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Phase II trial of docetaxel, bevacizumab, lenalidomide and prednisone in patients with metastatic castration-resistant prostate cancer

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Abstract

Objective—To determine the safety and clinical efficacy of two anti-angiogenic agents, bevacizumab and lenalidomide, with docetaxel and prednisone.

Patients and methods—Eligible patients with metastatic castration-resistant prostate cancer enrolled in this open-label, phase II study of lenalidomide with bevacizumab (15 mg/kg), docetaxel (75 mg/m^2) and prednisone (10 mg daily). Docetaxel and bevacizumab were administered on day 1 of a 3-week treatment cycle. To establish safety, lenalidomide dosing in this combination was escalated in a conventional 3 + 3 design (15, 20 and 25 mg daily for 2 weeks followed by 1 week off). Patients received supportive measures including prophylactic pegfilgrastim and enoxaparin. The primary endpoints were safety and clinical efficacy.

Results—A total of 63 patients enrolled in this trial. Toxicities were manageable with most common adverse events (AEs) being haematological, and were ascertained by weekly blood counts. Twenty-nine patients (46%) had grade 4 neutropenia, 20 (32%) had grade 3 anaemia and seven (11%) had grade 3 thrombocytopenia. Despite frequent neutropenia, serious infections were rare. Other common non-haematological grade 3 AES included fatigue (10%) and diarrhoea

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Conflict of Interest

None declared.

(10%). Grade 2 AES in of patients included anorexia, weight loss, constipation, osteonecrosis of the jaw, rash and dyspnoea. Of 61 evaluable patients, 57 (93%), 55 (90%) and 33 (54%) had PSA declines of >30, >50 and >90%, respectively. Of the 29 evaluable patients, 24 (86%) had a confirmed radiographic partial response. The median times to progression and overall survival were 18.2 and 24.6 months, respectively.

Conclusions—With appropriate supportive measures, combination angiogenesis inhibition can be safely administered and potentially provide clinical benefit. These hypothesis-generating data would require randomized trials to confirm the findings.

Keywords

prostate cancer; angiogenesis inhibition; combinationation therapy; metastatic castration resistant prostate cancer; docetaxel coimbination

Introduction

Up until 2010, docetaxel with prednisone was the only treatment that had been found to have a survival benefit in patients with metastatic castration-resistant prostate cancer (mCRPC), which annually claims more than 300 000 lives worldwide [1–3]. Recent advances in the treatment of mCRPC have revolutionized treatment algorithms [4]. Despite their impact on overall survival (OS), sipuleucel-T and Ra-223 have unknown impact in symptomatic patients or those with visceral metastasis, respectively. Abiraterone and enzalutamide have favourable toxicity profiles, but they share mechanisms of resistance that probably diminish the benefits of sequential use [5–7].

Given that current clinical studies are focusing on using many of these new treatments earlier in the disease process (at the non-metastatic stage or as neoadjuvant therapy), it is likely that future populations of patients with mCRPC may have disease with greater inherent androgen resistance based on earlier exposure to modern antiandrogens [7]. In this context, taxane-based chemotherapy remains a very relevant treatment, and efforts to maximize its benefit should continue. The therapeutic potential of docetaxel is exemplified by the significant clinical impact of limited docetaxel (for six cycles) when added to androgen deprivation therapy in patients with castration-sensitive, metastatic disease: a median improvement in OS of 13.6 months compared with androgen deprivation therapy alone (57.6 vs 44.0 months; hazard ratio [HR] 0.61; $P < 0.001$). [8] These findings have been supported by similar outcomes in the STAMPEDE trial [9].

