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Phase II, Multicenter, Randomized Trial of Docetaxel plus Prednisone with or Without Cediranib in Men with Chemotherapy-Naive Metastatic Castrate-Resistant Prostate Cancer

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT00527124
- **Sponsor(s):** National Cancer Institute
- **Principal Investigator:** Elisabeth Heath
- **IRB Approved:** Yes

Lessons Learned

- The negative results are consistent with the negative results of large phase III trials in which docetaxel plus anti-angiogenic agents were used in patients with metastatic castrate-resistant prostate cancer (mCRPC).
- The negative data underscore that, despite a sound biological rationale and supportive early-phase clinical results, adding antiangiogenic agents to docetaxel for mCRPC is a great challenge.

Abstract

Background. Inhibition of vascular endothelial growth factor (VEGF) signaling abrogates tumor-induced angiogenesis to constrain tumor growth, and can be exploited therapeutically by using cediranib, an oral tyrosine kinase inhibitor of VEGF receptor signaling. Our preliminary phase I trial data showed that adding cediranib to docetaxel plus prednisone (DP) was safe and feasible, with early evidence for efficacy in patients with metastatic castrate-resistant prostate cancer (mCRPC).
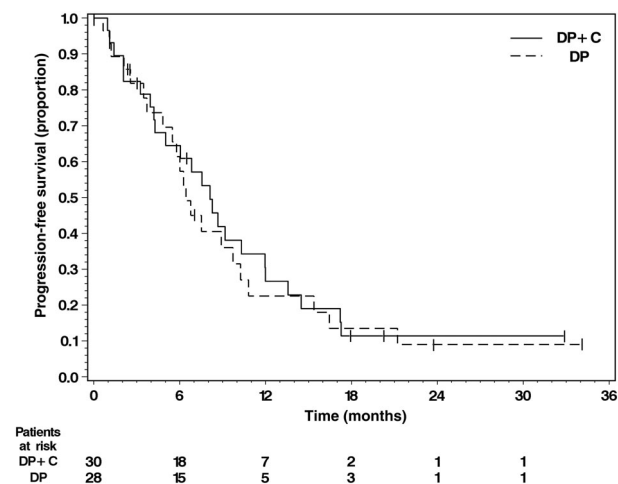
Methods. This multicenter phase II trial assessed whether adding cediranib to DP improves efficacy of DP in patients with mCRPC. Chemotherapy-naive patients with mCRPC were randomly assigned to receive either docetaxel (75 mg/m^2 intravenously every 3 weeks) with prednisone (5 mg twice daily) plus cediranib (30 mg once daily; the DP+C arm) or DP only (the DP arm). The primary endpoint was to compare 6-month progression-free survival (PFS) rate between the two arms. Secondary endpoints included 6-month overall survival (OS), objective tumor and prostate-specific antigen (PSA) response rates, biomarkers, and adverse events.

Results. The 6-month PFS rate in a total of 58 patients was only numerically higher in the DP+C arm (61%) compared with the DP arm (57%). Similarly, the 6-month OS rate, objective tumor and PSA response rates, and biomarkers were not significantly different between the two arms. Increased baseline levels of interleukin 6 (IL-6), however, were significantly associated with increased risk of progression. Neutropenia was the only grade 4 toxicity (38% in the DP+C arm vs. 18% in the DP arm).

Conclusion. Combining cediranib with docetaxel + prednisone failed to demonstrate superior efficacy, compared with docetaxel + prednisone, and added toxicity. Our data do not support pursuing the combination further in patients with mCRPC. *The Oncologist* 2019;24:1149–e807

Figure 1. Kaplan-Meier plot for progression-free survival by treatment arm. Censored (i.e., progression-free) patients are indicated by vertical marks in each curve.
Abbreviations: DP, docetaxel at 75 mg/m^2 intravenously over 1 hour on day one every three weeks plus prednisone at 5 mg orally twice per day on days 1-21; DP+C, docetaxel at 75 mg/m^2 intravenously over 1 hour on day one every three weeks plus prednisone at 5 mg orally twice per day on days 1-21 plus cediranib at 20 mg orally once daily on days 1-21.

DISCUSSION

We hypothesized that adding the antiangiogenic agent cediranib (AZD2171), an oral tyrosine kinase inhibitor of VEGF receptor signaling, to docetaxel may improve docetaxel's efficacy in mCRPC. We found in a phase I trial that adding cediranib to DP was safe and feasible with early evidence of efficacy in patients with mCRPC (data not shown). As a follow-up, we conducted a multicenter, randomized, phase II screening study to further evaluate safety and efficacy of the combination. The primary endpoint was to compare 6-month PFS rate between the two arms. Secondary endpoints included 6-month OS, objective tumor and PSA response rates, biomarkers, and adverse events.

