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Phase II clinical trial of cediranib in patients with metastatic castration-resistant prostate cancer

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Abstract

- To assess the efficacy and toxicity of cediranib, a highly potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with docetaxel-based therapy.
- The study used a Simon two-stage trial design, which required at least two of 12 patients in the first cohort to be progression-free at 6 months.
- We enrolled a total of 35 evaluable patients who all received cediranib 20 mg orally daily.
- In a second cohort, 23 additional patients received prednisone 10 mg daily with cediranib.
- Endpoints included tumour response, progression-free survival (PFS), overall survival (OS), vascular permeability via dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and toxicity.
- A total of 59 patients were enrolled, of whom 67% had received two or more previous chemotherapy regimens.
- Six of 39 patients with measurable disease had confirmed partial responses and one had an unconfirmed partial response.
- At 6 months, 43.9% of patients were progression-free; the median PFS and OS periods for all patients were 3.7 months and 10.1 months, respectively.

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We found that the DCE-MRI variables baseline transport constant (K_{trans}) and rate constant at day 28 were significantly associated with PFS in univariate analyses, but only baseline K_{trans} remained significant when considered jointly.

- The most frequent toxicities were hypertension, fatigue, anorexia and weight loss; the addition of prednisone reduced the incidence of constitutional toxicities.
- This study demonstrated that cediranib was generally well tolerated with some anti-tumour activity in highly pretreated patients with metastatic CRPC who had progressive disease after docetaxel-based therapy.

Keywords

castration-resistant prostate cancer; angiogenesis inhibitors; cediranib; AZD2171

Introduction

Prostate cancer is the most common non-dermatological cancer in men and has the second highest cancer-related death rates in men [1]. Docetaxel and prednisone are currently the standard of therapy for patients with symptomatic metastatic castration-resistant prostate cancer (CRPC). Cabazitaxel and abiraterone are approved as second-line treatment options for patients with post-docetaxel progressive metastatic disease, but the duration of response is generally short-lived with a modest survival benefit; therefore, more effective therapeutic approaches are still needed, especially in the post-docetaxel setting.

Vascular endothelial growth factor (VEGF), a pro-angiogenic factor, and its receptors have been shown to be important in promoting tumour angiogenesis, playing a critical role in prostate cancer development and progression [2–4]. In preclinical models, inhibition of angiogenesis has been shown to be an effective target in CRPC. VEGF expression is observed in prostate tumours and in plasma and urine from patients with metastatic disease, where increased expression is associated with disease progression [5, 6]. The fms-like tyrosine kinase/kinase insert domain receptor receptors are expressed in human prostate cancers and are correlated with higher grade lesions and outcome [7]. While targeting angiogenesis appears to be a rational and therapeutic approach for CRPC [8], recent phase III trial results of VEGF pathway inhibitors bevacizumab [9] and sunitinib [10] have shown no clinical benefit, suggesting the need for predictive biomarkers to identify appropriate subgroups that may more likely benefit from this targeted therapy.

Cediranib (AZD2171) is a potent oral small molecule inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3 [11, 12] and also of c-kit, to a lesser extent [12]. Cediranib has been investigated in clinical trials with multiple cancers including colorectal [13], lung [14, 15], ovarian [16] and renal [17] cancer, and glioblastoma [18, 19]. Cediranib has been reported to show activity in prostate cancer. Ryan et al. [20] reported a phase I trial that established a maximum tolerated dose of 20 mg with the dose-limiting toxicities of muscle weakness and hypertension. We conducted a phase II trial using cediranib 20 mg orally, once daily to assess the clinical efficacy and side-effect profile in patients with metastatic CRPC who have progressed after therapy with docetaxel. Previous studies have reported that serum PSA level has not been a dependable marker in assessing response using non-cytotoxic drugs [21, 22]. The present study used clinical and radiographical criteria to assess response. A second part of the study added prednisone in an attempt to limit the constitutional side effects that were associated with cediranib.

Patients and Methods

Patient selection

Patients were considered eligible if they had: a) histological confirmation of prostatic adenocarcinoma; b) metastatic CRPC with radiographic evidence of disease, with progression defined as an increase in radiographic lesions and/or PSA level rising on successive measurements; c) previously received a docetaxel-based chemotherapy regimen with no limit on subsequent treatments; and d) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1or 2. Patients were excluded if they had: a) QTc >470 ms; b) > 1+ proteinuria; c) uncontrolled hypertension; or d) abnormal haematological or biochemical characteristics and/or brain metastasis. Patients were not allowed to receive other anti-tumour therapy (including radiation therapy) except continuation of LHRH agonists. Concurrent use of bisphosphonates was allowed for patients with known bone metastases. All patients gave written informed consent in accordance with federal, state and institutional guidelines, and the National Cancer Institute (NCI) review board approved the study.

Study design

This was a single institution, single-arm, open-label phase II clinical trial with part one using a two-stage optimum design, as described by Simon [23]. The study was designed before the publication of the recent Prostate Cancer Working Group 2 criteria and was based on data from previous trials of NCI patients with similar eligibility requirements. The trial targeted 30% as the desirable proportion of patients who were progression-free, according to clinical and radiographic criteria, by the 6th monthly evaluation ($p1=0.30$); and results would be considered inadequate if only a fraction consistent with 10% were progression-free by the 6 month evaluation time ($p0=0.10$). With $\alpha=0.10$ and $\beta=0.10$ as acceptable error probabilities, initially 12 patients were enrolled and followed for progression. If 0–1 of the 12 patients was progression-free at 6 months, then no further patients were enrolled. If two or more of the first 12 patients were progression-free at 6 months, then enrolment was continued until a total of 35 evaluable patients had been entered. If five or fewer of the 35 patients were progression-free at 6 months, this would not be considered adequate responsiveness to treatment, while if six or more of the 35 patients were progression-free at 6 months, this would have indicated results consistent with an adequate progression-free survival (PFS) probability worthy of further investigation. Under the null hypothesis (10% of patients progression-free at 6 months), the probability of early termination after 12 patients had been evaluated at 6 months would be 66%.

