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Final Analysis Of A Phase II Trial Using Sorafenib For Metastatic Castration Resistant Prostate Cancer

Jeanny B. Aragon-Ching[1], **Lokesh Jain**[2,5], **James L. Gulley**[1], **Philip M. Arlen**[1], **John J. Wright**[3], **Seth M. Steinberg**[4], **David Draper**[1], **Jürgen Venitz**[5], **Elizabeth Jones**[6], **Clara C. Chen**[7], **William D. Figg**[1,2,5], and **William L. Dahut**[1]

[1]Medical Oncology Branch, National Cancer Institute, Bethesda, MD 20892, USA

[2]Section of Molecular Pharmacology, National Cancer Institute, Bethesda, MD 20892, USA

[3]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD 20892, USA

[4]Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA

[5]Department of Pharmaceutics, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA

[6]Department of Radiology, Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA

[7]Department of Nuclear Medicine, Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA

Abstract

OBJECTIVE—To determine if sorafenib is associated with an improved 4-month probability of progression-free survival using radiographic and clinical criteria alone, in patients with metastatic castration-resistant prostate cancer (CRPC). Secondary endpoints included pharmacokinetics, toxicity analysis and overall survival.

PATIENTS AND METHODS—This was an open-label, phase II, 2 stage design, focusing on the results from the second stage since criteria for progression were modified after completion of the first stage. Sorafenib was given daily at a dose of 400 mg orally twice daily in 28-day cycles. Clinical and laboratory assessments were done every 4 weeks, radiographic scans were obtained every 8 weeks.

RESULTS—Twenty-four patients were accrued in the second stage. Patient characteristics included a median (range) age of 66 (49 – 85), on-study PSA of 68.45 ng/mL (5.8 – 995), Gleason of 8 (6 – 9), and ECOG of 1 (n=17). 21/24 had prior chemotherapy with docetaxel. All patients had bony metastases, either alone (n=11) or with soft tissue disease (n=13). One patient had a partial response. Ten patients had stable disease (median duration: 18 weeks, range: 15 – 48 weeks). At a median potential follow-up of 27.2 months, the median progression-free survival was 3.7 months and the median overall survival was 18.0 months. For the whole trial of 46 patients, median survival was 18.3 months. Most frequent toxicities included hand-foot skin reaction (Grade 2 in 9 patients, Grade 3 in 3 patients), rash, LFT abnormalities, and fatigue.

CONCLUSIONS—Sorafenib has moderate activity as 2nd line treatment in metastatic CRPC.

Corresponding Author: Dr. William D. Figg, Medical Oncology Branch, CCR, NCI/NIH, 9000 Rockville Pike, Building 10, Room 5A01, Bethesda, Maryland 20892, Tel: +1-301-402-3622, Fax: +1 301-402-8606, wdfigg@helix.nih.gov.
Current address for J.B. Aragon-Ching: George Washington University Medical Center, Division of Hematology and Oncology, 2150 Pennsylvania Ave., Suite 3-428, Washington, DC 20037, USA

Keywords

castration resistant prostate cancer; angiogenesis; Raf-kinase inhibitor; sorafenib

INTRODUCTION

Sorafenib is an oral multi-kinase inhibitor that targets the Ras/Raf kinase pathway, vascular endothelial growth factor (VEGF), and platelet-derived growth factor receptor (PDGF) [1]. It has gained Food and Drug Administration approval for renal cell and hepatocellular cancer [2] and has shown promising activity in a variety of other cancers [3,4]. Angiogenesis has been shown to have a role in the progression of prostate cancer [5]. As such, a phase II study using sorafenib in patients with metastatic castration resistant prostate cancer (mCRPC) was designed to determine if sorafenib was associated with a potentially improved 4-month probability of progression-free survival as determined by clinical, radiographic and prostate-specific antigen (PSA) criteria. The first stage of this two-stage design study was recently reported [6]. Of the 22 patients accrued to the first stage, 13 progressed only by prostate specific antigen (PSA) criteria in the absence of clinical or radiologic progression. Furthermore, two patients had reduction of metastatic bone lesions in bone scintigraphy while meeting PSA progression criteria. We determined that PSA was not a good surrogate marker for sorafenib activity as evidenced by *in vitro* cumulative increase in PSA with increasing drug concentrations. The observed discordance between the PSA and radiographic response led to the amendment of the protocol to define progression based only on clinical or radiographic criteria alone. This report describes the final analysis of the second stage of this clinical trial (n=24), and reports the overall survival for the whole cohort (n=46).

