upon stratification by prior abiraterone or ketoconazole exposure. We believe that these results generate an interesting hypothesis: that prednisone may only enhance the efficacy of docetaxel in those who have not previously received corticosteroids. In current practice, patients are much more likely to have been treated with abiraterone than ketoconazole. Because abiraterone as a single-agent was found to cause symptoms of mineralocorticoid excess through its potent effects on adrenal steroid synthesis,[29] abiraterone was subsequently developed to be co-administered with a corticosteroid.[30] Therefore, patients with prior abiraterone exposure in this study would have also had prior chronic prednisone exposure.

Data in the literature about the efficacy of prednisone in various contexts support this hypothesis of reduced prednisone efficacy on subsequent re-challenge. While acknowledging the inherent difficulties of cross-study comparisons, the single-agent activity of prednisone appears reduced when used post-docetaxel. Prednisone was minimally effective, for example, in the control arm of the post-chemotherapy COU-AA-301 study of abiraterone/prednisone versus prednisone-alone.[31] Patients receiving 10mg prednisone daily

in that study had a >50% PSA response rate of only 6% and a PFS of only 3.6 months. One possible explanation for reduced efficacy of prednisone post-docetaxel is the development of generally more aggressive and refractory disease.[32] Another explanation is that these patients may have developed a glucocorticoid-resistant phenotype through progression on prior prednisone (co-administered with docetaxel).

The characteristics of corticosteroid-sensitive tumors are not well described. The glucocorticoid receptor (GR) is observed to be overexpressed in pre-treated and advanced prostate cancer.[33] However, steroid responsiveness in the setting of overexpressed or underexpressed GR has not been demonstrated. Therefore, a need exists for identification of a biomarker for glucocorticoid responsiveness, similar to ongoing work on biomarkers for AR-directed therapy resistance.[34] Such a marker might allow a clinician to decide whether to administer prednisone together with docetaxel or not.

This study has several important limitations. First, this data represents a single institution's retrospective experience, and prospective study in a multi-institutional manner would provide the strongest confirmation. Although PFS was the most appropriate endpoint for this study due to its timespan with different post-chemotherapy treatment options available, PFS can be confounded by non-standardized radiographic and clinical assessment schedules. In addition, LDH is a prognostic factor for patients with prostate cancer,[35] but this was not routinely measured for these patients and thus was unable to be included in our analysis.

In summary, this retrospective analysis suggests that patients who receive docetaxel together with prednisone may have superior outcomes than those receiving docetaxel alone. While this analysis did not address questions of safety, this putative benefit must be weighed against the potential side effects of prednisone in the individual patient. This study also generates a hypothesis that patients who have received prior prednisone (for example, with abiraterone) may not benefit from additional prednisone administration during docetaxel treatment. Judicious use of prednisone has been suggested based upon preclinical work showing reduced efficacy of enzalutamide in the setting of corticosteroid use,[36] as well as inferior outcomes for concurrent corticosteroid administration in a trial of enzalutamide.[37] Interactions between therapies will become increasingly relevant as the number of drugs available to patients with metastatic CRPC increases further in coming years. In this context, we postulate that prednisone may only be beneficial once during a patient's treatment course for advanced prostate cancer, and prospective confirmation of this hypothesis is needed.

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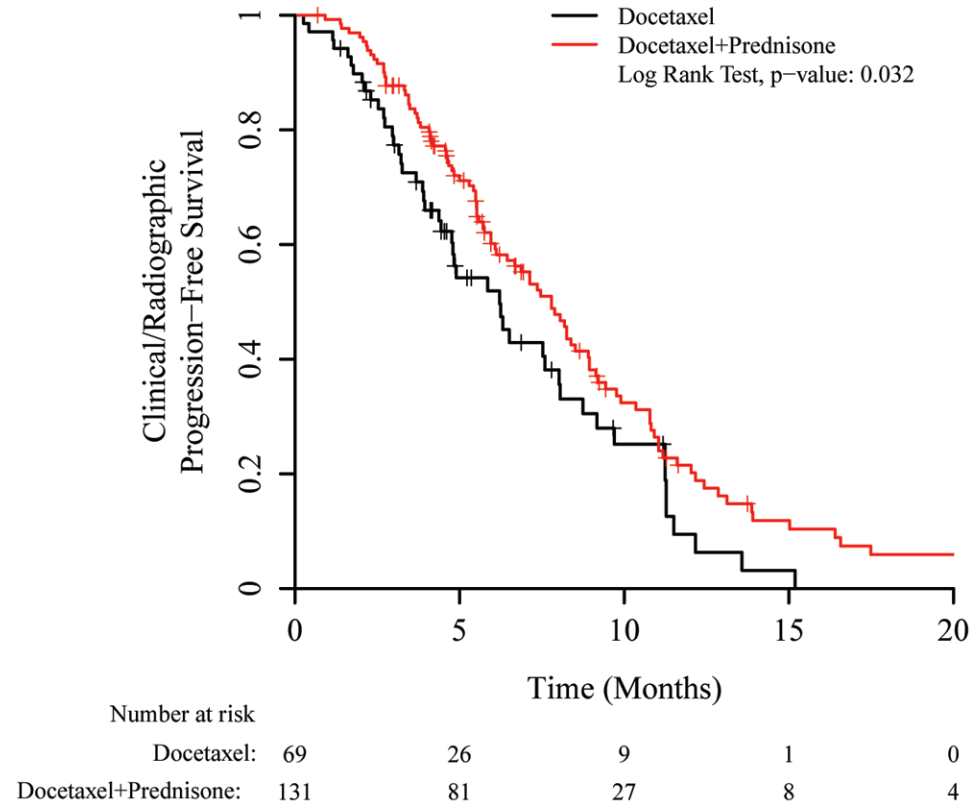