In the second portion of the study, 23 additional evaluable patients were enrolled in the trial and received prednisone and cediranib. This was done because a large proportion of patients from the first part of the study experienced grade ≥2 fatigue, anorexia and/or weight loss, many of whom appeared to be responding to therapy. To determine if adding prednisone was associated with an improvement in treatment response, a sample size calculation was carried out after evaluation of the first 28 patients. Using a one-sided $\alpha=0.05$ Fisher's exact test, we found that 23 patients would provide 80% power to detect a difference between 19/28 (68%) patients identified with grade ≥2 fatigue, anorexia and/or weight loss from the first part of the study, and 30% of patients with the same level and type of symptoms.

The secondary objective of the present study was to measure the overall response rate and overall survival (OS) rate. PSA progression may occur in the absence of radiological or clinical progression and response rate to therapy with cediranib, and demonstration of a pharmacodynamic effect by cediranib in the patient and on the tumour (when possible) via

dynamic contrast enhanced (DCE)-MRI) to determine early changes in tumour vascularity during treatment.

Treatment plan and toxicity evaluation

Patients were given cediranib 20mg orally for a 28-day cycle in the first stage of the study. Patients were evaluated in the clinic every 4 weeks, and radiographic assessments using CT and bone scintigraphy were obtained every 2 months. Blood tests including complete blood count, chemistry and PSA level were obtained at each monthly visit. Response and progression were evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 [24]. For bone scans, progression was defined as appearance of a new lesion, and improvement was defined as the complete resolution of at least one lesion. PSA values were recorded but not used as a criterion for progression. Echocardiograms and electrocardiograms were carried out and patients' troponin levels were measured monthly owing to previous reports of cardiotoxicity [25]. The dose of cediranib was adjusted based on NCI Common Toxicity Criteria for Adverse Events (CTCAE version 3.0). Briefly, patients found to have grade 1 toxicity had no dose adjustment or interruptions. Cediranib was decreased by 25% for persistent grade 2 nausea, vomiting, diarrhoea or other intolerable grade 2 side effects. Cediranib was held for Grade 3 non-haematological toxicity or Grade 4 haematological toxicity until resolution of side effects ≤ Grade 1. After resolution, the dose was decreased by 25%. If a patient's side effects did not resolve, the patient was withdrawn from the study. Patients with Grade 4 non-haematological toxicity were to be withdrawn from the study. Hypertension was managed using therapy and toxicity grading specific for anti-angiogenic therapies. Proteinuria, analysed by dipstick, required confirmation with a dose adjustment of 25% for >1 g of protein in 24-h urine. All patients in the second stage of the trial received prednisone 10 mg orally daily and cediranib 20 mg orally daily. Both drugs were taken together in the morning. Cortisol levels were checked in patients who were not on steroids at the time of enrolment.

Response evaluation

Patients were evaluated based on RECIST every two cycles. Patients remained enrolled in the study unless: a) they had radiological disease progression; b) they had intercurrent illness requiring cessation of cediranib; c) they decided to withdraw from the study; or d) they had unacceptable side effects. Patients with bone-only disease were considered to have progressed if they had new lesions or clinical signs of progression. Bone scans with a disappearance of any bone lesion were recorded. Patients who had a rising PSA level were still included in the study if they did not meet the above criteria [22].

Dynamic contrast-enhanced MRI

Dynamic contrast-enhanced MRI was obtained using T1-weighted gradient echo images after injection of a bolus of a low-molecular-weight gadolinium chelates. DCE-MRI scans were obtained before treatment (preferably < 7 days before treatment start), 24–36 h after starting daily oral dosing, and at 28 and 56 ± 2 days, subsequently doubling the time before follow-up scans (e.g. 112 and 224 days), while patients remained enrolled in the study, and depending on the study design. The initial area under the gadolinium curve measured over 60 s ($iAUC_{60}$) and the transport constant (K_{trans}) from a region-of-interest analysis, averaged over the whole tumour volume (using three-dimensional techniques) or over the tumour area (using two-dimensional techniques), were measured and provided basic measurements for collation of DCE-MRI data. Both $iAUC_{60}$ and K_{trans} require calculation of instantaneous tumour gadolinium concentration based on the change in relaxivity due to contrast uptake $\Delta R1$. Manual region-of-interest measurements were obtained from the target lesion. Baseline and follow-up after treatment cycles of additional DCE-MRI variables,

including tumour volumes, the rate constant (K_{ep}) and the extravascular fraction V_e, were also obtained.

Echocardiograms

Recent data from breast cancer trials using cediranib and doxorubicin at the NCI identified two patients who experienced asymptomatic ejection fraction decreases that were reversible upon withdrawal of cediranib [25]. As it is difficult to determine whether this was a toxicity that was associated with VEGF inhibitor monotherapy or with concurrent regimens including VEGF inhibitors, echocardiograms were obtained for patients concurrently with CT scans and bone scans. As there are currently no guidelines on the evaluation and management of ejection fraction in the setting of cediranib use, similar criteria to those previously used for trastuzumab, which is known to decrease ejection fraction, and to those used in the NCI breast cancer trials were applied [26].

Statistical analysis

Time to progression was defined as the time from the date of enrolment in the study to the date of first observation of disease progression, death while enrolled in the study, or to the time when the patient was removed from the study at the PI's discretion. Other reasons for a patient being removed from the study, such as adverse events, patient decision, or intercurrent illness, were used to censor the time to progression. OS was defined as the time from the date of enrolment in the study to the date of death from any cause. Patients remaining enrolled in the study or alive at time of analyses were censored at date of last follow-up. The probability of PFS or OS as a function of time was determined using the Kaplan–Meier method.