PATIENTS AND METHODS

Patient selection

All patients had histologically confirmed prostate adenocarcinoma and had progressive mCRPC as evidenced by any expanding measurable lesion, appearance of a new lesion, and/or an increasing PSA concentration on successive measurements. Patients were allowed to have no more than one prior cytotoxic chemotherapeutic regimen; Eastern Cooperative Oncology Group status of 0 to 2; life expectancy of $\geq$ 12 weeks; adequate organ function; and castrate levels of testosterone achieved either by surgical orchiectomy or administration of a gonadotropin releasing hormone agonist. Other eligibility criteria included being off prior chemotherapy for 4 weeks, absence of brain metastasis, bleeding diathesis or uncontrolled illnesses; well-controlled hypertension, if present.

Study design

This was an open-label, single-center, phase II clinical trial using an optimal two-stage design [7] with the first stage as previously published [6] and the second stage being presently reported. All patients gave written informed consent in accordance with federal, state, and institutional guidelines and the study was approved by the National Cancer Institute (NCI) Institutional Review Board. Patients received 400 mg of sorafenib orally twice daily each day of a 28-day cycle. Patients were evaluated in the clinic every 4 weeks, and radiographic assessments using computed tomography (CT) and bone scintigraphy were obtained every 2 months. Blood tests including complete blood count, chemistry, and PSA were obtained at each monthly visit. Response and progression was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST).[8] 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 response was recorded but not used as a criterion for progression.

The primary endpoint was disease progression defined as either the appearance of new lesions on bone scan or progression by RECIST criteria. Secondary endpoints included measurement of overall response, pharmacokinetics, toxicity analysis, and pharmacodynamics.

Statistical considerations

The Simon two-stage design [7] was used in order to rule out a 30% probability of 4 month progression free survival while targeting a 50% probability of patients having 4 month progression free survival. Conventional error probabilities of alpha=0.10 and beta=0.10 were employed. Based on this design, during the first stage, 22 patients were enrolled and progression at four months was evaluated. Per the protocol, if 7 or fewer patients were found to be progression free at the 4 month evaluation, then no further patients were to be enrolled. However, the PSA and radiographic discordance noted during the first stage of the study allowed for the accrual to the full 46 patients following a change of endpoint evaluation felt to be desirable in view of the initial findings. The Kaplan-Meier method was used to calculate the progression-free survival for the second stage of accrued patients, as well as the overall survival.

Pharmacokinetics – Sample collection and analysis

Sorafenib doses and pharmacokinetic sample collection points were similar to stage 1 of this trial. Sorafenib was administered orally at 400 mg twice daily dose. The blood samples were collected at baseline and at 0.25, 0.50, 1, 2, 4, 6, 8, 12, and 24 hrs after the ingestion of initial doses. Immediately after collection samples were processed, plasma was separated and stored at −80 ° C. A validated LC-MS/MS method was used for determination of sorafenib concentration in plasma samples [9].

The samples were prepared by protein precipitation using acetonitrile and radiolabeled sorafenib was used as internal standard. The workable concentration range was 5–2000 ng/mL with mean accuracy and imprecision ranging from 92.86–99.88% and 1.19–4.53%. Pharmacokinetic parameters area under the curve (AUC_{0-12}), maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}) were calculated by non-compartmental analysis using WinNonlin professional v5.0 (Pharsight Corporation, Mountain View, CA, USA).

Toxicity analysis and dose modifications

Adverse events were recorded using the NCI Common Terminology Criteria (NCI CTC) version 3 and dose adjustments made as previously described.[6] Briefly, no dose interruptions were required for grade 1 or 2 toxicities unless they were deemed intolerable by the patient and treatment was discontinued if ≥ grade 3 or grade 4 toxicities occurred and did not resolve to grade ≤ 1 or baseline within 3 weeks. Dose reductions by 200 mg/d were made but any subsequent dose reductions beyond 75% was not allowed.