Because of poor accrual, the study was discontinued prior to full enrollment of 104 patients. The data that were obtained from 58 chemotherapy-naive patients with mCRPC recruited in nine participating institutions from December 2007 until December 2011 are reported herein. Thirty patients were randomized to the DP+C arm, of whom 29 received treatment. All 28 patients randomized to the DP arm were treated. The median age was 68 years (range, 52–82 years) in the DP+C arm versus 66 years (range, 51–84 years) in the DP arm.

Chemotherapy-naive patients with mCRPC were randomly assigned to receive either docetaxel (75 mg/m^2 intravenously every 3 weeks) with prednisone (5 mg twice daily) plus cediranib (once daily; the DP+C arm) or DP only (the DP arm). Because of the observed toxic effects, the starting dose of cediranib, 30 mg/daily, was reduced to a 20-mg daily dose.

The 6-month PFS rate was slightly numerically improved in the DP+C arm compared with the DP arm. This was not statistically significant, however, given the extensive overlap of the arm-specific 95% confidence intervals (CIs; 61%, 43%–79% for the DP+C arm vs. 57%, 38%-77% for the DP arm). Similarly, the duration of censored PFS was slightly longer in the DP+C arm, but this was not statistically significant (hazard ratio [HR] for the DP+C arm, 0.91; 95% CI, 0.51–1.62; p = .74; Fig. 1). Adjustment for age, race, and baseline PSA had a negligible effect (HR, 0.94; 95% CI, 0.52–1.70; p = .84). Moreover, median PFS estimates were not significantly different between the two arms, as evidenced by overlapping 95% CIs (8.0 months, 4.2–11.9 months in the DP+C arm and 6.4 months, 4.8–10.2 months in the DP arm). Similarly, 12-month PFS rates were not significantly different between the two arms.

The 6-month OS rate and the duration of censored OS were numerically improved but not significantly different in the DP arm compared with the DP+C arm. The partial tumor and complete PSA response rates were only numerically higher in the DP+C arm compared with the DP arm (53% and 35% vs. 33% and 12%, respectively).

There were no significant interactions observed for biomarkers by treatment arm. For IL-6, however, a 10 pg/mL increase in the baseline level was significantly associated with an 18% increase in the risk of a progression event. The primary grade 4 toxicity neutropenia was observed in 11/29 (38%) patients in the DP+C arm and in 5/28 (18%) patients in the DP arm.

Overall, adding cediranib to docetaxel + prednisone in patients with mCRPC was associated with numerically higher partial tumor and complete PSA response rates, but without any significant improvement in PFS or OS, and with added toxicity. Our data do not support pursuing the combination further in patients with mCRPC.

TRIAL INFORMATION	
Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Randomized
Primary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Objective tumor responses
Secondary Endpoint	Prostate-specific antigen
Secondary Endpoint	Correlative endpoints
Secondary Endpoint	Safety

Additional Details of Endpoints or Study Design

Study Design and Oversight

This multicenter, randomized, open-label, phase II screening trial enrolled patients with mCRPC who had no prior chemotherapy and whose performance status and organ function were suitable for docetaxel. The study was approved by the National Cancer Institute and the institutional review board at each participating institution. The trial was coordinated by the Karmanos Cancer Institute (Wayne State University, Detroit, MI). The Biostatistical Core at the Karmanos Cancer Institute was the data collector and the coordinating center. All patients provided written and signed informed consent before trial entry.

Procedures

Eligible patients were randomly assigned at a one-to-one ratio to docetaxel, at a dose of 75 mg/m^2 intravenously every 3 weeks, with prednisone, at a dose of 5 mg orally twice per day, and cediranib, at a dose of 30 mg orally once a day (the DP +C arm), versus docetaxel plus prednisone alone (the DP arm). Initially, the cediranib dose was used at the recommended phase II dose of 30 mg daily, but it was reduced to 20 mg, or even 15 mg, daily because of toxicities, including fatigue and hematologic effects. For docetaxel, the starting dose of 75 mg/m^2 was subsequently reduced to 55 and 40 mg/m^2. Dose reductions of both treatments were detailed and recorded in protocol amendments. Randomization was stratified by each of the nine participating institutions. The procedure incorporated random permuted blocks to minimize the differences in the number of patients assigned to the two treatment arms for any given institution. The block sizes were chosen by the study biostatistician and were not revealed until patient accrual was closed.

Study Assessments

Patients receiving cediranib with or without docetaxel plus prednisone were evaluated every three cycles (i.e., every 9 weeks) during treatment and every 3 months thereafter. Radiographic disease assessment (with computed tomography of abdomen and pelvis and bone scan) was carried out at baseline and every three cycles. For patients with measurable disease, disease evaluation was based on RECIST version 1.0 and on the Prostate Cancer Working Group 2 (PCWG2) criteria [1, 2]. For patients with non-measurable disease, in addition to RECIST 1.0, the PCWG2 PSA criteria were used for disease evaluation [2, 3].