For the DCE-MRI analyses, changes from baseline were reported as the relative change, which was the value at (day 28 – day 0)/day 0 for each of the variables evaluated. This was done because the relative changes were less associated with the baseline values than were the absolute changes; thus, the relative change × 100% would represent the percentage change from baseline. The association between DCE-MRI variables and PFS or OS as determined by the Kaplan–Meier method was assessed. Initially, in univariate analyses, the significance of a difference in a pair of Kaplan–Meier curves, or among a set of curves, was determined using the log rank test. Initial exploratory evaluations were carried out to determine the association between the variables divided at their quartiles and survival or PFS. When an evaluation of the survival or PFS analyses suggested that there would be a potentially significant effect when the data were re-divided into the two groups suggested by the data, the resulting *P* value was adjusted by multiplying the unadjusted value by 3 to account for the implicit comparisons involved in deciding to use a single division of the data. Cox proportional hazards model analysis was used to determine the hazard ratio of any DCE-MRI variable found to be potentially significantly associated with outcome in the univariate analyses, as well as to determine the joint effect of the variables found to be significant. Spearman correlation was used to describe the association between change in tumour volume and the DCE-MRI variables. All *P* values were two-tailed, and except as noted above, were reported without any correction for multiple testing, and the results of these analyses were considered hypothesis-generating.

Results

A total of 59 patients were enrolled in the present study: 36 patients in the first cohort and 23 in the second cohort of the trial, between February 2007 and February 2010. The study demographics and baseline characteristics of all patients are shown in Table 1. Many patients had unfavourable prognostic factors, as evidenced by visceral disease, a high

Gleason score at diagnosis, and previous treatment with two or more chemotherapy regimens. Eighteen patients (31%) had received previous treatment with at least one anti-angiogenic agent. The majority (n=47) had an ECOG performance status of 1.

Of the 59 patients who were enrolled, 39 had measurable disease. One patient in the first cohort was not evaluable owing to the development of a cord compression on day 2 of therapy and was subsequently removed from the trial. Among those with measurable disease, six patients had confirmed partial responses and one had an unconfirmed partial response. The probability of PFS was 43.9% at 6 months. After a median potential follow-up of 33.5 months, nine patients of 58 evaluable patients remained alive as of the last follow-up. The median PFS was 3.6 months for the first cohort (n=35) and 3.7 months for the second cohort (n=23 [P=0.79; data not shown]). The median PFS for all patients (n=58) was 3.7 months (Fig. 1A). The median OS was 10.9 months for the first cohort and 9.6 months for the second cohort (P=0.23; data not shown), and for the whole cohort of 58 patients it was 10.1 months (Fig. 1B).

Of the 59 patients enrolled in the study, 49 had DCE-MRI scans that were available for assessment: six patients were evaluated up to day 2, eight up to day 28, 16 up to day 56, 14 up to day 112, four up to day 224, and one up to day 448 (48 patients were evaluated on day 2, 43 on day 28, 33 on day 56, 18 on day 112, 5 on day 224, and one on days 336 and 448). A rapid reduction in the primary DCE-MRI variables K_{trans} and $iAUC_{60}$ was observed for the majority of patients within 24 h of the first dose (median reductions of 17.65 and 14.50%, respectively). The magnitude of change in either median K_{trans} or $iAUC_{60}$ observed after 28 days was greater overall than at 24 h (P = 0.001 and P = 0.015 respectively, Wilcoxon signed-rank test, n=40). Based on previous studies with cediranib, we considered a > 30% reduction in primary DCE-MRI variables to be representative of a positive pharmacodynamic response to anti-vascular therapy [24]. After one cycle of therapy, 60% of patients experienced a vascular response with > 30% reductions in K_{trans}, where the mean reduction was 66%. Figure 2A shows the distribution of patients with minor to major reductions in DCE-MRI variables at day 28. Over 65% of patients experienced at least minor reductions from baseline in K_{trans} and $iAUC_{60}$, observed at the end of cycle 1. The proportion of patients with reductions in DCE-MRI variables began to decrease at 56 days after the initiation of therapy, for patients who remained on cediranib (data not shown).

The change in vascular response to cediranib over the course of four cycles as percent reductions in DCE-MRI variables is shown in Fig. 2B. In the present study, the vascular response tended to reach a maximum at 28 days after initiation of treatment. The distribution of the largest percent change from baseline in lesion volume during 1–2 cycles of therapy is shown in Fig. 2C. Approximately 40% of patients had maximum lesion volume reductions of > 25% (i.e. 28–84% decreases in lesion volume). The compound daily growth rate (%) is a more relative indicator for comparing patients who may have either fast or slow growth in lesion volume. For example, patients #1 and #4 in Fig. 3 had the same percent growth rate; however, patient #4 had a maximum reduction at 28 days compared with 56 days for patient #1. Also, the figure depicts only three patients who experienced maximum changes in lesion volume beyond two cycles (represented as spikes), for those patients who remained on therapy.

The K_{trans}, K_{ep} and $iAUC_{60}$ measurements at day 0 (baseline), day 28, and the difference between the day 28 and the day 0 measurements (day 28 – day 0), were evaluated for their association with tumour volume. There was no evidence of any association between change in tumour volume or relative change in volume and the DCE-MRI variables evaluated (data not shown). These same measurements were divided into quartiles and the relationship between these variables and PFS and OS was determined. When associations were

identified, the data were re-divided at the quartile associated with a difference in the prognostic ability of the variables, and the association with outcome was re-determined. Only baseline K_{trans} and K_{ep} at day 28, divided as indicated, were found to be significantly associated with PFS in univariate analyses (Fig. 3), while none of the variables examined were significantly associated with OS. As shown in Table 2, using Cox hazards models for each variable individually, a baseline $K_{trans} > 0.22$ was significantly associated with a lower probability of PFS than a K_{trans} of < 0.22 (P=0.02), with a hazard ratio of 3.26 (95% CI: 1.22–8.76). A K_{ep} at day 28 of > 0.35 was associated with significantly lower probability of PFS than a K_{ep} of < 0.35 (P=0.02), with a hazard ratio of 2.40 (95% CI: 1.14–5.03). When the two DCE-MRI variables were considered jointly, K_{ep} at day 28 lost its significance in the presence of baseline K_{trans}.

