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Phase II trial of bevacizumab and satraplatin in docetaxel-pretreated metastatic castrate-resistant prostate cancer

Ulka N. Vaishampayan, M.D.^{a,*}, Joseph Fontana, M.D.^a, Lance K. Heilbrun, Ph.D.^b, Daryn Smith, M.S.^b, Elisabeth Heath, M.D.^a, Brenda Dickow, R.N.^c, and William D. Figg, Pharm.D.^d

^aDepartment of Oncology, Department of Medicine, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI

^bBiostatistics Core, Barbara Ann Karmanos Cancer Institute, Detroit, MI

^cClinical Trials Office, Barbara Ann Karmanos Cancer Institute, Detroit, MI

^dMedical Oncology Branch, National Cancer Institute, Bethesda, MD

Abstract

Background—Satraplatin is an oral platinum compound that has demonstrated efficacy and tolerability in prostate cancer. Preclinical synergy between bevacizumab and platinum has been noted.

Methods—Docetaxel-pretreated metastatic castrate-resistant prostate cancer patients with disease progression were eligible. Satraplatin 80 mg/m² orally on days 1 to 5, prednisone 5 mg twice daily, and bevacizumab 10 mg/kg on day 1, and 15 mg/kg on day 15 were administered in 35-day cycles.

Results—Thirty one patients were enrolled. Grade 3 or 4 toxicities were pulmonary embolism in 2 patients and thrombocytopenia in 1 patient. 31% of the patients had a ≥30% decline in prostate-specific antigen. Median time to progression was 7.0 months (90% confidence interval [CI] 4.7–8.5 mo) and median overall survival was 11.2 months (90% CI 9.1–16.4 mo). Polymorphism in the excision repair cross-complementation-1 (ERCC-1) gene was associated with time to progression (hazard ratio = 1.91). A circulating tumor cell count ≥5 was moderately prognostic of overall survival (hazard ratio = 1.49) as compared with CTC <5.

Conclusions—The combination was tolerable, and revealed promising efficacy in metastatic castrate-resistant prostate cancer. ERCC1 genotype maybe predictive of clinical benefit with platinum-based therapy in metastatic prostate cancer.

Keywords

Excision repair polymorphism; Prostate cancer; Chemotherapy; Phase II clinical trial

1. Introduction

Docetaxel-based chemotherapy was the first systemic regimen to confer an overall survival benefit in metastatic castrate-resistant prostate cancer (CRPC) [1,2]. About 50% of the patients are unresponsive and all patients eventually progress on docetaxel therapy. Platinum-based therapies have been utilized in this setting. Clinical trials conducted using

carboplatin demonstrated a promising efficacy and favorable responses [3,4]. Another platinum agent that has been extensively tested in metastatic CRPC is satraplatin.

Satraplatin is an oral, third-generation platinum compound noted to have preclinical efficacy in platinum-resistant cell lines, and clinical efficacy in metastatic CRPC [5]. Preliminary results of phase I and II trials established the safety of the agent, with the severe toxicities noted being neutropenia, thrombocytopenia, and diarrhea [6,7]. Cisplatin side effects such as nephrotoxicity, neuropathy, and ototoxicity were not observed with satraplatin. The results of a phase II trial of satraplatin and prednisone compared with prednisone alone, revealed that the treatment was well tolerated with a promising prostate-specific antigen (PSA) response rate of 33%, and median progression-free survival (PFS) of 5.2 months in the satraplatin and prednisone arm as compared with a response rate of 9%, and median PFS of 2.5 months, in the prednisone arm [7]. Median overall survival (OS) estimates were 14.9 months and 11.9 months in the satraplatin and prednisone and the prednisone alone arms, respectively. The Satraplatin and Prednisone Against Refractory Cancer (SPARC) [8] trial evaluated satraplatin plus prednisone vs. placebo plus prednisone as a second-line treatment in 950 patients with metastatic CRPC. The PFS was significantly better ($P < 0.0000003$) in favor of satraplatin [8]. However, the OS analysis revealed no benefit leading to lack of regulatory approval of the agent.