RESULTS

Patient characteristics

Twenty-four patients were enrolled into the second stage of the trial between January 2006 and September 2007. The baseline characteristics are presented in Table 1. Twenty-one of 24 (87.5%) patients in the second stage had received prior chemotherapy with docetaxel compared to only 55% (12 of 22 patients) in stage 1. Majority had ECOG status of 1 (n=17).

Pharmacokinetics

Plasma-concentration time profile for patients on the second stage of this trial is shown in Figure 1. Following administration of first dose, the geometric mean for exposure ($AUC_{0–12}$) was 18.63 mg/L*hr (95% CI, 13.1–26.4; %CV, 69 %) and for C_{max} was 2.57 mg/L (95% CI, 1.9–3.5; %CV, 71 %). The t_{max} ranged from 2–12.2 hr with a median value of 8 hr. The geometric mean $AUC_{0–12}$ and C_{max} for the second stage were found to be significantly higher than those reported for the first stage, perhaps due to three patients who had significantly higher AUCs (> 2 times mean AUC) than the rest of patients in stage 2. Of these 3 patients with the highest AUC, one patient had UGT1A9*3/*3 homozygous variant polymorphism, the second one was the oldest with the lowest body surface area, and the third one had high alkaline phosphatase levels. However, comparison between the two stages between patient demographics (weight, age, BSA), liver function markers (albumin, total protein, SGOT, SGPT) and serum creatinine were not found to be significantly different. The median accumulation (concentration at 24^{th} hr/ concentration at 12^{th} hr) after second dose was 1.46 and ranged from 0.54 – 4.41.

Toxicities

All patients who received treatment were analyzed for toxicity. Patients received a median of 2.5 cycles (range <1 – 12). However, of the 24 patients, 5 discontinued drug treatment prior to the radiographic evaluation at 8 weeks secondary to refusal (n=3), adverse event (n=1), and death (n=1). The patient who died on-study was an 85 year-old patient with pre-existing cerebrovascular accident within the past 5 years, and was on-study for only 20 days when he suffered from a recurrent hemorrhagic cerebrovascular accident. Of note, this patient was one of the three who had the highest sorafenib AUC. Table 2 lists the most common treatment-related adverse events occurring in > 10% of patients enrolled in the second stage and all grade 3 or 4 events. The incidence of hand-foot skin reaction (HFSR) was notably higher in patients in the second stage (3 patients with Grade 3 and 9 patients with Grade 2) as compared with the first stage where only one patient each had Grade 2 and 3 HFSR. The second stage patients also experienced a higher incidence of LFT abnormalities and more severe fatigue but less hypertension compared to those in the first stage. Dose reductions occurred in 54% (13 of 24) patients in the second stage.

Response, progression free survival, and overall survival

Of the 13 patients enrolled in the second stage who had measurable disease, one patient had a partial response (PR) by RECIST criteria. Of the 24 patients in the second stage, 10 patients had stable disease. The median duration of stable disease is 18 weeks, currently with a range of 15 to 48 weeks, including two patients still stable at 35 and 37 weeks. No PSA responses were noted, the one patient who had PR on CT scan had a 48% reduction in PSA after 2 cycles of sorafenib. This patient received a total of 6 cycles before disease progression was noted. At a median potential follow-up of 27.2 months, the median progression-free survival (PFS) for patients in the second stage was 3.7 months (Figure 2A). The median overall survival (OS) for patients in the second stage was 18 months while the median OS for the whole cohort of 46 patients was 18.3 months (Figure 2B).

DISCUSSION

We have previously reported the results of the first stage of this phase II trial of sorafenib [6] in metastatic castration resistant prostate cancer. Of the 22 patients in the first stage, 13 patients progressed by PSA alone and of all patients with bony lesions, only 4 had progressive disease. *In vitro* experiments showed that sorafenib treatment in LNCaP prostate cancer cell lines showed growth inhibition but increased cumulative PSA secretion over time. The observed discordance between the PSA increase and improvement in bone scans brought about a protocol

amendment that resulted in further accrual of the trial to investigate the effect of targeting the Ras/Raf/Extracellular signal regulated kinase (ERK)/mitogen activated protein kinase (MAPK) signaling pathway and vascular endothelial growth factor (VEGF) in metastatic CRPC.

