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A Phase II clinical trial of everolimus plus bicalutamide for castration-resistant prostate cancer

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Abstract

Background—The mammalian target of rapamycin (mTOR) pathway is up-regulated in castration-resistant prostate cancer (CRPC). Nevertheless, inhibition of mTOR is ineffective in inducing apoptosis in prostate cancer cells likely due to the compensatory up-regulation of the androgen receptor (AR) pathway.

Methods—Eligible patients must have progressive CRPC with serum testosterone <50 ng/dl. No prior bicalutamide (except to prevent flare) or everolimus was allowed. Treatment included bicalutamide 50 mg and everolimus 10 mg oral, both once daily. Primary endpoint was prostate specific antigen (PSA) response (≥30% reduction) from baseline A sample size of 23 patients would have power of 0.8 and α error of 0.05 (one-sided) if the combination had a PSA response rate of 50% versus a historical rate of 25% with bicalutamide alone.

Results—Twenty-four patients were enrolled. Mean age was 71.1 years (range: 53.0–87.0). Mean PSA at the study entry was 43.4 ng/dl (2.5–556.9). Mean length of treatment was 8 cycles (1.0–23.0). Of 24 patients, 18 had a PSA response (75%, 95% CI: 0.53–0.90) while 15 had a PSA decrease of ≥ 50% (62.5%, 95% CI 0.41–0.81). Median overall survival was 28 months (95% CI 14.1–42.7). Fourteen patients (54%, 95% CI 0.37–0.78) developed Grade 3 (13 patients) or Grade 4 (1 patient with sepsis) adverse events attributable to treatment.

Conclusions—The combination of bicalutamide and everolimus has encouraging efficacy in men with bicalutamide-naïve CRPC, thus warranting further investigation. A substantial number of patients experienced everolimus-related toxicity.

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Keywords

castration-resistant prostate cancer; everolimus; bicalutamide; mTOR; urology

INTRODUCTION

Cancer of the prostate (CaP) is the most common cancer and the second leading cause of cancer death in American men. It is estimated that 233,000 new cases of CaP were diagnosed in the USA in 2014 [1]. Over 80% of newly diagnosed CaP patients have localized disease and choose between the two standard forms of curative therapy, radical prostatectomy or radiation therapy. Approximately one-third of patients treated with localized therapies will have a biochemical recurrence[2,3]. Some of these patients can be salvaged with either radiotherapy or rarely surgery depending on prior therapy received. The remaining recurrent CaP patients and those presented with metastatic CaP are usually treated with androgen deprivation therapy (ADT) which is initially highly effective[4]. However, most patients will develop castration-resistant prostate cancer (CRPC) within 18–24 months[5]. Second-line therapy with an androgen receptor (AR) modulator, such as bicalutamide, is associated with a response rate around 25% and the duration of response of a few months[4,6]. Even though new medications, such as enzalutamide and abiraterone, have been approved after bicalutamide, long-term survival is extremely rare. Most patients will become resistant to the treatment and estimated at least 27,540 patients died from this disease[7]. Therefore, there is a substantial need to improve upon new treatment options.

Several mechanisms have been proposed to explain castration-resistance, such as over-expression of AR, AR mutation, auto- or paracrine production of androgen, and alternative signaling pathways among others. We previously report upregulation of the mammalian target of rapamycin (mTOR) pathway in CRPC cell lines, as well as in CaP cells treated with ADT[8]. mTOR is a key serine-threonine kinase regulating protein synthesis and ultimately results in cell growth, proliferation, angiogenesis and survival. However, a previous study demonstrated that inhibition of the mTOR signaling pathway also up-regulates the AR signaling pathway[8]. This compensatory mechanism explains why an mTOR inhibitor would have little therapeutic effect in CRPC[9]. We found that inhibition of the mTOR signaling pathway unregulated the AR signaling pathway, which compensated the therapeutic effect of an mTOR inhibitor[8]. In addition, bicalutamide inhibits AR transcriptional activity stimulated by rapamycin without affecting the inhibition of the mTOR pathway. Simultaneous treatment with the mTOR inhibitor rapamycin and the AR inhibitor bicalutamide apparently enhanced growth-inhibition by rapamycin in both androgen dependent and –independent sublines of LNCaP cells despite bicalutamide having no effect on the growth of CRPC cells as a single agent. Similar synergistic effects of the combination of an AR antagonist and an mTOR antagonist were also observed with *in vivo* xenograft models[10–12].