Subsequently, numerous docetaxel-based combination studies failed to improve on the benefits of docetaxel and prednisone [10]. Despite a strong preclinical rationale with preliminary clinical data, the list of failed studies includes several phase Ill trials which combined docetaxel with a single angiogenesis inhibitor, including bevacizumab, lenalidomide and vascular endothelial growth factor (VEGF)-trap (aflibercept) [11–13]. The toxicity for these combination regimens could have curtailed treatment exposure, limiting clinical benefit compared with docetaxel alone. Another possible explanation for the failure of these trials was that, over time, resistance mechanisms, such as upregulation of proangiogenesis factors, ultimately circumvented the benefits of these anti-angiogenic

therapies, thereby limiting their potential clinical benefit [14]. An earlier phase II trial suggested that an approach using a combination of antiangiogenic agents could limit such treatment resistance. The study evaluated the combination of thalidomide, bevacizumab, docetaxel and prednisone which resulted in a median progression-free survival (PFS) of 18.3 months and a median OS of 28.2 months.[15]

In the present study, patients with mCRPC were treated with docetaxel, prednisone, bevacizumab and lenalidomide. Lenalidomide was substituted for thalidomide in this regimen because of the reduced side effect profile, namely it is not associated with fatigue and neuropathy. Patients were also given broad supportive measures (growth factor and anticoagulation) in an attempt to mitigate morbidity and treatment-limiting toxicities.

Patients and Methods

Study Population

Eligible patients were required to have progressive mCRPC as defined by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) [16]. Patients were aged ≥18 years with Eastern Cooperative Oncology Group performance status of ≤2, and adequate organ and bone marrow functions. Previous use of chemotherapy or anti-angiogenic therapy for mCRPC was an exclusion criterion. Patients with brain metastases, congestive heart failure, unstable angina, history of hypertensive encephalopathy, proteinuria ≥2 g/24 h, non-healing ulcers, bleeding diathesis and peripheral neuropathy ≥grade 2 were not eligible for enrolment. Patients on active treatment for venous thromboembolism, and those with abdominal fistula or gastrointestinal perforation within the previous 6 months were also not eligible.

The protocol was approved by the National Cancer Institute's Institutional Review Committee and written informed consent was obtained from all patients. The protocol was registered with the US National Clinical Trials Registry (NCT00942578).

Study Design and Statistical Methods

After a brief dose escalation portion, the study was designed to be a single-arm, open-label phase II study of lenalidomide and bevacizumab with docetaxel and prednisone in patients with mCRPC. The initial dose escalation portion was planned to enroll three to six patients at each of 15, 20 and 25 mg of lenalidomide. (Dose-limiting toxicity was defined as a ≥grade 3 non-haematological toxicity related to lenalidomide.) Then, 45 planned patients were to be enrolled at 25 mg lenalidomide to exclude 25% of patients with grade 4 non-haematological toxicity attributable to that dose level of lenalidomide. See the supplemental statistical methods in Supporting Information Appendix S1 for more details.

The primary objectives were safety of the treatment regimen and clinical efficacy, including response rate and time to progression (TTP) using PCWG2 criteria. [16] TTP was determined from the on-study date until the date of progression or last follow-up without progression, while survival was determined from the on-study date until the date of death or last follow-up. Patients who did not progress but were removed from treatment for adverse effects, preference and other reasons had follow-up for TTP censored at that time.

Additional objectives included evaluation of OS and the impact of changes in immune cells, circulating endothelial cells (CECs) and genotype on outcomes.

All *P* values are two-tailed and, except as noted in the supplemental statistical methods, are presented without any adjustments for multiple comparisons.

Drug Administration

All patients received i.v. docetaxel 75 mg/m^2 and bevacizumab 15 mg/kg on day 1 of each 21-day cycle. Lenalidomide was taken orally for the first 14 days of each cycle, while 10 mg prednisone was taken daily throughout the cycle. All patients received pegfilgrastim 6 mg s.c. on day 2, enoxaparin 1 mg/kg/day s.c. starting on day 1 for thromboembolic prophylaxis, and continued androgen deprivation therapy. Oral dexamethasone 8 mg was administered at 12, 3 and 1 h before docetaxel infusion, except in cases where i.v. infusions were required because of patient non-compliance. Patients receiving bisphosphonate before study enrolment were allowed to continue the drug. Because of potential concerns about the development of osteonecrosis of the jaw, bisphosphonate treatment was initiated after cycle 5 among patients with bone metastases who were not on bisphosphonate therapy before study enrolment. (Treatment modifications are described in the Supporting Information Appendix S2.)