All patients who received treatment were analysed for toxicity. Patients received a median (range) of 3 (<1 – 16) cycles. Of the 58 patients, 30 (52%) discontinued therapy because of disease progression, 10 (17%) owing to toxicity, and 16 (28%) as a result of the physician's or the patient's own decision, but were not required by the protocol to discontinue. One patient discontinued therapy because of intercurrent illness not related to prostate cancer and one patient died during treatment from a cerebral haemorrhage complicated by disseminated intravascular coagulation. Protocol-required dose reductions for the management of cediranib toxicity were necessary for five patients.

Table 3A shows the most common grade 2 toxicities that occurred in >10% of patients and all grade 3 and 4 toxicities. Significant grade 2 adverse events included hypertension (43%), fatigue (33%), anorexia (31%) and weight loss (27%). The intensity of these events was usually mild to moderate. Most side effects were of short duration and resolved without incident. Severe grade 3 toxicities included fatigue (10%), dehydration (10%), elevated alkaline phosphatase (9%) and muscle weakness (7%). There was a low overall incidence of Common Toxicity Criteria grade 4 toxicity that included thrombosis/embolism (n=2) and CNS haemorrhage (n=1). The addition of prednisone in the second stage of the study reduced the overall incidence of grade 2 constitutional toxicities of fatigue (43% in cohort 1 vs 17% in cohort 2), anorexia (34% in cohort 1 vs 26% in cohort 2), and weight loss (31% in cohort 1 vs 17% in cohort 2) as well as grade 2 dehydration, grade 2 prolonged QTc, and grade 3 elevated alkaline phosphatase (Table 3B).

A total of 38 patients had echocardiograms. The median (range) ejection fraction on study entry was 65 (43–79)%. No patient had any clinical signs or symptoms of congestive heart failure and there were no clinically significant decreases in ejection fraction.

Discussion

Cediranib has been shown to inhibit the growth of bone and brain metastases in a preclinical model of advanced prostate cancer [27]. A phase I study of cediranib was previously conducted in 83 patients with advanced solid tumours, with the primary objective of determining the maximum tolerated dose. The most common dose-limiting toxicity was hypertension (n=7) occurring at doses of ≥20 mg [28]. A separate phase I dose-escalation study was performed in patients with CRPC and showed good tolerability overall and an acceptable cediranib toxicity profile when given at therapeutic doses [20]. Doses of 1, 2.5, 5, 10, 15, 20 and 30 mg were administered to 26 patients. Dose-limiting toxicities occurred at the 30 mg dose and the maximum tolerated dose was identified as 20 mg. Although safety, tolerability and DCE-MRI pharmacodynamic responses were the main objectives of the phase I study, an objective clinical response was observed in one patient whereas four patients experienced PSA level reductions after drug discontinuation.

In the current phase II study of patients with metastatic CRPC who have progressed after docetaxel therapy, cediranib, given at 20 mg daily, was generally well tolerated. The primary objective of the present study was met, as the probability of remaining progression-free at 6 months was 43.9%. The most common adverse events reported were hypertension, fatigue, anorexia and weight loss. Unlike Ryan et al. [20], we did not observe any grade 3 hypertension at the 20 mg dose in the present study. The most common grade 3 toxicities included fatigue, dehydration and elevated alkaline phosphatase. Grade 3/4 hromboembolism was observed in three patients and one patient experienced a grade 4 CNS haemorrhage that resulted in death. The addition of prednisone in the second cohort reduced the overall incidence of constitutional toxicities.

Until recently, life-prolonging therapies for patients with metastatic CRPC were limited to docetaxel-based regimens [29], which received US Food and Drug Administration (FDA) approval in 2004 as first-line chemotherapy for metastatic CRPC, whereas mitoxantrone had previously been approved based on improvements in quality of life [30]. In 2010–2011, three more FDA-approved therapies were added to the CRPC treatment armamentarium: the autologous cellular immunotherapy product sipuleucel-T (indicated for men with minimal or no symptoms) [31], the chemotherapy agent cabazitaxel [32] and the targeted therapy abiraterone acetate (indicated for men with disease progression after docetaxel chemotherapy) [33]. Although it appears that treatment options for patients with metastatic CRPC have increased and outcomes have improved, specifically for those in the post-docetaxel setting, the duration of PFS and OS still remains relatively short.

The median OS for the current study involving cediranib was 10.1 months and was shorter than that reported for phase III trials involving cabazitaxel (OS=15.1 months) [32] or abiraterone (OS=14.8 months) [33]; however, direct comparisons among the three studies should be tempered by the fact that patients in the present study were exposed to more previous chemotherapy regimens, thereby potentially affecting the benefit derived from cediranib. Although all three studies evaluated patients who had already had progressive disease after docetaxel, the majority of patients (67%) in present study of cederanib had undergone more than two previous chemotherapy regimens, including 31% who had undergone three or more. Patients in the abiraterone phase III trial were limited to only two previous chemotherapy regimens with only 30% of these patients having had more than one cytotoxic therapy [33]. Similarly, only 15% of patients enrolled in the cabazitaxel phase III trial had had exposure to more than one previous chemotherapy regimen [32].

The present study used DCE-MRI to investigate the effect of once-daily 20mg dosing on tumour vascular permeability. The primary DCE-MRI variables $iAUC_{60}$ and K_{trans} revealed rapid and sustained reductions from baseline up to two or more cycles in the majority of patients. The results support the hypothesis that cediranib has effects on tumour vasculature, as evidenced by statistically significant reductions in gadolinium uptake, by as much as 97%, and across large proportions of patients in the study. Moreover, vascular permeability and perfusion of gadolinium remained decreased up to day 112; however, no correlation was found between RECIST and changes in DCE-MRI primary or exploratory variables. High baseline K_{trans} and post-therapy (day 28) K_{ep} were found to be significantly associated with PFS, indicating that DCE-MRI variables may prove effective as pharmacodynamic predictive biomarkers of clinical outcome for cediranib, as previously shown for sorafenib (34, 35). The clinical relevance of these findings and their predictive value remain to be determined and validated prospectively, especially given the recent studies showing higher morbidity in patients receiving anti-angiogenic therapy [36].