Based on these pre-clinical studies, we evaluated the combination of bicalutamide and everolimus (RAD001, an mTOR inhibitor) in treating CRPC. We hypothesize that simultaneous blockade of the mTOR and AR pathways are synergistic against CRPC cells and that this can be demonstrated in a clinical trial. The primary objective of this trial is to

determine the prostate specific antigen (PSA) response rate of bicalutamide plus everolimus in the treatment of CRPC after the first-line androgen deprivation therapy.

PATIENTS AND METHODS

Patient Eligibility

Patients are eligible for enrollment if they have age >18 years, have a histologically or cytological confirmed diagnosis of CaP, and castrate levels of testosterone (<50 ng per deciliter or 1.7 nmol per liter) within 3 months prior to registration. Patients must have CaP deemed to be castration-resistant by (1) progression of uni-dimensionally measurable disease assessed within 42 days prior to initial administration of drug; (2) progression of evaluable but not measurable disease assessed within 42 days prior to initial administration of drug for PSA evaluation and for imaging studies; or (3) at least two consecutive rises in PSA measured at least one week apart. Patients must remain on androgen deprivation therapy and must have an ECOG performance status of 0 to 2, adequate vital organ function and marrow function as defined below: leukocytes ≥3,000/L, absolute neutrophil count ≥1,500/L, platelets ≥ 100,000/L, total bilirubin ≤1.5 mg/dL, aspartate transaminase (AST) and alanine transaminase (ALT) ≥2.5 X institutional upper normal limit and creatinine ≤1.5 X institutional upper normal limit. Men enrolled in this trial must agree to use adequate contraception prior to study entry and for the duration of study participation. A complete list of inclusion and exclusion criteria is provided in the protocol (supplement Information #1).

Exclusion criteria for the study included: any hormonal therapy other than surgical castration with orchiectomy or medical castration with luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide or goserelin) or antagonist (degarelix); or prior therapy with androgen receptor antagonists (except to prevent flare) or mTOR inhibitors. Patients with the following condition were also excluded from this study: uncontrolled serious concurrent illness, treatment with combination anti-retroviral therapy for HIV infection, other anticancer therapies, or any major surgery or significant traumatic injury within the previous 4 weeks of the start of study drug. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent were also excluded, except corticosteroids with a daily dosage equivalent to prednisone ≤ 20 mg. Patients should not have received immunization with attenuated live vaccines within one week of study entry or during study period. Patients were also excluded if they were on herbs or other alternative medicines for the treatment of CaP, uncontrolled brain or leptomeningeal metastases, other malignancies within the past 3 years, impairment of gastrointestinal function/disease or active, bleeding diathesis. This study was approved by the UC Davis Institutional Review Board. All patients provided written informed consent before treatment initiation. This clinical trial was registered at Clinicaltrials.gov (clinicaltrials.gov registration # NCT00814788).

Study Design and Treatment

This clinical trial was originally designed as a Phase Ib lead-in safety trial followed by a randomized, double-blinded, placebo-controlled Phase II trial in patients with CRPC. Because there was administrative delay in obtaining matched placebo tablets, this trial was

converted to a single-arm Phase II trial comparing results to a historical control of bicalutamide as second-line hormonal therapy. During the lead-in safety trial, eight patients were recruited at the dose of bicalutamide 50 mg oral once daily plus everolimus 10 mg oral once daily. Each cycle is defined as 4 weeks. At each cycle, patients will be evaluated clinically for side effects and response, and undergo laboratory tests (PSA, CBC and CMP). If patients have measurable lesions, imaging studies (chest X-ray, bone scan, CT and/or MRI) are performed every two cycles. If patients do not have any measurable lesions, imaging studies are not required unless clinically indicated. After 4 cycles, patients will be followed every 2 cycles (8 weeks). After no grade III or higher toxicity was observed during the first 4 weeks, this trial entered Phase II; eight patients recruited in the lead-in safety phase were included in the final efficacy analysis.