Results

Patient Characteristics

In the dose escalation portion of the study, cohorts of three patients were treated with lenalidomide at 15, 20 and 25 mg daily, respectively, in combination with docetaxel, bevacizumab and prednisone. In the second part of the study, a total of 43 patients received a 25-mg dose of lenalidomide, and 11 patients in the expansion cohort received the 15-mg lenalidomide dose in the combination regimen. Patient characteristics for all 63 patients are shown in Table 1.

Clinical Response, Time to Progression and Overall Survival

Of 61 evaluable patients, 57 (93%) had confirmed PSA declines >30%, of which 55 (90%) and 33 (54%) had confirmed PSA declines >50 and >90%, respectively (Fig. 1A) In addition, 29 patients were evaluable for radiographic responses based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Twenty-four patients (84%) met the criteria for confirmed partial (>30%) radiographic response (Fig. 1B).

With a median time of potential follow-up of 47.5 months, the median TTP for all 63 enrolled patients was 18.2 months and the median OS was 24.6 months (Fig. 2). There were no significant differences noted with regard to lenalidomide dose levels and thus we reported these results in a combined fashion. There was no clear association between magnitude of PSA decline or rapidity of PSA decline and survival.

Toxicity

The dose escalation of lenalidomide did not reveal any dose-limiting toxicities, making 25 mg the recommended phase II dose in this combination. For all patients enrolled in the study, the most common adverse events (AEs) were haematological (Table 2). There were 29 patients (46%) with grade 4 neutropenia (ascertained by weekly complete blood counts). Non-heme grade 4 toxicities were seen in eight patients (13%), with neutropenic fever the most common ($n = 4$; 6%). Twenty patients (32%) and seven patients (11%) had grade 3 anaemia and thrombocytopenia, respectively. Although one patient had sepsis, most other infections were common respiratory infections, including five that were grade 3. Other frequent grade 3 AES included fatigue (10%) and diarrhoea (10%). Additional grade 2 AES experienced by >10% of the patients included anorexia, weight loss, constipation, osteonecrosis of the jaw, rash and dyspnoea. Clinically significant AES seen in a minority of patients included arrhythmia ($n = 2$), transient ischaemic attack ($n = 2$), thromboembolic event ($n = 2$) and rectal fistula ($n = 1$). There was one sudden death of unknown aetiology during the study in a patient with multiple cardiac risk factors including diabetes, hypertension and hyperlipidaemia. Nonetheless, attribution to study drugs could not be excluded. Forty-five of 61 patients (73.8%) required dose reductions or discontinuations of lenalidomide, bevacizumab or docetaxel (Table 3). Lenalidomide and docetaxel dose reductions were most frequently attributable to cytopenias, while bevacizumab discontinuation was often related to bleeding or tissue ulceration. Only one patient required docetaxel discontinuation.

Genetic Analysis

Inter-individual variation in the gene expression and plasma levels of VEGF has been attributed to single nucleotide polymorphisms (SNPs) in the *VEGF* gene [17]; therefore, the *VEGF* −634G>C SNP (rs2010963) was evaluated in 54 patients as it has been associated with a more aggressive phenotype of prostate cancer, altered-VEGF binding affinity, bevacizumab toxicity, and altered response to thalidomide-based therapy [18–20]. Cereblon (encoded by *CRBN*) is considered to be the target of lenalidomide, and SNPs in CRBN (rs1714327G>C, rs1705814T>C, and rs1672753G>A) have been associated with lenalidomide efficacy [21–23].