Although targeting angiogenesis appears to be a rational therapeutic approach for CRPC, there are still major obstacles to identifying the appropriate subgroups that may benefit more

from these agents. Monotherapy with sunitinib, another small molecule tyrosine kinase inhibitor, despite supportive phase II data in patients with progressive metastatic CRPC after docetaxel treatment [37], recently failed in a phase III trial of the same patient population [10]. It would be reasonable to expect that the use of angiogenesis inhibitors in combination with chemotherapy would prove to be more efficacious than monotherapy with anti-angiogenic agents; however, results from another recent phase III study showed that the addition of bevacizumab may add little clinical benefit in OS to docetaxel in chemotherapy-naïve patients with CRPC [9]. The role that anti-angiogenic agents have in docetaxel-refractory mCRPC remains to be determined with the most promising candidate being cabozantinib, an oral small molecule inhibitor of multiple kinase signalling pathways including c-MET and VEGFR2. A phase II study investigating the use of cediranib in combination with or without dasatinib, an oral Src family kinase inhibitor, in patients with docetaxel-refractory metastatic CRPC is currently underway (clinicaltrials.gov identifier NCT01260688) as well as a phase II study of docetaxel with or without cediranib in chemotherapy-naïve patients with CRPC (NCT00527124). The challenge lies in how to best combine these agents and how to measure the responses seen with these treatments.

In conclusion, this phase II study showed that cediranib, 20mg daily, in 58 patients with docetaxel-refractory metastatic CRPC, results in perturbations in tumour vasculature, >30% PFS at 6 months, and a median OS of 10.1 months. There remains a clear need to define the most appropriate treatment approach for patients with metastatic CRPC in light of new second-line treatment options becoming available, especially those who have progressive disease after docetaxel therapy. Future studies will need to focus on determining the optimum sequence and combination of new anti-angiogenics and other investigational agents with conventional chemotherapy. Further investigation into the potential predictive value of DCE-MRI parameters as biomarkers for anti-angiogenic therapy is warranted.

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Abbreviations

CRPC	castration-resistant prostate cancer
ECOG	Eastern Cooperative Oncology Group
PFS	progression-free survival

OS	overall survival
DCE-MRI	dynamic contrast-enhanced MRI
K_{trans}	transport constant
K_{ep}	rate constant
VEGF	vascular endothelial growth factor
NCI	National Cancer Institute
RECIST	Response Evaluation Criteria in Solid Tumours
$iAUC_{60}$	area under the curve measured over 60 seconds
FDA	Food and Drug Administration

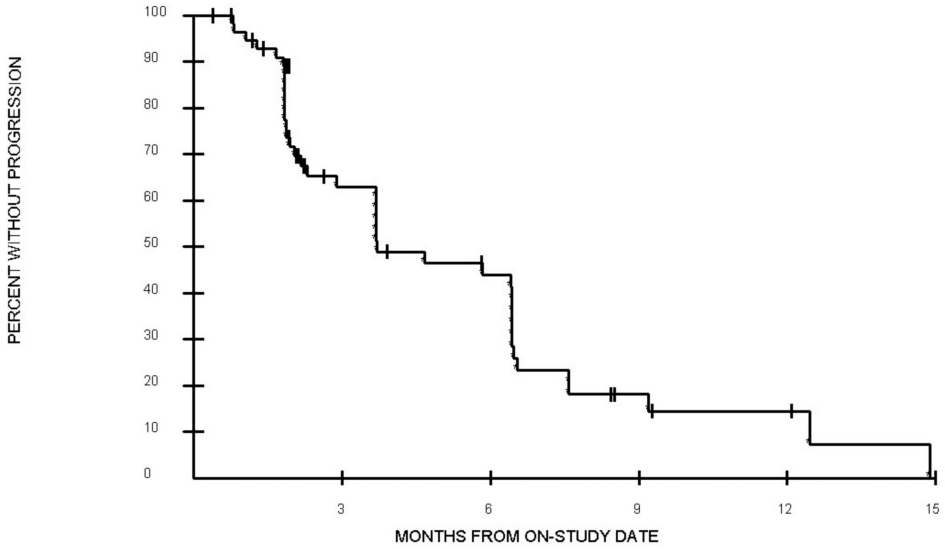
What's known on the subject?

Recent advances in the treatment of metastatic castration-resistant prostate cancer (CRPC) have resulted in improved outcomes; however, the effects have not proved to be long term, highlighting the need for new therapies, particularly in patients with docetaxel-refractory metastatic CRPC. Angiogenesis has been shown to play an important role in the development and progression of prostate cancer. Although targeting angiogenesis appears to be a rational and therapeutic approach for metastatic CRPC, identifying the appropriate subgroups that may benefit from anti-angiogenic therapy remains a challenge.

What does the study add?

The study demonstrates the potential use of dynamic contrast-enhanced (DCE)-MRI variables as pharmacodynamic endpoints in predicting the clinical outcomes associated with anti-angiogenic agents such as cediranib. Further investigation into the potential predictive value of DCE-MRI variables as biomarkers for antiangiogenic therapy is warranted.