Study Endpoints

The primary objective of the trial was to determine the PSA response rate of bicalutamide plus everolimus in the treatment of CRPC after the first-line androgen deprivation therapy. PSA response rate was defined as a 30% reduction in the PSA level from baseline. A 30% reduction was selected as the principal response discriminant (instead of 50% as per the Bubley criteria) because of data from the SWOG 9916 trial of docetaxel/estramustine versus mitoxantrone/prednisone demonstrating that it was the 30% level which met Prentice's criteria for survival surrogacy [13]. However, patients experiencing a greater than or equal to 50% reduction in PSA level, as per Bubley criteria [14,15], were also recorded in the database and included for the final analysis.

Secondary objectives were to evaluate the time to treatment failure and overall survival of patients with CRPC treated with bicalutamide + everolimus; and to assess the toxicity of bicalutamide and Everolimus.

Efficacy Assessment

We used the PSA Working Group consensus criteria[15] combined with radiographic studies to determine the proportion of patients with a PSA decline and time to progression. Response and progression were evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [16]. PSA criteria for response and progression were based on the PSA Working Group consensus criteria[15]. PSA declines of at least 30% (confirmed by a second value at least 4 weeks after the first) with no other evidence of disease progression were recorded for each cohort. We also recorded PSA response of at least 50% decline. Progressive disease was defined by any of the following criteria: (1) 25% increase in the size of all soft tissue masses and/or the appearance of new lesions; (2) the need for radiation therapy; and (3) two consecutively increasing PSA measurements by greater than 50% of the nadir PSA for patients with PSA response, or by greater than 25% of the nadir or baseline (whichever is lower) PSA for patients without PSA response. Patients were not declared to have disease progression based on PSA alone until the PSA had increased by an absolute value of 5 ng/mL or more. There were no minimum PSA required. At baseline, PSA test, computed tomography of the chest, abdomen and pelvis, bone scan and a clinical disease assessment for palpable lesions were performed. Post-baseline imaging studies and PSA tests were performed every 8 weeks. Standard RECIST objective

criteria were used to assess soft tissue lesion changes. Measurable and non-measurable lesions as well as PSA changes were all used to evaluate response. Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions were used in the RECIST criteria.

Safety Assessment

The study utilized the NCI Common Terminology Criteria (CTC) for Adverse Events 3.0 for toxicity and adverse event (AE) reporting. Safety assessments included history, physical examination, AE/serious AE (SAE) documentation, laboratory tests, ECG and echocardiogram (if indicated). AEs and SAEs were recorded from the first study medication dose until the first visit (1–3 months) after discontinuation.

Statistical Analysis

All patients who received any study drugs were assessable for toxicity and disease response. In total, 24 patients were included in analyses. The primary analysis was to calculate the PSA decrease from baseline and determine PSA response of >= 30%. Sample size was determined with the hypothesis that addition of everolimus would increase the PSA response rate from 25% with bicalutamide alone (historical control) to 50% with the bicalutamide and everolimus combination[17]. A total of 24 patients were needed with a power of 0.8 and Type I error α of 0.05 (one-sided) to detect this difference. Descriptive summaries (mean, standard deviation, minimum, maximum) were completed for quantitative variables (age, PSA at baseline and follow-up and treatments completed) followed by frequencies percentages for categorical variables (treatment, treatment frequency, best response, survival status, ethnicity, race). The observed proportion, with exact 95% confidence interval (CI), was calculated for each response level: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The overall survival (OS) time and progression-free survival (PFS) were estimated by the Kaplan-Meier method. The percent PSA decrease from baseline was defined at each follow-up as 100% x (baseline PSA – PSA at follow-up)/ baseline PSA. The number and proportion of patients whose PSA decrease was at least 30% for at least one follow-up was calculated as the primary response and the number with PSA decrease exceeding 50% as a secondary response. The number of adverse responses was summarized by type and severity.