Figure 1.

Kaplan-Meier plot for clinical/radiographic progression-free survival (PFS), based on whether or not prednisone was co-administered with docetaxel. Hazard ratio = 0.68 (0.48 – 0.97).

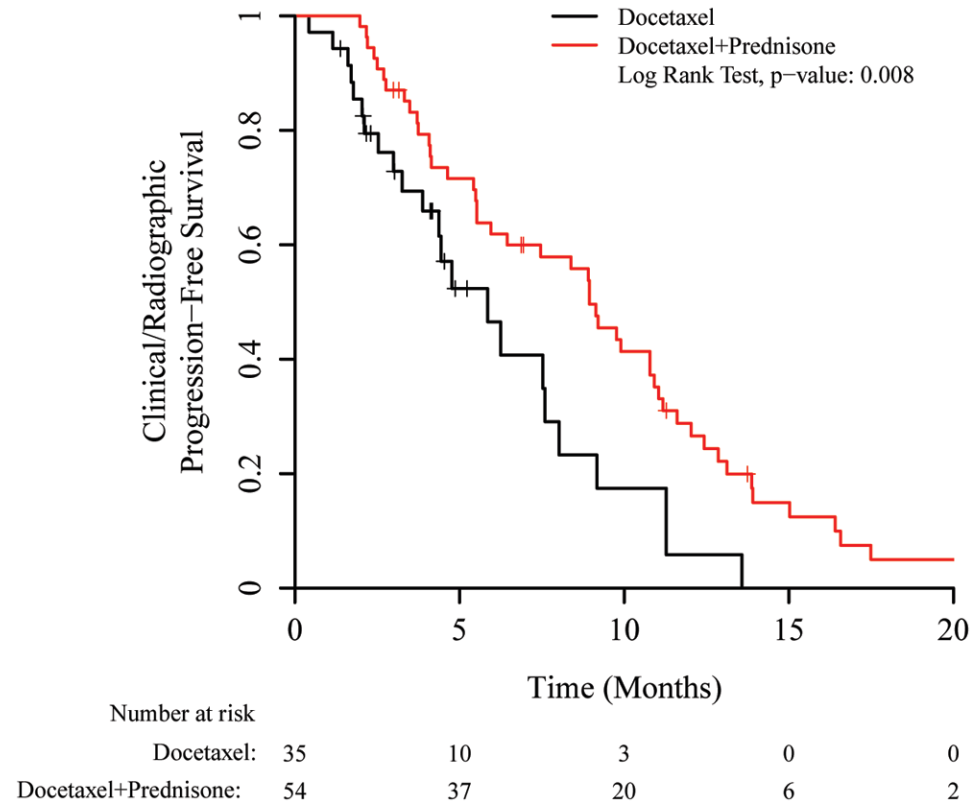

Figure 2a

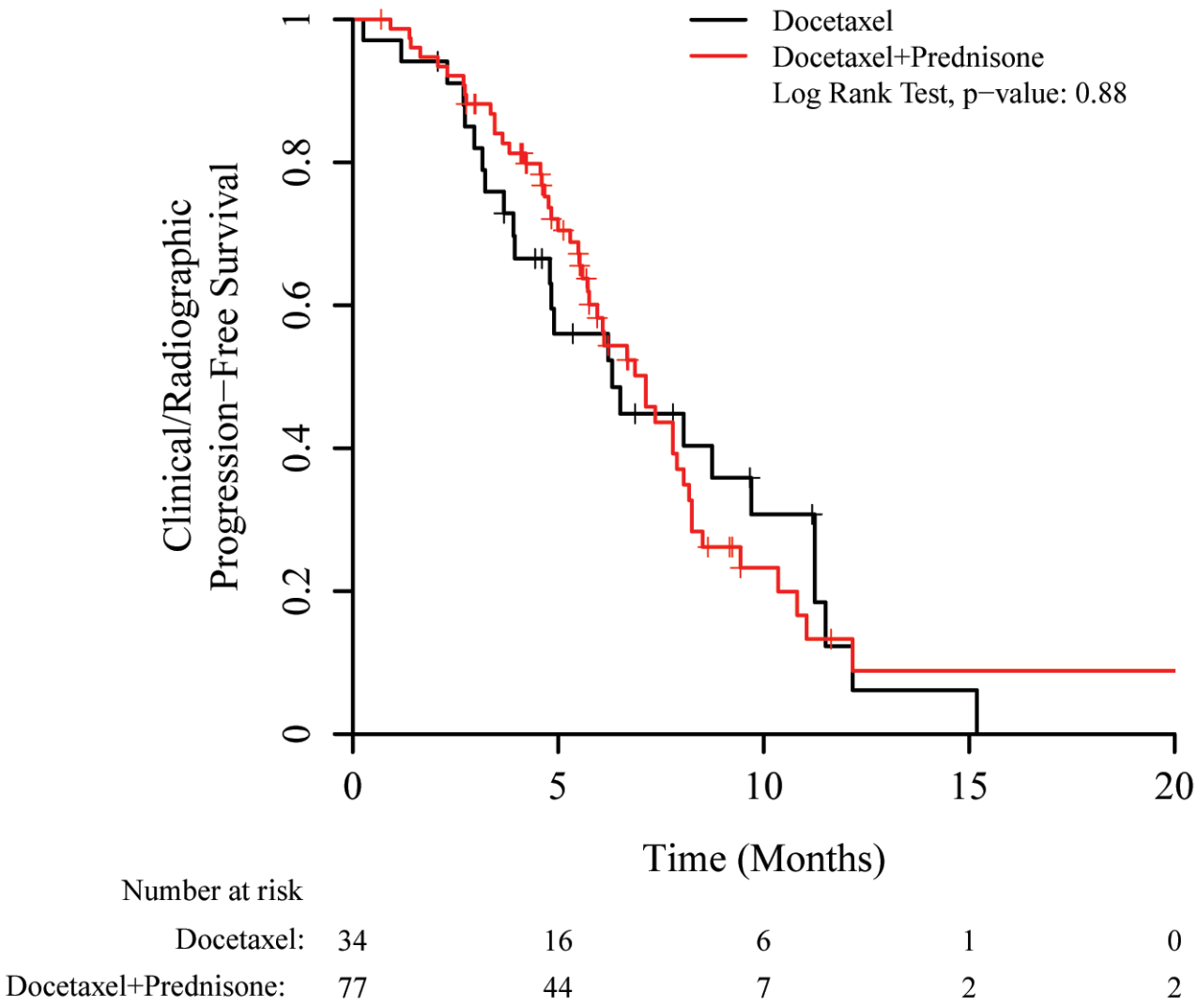

Figure 2b

Figure 2.

Kaplan-Meier plots for clinical/radiographic PFS, showing subsets according to prior use of abiraterone or ketoconazole. A) No prior use of abiraterone or ketoconazole (hazard ratio 0.49 [0.29–0.84]), B) Prior use of abiraterone or ketoconazole (hazard ratio 0.96 [0.59–1.57]).