Serum PSA levels were checked with every 3-week visit. Complete PSA response was defined as a decrease to ≤4 ng/mL confirmed by a second PSA measurement 4–6 weeks later. Disease progression by PSA was defined as an increase in the PSA concentration by ≥25% above nadir (or baseline, if PSA never decreased below the baseline), with an absolute increase in the PSA level by 2 ng/mL, confirmed by a second value 3 or more weeks later. If the PSA did not increase, and the bone scan alone was the indicator for progression, the presence of at least two or more new lesions was required to confirm progression in bone.

The primary objective of the trial was to compare 6-month PFS rate between the two treatment arms. PFS was defined as the time from study registration until documented disease progression according to PCWG2 [1] or death resulting from any cause, whichever occurred first. Patients still alive were censored as of the date of their last vital status determination. Secondary endpoints included OS and objective tumor response rates, PSA, biomarkers as correlative endpoints, and safety data. OS was defined as the time from study registration until death resulting from any cause.

Blood Samples and Biomarker Analysis

For biomarker analyses, blood samples (10 mL) were withdrawn from patients at baseline, after cycles two and three, and after drug cessation. The biomarkers assessed in the study included VEGF, VEGF-C, VEGF-D, IL-6, and IL-8. Duplicates of 50-μL plasma per sample were aliquoted and assayed using a Magnetic Luminex Assay multiplex kit (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. A multiplex protein analysis platform (Bio-Plex 100, Bio-Rad, Hercules, CA) and a software (Bio-Plex® Manager 6.1; Bio-Rad) were used for measurement of biomarker levels and their quantification, respectively.

Statistical Analysis

A randomized phase II screening design that uses a nondefinitive comparison of a new experimental regimen with a standard active control regimen was used. [4] On the basis of an assumed 6-month PFS rate of 50% on the DP arm, the study was designed to detect an improvement of 20 percentage points (i.e., to 70%) on the DP+C arm. The nondefinitive comparison allows larger than usual type I (α) and type II (β) error limits so as to identify even a weak signal of efficacy improvement in the experimental regimen [4]. With a total of 104 patients (52 per arm), the study was designed to have 80% power to detect a 20% absolute increase in 6-month PFS with one-sided $\alpha = 0.15$ and $\beta = 0.20$. The sample size calculation and power analysis of two proportions was determined using the Continuity Corrected Z-Test with Pooled Variance program in the Power and Sample Size statistical software. However, as a result of slow accrual, the protocol was administratively closed to accrual in December 2011 after a total enrollment of 58 patients (30 on the DP+C arm and 28 on the DP arm). With those sample sizes and the original statistical design parameters, the resulting power to detect the hypothesized improvement in 6-month PFS rate was 60.1%.

The PFS and OS distributions were subject to censoring and were estimated by the standard Kaplan-Meier methodology [5]. Cox proportional hazards models [6] were employed to estimate HRs and their (two-sided) 95% CIs. Response rates were summarized with point estimates and (two-sided) 95% CI estimates by the Wilson method.

Correlative biomarkers were analyzed using descriptive statistics, box plots, and Spearman rank correlations (rho). Exploratory Cox models were fit to determine the association of each baseline correlative biomarker with PFS and OS. Biomarker association multiple comparison adjustments were performed using the false discovery rate method of Benjamini and Hochberg [7].

Correlations Among the Biomarkers

VEGF and IL-6 were moderately positive at the baseline visit (rho = 0.51, p = .001) and after cycle 1 (rho = 0.50, p = .002; data not shown). Ignoring treatment arm, the levels of VEGF and VEGF-C were positively correlated, with rho values of 0.51 to

0.67 over four time points (p < .002 for each time point; data not shown). In contrast, correlation between the levels of VEGF-C and IL-8 was moderately negative at the end of treatment (rho = −0.63, p = .0002; data not shown).

PFS Modeled as a Function of Individual Baseline Biomarkers

The risk of progression was calculated for a 10 pg/mL increase in the baseline biomarker levels (with the exception of VEGF-C, for which a 100 pg/mL increase was used). Univariate and bivariate (biomarker and treatment arm) Cox models showed that baseline levels of all biomarkers were weakly positively associated with the risk of progression (HRs ≥1.00), with the exception of VEGF-C, for which the association was weakly negative (HRs <1.00). There was no statistically significant association of the specified X-unit increase in the baseline level of any of the biomarkers with the risk of progression. The only exception was IL-6, for which a 10 pg/mL increase in the baseline level was significantly associated with an 18% increase in the risk of a progression event. Covariate adjustment for treatment arm did not change the IL-6-associated HR or its 95% CI. In addition, after adjusting for multiple comparisons, only two HRs for baseline levels of IL-6 (from both the univariate and the bivariate models) were still statistically significant, each one with an adjusted p = .06. Thus, increased baseline levels of IL-6 were indicative of an increased risk of progression. There were no significant interactions for biomarkers by treatment arm observed (all interactions had p > .28).