Twenty-four patients were found to have at least one VEGF-634 C allele (CC or CG), while 30 patients were carriers of the GG genotype. The median TTP for patients with the C allele (CC or CG) was 15.5 months, compared with 22.2 months for patients without the C allele (GG; $P = 0.014$ unadjusted; $P = 0.027$ adjusted; Fig. S1). According to a multivariate Cox analysis, after univariate analyses had shown that albumin (2.4–3.4 g/DL vs > 3.5 g/DL) and Halabi predicted survival (< 8 months vs ≥ 8 months) were the only clinical factors to consider for inclusion in modelling, the VEGF-634 C allele retained its significance ($P < 0.009$, HR 0.41; 95% CI for HR 0.21–0.80) after adjusting for albumin ($P = 0.006$; HR 0.28; Cl for HR 0.19–0.76). Univariate analysis of OS also favoured patients who had the VEGF-634G (CG or GG) allele, with median OS of 25.7 vs 17.3 months ($P = 0.037$ unadjusted; $P = 0.073$ adjusted), although significance was not retained for CC or CG vs GG ($P = 0.19$), with medians of 26.2 vs 23.2 months. Cox model analysis for OS failed to show an association of the VEGF-634 C allele when other clinical factors were taken into

consideration (data not shown). None of the CRBN SNPs were associated with TTP or OS (all $P > 0.20$; data not shown).

Immune Analysis

Immune subsets were evaluated by flow cytometry to assess for T-cells, regulatory T -cells, myeloid-derived suppressor cells and cd14+monocytes. Associations were seen with high expression of markers linked with T-cell exhaustion and dysfunction [24]. Forty-nine patients were evaluable for T-cell PD-I expression at baseline and those whose PD-I expression was lower than the median value had greater TTP (medians 27.6 vs 16.1 months; $P = 0.007$). Similarly, individuals with lower Tim-3 expression than the median at baseline had better TTP (median 22.3 vs 15.2 months; $P = 0.031$ [Fig. S2]). In addition, patients who had increases at 3 months in $CD45^{+}CD14^{+}$ HLA-DR^{high} monocytes were associated with longer survival than patients who had declines (P = 0.028). This population of cells has been associated with higher tumour necrosis factor production which could assist in an anti-tumour response [25].

Circulating Endothelial Cells

While baseline CECs were not predictive of TTP or OS, post-treatment changes in CECs were associated with improved OS. Patients with a decrease in CECs after 3 months of therapy had improved OS compared to those ($n = 20$) with increases in CECs ($P = 0.048$; Fig. S3).

Discussion

Findings from the present study suggest that simultaneous treatment with two angiogenesis inhibitors can be safely combined with standard docetaxel and prednisone in mCRPC, with the potential for clinical benefit. One of the noteworthy aspects of previous phase Ill trials of docetaxel with angiogenesis inhibitors was the risk of increased toxicity. In the MAINSAIL trial (docetaxel ± lenalidomide) investigators noted substantial toxicity and postulated that this limited treatment in patients randomized to lenalidomide [12]. The most striking toxicities limiting treatment were neutropenia and pulmonary embolism. Similarly, CALGB 90401 (docetaxel ± bevacizumab) and the VENICE trial (docetaxel ± aflibercept) attributed increased treatmentrelated deaths primarily to infections [11,13]. The present study had one possible treatment-related death, but this was in a patient with multiple cardiac risk factors (diabetes, hypertension, hyperlipidaemia) who experienced sudden death. Furthermore, the study protocol necessitated supportive measures (daily anticoagulation with low molecular weight heparin and granulocyte colony-stimulating factor), which might have minimized the treatment toxicity that was seen in other studies. It is important to note that, although the incidence of grade 3 and 4 neutropenia was higher in the present trial than in previous studies, this was probably attributable to ascertainment bias because this protocol required weekly complete blood counts, while the other studies evaluated blood counts less frequently [11]. Furthermore, the trial allowed treatment holidays, in which patients may hold therapy to recover from toxicities and then continue as long as they had not met progression criteria. This strategy may minimize the burden of chronic toxicities and

maximize drug efficacy. Nonetheless, as with many combination chemotherapy regimens, toxicities were seen with this regimen and do require management considerations.