Increased expression of vascular endothelial growth factor (VEGF) contributes to prostate cancer progression, by up-regulating microvessel density, and increasing expressions of VEGF-C and VEGFR-3 with enhanced lymphangiogenesis [9,10]. Bevacizumab is an antiangiogenic, monoclonal antibody that inhibits VEGF and improves the efficiency of the local vasculature, thereby improving chemotherapy penetration and delivery [11-13]. Due to the individual efficacy and tolerability of satraplatin and bevacizumab and the clinical synergy noted between platinum-based chemotherapies and antiangiogenic therapy we conducted a phase II trial of the combination of satraplatin and bevacizumab in pretreated metastatic CRPC.

2. Patients and Methods

The protocol and the informed consent form were approved and reviewed annually by the Wayne State University Institutional Review Board. Eligibility criteria included histologically confirmed prostate adenocarcinoma with radiologically evident metastases and testosterone < 50 ng/ml. Objective evidence of progression was required. Prior docetaxel-based chemotherapy was required but not more than 1 prior chemotherapy (unless given in combination with docetaxel) for metastatic disease was allowed. Concomitant bisphosphonate therapy was allowed. Prestudy imaging for disease assessment was performed within 28 days of treatment. Antiandrogen withdrawal was required for 4 weeks prior to treatment with flutamide and for 6 weeks prior to treatment with bicalutamide or nilutamide. Radiation therapy had to be completed at least 28 days prior to enrollment. Performance status of 0 to 2 by Zubrod criteria, life expectancy of at least 12 weeks, and normal renal, liver, and bone marrow function were required. Patients on anticoagulants were allowed if treated adequately and if no ongoing acute thromboembolic activity was noted. At least 28 days had to have elapsed from a major surgical procedure, open biopsy, or significant traumatic injury. Patients with severe congestive heart failure, arrhythmias, or a myocardial infarction within 3 months of registration, were excluded. Patients with urinary protein and creatinine ratio > 1 , or 24-hour urine protein greater than or equal to 1 g/dl were ineligible. All patients were required to provide a written informed consent.

2.1. Treatment plan

Bevacizumab treatment was administered at 10 mg/kg intravenously on day 1, and 15 mg/kg on day 15, of each 35-day cycle. Premedications were allowed at the treating physician's discretion. Satraplatin 80 mg/m² was taken orally with fasting for 1 hour prior, and 2 hours after dosing. Prednisone 5 mg twice daily was taken with meal.

Dose adjustments were made for severe hematologic and nonhematologic toxicities. Treatment was discontinued if there was evidence of disease progression, unacceptable or severe grade 3 or 4 toxicity, or delay in treatment by 4 weeks or more.

2.2. Correlative tests

2.2.1. ERCC1—Approximately 10 ml of blood was drawn using a 10 ml ethylenediaminetetraacetic acid tube for DNA extraction. Genomic DNA was extracted from the serum or the white blood cells present in the buffy coat layers of the whole blood of patients according to the manufacturer's instructions using the UltraSens Virus Kit (Qiagen, CA). Polymerase chain reaction (PCR) was done using the Platinum Taq PCR Kit (Invitrogen, CA) with gene-specific primers. PCR was carried out by denaturation at 94°C for 5 minutes followed by denaturation at 94°C for 30 seconds, annealing at optimal temperature for each pair of primers for 30 seconds, and synthesis for 30 seconds at 72°C for 40 cycles; the final extension was carried out at 72°C for 7 minutes. Direct nucleotide sequencing PCR was conducted using the Big Dye Terminator Cycle Sequencing Ready Reaction kit V3.1 (Applied Biosystems, CA) and an ABI Prism 3130 Genetic Analyzer using the manufacturer's instructions. Immunohistochemical phenotyping of normal peripheral blood leukocytes (PBLs) was done to check for polymorphisms of the (ERCC1) enzyme [14].