Odds Ratio for a Target Lesion Partial Response as a Function of Each Baseline Biomarker

We found that for a 25% increase in baseline VEGF-C, the odds ratio for the target lesion partial response in the DP+C arm was 0.62 (80% CI, 0.39–0.96). The data suggest that the likelihood of the response in the DP+C arm is decreased by 38% for a 25% increase in baseline VEGF-C levels. We also found that for a 10 pg/mL increase in baseline IL-8, the odds ratio for the target lesion partial response in the DP+C arm was 0.43 (80% CI, 0.20–0.93). The results indicate that the likelihood of the response in the DP+C arm is decreased by 57% for every 10 pg/mL increase in baseline IL-8 levels. In addition, using the same exploratory approach, we assessed the odds for grade 3 hypertension in the DP+C arm. We found that for every 100 pg/mL increase in baseline VEGF-C levels, the odds ratio for grade 3 hypertension was 1.22 (80% CI, 0.95–1.57). The results suggest a 22% increase in the odds for grade 3 hypertension in the DP+C arm for every 100 pg/mL increase in baseline VEGF-C. These associations with the odds of target lesion partial responses are weak, based on small sample sizes, and are purely exploratory.

Investigator's Analysis	Our data do not support pursuing the combination further in mCRPC.

DRUG INFORMATION: CEDIRANIB + DOCETAXEL + PREDNISONE

Drug 1

Generic/Working Name	Docetaxel/RP 56976
Trade Name	Taxotere
Drug Type	Small molecule
Drug Class	Microtubule-targeting agent
Dose	75 mg/m^2
Route	IV
Schedule of Administration	Docetaxel at 75 mg/m^2 over 1 hour on day 1 every 3 weeks

Drug 2

Generic/Working Name	Prednisone
Trade Name	DeCortin/Delta
Drug Type	Small molecule
Drug Class	Corticosteroid
Dose	5 mg per flat dose
Route	p.o.
Schedule of Administration	Prednisone at 5 mg twice daily on days 1–21

Drug 3

Generic/Working Name	Cediranib/AZD2171
Trade Name	Recentin
Company Name	AstraZeneca
Drug Type	Small molecule
Drug Class	VEGFR
Dose	30 mg per flat dose
Route	p.o.
Schedule of Administration	Cediranib 30 mg once daily on days 1–21. Reduced to 20 mg once daily by amendment

DRUG INFORMATION: DOCETAXEL + PREDNISONE	
Drug 1	
Generic/Working Name	Docetaxel/RP 56976
Trade Name	Taxotere
Drug Type	Small molecule
Drug Class	Microtubule-targeting agent
Dose	75 mg/m^2
Route	IV
Schedule of Administration	Docetaxel at 75 mg/m^2 over 1 hour on day 1 every 3 weeks
Drug 2	
Generic/Working Name	Prednisone
Trade Name	DeCortin/Delta
Drug Type	Small molecule
Drug Class	Corticosteroid
Dose	5 mg per flat dose
Route	p.o.
Schedule of Administration	Prednisone at 5 mg twice daily on days 1–21

PATIENT CHARACTERISTICS: CEDIRANIB + DOCETAXEL + PREDNISONE	
Number of Patients, Male	29
Number of Patients, Female	0
Stage	Metastatic castrate-resistant prostate cancer (stage IV)
Age	Median (range): 68 years (52–82 years)
Number of Prior Systemic Therapies	Median (range): none
Performance Status: ECOG	0 — 12 1 — 17 2 — 0 3 — 0 Unknown — 0
Other	Complete details of patient characteristics are shown in Table 1.
Cancer Types or Histologic Subtypes	Gleason grade <7, *n* (%): 2 (7) Gleason grade = 7, *n* (%): 10 (37) Gleason grade >7, *n* (%): 15 (56) Unknown Gleason grade, *n* = 2

PATIENT CHARACTERISTICS: DOCETAXEL + PREDNISONE	
Number of Patients, Male	28
Number of Patients, Female	0
Stage	Metastatic castrate-resistant prostate cancer (stage IV)
Age	Median (range): 66 years (51–84 years)
Number of Prior Systemic Therapies	Median (range): none
Performance Status: ECOG	0 — 10 1 — 17 2 — 1 3 — 0 Unknown — 0
Other	Complete details of patient characteristics are shown in Table 1.
Cancer Types or Histologic Subtypes	Gleason grade <7, *n* (%): 2 (8) Gleason grade = 7, *n* (%): 9 (35) Gleason grade >7, *n* (%): 15 (58) Unknown Gleason grade, *n* = 2

PRIMARY ASSESSMENT METHOD: CEDIRANIB + DOCETAXEL + PREDNISONE		
Title	PFS	
Number of Patients Evaluated for Efficacy	30	
Evaluation Method	Kaplan-Meier	
(Median) Duration Assessments PFS	8 months, CI: 95	
Outcome Notes	A total of 85 patients were screened.	
Number of patients	**DP+C**	**DP**
Enrolled	30	28
Evaluable for toxicity	29	28
Evaluated for efficacy, PFS and OS	30	28
Evaluated for efficacy, responses	29	28

PFS, OS, and objective tumor and PSA responses of patients by treatment arm are shown in Table 2.