The potential short-term clinical impact in the present trial can be shown by substantial PSA declines (≥80% in 75% of patients), confirmed partial responses in 24 of 29 patients (83%) with evaluable disease as per RECIST 1.1, and a median TTP >18 months. Compared with previous phase Ill docetaxel plus angiogenesis inhibitor trials, the proportion of patients with 50% PSA declines is substantially greater in the present trial (90% in the present study vs 59–70% in previous studies) [11–13]. The objective response rate is also greater than the only other study to use RECIST 1.1 (MAINSAIL, responses <25% in both arms) and compares favourably with the chemotherapy-naïve abiraterone (36%) and enzalutamide (59%) trials [5,6,12]. Although TTP was substantially longer in the present study compared with that reported in the other docetaxel/anti-angiogenic combination trials, progression criteria varied across all the studies making definitive comparisons difficult [11–13]. (The use of PSA progression parameters in other trials could have limited drug exposure and thus clinical benefit.) The criteria used in the present study, however, are similar to those used in trials evaluating abiraterone and enzalutamide in chemotherapy-naïve patients, and the 18.2-month TTP seen in the present trial compares favourably with those antiandrogen agents [5,6].

The survival data from the present trial also compare favourably with the previous trials although the difference is not as substantial as intermediate surrogates (e.g. PFS or responses). The median OS in the present study was 24.6 months compared with 22.6 months in the CALGB 90 401 trial, 22.1 months in the VENICE study and 17.1 months in the MAINSAIL trial [11–13]. Although caution should be taken with such comparisons, recent analyses have suggested that patients with more aggressive mCRPC may benefit most from chemotherapy, perhaps providing an explanation for the relatively prolonged OS seen in the present study [26].

The OS in the present trial, however, is shorter than previously reported for the combination angiogenesis trial performed here at the National Cancer Institute (NCI; docetaxel, bevacizumab, thalidomide; OS 28.2 months) [15]. Although lenalidomide was developed as a next-generation version of thalidomide, the exact antineoplastic mechanisms for both agents remain undefined; it is possible that the substitution of lenalidomide for thalidomide may have compromised some anti-cancer activity. The principal toxicities of thalidomide (fatigue and neurotoxicity) were substantially reduced in the present study, and thus in combination with docetaxel and bevacizumab, lenalidomide appears to be more tolerable. In addition, it is unclear why the PFS was similar between these two trials (≈18 months) but OS was shorter in the lenalidomide trial compared with the thalidomide trial (24.6 vs 28.2 months), given that both study populations had similar characteristics. Possible explanations include cumulative toxicity that was not captured within the follow-up timeframe of the present trial, treatment selection of particularly malignant/aggressive clones in patients treated in the lenalidomide trial, or a pro-angiogenesis rebound that has been postulated in previous trials [11,27].

The correlative studies provide some hypothesis-generating data. Tim-3 and PD-I expression on T-cells has previously been associated with T-cell exhaustion/dysfunction [24]. That could explain why patients with lower levels of expression of Tim-3 and PD-I had better responses to therapy, especially given the postulated immune effects of docetaxel, lenalidomide and bevacizumab [28–30]. Analysis of the *VEGF*-634G>C polymorphism suggested an association between clinical benefit (PFS) and patients with the C allele (CC or CG). Further evaluation is required to determine whether they can be reliable predictive markers of response.

Although the clinical responses seen in the present trial are compelling, the study has shortcomings inherent to single-institution, non-randomized trials. While toxicity was improved with the addition of supportive care measures, it is unclear if such trends would hold true in a larger, multicentre trial. Similarly, the survival trends reported in the present study should also be considered in that context. Additionally, the criteria for assessing disease progression differed between the present trial and several previous trials of docetaxel plus angiogenesis inhibitors, and it is not certain how that could have influenced the survival data.