2.2.2. Circulating tumor cell (CTC) counts—A single sample of approximately 22.5 ml (three 7.5 ml tubes) of blood was collected from the patients who consented and were treated on the study. Blood collection kits and instructions were provided by CARIS Labs and were performed by CARIS/Veridex (Caris Diagnostics, Irving, TX). Samples were only collected posttherapy, and not at baseline due to funding delays.

2.2.3. Evaluation—Toxicity was categorized according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). All patients who were starting the therapy were considered to be toxicity evaluable. Patients completing a minimum of 1 cycle of therapy followed by assessment were considered to be response evaluable. Imaging studies for tumor assessment were conducted at baseline and every 2 cycles. RECIST criteria were used to categorize measurable disease responses [15]. PSA working group criteria were used to measure PSA response [16].

2.2.4. Statistical methods—We had a directional hypothesis that the median time to progression (TTP) achievable with satraplatin and bevacizumab might exceed an assumed population reference (i.e., control) value of 3 months. A clinically meaningful improvement in median TTP would be at least 2 months over that, i.e., if satraplatin and bevacizumab had a true median TTP of 5 months (i.e., a 67% improvement). A 1-sample survival-type design was used based on the methods of Lawless [17]. With an assumed accrual time of 24 months, no additional follow-up time, power of 90%, and α error of 0.15, the required sample size was 28 evaluable patients.

Standard Kaplan-Meier (K-M) estimates of the censored TTP and OS distributions were computed. Due to the small sample sizes, survival statistics (e.g., median) were estimated more conservatively using linear interpolation among successive event times on the K-M

curves [18]. CTC count was dichotomized as <5 CTCs vs. ≥ 5 CTCs. ERCC1 genotype category was dichotomized as CC vs. TT/CT. Extent of disease at baseline was dichotomized as minimal vs. extensive. With CTCs <5 as the reference group, the progression and OS hazard ratio (HR) was estimated from a univariate Cox proportional hazards model. Similar Cox model analyses of TTP and OS were performed with ERCC1, using ERCC1 = CC (wild type) as the reference group. Cox model analyses of TTP and OS were also performed with extent of disease at baseline, using minimal disease as the reference group. The univariable relationships of CTC count, ERCC1 genotype, and disease extent with TTP and with OS are reported as exploratory analyses only, without significance testing. The proportional hazards assumption was checked via plots of $\log(-\log)$ of TTP (and OS), and via smoothed hazard function plots.

3. Results

3.1. Clinical results

Patient characteristics are summarized in Table 1. Bone pain was noted in 21 (68%) and Gleason score ≥ 8 was noted in 20 patients (67%). A median of 4 cycles (range 1–12 cycles) was administered among the 30 treated patients. The only grade 4 toxicities were venous thromboembolism in 2 patients and thrombocytopenia in 1 patient (3%, 90% CI: 0.01–0.14), with no clinical evidence of bleeding (Table 2). No treatment-related deaths occurred. Treatment-related hospitalizations occurred in 2 patients (7%, 90% CI: 0.02–0.18) due to dehydration and diarrhea.

Of 31 patients, 30 were deemed response evaluable; 1 patient did not receive therapy due to obstructive renal failure related to disease progression. PSA response ($\geq 30\%$ decline) was noted in 9 (30%, 90% CI: 0.18–0.45) patients, of which 5 patients (17%, 90% CI: 0.08–0.30) had a $\geq 50\%$ PSA decline and 3 (10%, 90% CI: 0.04–0.23) patients demonstrated a $\geq 90\%$ PSA decline. Partial response by RECIST 1.0 criteria was noted in 2 (15%, 90% CI: 0.05–0.37) of the 12 patients with measurable disease and stable disease was noted in 7 patients. Median TTP was 7.0 months (90% CI: 4.7–8.5 mo), and the median OS was 11.2 months (90% CI: 9.1–16.4 mo) (Tables 3 and 4, Figs. 1 and 2). One-year TTP and OS rates were 35% (90% CI: 20%–50%) and 47% (90% CI: 32%–62%), respectively.