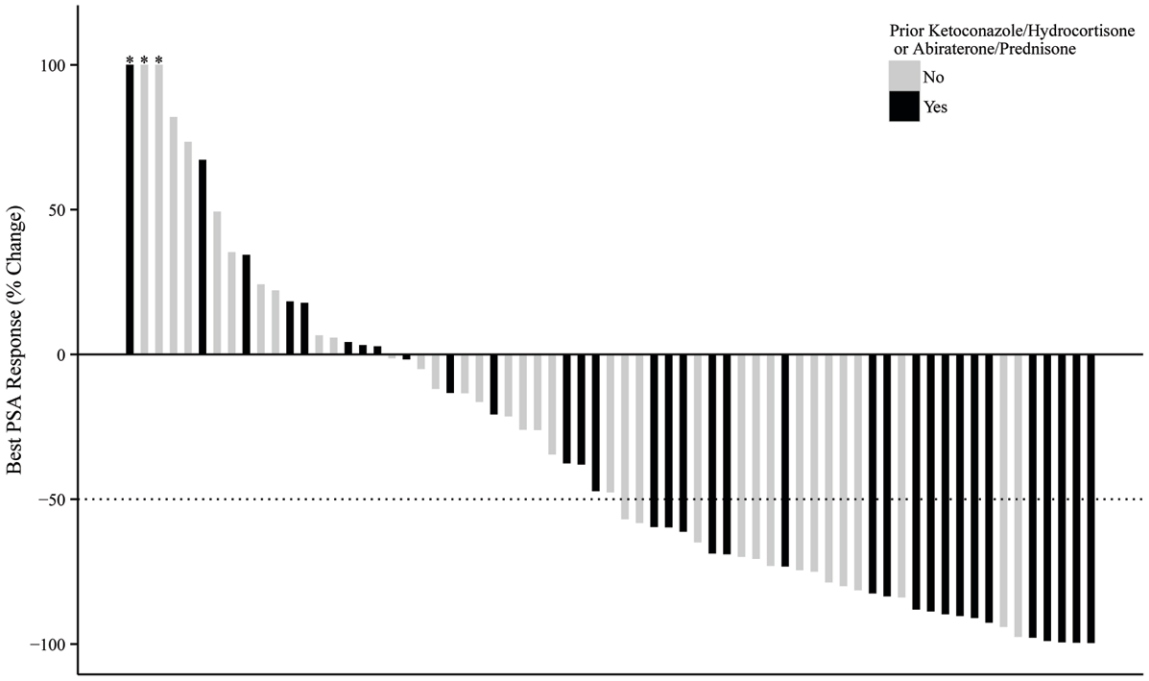

Figure 3a

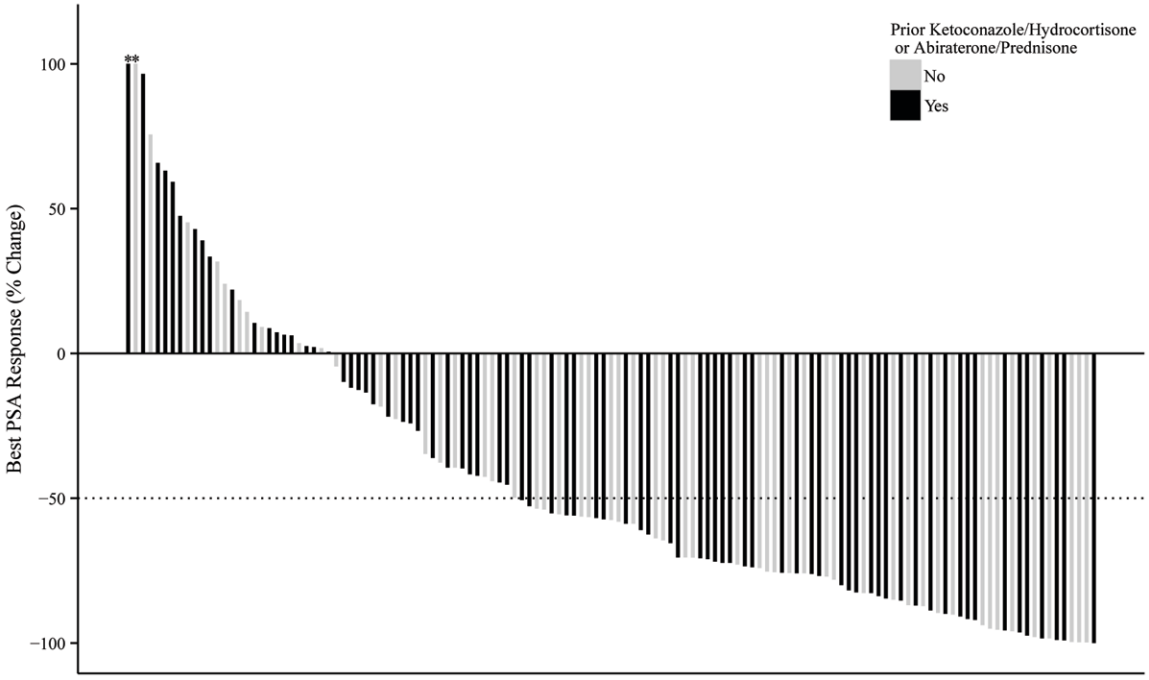

Figure 3b

Figure 3.