Indeed, the interpretation of post-therapy PSA changes as a measure of response in the era of targeted agents is of unclear clinical significance, especially since noncytotoxic agents may modulate PSA secretion independent of its activity on tumor suppression [10]. Two other clinical studies using sorafenib for prostate cancer has shown similar results with sorafenib exhibiting limited activity using PSA-defined criteria for progression [11,12]. In the first study, the primary endpoint of progression-free survival of ≥ 12 weeks using sorafenib was achieved with 4 of 55 evaluable patients achieving SD by RECIST criteria, 2 patients with PSA response, and 11 patients with stable PSA [11], while a 3.8% PSA response was seen in the study by Chi et. al. [12], thereby not meeting the primary end point of > 20% possibility of a PSA response as defined by 50% decline in ≥ 4 weeks. The conclusion for both of these trials, including our previous published first stage, was that while sorafenib did exhibit some activity in prostate cancer, PSA was not a reliable marker for disease progression. However, no reliable surrogate marker has yet been established. Analysis of phospho-ERK levels did not show a correlative reduction in the obtained samples of patients treated with sorafenib [6]. Therefore, subsequent bone marrow biopsies were not performed. Of note, the two previous clinical studies using sorafenib enrolled patients who were chemotherapy-naïve [11,12]. In comparison, the majority of patients in the second stage of this trial had prior docetaxel (21 of 24 patients) since the accrual began in January 2006, long after docetaxel and prednisone had become standard of care [13].

Second line treatment after docetaxel failure has been studied using several agents including mitoxantrone [14], ixabepilone [15], carboplatin [16], and satraplatin [17], with reported median overall survival using these agents in the range of 9.8 months to 17 months. The median overall survival for sorafenib is 18.3 months in this study, comparable to other 2^{nd} line cytotoxic regimens. In addition, there was one PR and 10 patients with SD. The modest activity seen warrants further study of sorafenib, perhaps in the docetaxel-failure population.

Sorafenib is fairly well tolerated, although an increase in patients who had to discontinue treatment in the second stage compared to the first stage was noted. More patients experienced hand-foot skin reaction (HFSR) with Grade 3 toxicity occurring in 3 patients and Grade 2 toxicity in 9 patients in contrast to the first stage in which only one patient each developed Grade 2 and 3 HFSR. Further explorations of risk factors associated with the dermatologic toxicities are reported elsewhere (personal communication). Although high variability was observed in rate and extent of sorafenib absorption for the second stage of this trial, this was consistent with the first stage and other reported pharmacokinetics trials [18–20] where geometric mean on exposure and C_{max} ranges from 9.76–71.7 hr*mg/L and 1.28–9.35 mg/L, respectively and the corresponding % CV ranges from 43–90% and 44–106%. The variability in exposure and Cmax does not account for the higher frequency of HFSR observed in the second stage. Exploration of covariate factors that might explain variability in individual response or toxicity to sorafenib is ongoing. One possible example of sources of variability is polymorphism in UGT1A9 enzyme which may influence the sorafenib blood levels by altering its elimination. In the current analysis, the patient with UGT1A9*3/*3 polymorphism (only 1) had significantly higher exposure and was the only patient who had grade 3 skin rash/ desquamation toxicity.

CONCLUSIONS

While it is difficult to compare the two stages of this phase II trial since the PSA-defined progression endpoint was no longer considered in the second stage as a progression criterion, sorafenib in prostate cancer seems to benefit a select population of patients. Also, the assessment used in the second stage of this trial is in line with the evolving concept that in the absence of a clinically compelling indicator of progression, early changes in the PSA should not be heavily weighed upon in the decision to withhold or discontinue treatment [10]. However, ongoing challenges remain as we attempt to identify the appropriate early outcome measures that may be used in the assessment of response using these newly available targeted agents.