SECONDARY ASSESSMENT METHOD: CEDIRANIB + DOCETAXEL + PREDNISONE	
Title	Correlative endpoints
Evaluation Method	Serum markers
Outcome Notes	See Figure 3 and Table 4
Title	Median OS
Number of Patients Evaluated for Efficacy	30
Evaluation Method	Kaplan-Meier
Outcome Notes	Not reached
Title	Objective tumor responses
Number of Patients Evaluated for Efficacy	15
Evaluation Method	RECIST 1.0
Response Assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 8$ (53%)
Response assessment SD	$n = 6$ (40%)
Response assessment PD	$n = 1$ (7%)
Response assessment OTHER	$n = 14$
Title	Serum PSA
Number of Patients Evaluated for Efficacy	26
Evaluation Method	PCWG2 criteria
Response Assessment CR	$n = 9$ (35%)
Response Assessment PR	$n = 7$ (27%)
Response Assessment SD	$n = 9$ (35%)
Response Assessment PD	$n = 1$ (4%)
Response Assessment OTHER	$n = 3$

PRIMARY ASSESSMENT METHOD FOR PHASE II DOCETAXEL + PREDNISONE		
Title	PFS	
Number of Patients Evaluated for Efficacy	28	
Evaluation Method	Kaplan-Meier	
(Median) Duration Assessments PFS	6 months, CI: 95	
Outcome Notes	A total of 85 patients were screened.	
Number of patients	**DP+C**	**DP**
Enrolled	30	28

Evaluable for toxicity	29	28
Evaluated for efficacy, PFS and OS	30	28
Evaluated for efficacy, responses	29	28

PFS, OS, and objective tumor and PSA responses of patients by treatment arm are shown in Table 2.

SECONDARY ASSESSMENT METHOD FOR PHASE II DOCETAXEL + PREDNISONE	
Title	Correlative endpoints
Evaluation Method	Serum markers
Outcome Notes	See Figure 3 and Table 4
Title	Median OS
Number of Patients Evaluated for Efficacy	28
Evaluation Method	Kaplan-Meier
Outcome Notes	Not reached
Title	Objective tumor responses
Number of Patients Evaluated for Efficacy	9
Evaluation Method	RECIST 1.0
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 3$ (33%)
Response Assessment SD	$n = 6$ (67%)
Response Assessment PD	$n = 0$ (0%)
Response Assessment OTHER	$n = 19$
Title	Serum PSA
Number of Patients Evaluated for Efficacy	26
Evaluation Method	PCWG2 criteria
Response Assessment CR	$n = 3$ (12%)
Response Assessment PR	$n = 14$ (54%)
Response Assessment SD	$n = 8$ (31%)
Response Assessment PD	$n = 1$ (4%)
Response Assessment OTHER	$n = 2$
Adverse Events	Adverse events are shown in Table 3.

ASSESSMENT, ANALYSIS, AND DISCUSSION	
Completion	Study terminated before completion
Terminated Reason	Did not fully accrue
Investigator's Assessment	Our data do not support pursuing the combination further in mCRPC.

This randomized phase II screening trial included two well-balanced treatment groups with comparable patient demographics and biological characteristics (Table 1; Fig. 2). No statistical differences, however, were found between the two treatment groups in any of the tested outcome parameters (Figs. 1, 3; Table 2). There were no differences in the extent of disease in either arm. Thus, the data do not support our hypothesis that adding the antiangiogenic cediranib to docetaxel plus prednisone (DP) would improve DP efficacy in metastatic castrate-resistant prostate cancer (mCRPC). Although the results were disappointing, they are consistent with the negative results of large phase III trials of docetaxel and antiangiogenic combination therapy in patients with mCRPC that have been reported since the initiation of our clinical trial [8].

This clinical trial had to close early because of slow accrual. Accrual was ultimately very challenging because of the rapidly changing treatment landscape, which at the time included emerging oral androgen receptor-targeted agents in competing clinical trials. Such oral drugs held additional appeal for patients with mCRPC, whose only available option at that time was intravenous chemotherapy. Notably, as reported by Massett et al. [9], the National Cancer Institute recognized competing trials as a reason for

slow accrual in phase II studies. They proposed to invest in earlier accrual planning as a better strategy for future trials.