Several antiangiogenic phase Ill trials have failed to show a survival benefit in mCRPC [11–13]. Toxicity was a critical obstacle in those trials. Two trials at the NCI have suggested the potential clinical benefits of using multiple angiogenesis inhibitors in combination with docetaxel, perhaps enhancing outcomes by suppressing compensatory pro-angiogenic factors. Moreover, the use of supportive measures in both NCI trials appears to mitigate the toxicity to a large degree. Despite the negative survival data from previous trials, preclinical and clinical evidence indicate the importance of angiogenesis in mCRPC biology, thus developing newer agents with improved or broader antiangiogenic properties could be considered for future investigations. Alternatively, given the sharp PSA declines and high proportion of objective responses, a similar docetaxel regimen with multiple anti-angiogenic agents could enhance the benefits produced in the CHAARTED study [8] when given earlier in the disease process, for a short course. Despite the development of modern antiandrogens, such as enzalutamide and abiraterone, emerging resistance patterns to those agents should serve as a reminder that docetaxel continues to have a substantial therapeutic role in mCRPC, and building on that regimen should remain a priority in future studies, which could include docetaxel and combination angiogenesis inhibitors with appropriate supportive measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

mCRPC	metastatic castration-resistant prostate cancer
OS	overall survival
HR	hazard ratio

VEGF	vascular endothelial growth factor
PFS	progression-free survival
TTP	time to progression
RECIST	Response Evaluation Criteria In Solid Tumors
AE	adverse event
SNP	single nucleotide polymorphism
CEC	circulating endothelial cell
NCI	National Cancer Institute

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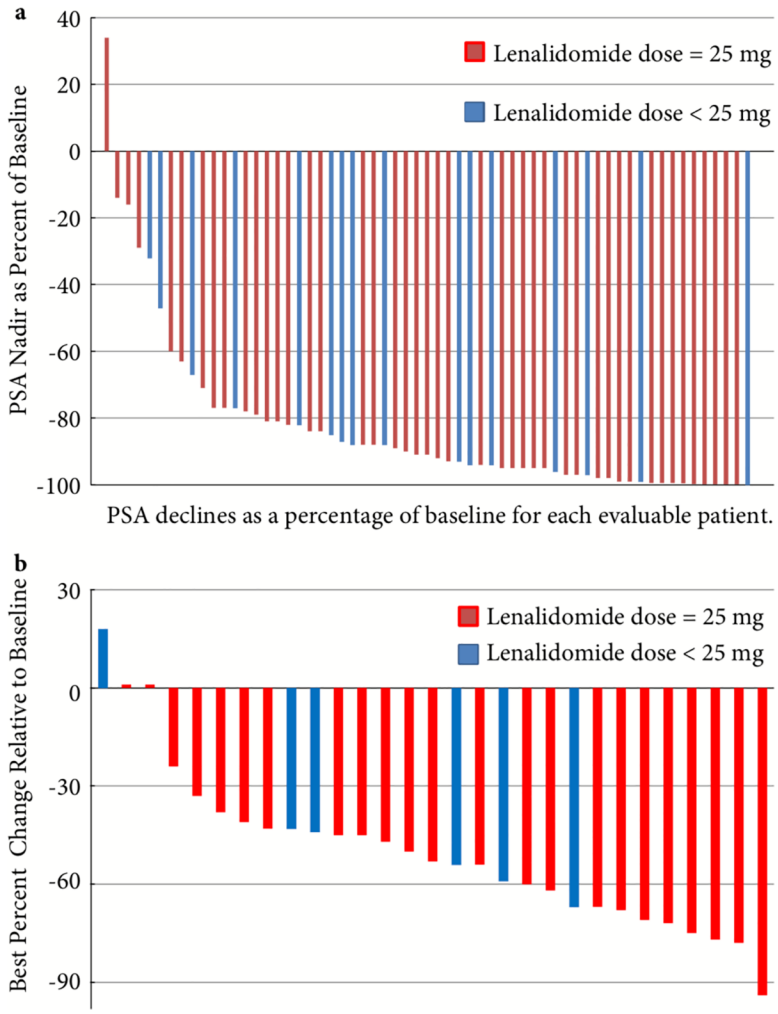

Fig. 1.