RESULTS

Patient Characteristics

A total of 24 patients were recruited from February 20, 2009 to January 4, 2013 and were treated with the bicalutamide and everolimus combination. Patients' baseline demographic data are summarized in Table 1. All treated patients were included in the assessment of efficacy and toxicity and in the analysis of survival. Mean age was 71.1 years (range: 53.0 – 87.0) and the mean number of treatments completed was 8 cycles (range, 1 – 23 cycles). Mean PSA at the study entry was 43.4 ng/dl (2.5 – 556.9). The maximum percent PSA decrease was calculated as the baseline PSA value minus the nadir PSA value divided by the baseline PSA value. On average, patients received 2.7 years (1 – 6) of androgen deprivation treatment prior to entering the clinical trial. Bone and lymph nodes were the most frequent

sites of metastasis. Fourteen patients had bone metastases and three patients with lymph node involvement only (58% and 13%, respectively). Three patients had both bone and lymph node metastases (13%). Furthermore, only one patient (4%) received one prior chemotherapeutic regimen with docetaxel-based chemotherapy. It should be noted that 20 out of 24 patients (83%) received further treatments (hormone and/or chemotherapy) after disease progression; only 5 patients (21%) were treated with two or more lines of chemotherapy regimen and 16 patients (67%) received further hormonal manipulation. At the time of data collection cutoff on 7/31/2013, 4 patients (17%) ultimately had progressive disease; two (8%) were removed from the trial due to excessive toxicities; one (4%) was removed due to unrelated renal artery stenosis; 5 patients decided to (21%) withdraw from the study; two (8%) died from causes other than CRPC; and 3 (12%) patients were still receiving treatment. Among these patients, 87% were of Caucasian descent, 4% Asian and 8% African American population.

Efficacy

First, we determined the PSA response. Of 24 patients, 18 (75%, 95% CI 0.53–0.90) patients had a maximum PSA decrease of ≥30% as per the proposed study protocol (Figure 1). The range of response duration of these 18 patients was 0 to 21.6 months (median: 5.6 months) as compared to 3.1 months in the bicalutamide alone [18]. Of the 24 patients, 18 (75%) patients reached PSA decrease rate over 30%.Of these 18 patients, the duration for the 30% PSA drop ranged from 0.3 to 34 months; the earliest starting time was at 0.3 month after baseline. Of the 24 patients, 15 (62.5%, 95% CI 0.41–0.81) patients had PSA decrease of 50% or higher.

In addition to the PSA response, we also evaluated the response by the RECIST criteria (Table 2). Of the 24 patients, 1(4%) had complete remission (CR, 95% CI 0.1, 21%); 4(17%) had partial response (PR, 95% CI 5–37%); 14(58%) had stable disease (SD, 95% CI 37–78%); 4 (17%) had progressive disease (PD, 95% CI 5–37%); and 1(4%) had missing value (Table 2).

For updated survival status with cut-off on February 2015, 11 (46%) were still alive and 13 (54%) were expired. Two died of other causes, therefore, 11 patients died of progressive disease. The Kaplan Meier curve (Figure 2) showed that the median overall survival time was 28 months, with 95% confidence interval (14.1–42.7**).** The median progression-free survival time was 9.4 months with 95% confidence interval (4.0–25.0) (Figure 3) as compare to bicalutamide alone of 5.8 months historically[17].

Toxicities

All patients who received treatment were evaluated for toxic effects. Observed Grade 3 and 4 toxicities are summarized in Table 3. There were 13 of 24 patients (54.2%, 95% CI 0.328–0.745) with Grade 3 toxicity and one of 24 patients (4.2 %, 95% CI 0.001–0.2112) with Grade 4 toxicity. Two patients discontinued treatment secondary to toxicity. Most of the hematologic toxicities were mild with one grade 3 neutropenia; two grade 3 anemia and one grade 3 thrombocytopenia. Two patients developed grade 3 lymphopenia while on treatment.

One patient had grade 4 non-neutropenic sepsis and one patient had non-neutropenic grade 3 pneumonia.

Of the non-hematologic toxicities (Table 3), the most common adverse events were Grade 3 oral mucositis (4 patients) and hyperglycemia (2 patients). These symptoms improved after dose reduction of everolimus. Other significant toxicity included one patient with Grade 3 pneumonitis attributed to everolimus and another patient with Grade 3 thromboembolic incidence.

DISCUSSION

This single institutional, single arm phase II study with a lead-in safety phase was conducted to assess the efficacy and tolerability of everolimus in combination with bicalutamide in 24 men with CRPC. This trial showed encouraging clinical activity with a PSA response (decrease by 30% or more) observed in 75% patients treated with the combination therapy of an AR agent bicalutamide and mTOR inhibitor everolimus. However, this regimen was also associated with significant toxicity with 58.3% (14/24) Grade 3 or 4 toxicity.