It is doubtful, however, that additional patients would have changed the outcome of our study. In patients with mCRPC, there have been 11 randomized phase III trials of docetaxel combined with GVAX, calcitriol, bevacizumab, aflibercept, dasatinib, atrasentan, zibotentan, lenalidomide, or custirsen, with no difference in overall survival (OS) noted between the treatment arms [10–20], notwithstanding promising early-phase data of docetaxel combined with sunitinib [21]. Specifically, phase III trials undertaken in patients with mCRPC using docetaxel combined with the antiangiogenic agents bevacizumab [12] or aflibercept [13] did not meet the primary endpoint of improving OS. Moreover, these combinations were associated with greater toxicity compared with the control arms. Similarly, in a phase III trial in patients with mCRPC, the combination of docetaxel with dasatinib, an SRC inhibitor and an antiangiogenic agent, did not improve OS and added toxicity compared with the active control arm [14]. Another combination tested in the phase III clinical trial setting that worsened not only the toxicity but also the OS in patients with mCRPC was docetaxel plus lenalidomide, an immunomodulatory agent with antiangiogenic properties [18]. Other agents that showed a lack of benefit in mCRPC when combined with docetaxel in the phase III setting include atrasentan, an endothelin receptor antagonist, and custirsen (OGX-011), a second-generation antisense oligonucleotide designed to inhibit production of the cytoprotective clusterin that is associated with resistance to chemotherapy [20]. Similarly, the second-generation taxane cabazitaxel, approved as a second-line treatment after docetaxel failure, when combined with custirsen did not improve OS in patients with mCRPC [19].

In our trial, the adverse events noted in both arms were as anticipated, with the majority of them likely related to docetaxel (Table 3). Grade 4 neutropenia was higher in the DP+C arm compared with the DP arm. Treatment with cediranib also resulted in considerable fatigue and hypertension that led to permanent dose reduction. As the cediranib dose was reduced, adverse events became somewhat more manageable.

We showed that increased basal blood levels of interleukin 6 (IL-6; Table 4) were significantly positively associated with PFS, suggesting potential prognostic value of IL-6. Elevated blood levels of IL-6 were associated with castration-resistant prostate cancer or prostate cancer metastatic to bone, and correlated negatively with tumor survival [22–24]. In addition, blood IL-6 levels were associated with resistance to chemotherapy in prostate cancer [24, 25]. In our study, however, neither IL-6 levels nor the levels of any of the other four biomarkers (i.e., vascular endothelial growth factor [VEGF], VEGF-C, VEGF-D, and IL-8) were affected by treatment. It is likely that the short duration of our study and the small number of tested samples were not adequate to identify potential predictive biomarkers of responsiveness to cediranib in combination with docetaxel.

Biomarkers are usually used in selecting patients when administering targeted drugs, and this approach can improve treatment outcome. A distinguishing feature between antiangiogenic drugs and other targeted therapies, however, is that the former are administered to unselected patients within approved indications [26]. There is a need, therefore, to develop predictive biomarkers to identify patients with mCRPC who are more likely to respond to antiangiogenic drugs. As suggested by Kelly et al. [12] the success of future phase III trials in mCRPC depends on identifying critical biomarkers that enrich the study population for the targeted therapy in order to better understand the association between PFS, prostate-specific antigen response, and objective tumor response as intermediate markers for OS in this patient population.

Overall, our study provides additional evidence supporting the view that docetaxel in combination with any targeted agent has not been successful in patients with mCRPC. The negative data from our study underscore the challenges of adding novel agents to standard treatments for mCRPC, particularly docetaxel, even in the context of a sound biological rationale and supportive early-phase clinical results. Because promising preclinical data do not often translate to an OS benefit in the clinic, additional preclinical and early-phase studies for docetaxel combinations are warranted. Heterogeneity of mCRPC is a key factor contributing to poor correlation between preclinical findings and patient data. To meet this challenge, novel targeted agents with complementary mechanisms of action may improve outcomes of docetaxel-based therapies [27]. The importance of carrying out additional preclinical and early-phase studies for docetaxel combinations cannot be overemphasized to inform future trial design, such as an ongoing phase III trial (ARASENS; ClinicalTrials.gov identifier NCT02799602) using docetaxel plus darolutamide (ODM-201), an oral investigational high-affinity androgen receptor antagonist, in patients with metastatic castration-sensitive prostate cancer [28].

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Assessed for eligibility ($n = 85$)

Excluded ($n = 27$)
   Not meeting inclusion criteria ($n = 23$)
   Refused to participate ($n = 4$)

Patients randomly assigned ($n = 58$)

Allocated to DP+C arm ($n = 30$)
   Received allocated intervention ($n = 29$)
   Did not receive allocated intervention ($n = 1$)

Allocated to DP arm ($n = 28$)
   Received allocated intervention ($n = 28$)
   Did not receive allocated intervention ($n = 0$)

Lost to follow-up ($n = 1$)
Discontinued intervention ($n = 29$)
   Toxicity ($n = 5$)
   Refused further treatment ($n = 3$)
   Progression ($n = 13$)
   Expired ($n = 1$)
   Developed inter-current illness ($n = 2$)
   Patient decision ($n = 2$)
   Physician decision ($n = 3$)