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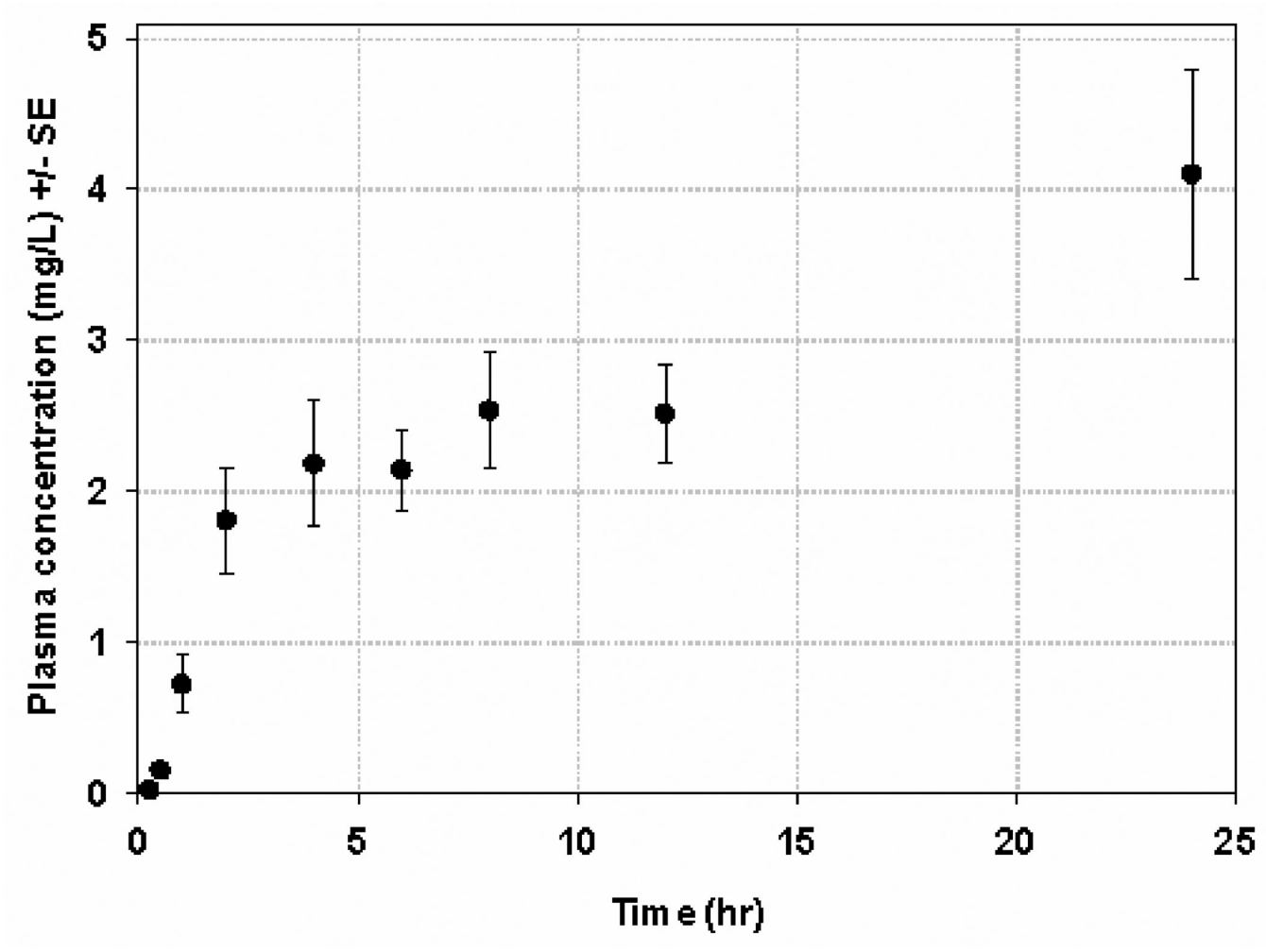
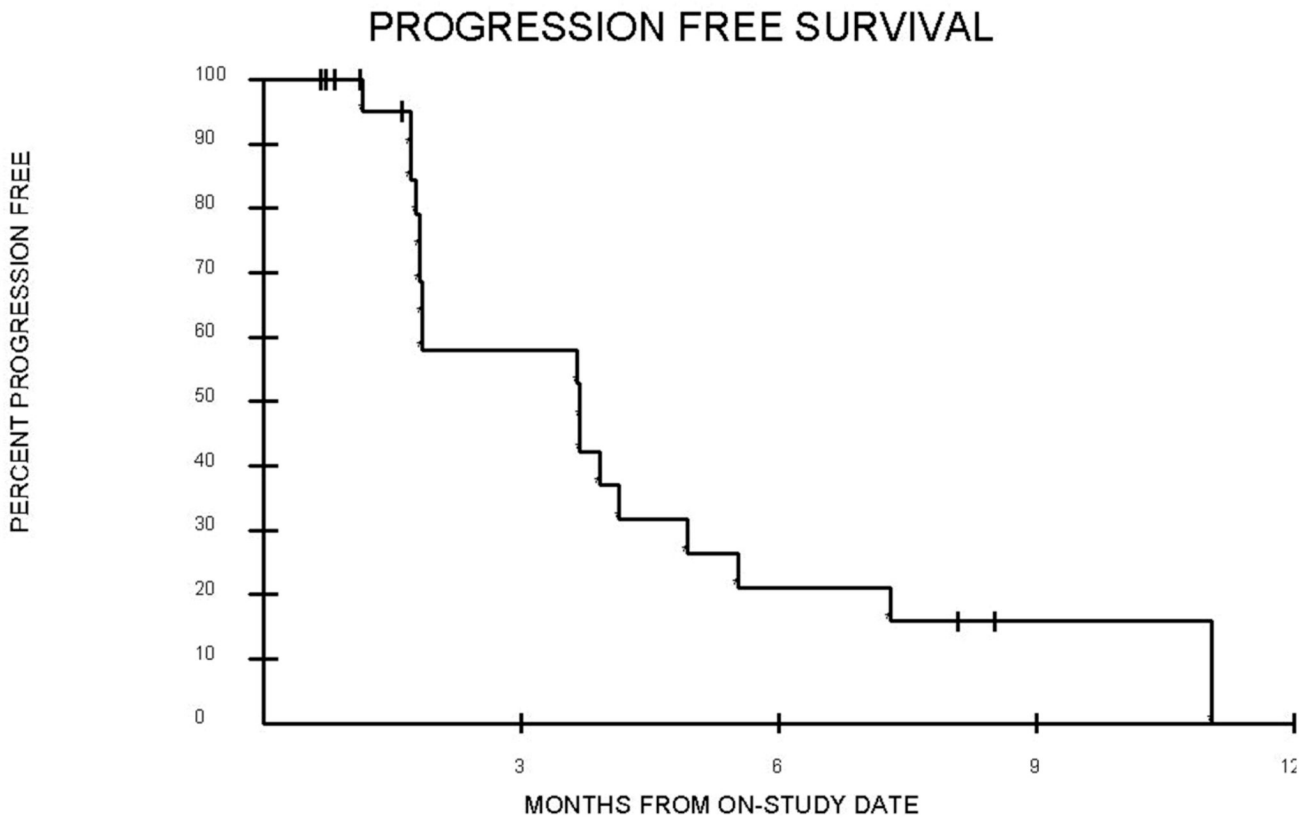