The results of this study contrast with what has been reported in a clinical trial reported by Nakabayashi et al [19], showing that the addition of everolimus to patients resistant to bicalutamide was ineffective in patients with CRPC. The major difference between these two trials is that 31 (86%) patients in that trial had previously been treated with bicalutamide for a median duration of 7.4 months when everolimus was added[19]. The response rate to bicalutamide alone in CRPC is less than 25%, and the duration of response to bicalutamide is 3.1 months[18] . Therefore, in the trial performed by Nakabayshi et al, by the time everolimus was added, almost all patients have already developed resistance to bicalutamide. In other words, functionally, that clinical trial is equivalent to inhibiting the mTOR pathway as a single treatment modality. Considering our previous findings that inhibition of the mTOR pathway upregulated the AR pathway and PSA production, it is not surprising that only two out of 36 patients had a PSA response of ≥50%.

The response rate observed in this study is comparable to that observed with newer agents targeting the androgen signaling pathway. In the study with abiraterone in chemotherapy-naïve CRPC patients, a PSA reduction of ≥50% from baseline was observed in 62% of the patients. [20] In another study with enzalutamide in a similar population of chemotherapy-naïve CRPC patients, a PSA decline of ≥50% from baseline was observed in 78 % of the patients[21]. However, despite the addition of enzalutamide to the repertoire of treatment for CRPC, the drug is not yet available in much of the world and due to cost may not be available to many patients. As such, this bicalutamide and everolimus combination is a potentially cost effect option.

One major strength of this bench-to-bedside clinical trial is the design which is based on our previous strong preclinical studies. Everolimus is a novel oral derivative of rapamycin. At the cellular and molecular level, mTOR is a key and highly conservative serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. Studies in both

cancer cell lines and animal models show that treatment with rapamycin delayed but did not completely prevent tumor growth[22,23]. Incomplete growth inhibition with rapamycin is due to stimulation of AR expression and transcriptional activity in CaP cells lines[24]. Rapamycin-induced AR transcriptional activity promotes cell growth in CaP, and inhibition of this activity prevents the recurrence of cell growth seen in the presence of rapamycin. This activity is observed in both androgen dependent and –independent sublines of CaP cells, despite bicalutamide having no effect on the growth of CRPC cells as a single agent.

Even though this clinical trial showed promising clinical activity, it was also associated with significant toxicity. Fifty-eight percent (14/24) of patients developed Grade 3 or 4 toxicity. Most of these toxicities were attributed to everolimus as patients improve after dose reduction or temporary withholding of everolimus. Even though the toxicity profile of everolimus in this study was similar to that in the treatment of kidney cancer patients, more patients developed grade 3–4 toxicities: 58.3 % versus 19%[25]. One possible explanation was that more patients at advanced age were recruited in this study. The median age of patients in this study was 71.1 years (range: 53.0–87.0), compared to 61 years old in the trial with kidney cancer. Another possibility is that androgen deprivation and anti-androgen therapy sensitize patients to everolimus. A third possibility is that bicalutamide has changed the drug metabolism of everolimus. Both bicalutamide and everolimus are metabolized by cytochrome P450 CYP3A4 and competitive inhibition can occur when the two drugs are combined together [26].

Like most Phase II clinical trials, one major limitation of this study is its small sample size. Hence, any random events can dramatically change the final response rate. However, the patient number was decided based on our strong preclinical data and historical control. Even with this small number of subjects, the response data suggest that this combination was indeed effective in CRPC.

In summary, combination therapy with everolimus and bicalutamide represents a promising new area of treatment for bicalutamide-naïve CRPC. A randomized Phase III trial with everolimus in combination with anti-androgen therapy in CRPC is warranted. However, due to significant toxicity, modification of the study designed is needed. One option is to reduce everolimus dose as toxicity improved in a vast majority of patients after the dose of everolimus, but not bicalutamide, was reduced. As newer anti-androgen therapies with abiraterone and enzalutamide are more effective than bicalutamide in CRPC, a modified clinical trial design with everolimus in combination with abiraterone or enzalutamide can also be considered. (This clinical trial is registered at Clinicaltrials.gov. registration # NCT00814788).