Lost to follow-up ($n = 1$)
Discontinued intervention ($n = 28$)
   Toxicity ($n = 3$)
   Refused further treatment ($n = 2$)
   Progression ($n = 16$)
   Patient decision ($n = 5$)
   Physician decision ($n = 2$)

Analyzed ($n = 30$) (by intention to treat)
   Excluded from analysis ($n = 0$)

Analyzed ($n = 28$) (by intention to treat)
   Excluded from analysis ($n = 0$)

DP+C arm = Docetaxel+prednisone+cediranib   DP arm = Docetaxel+prednisone

Figure 2. Consolidated Standards of Reporting Trials diagram. Overview of screened and randomly assigned patients.
Abbreviations: DP, docetaxel plus prednisone; DP+C, docetaxel plus prednisone plus cediranib.
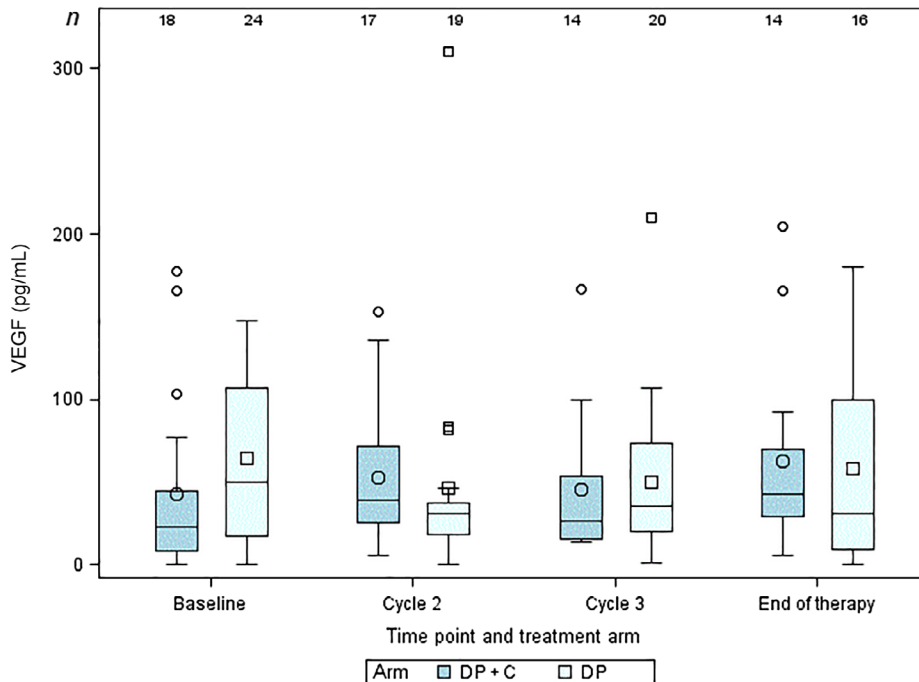
Figure 3. VEGF levels by treatment arm and time point. Multiple box plot of VEGF levels (in pg/mL) for each treatment arm is shown at all four time points of measurement. The effective sample size (n) is shown above each individual box plot.
Abbreviations: DP, docetaxel at 75 mg/m^2 intravenously over 1 hour on day one every three weeks plus prednisone at 5 mg orally twice per day on days 1-21; DP+C, docetaxel at 75 mg/m^2 intravenously over 1 hour on day one every three weeks plus prednisone at 5 mg orally once daily on days 1-21 plus cediranib at 20 mg orally once daily on days 1-21; VEGF, vascular endothelial growth factor.

Table 1. Baseline and clinical characteristics of patients by treatment arm

Variable	DP+C (n = 29)[a]	DP (n = 28)[b]
Median age, years (range)	68 (52–82)	66 (51–84)
Race, n[c]		
White	19	16
Black	9	10
Other	1	1
ECOG PS, n		
0	12	10
1	17	17
2	0	1
Gleason grade, n (%)		
<7	2 (7)	2 (8)
7	10 (37)	9 (35)
>7	15 (56)	15 (58)
Unknown, n	2	2
Extent of disease, n (%)		
Bone only	15 (52)	15 (54)
Viscera only	3 (10)	1 (4)
Bone and viscera	11 (38)	12 (43)
Prior treatment, n (%)		
Radical prostatectomy	12 (41)	6 (21)
Primary prostate radiotherapy	18 (62)	18 (64)
Baseline PSA, median (range), ng/mL	125 (0.1–3,650)	136 (5.5–3,000)

[a]DP+C, docetaxel at 75 mg/m^2 intravenously over 1 hour on day 1 every 3 weeks + prednisone at 5 mg orally twice daily on days 1–21 + cediranib at 20 mg orally once daily on days 1–21.
[b]DP, docetaxel at 75 mg/m^2 intravenously over 1 hour on day 1 every 3 weeks + prednisone at 5 mg orally twice daily on days 1–21.
[c]Race data were missing for one patient in the DP arm.
Abbreviations: C, cediranib; D, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; P, prednisone; PSA, prostate-specific antigen.