Clinical responses. (**a**) Maximum PSA declines and (**b**) radiographic responses.

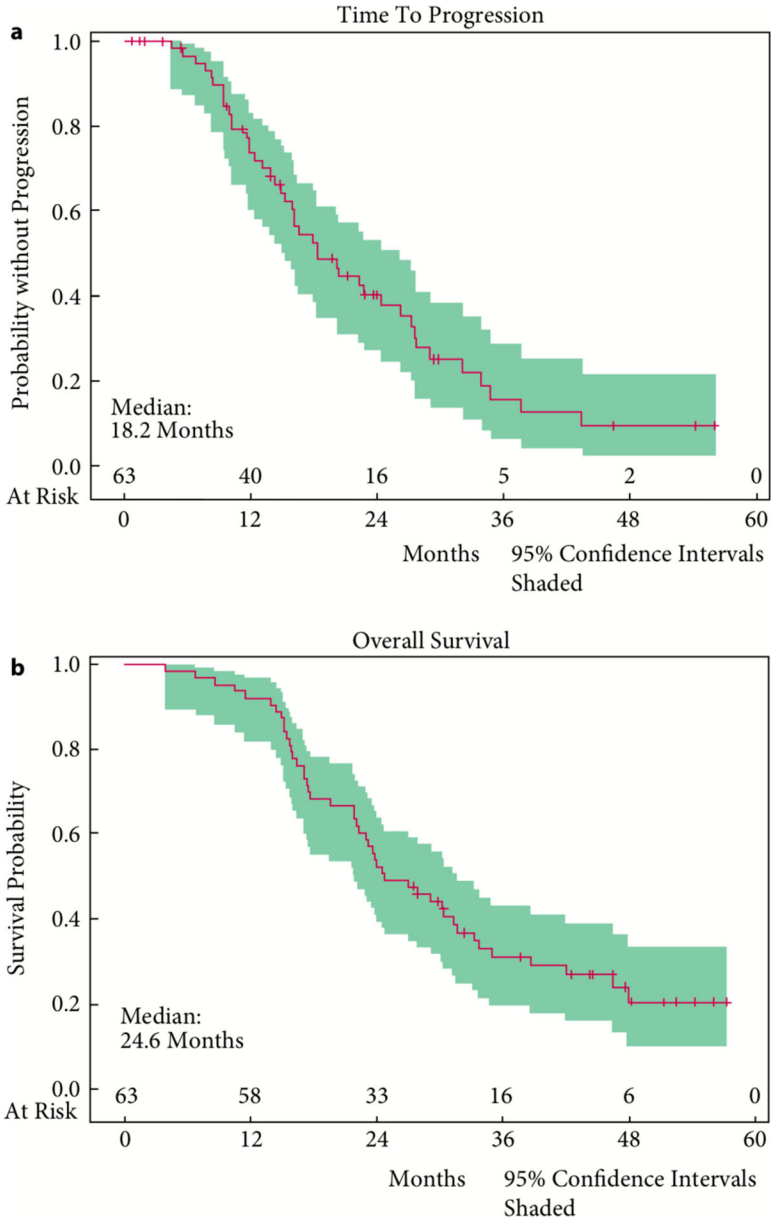

Fig. 2.

Clinical outcomes. (**a**)Time to progression and (**b**) Overall survival.

Table 1

Baseline characteristics ($N = 63$).