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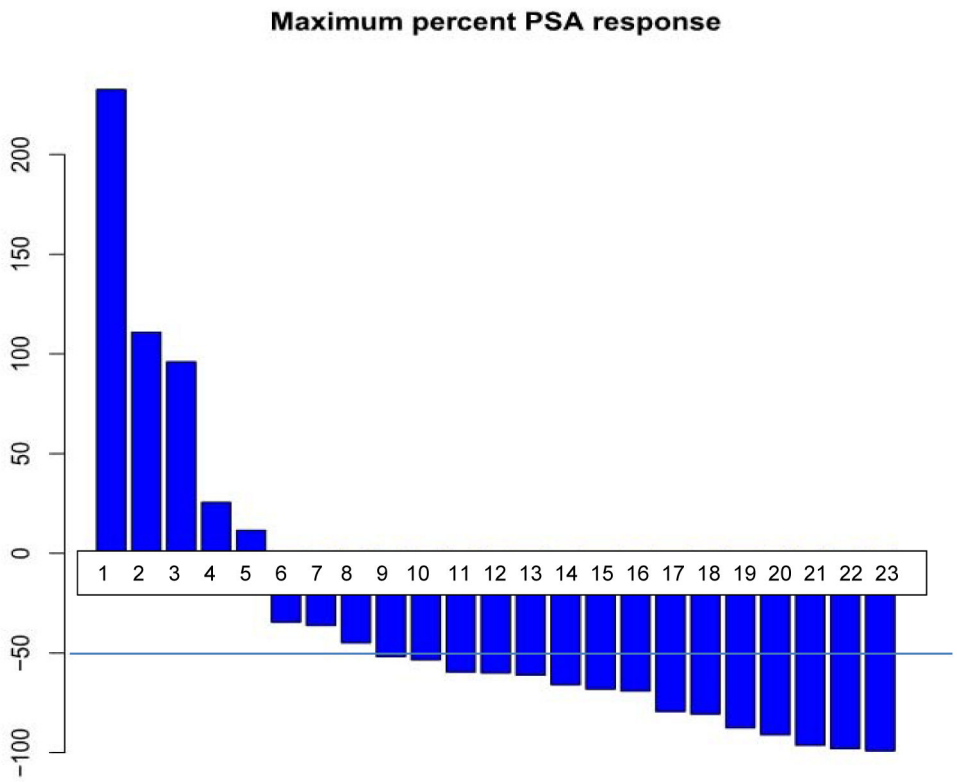

Figure 1. Waterfall plot of PSA response of all patients

Of 24 patients treated in this study, 18 (75%, 95% CI 0.53–0.90) patients had maximum PSA decrease of 30% or more, and 15 (62.5%, 95% 0.41–0.81) patients had PSA decrease of 50% or higher. (Only 23 patients plotted as one patient did not have 2 time point before PSA prior to dis-enroll in trial).