Waterfall plots depicting best PSA response, according to whether or not prednisone was co-administered with docetaxel. The proportion of men with >50% PSA responses was 48% for those receiving docetaxel alone (A) and was 60% for those receiving docetaxel plus

prednisone (p = 0.14) (B). Dark bars indicate patients who had received prior abiraterone or ketoconazole; light bars indicate those who had not received prior abiraterone or ketoconazole. Values >100% are truncated (as depicted by the asterisks).

Table 1

Baseline characteristics.

Characteristic	All Patients (n = 200)	Docetaxel Alone (n = 69)	Docetaxel + Prednisone (n = 131)	P-value
Age (years)	68 (45 – 85)	68 (52 – 85)	69 (45 – 85)	0.45
Performance Status				
0	75 (38%)	22 (32%)	53 (40%)	0.001
1 – 2	86 (43%)	21 (30%)	50 (50%)	
Missing	39 (20%)	26 (38%)	13 (10%)	
Hemoglobin (g/dL)	11.9 (7.7 – 15.9)	11.9 (7.7 – 15.9)	11.9 (8.1 – 15.3)	0.49
Creatinine (mg/dL)	0.9 (0.5 – 3.5)	1.0 (0.5 – 3.5)	0.9 (0.5 – 2.1)	0.08
Alkaline Phosphatase (IU/L)	137 (39 – 2109)	125 (44 – 684)	149 (39 – 2109)	0.22
PSA (ng/dL)	153 (1.2 – 5327)	131.1 (2.9 – 4861)	155.7 (1.2 – 5327)	0.96
Gleason score sum				
6	13 (6%)	5 (7%)	8 (6%)	0.56
7	50 (25%)	17 (25%)	33 (25%)	
8 – 10	116 (58%)	37 (54%)	79 (60%)	
Missing	21 (10%)	10 (14%)	11 (8%)	
Presence of visceral metastasis				
Liver	30 (15%)	10 (14%)	20 (15%)	0.99
Lung	24 (12%)	6 (9%)	18 (14%)	0.36
Presence of pain	82 (41%)	26 (38%)	56 (43%)	0.55
Number of prior hormonal therapies	3 (1 – 5)	2 (1 – 5)	3 (1 – 5)	0.45
Prior Abiraterone – Prednisone	46 (23%)	9 (13%)	37 (28%)	0.02
Prior Ketoconazole – Hydrocortisone	77 (38%)	26 (38%)	51 (39%)	0.88
Prior Enzalutamide	14 (7%)	2 (3%)	12 (9%)	0.15

Data reported as median (range) or percentages. P-values for categorical variables are based on Fisher's Exact test, and for continuous variables are based on Wilcoxon-Mann Whitney test.

Table 2

Propensity Score-Weighted Multivariable Cox Model for Clinical/Radiographic Progression-Free Survival (PFS).

	Hazard Ratio (95% C.I.)	P-value
Treatment		
Docetaxel Alone	1.0 [Ref]	
Docetaxel + Prednisone	0.53 (0.35 – 0.80)	0.002
Performance Status		
0	1.0 [Ref]	
1 – 2	1.37 (1.003 – 1.87)	0.05
Presence of Pain		
No	1.0 [Ref]	
Yes	1.15 (0.86 – 1.55)	0.36
PSA	1 [Based upon 1 unit change]	0.91
Alkaline Phosphatase	1	0.83
Gleason Score		
6	1.0 [Ref]	
7	0.57 (0.33 – 0.99)	0.04
8 – 10	0.60 (0.36 – 0.99)	0.05
Visceral Metastasis: Liver		
No	1.0 [Ref]	
Yes	1.22 (0.80 – 1.84)	0.36
Visceral Metastasis: Lung		
No	1.0 [Ref]	
Yes	1.07 (067 – 1.69)	0.78
Prior Abi/Keto.		
No	1.0 [Ref]	
Yes	0.73 (0.46 – 1.16)	0.18
Interaction		
Treatment * Prior Abi/Keto	1.79 (1.001 – 3.19)	0.05

Table 3

Proportion of Patients Achieving a >50% PSA Response, According to Prior Abiraterone or Ketoconazole Use.

	All Patients (n = 200)	Docetaxel Alone (n = 69)	Docetaxel + Prednisone (n = 131)	P-value
No Prior Abi/Keto (n = 89)	49 / 89 (55%)	14 / 35 (40%)	35 / 54 (65%)	0.03
Prior Abi/Keto (n = 111)	62 / 111 (56%)	19 / 34 (56%)	43 / 77 (56%)	>0.99

P-values are based on Fisher's Exact test.