Table 2. PFS, OS, and objective tumor and PSA responses of patients by treatment arm

Endpoint	DP+C (n = 29)[a]	DP (n = 28)[b]
Median PFS (95% CI), months	8.0 (4.2–11.9)	6.4 (4.8–10.2)
6-month PFS (95% CI), %[c]	61 (43–79)	57 (38–77)
12-month PFS (95% CI), %[c]	27 (10–43)	21 (4.0–38)
Median OS	Not reached	Not reached
6-month OS (95% CI), %[c]	84 (70–98)	88 (74–100)
12-month OS (95% CI), %[c]	71 (54–88)	76 (59–93)
Objective tumor responses, n (%) [95% CI][d]		
CR	0 (0) [0–20]	0 (0) [0–30]
PR	8 (53) [30–75]	3 (33) [12–65]
SD	6 (40) [20–64]	6 (67) [35–88]
PD	1 (7) [1–30]	0 (0) [0–30]
Nonmeasurable, n	14	19
PSA responses, n (%) [95% CI][e]		
CR, PSA	9 (35) [19–54]	3 (12) [4–29]
PR, PSA	7 (27) [14–46]	14 (54) [35–71]
SD, PSA	9 (35) [19–54]	8 (31) [17–50]
PD, PSA	1 (4) [1–19]	1 (4) [1–19]
Inevaluable, n	3	2

[a]DP+C, docetaxel at 75 mg/m^2 intravenously over 1 hour on day 1 every 3 weeks + prednisone at 5 mg orally twice daily on days 1–21 + cediranib at 20 mg orally once daily on days 1–21.
[b]DP, docetaxel at 75 mg/m^2 intravenously over 1 hour on day 1 every 3 weeks + prednisone at 5 mg orally twice daily on days 1–21.
[c]PFS and OS (6-month and 12-month values) are shown as rates in percentages.
[d]Objective tumor responses are shown as number of patients and percentages of patients with measurable disease (15 and 9 on the DP+C and the DP arm, respectively).
[e]PSA responses by PCWG2 criteria are shown as number of patients and percentages of evaluables (26 per each arm).
Abbreviations: C, cediranib; CI, confidence interval; CR, complete response; D, docetaxel; P, prednisone; PD, progressive disease; PCWG2, Prostate Cancer Working Group; PFS, progression-free survival; PR, partial response; PSA, prostate-specific antigen; OS, overall survival; SD, stable disease.

Table 3. Grade 3 and 4 adverse events by treatment arm

Adverse event	DP+C (*n* = 29)[a]	DP (*n* = 28)[b]
Grade 4, *n* (%)		
Neutropenia	11 (38)	5 (18)
Grade 3, *n* (%)		
Anemia	6 (21)	2 (7)
Deep vein thrombosis	2 (7)	1 (4)
Diarrhea	3 (10)	1 (4)
Fatigue	9 (31)	1 (4)
Hypertension	8 (28)	1 (4)
Mucositis	2 (7)	0 (0)
Neuropathy	2 (7)	0 (0)
Neutropenia	4 (14)	6 (21)
Thrombocytopenia	0 (0)	1 (4)

[a]DP+C, docetaxel at 75 mg/m^2 intravenously over 1 hour on day 1 every 3 weeks + prednisone at 5 mg orally twice daily on days 1–21 + cediranib at 20 mg orally once daily on days 1–21.
[b]DP, docetaxel at 75 mg/m^2 intravenously over 1 hour on day 1 every 3 weeks + prednisone at 5 mg orally twice daily on days 1–21.
Abbreviations: C, cediranib; D, docetaxel; P, prednisone.

Table 4. Hazard ratios for progression by each baseline biomarker

Baseline biomarker	Univariate model[a]	Bivariate model[b]
VEGF, pg/mL	1.04 (0.97–1.11)	1.04 (0.97–1.11)
VEGF-C, pg/mL	0.92 (0.80–1.05)	0.91 (0.79–1.05)
VEGF-D, pg/mL	1.04 (0.69–1.57)	1.04 (0.68–1.60)
IL-6, pg/mL	1.18 (1.05–1.34)[c]	1.18 (1.05–1.34)[c]
IL-8, pg/mL	1.16 (0.94–1.42)	1.16 (0.95–1.43)

The data for both univariate and bivariate models are shown as hazard ratios (95% CI). Each hazard ratio shows the multiplicative change in the risk of a progression event associated with a 10 pg/mL increase in the level of each biomarker, except for VEGF-C, for which a 100 pg/mL increase was used.
[a]The univariate model includes only a biomarker.
[b]The biovariate model includes both a biomarker and a treatment arm.
[c]HR significantly different from unity before adjustment for multiple comparisons (*p* = .01).
Abbreviations: CI, confidence interval; IL, interleukin; VEGF, vascular endothelial growth factor.

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