(A) Progression-free survival



(B) Overall Survival

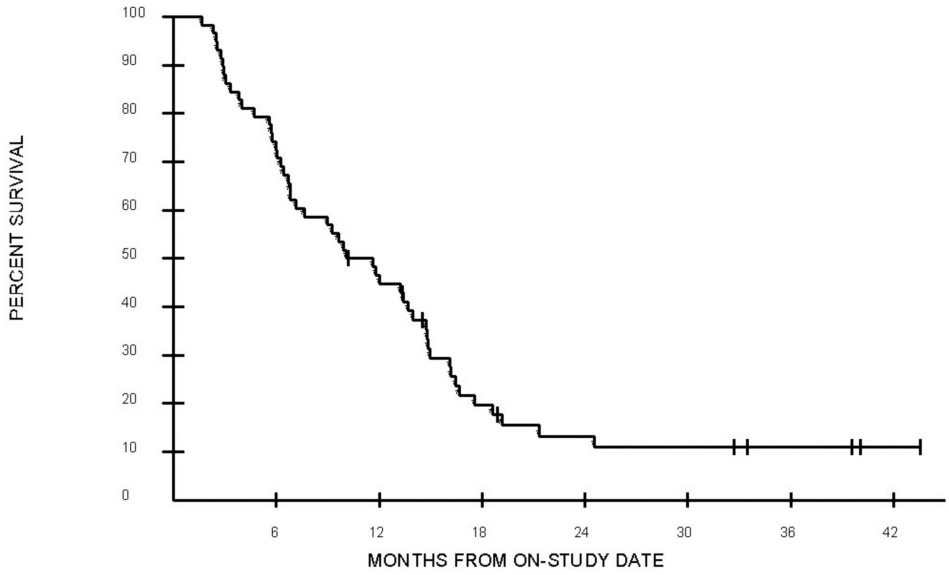
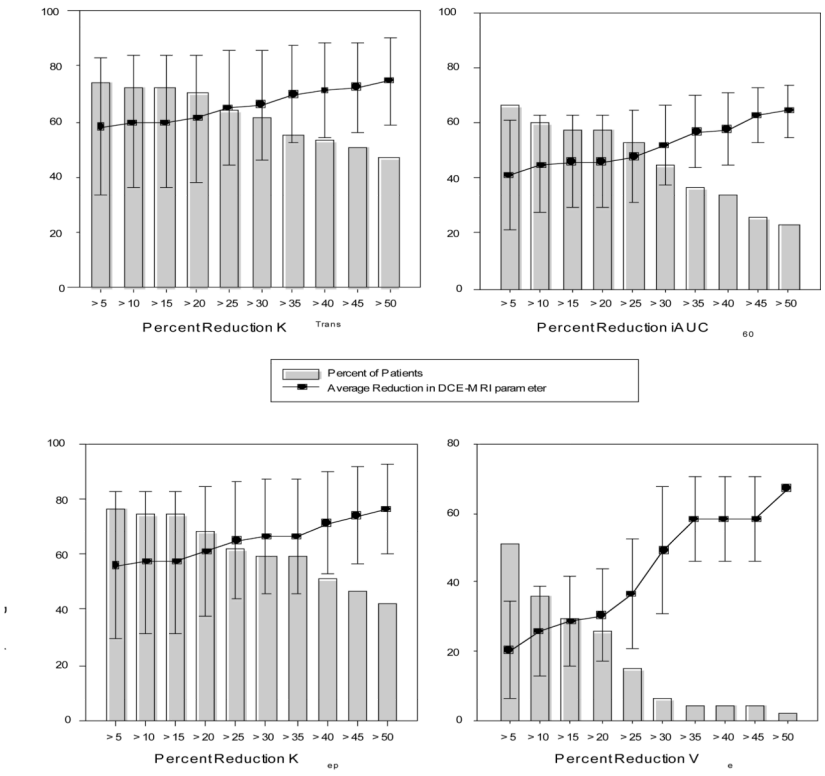
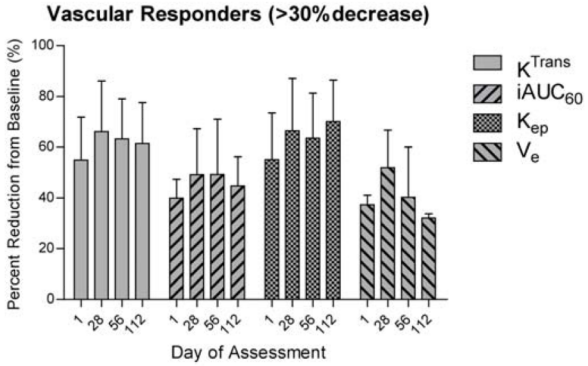


Fig. 1.
Kaplan–Meier analysis of **A**, PFS and **B,** OS for all patients (n=58) included in the study.

(A)



(B)



(C)