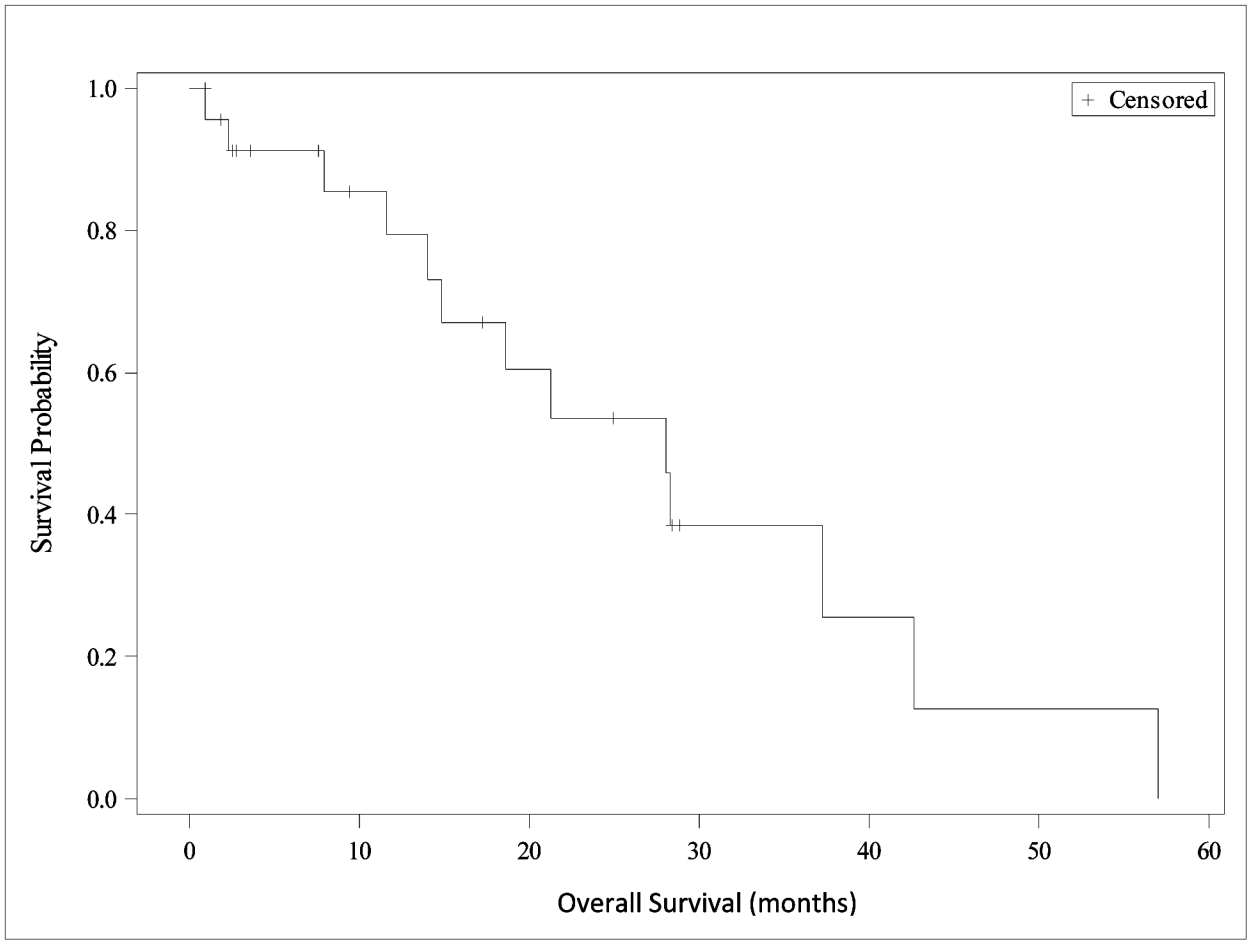

Figure 2.
Overall survival of all patients

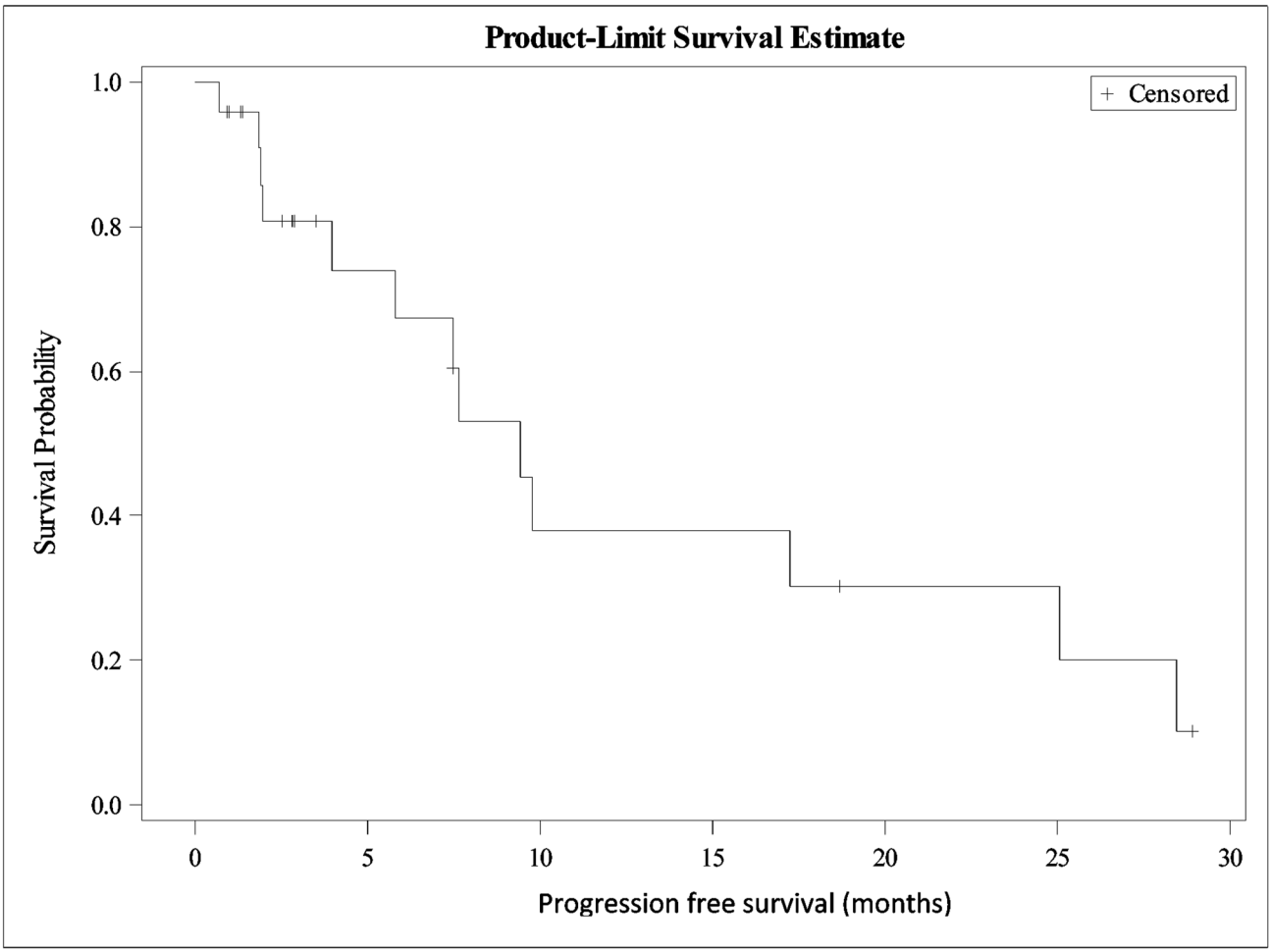

Figure 3.

Progression free survival of all patients Table 1. Patient characteristics Table 2. Response determined by the RECIST criteria.

Table 1

Patient characteristics

Characteristics (N= 24)	Value
Age (years): Mean (range)	71.1 (53–87)
Treatment completed (cycles): Mean (range)	7.9 (1–23)
PSA level (ng/mL): Mean (range)	43.4 (2.5–556.9)
Race, number (%)	
Caucasian	20 (87.5%)
African-American	3 (8.33%)
Asian	1 (4.17%)
Gleason Score	
<7	1 (4%)
7–10	21(88%)
Not available	2 (8%)
Site of Disease: prior to treatment	
Bone	14 (58%)
Nodes	3 (13%)
Bone and Nodes	3 (13%)
PSA only	2 (8%)
Bladder	1 (4%)
Liver	1 (4%)
Prior chemotherapy	
1 Line (docetaxel)	1 (4%)
2 Lines or more	0 (0%)

Table 2

Response by RECIST criteria

Best response		Patient numbers	% (95% CI)	Combined Percent
Response	**CR**	1	4.2 (0.1–21.1%)	20.8
	PR	4	16.7 (4.7–37.4%	
SD		14	58.3 (36.6–77.9%)	58.3
PD		4	16.7 (4.7–37.4%)	16.7
NA		1	4.2 (0.1–21.1%)	4.2

Table 3

Grade 3 and 4 Toxicity profiles (CTCAE version 3.0)

Toxicity	Grade	Number of patients (n)
Anemia	3	2
Anorexia	3	1
Abdominal pain	3	1
DVT/PE	3	1
Hyperglycemia	3	2
Lymphopenia	3	3
Oral Mucositis	3	4
Neutropenia	3	1
Nausea	3	1
Pneumonitis	3	1
Pneumonia	3	1
Right hip pain	3	1
Renal failure	3	1
Thrombocytopenia	3	1
Sepsis	4	1