Median (range) age (years)	65.6 (51.3–82.4)
Gleason score, *n*	
≤6	4
7	15
8	15
9	23
10	6
Median (range) PSA (ng/mL)	90.36 (0.14–3 520)
Median (range) alkaline phosphatase, U/L	436.5 (53–956)
Median (range) lactate dehydrogenase, U/L	206 (127–2 305)
Median (range) haemoglobin (g/dL)	11.8 (7.4–14.8)
ECOG performance status, *n*	
0	10
1	50
2	3
Patients requiring opiates for pain relief, *n*	49
Location of disease, *n*	
Bone only	24
Bone and lymph nodes	27
Bone and visceral	7 (3 hepatic)
Lymph node alone	3
Visceral alone	2 (bladder and lung)

ECOG, Eastern Cooperative Oncology Group.

Table 2

Adverse events of interest.

	Grade 2, *n*(%)	Grade 3, *n*(%)	Grade 4, *n*(%)
Haematological *			
Anaemia	14 (22)	20 (32)	0
Lymphopenia	1 (2)	0	0
Neutropenia	11 (17)	32 (50)	29 (46)
Thrombocytopenia	3 (14)	7 (11)	0
Total haematological adverse events	25 (40)	45 (71)	29 (46)
Constitutional			
Fatigue	18 (29)	6 (11)	0
Weight loss	8 (13)	1 (2)	0
Infection			
Febrile neutropenia	n/a	9 (14)	4 (6)
Respiratory	14 (22)	5 (8)	0
Tooth/gum infection	4 (6)	0	0
Skin	6 (10)	3 (5)	0
UTI	6 (10)	2 (3)	0
Infection: other	10 (16)	5 (8)	1 (2)
Cardiopulmonary			
Arrythmia	2 (3)	0	0
Dyspnoea	8 (13)	2 (3)	0
Hypoxia	1 (2)	0	0
Thromboembolic event	2 (3)	0	0
Gastrointestinal/digestive			
Anorexia	9 (14)	1 (2)	0
Constipation	9 (14)	0	0
Diarrhoea	12 (19)	6 (10)	0
Rectal Fistula	1 (2)	0	0
Neurological			
Dizziness	2 (3)	0	0

	Grade 2, *n*(%)	Grade 3, *n*(%)	Grade 4, *n*(%)
Neuropathy	2 (3)	2 (3)	0
Syncope	n/a	1 (2)	0
Transient ischaemic attack	2 (3)	0	0
Dermatological			
Palmar plantar erythrodysesthesia	2 (3)	1 (2)	0
Pruritis	3 (14)	0	0
Rash	9 (14)	0	0
Skin ulceration	2 (3)	0	0
Dental/oral			
Osteonecrosis of Jaw	10 (16)	3 (5)	0
Oral Mucositis	5 (8)	1 (2)	0
Oral Pain	3 (14)	0	0
Renal/electrolytes			
Dehydration	1 (2)	2 (3)	0
Haematuria	0	1 (2)	0
Hypokalaemia	1 (2)	1 (2)	1 (2)
Hypophosphataemia	2 (3)	2 (3)	0
Total non-heme adverse events	61 (97)	52 (83)	8 (13)

Adverse events determined using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

*Haematological toxicities acquired from weekly complete blood counts.

Table 3

Dose modifications and discontinuations.

	n/N	**%**
Participants requiring dose reduction and/or discontinuation	45/61	73.8
Lenalidomide only dose reduction and/or discontinuation	12/61	19.7
Bevacizumab only dose reduction and/or discontinuation	6/61	9.8
Docetaxel only dose reduction and/or discontinuation	1/61	1.6
>1 medications requiring dose reduction and/or discontinuation	26/61	42.6
Participants requiring dose reduction for one or more medications	35/61	57.4
Lenalidomide dose reduction	34/61	55.7
Bevacizumab dose reduction	N/A	N/A
Docetaxel dose reduction	19/61	31.1
Participants requiring one or more medications discontinued	21/61	34.4
Lenalidomide discontinued	12/61	19.7
Bevacizumab discontinued	16/61	26.2
Docetaxel discontinued	1/61	1.6