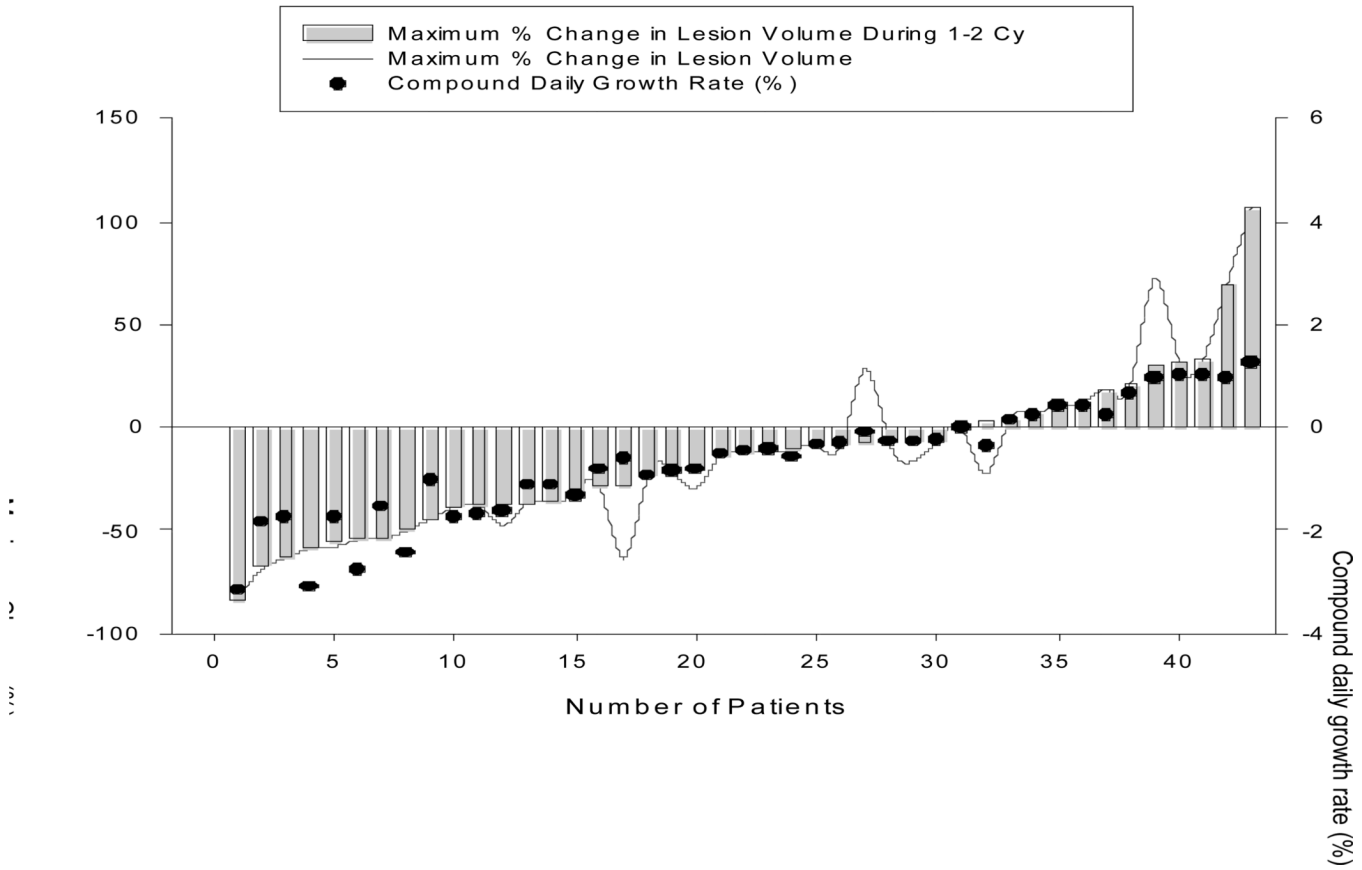


Fig. 2.

A, The percent of patients, and reductions, (mean ± SD) in DCE-MRI variables after one cycle of therapy. **B**, The percent change in DCE-MRI variables during four cycles of cediranib therapy (median ± 95% CI). **C,** Maximum percent change in lesion volume through all cycles and maximum percent change during 1–2 cycles of cediranib therapy in 43 patients. Compound daily growth rate represents the maximum percent change normalized by 28 or 56 days on therapy.

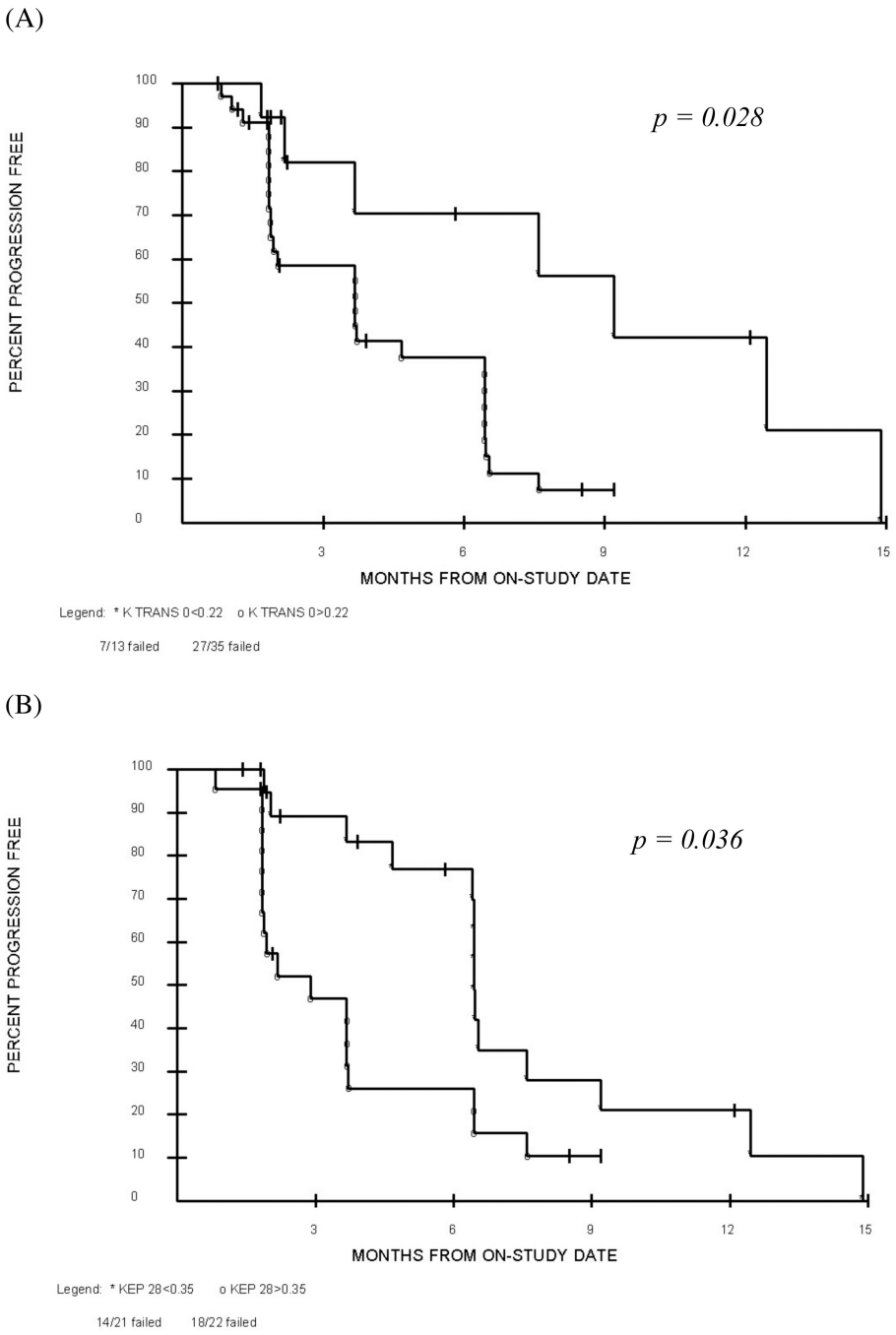


Fig. 3.