Figure 1.
Plasma concentration time profile for patients in stage 2



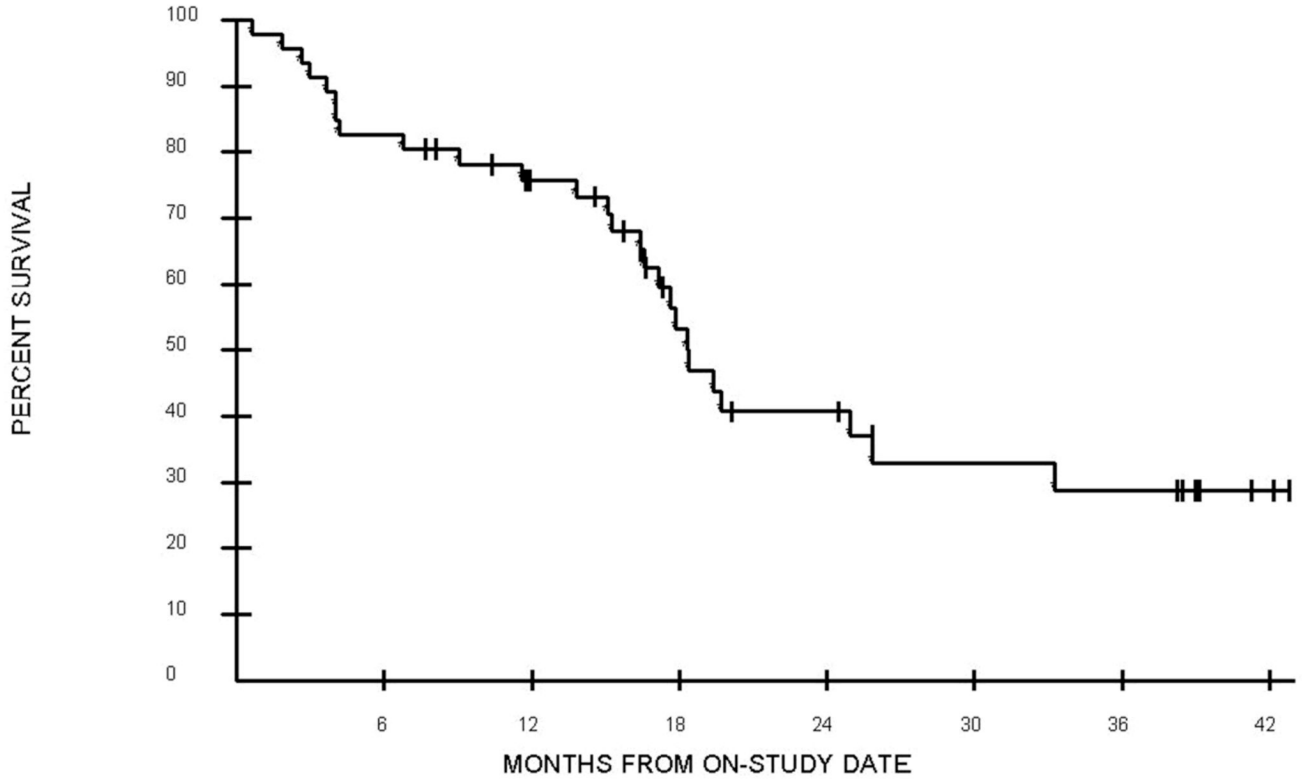


Figure 2.

Figure 2A. Kaplan-Meier curve for the progression-free survival of 24 patients enrolled in stage 2

Figure 2B. Kaplan-Meier curve for the Overall Survival of the whole cohort of 46 patients

Table 1

Patients Demographics and Characteristics

Characteristics	
Total number of patients	24
Age, yrs	
Median	66
Range	49 – 87
Race	
Caucasian	18
African American	5
Hispanic	1
Gleason score	
Median	8
Range	6 – 9
ECOG performance status	
0	7
1	17
Median	1
PSA on-study ng/ml	
Median	68.45
Range	5.8 – 995
Hemoglobin g/dL	
Median	12.35
Range	10.4 – 14.2
Alkaline phosphatase	
Median	83
Range	45 – 414
Sites of metastasis	
Bone only	11
Bone and soft tissue	13
Prior chemotherapy	
Docetaxel, n (%)	21 (87.5%)

Table 2

Treatment-related adverse events (n = 24 patients)

Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Blood/Bone Marrow				
Anemia	2	1	1	
Thrombocytopenia	2			1
Cardiovascular				
CNS cerebrovascular ischemia				1
Hypertension		3		
Thrombosis/embolism (vascular access-related)		1	1	
Constitutional symptoms				
Fatigue	10	2	2	
Weight loss	3	2		
Dermatology/skin				
Hand-foot skin reaction	1	9	3	
Rash/desquamation	11	3	1	
Gastrointestinal				
Diarrhea	6	2		
Nausea	1	1	1	
Infection			1	
Metabolic/Laboratory				
ALT,SGPT	6	2		
AST,SGOT	8		1	
Alkaline phosphatase	1	4	1	
Hyperkalemia			1	
Hyponatremia	1		1	
Hypophosphatemia		3	5	
Pain				
Musculoskeletal	3	7		
Throat/larynx	1		1	
Pulmonary/Upper respiratory				
Voice changes	3			