Kaplan–Meier estimates for PFS of patients with DCE-MRI variables. **A**, K_{trans} (threshold defined as baseline K_{trans} = 0.22). **B,** K_{ep} (threshold defined as the post-therapy day 28 K_{ep} = 0.35). Log rank *P* values shown have been adjusted for the effect of exploratory analyses used to determine the preferred quartile at which to divide the data for evaluation.

Table 1

Demographics and disease characteristics of enrolled patients (n = 59) patient demographics and clinical characteristics

Characteristic	
Median (range) age, years	68.9 (51.4 – 79.8)
Race, n (%)	
White	52 (88)
African-American	3 (5)
Hispanic	3 (5)
Asian	1 (2)
ECOG performance status, n (%)	
0	2 (3)
1	48 (81)
2	9 (16)
Median (range) Gleason score at diagnosis	8 (4–10)
Gleason score at diagnosis, n (%)	
≥8	32 (54)
≤ 7	26 (44)
Unclassified	1 (2)
PSA level during study, ng/mL	
Median (range)	175.45 (4.94–1587)
Haemoglobin, g/dL	
Median (range)	11.8 (6.7–14.9)
Lactate dehydrogenase, U/L	
Median (range)	235.5 (124–3344)
Alkaline phosphatase, U/L	
Median (range)	141 (46–1244)
Metastases, n (%)	
Bone only	19 (33)
Soft tissue and bone	36 (62)
Liver	9 (15)
Lung	1 (2)
Pain at baseline, n (%)	40 (69)
Previous chemotherapy regimens, n (%)	
1	19 (33)
2	21 (36)
≥ 3	18 (31)

Table 2

Cox model analysis for the individual effects of baseline K_{trans} <0.22 vs >0.22, K_{ep} at day 28 <0.35 vs >0.35, and for the joint effects of these variables

Variable	DF	Parameter estimate	SE	Chisquare	Pr > Chisquare	HR	95% HR CI
K_{trans} at day 0	1	0.874	0.378	5.340	0.021	2.396	1.142– 5.029
K_{ep} at day 28	1	1.182	0.504	5.506	0.019	3.262	1.215– 8.759
Joint effect of the parameters							
K_{trans} at day 0	1	1.389	0.695	3.990	0.046	4.011	1.026– 15.672
K_{ep} at day 28	1	0.348	0.432	0.648	0.42	1.417	0.607–3.306

DF, degrees of freedom; HR, hazard ratio.

Table 3

A. NCI Common Toxicity Criteria grade 2, 3 or 4 toxicities possibly, probably or definitely related to cediranib

Toxicity*	Grade *n* (%)	Grade *n* (%)	Grade 4 *n* (%)
Hypertension	25 (43)	0 (0)	0 (0)
Fatigue	19 (33)	6 (10)	0 (0)
Anorexia	18 (31)	2 (3)	0 (0)
Weight loss	15 (27)	2 (3)	0 (0)
Hypothyroidism	13 (22)	0 (0)	0 (0)
Dehydration	10 (17)	6 (10)	0 (0)
Prolonged QTc	10 (17)	2 (3)	0 (0)
Nausea	10 (17)	1 (2)	0 (0)
Diarrhoea	8 (14)	0 (0)	0 (0)
Hypoalbuminaemia	8 (14)	0 (0)	0 (0)
Proteinuria	8 (14)	0 (0)	0 (0)
Elevated alkaline phosphatase	6 (10)	5 (9)	0 (0)
AST	6 (10)	2 (3)	0 (0)
Vomiting	6 (10)	1 (2)	0 (0)
Hyperbilirubinemia	5 (9)	1 (2)	0 (0)
Muscle weakness	3 (5)	4 (7)	0 (0)
Haemoglobin, anaemia	3 (5)	1 (2)	0 (0)
Lymphopenia	2 (3)	3 (5)	0 (0)
Platelets	2 (3)	1 (2)	0 (0)
ALT	2 (3)	1 (2)	0 (0)
Pain	1 (2)	2 (3)	0 (0)
Hypoxia	0 (0)	2 (3)	0 (0)
Thrombosis/embolism	0 (0)	1 (2)	2 (3)
Hyponatremia	0 (0)	1 (2)	0 (0)
Renal failure	0 (0)	1 (2)	0 (0)
Hypokalemia	0 (0)	1 (2)	0 (0)
PTT	0 (0)	1 (2)	0 (0)
CNS haemorrhage	0 (0)	0 (0)	1 (2)

B. Number of toxicities in each cohort

	Cohort 1 (*n*=35)		Cohort 2 (*n*=23)	
Toxicity	**Grade 2**	**Grade 3**	**Grade 2**	**Grade 3**
Hypertension	17	0	8	0
Fatigue	15	4	4	2
Anorexia	12	1	6	1
Weight loss	11	2	4	0
Hypothyroidism	7	0	6	0
Dehydration	8	3	2	3

B. Number of toxicities in each cohort

	Cohort 1 (*n*=35)		Cohort 2 (*n*=23)	
Toxicity	**Grade 2**	**Grade 3**	**Grade 2**	**Grade 3**
Prolonged QTc	8	1	2	1
Nausea	7	1	3	0
Diarrhea	8	0	0	0
Hypoalbuminemia	5	0	3	0
Proteinuria	5	0	3	0
Elevated alkaline phosphatase	4	5	2	0
AST	3	2	3	0
Vomiting	4	1	2	0
Hyperbilirubinemia	4	1	1	0
Muscle weakness	2	3	1	1

* Toxicities occurring in > 10% of patients and any grade 3 and 4 toxicities in patients who received study drug ($n = 58$).