3.1.1. Biomarker results—CTC results are summarized in Tables 3 and 4. The patients with CTC ≥ 5 revealed a median OS of 5.7 months as compared with a median OS of 15.4 months in patients with CTC < 5 (HR = 1.49, 90% CI: 0.58–3.85). With CTC < 5 chosen as the reference group, an exploratory Cox model of censored TTP estimated a progression HR = 1.91 (90% CI: 0.54–6.77) for the patients with CTC ≥ 5 (Fig. 3).

Median TTP among the CC patients was 12.7 months (90% CI: 5.6–16.7 mo) vs. 6.7 months (90% CI: 0.3–13.6 mo) among the TT/CT patients (Table 3, Fig. 4).

ERCC1 was dichotomized into CC (wild type) vs. TT/CT genotype categories. Median TTP among the CC patients was 12.7 months (90% CI: 5.6–16.7 mo) vs. 6.7 months (90% CI: 0.3–13.6 mo) among the TT/CT patients (Table 3, Fig. 4).

With ERCC1 dichotomized as TT/CT vs. CC, and CC (arbitrarily) chosen as the reference group, an exploratory Cox model of censored TTP estimated a progression HR = 1.91 (90% CI: 0.70–5.18) for the TT/CT patients. This suggests a statistically weak association, with ERCC1 genotype. TT/CT patients demonstrated (numerically) increased risk of progression compared with the CC patients. The analogous exploratory Cox model of censored OS estimated a death HR = 0.70 (90% CI: 0.23–2.20) for the TT/CT patients. This suggests a statistically weak association of OS with ERCC1 genotype status, however the majority of

the patients were treated with other salvage therapies and that could have affected OS outcomes.

3.1.2. Extent of disease results—PSA response (≥30% decline) was noted in 3 of 4 minimal disease extent patients (75%, 90% CI: 0.36–0.94), compared with only 6 of 25 extensive disease extent patients (24%, 90% CI: 0.13–0.40). As shown in Table 5, the 25 patients with extensive disease at baseline had (numerically) shorter TTP and shorter OS than did the 4 minimal disease patients. An exploratory Cox model of censored TTP estimated a progression HR = 1.38 (90% CI: 0.55–3.46) for the extensive disease patients compared with the minimal disease patients. For OS, the extensive disease patients' HR = 1.05 (90% CI: 0.42–2.62). Taken together with the PSA response results, it was clear that extensive disease worsened prognosis.

4. Discussion

The establishment of therapies such as abiraterone, MDV-3100, and alpharadin [19-21] is likely to shift the initial focus of therapy in metastatic CRPC, to the nonchemotherapy-based agents. Docetaxel-based chemotherapy remains the current standard front-line chemotherapy in metastatic CRPC. However, about 50% of the patients treated do not respond to docetaxel and prednisone. Docetaxel-refractory disease within metastatic CRPC has a dismal prognosis and presents a serious therapeutic challenge. In our trial, 7 patients (23%) had received ≥4 cycles of docetaxel and were considered refractory to taxanes. Platinum-based therapy has demonstrated clinical efficacy in docetaxel-refractory patients [3,4]. Our study met the primary goal of median TTP exceeding 5 months even in this predominantly extensive disease patient population. The clinical relevance of this finding is minimal, due to recent availability of multiple effective nonchemotherapy-based agents. Along with PSA response, we also noted a dramatic clinical improvement in bone pain and performance status, measurable disease responses, and stabilization of bone metastases. This indicates meaningful clinical benefit, in addition to the favorable OS and TTP, compared with that seen with other postdocetaxel chemotherapy regimens tested in phase II trials. The addition of bevacizumab however has not been shown to confer an OS advantage in metastatic CRPC. The phase III trial comparing docetaxel and prednisone with or without bevacizumab revealed no survival benefit (median OS 22.6 mo vs. 21.5 mo, $P = 0.18$) [22].

Ideally, selection of a patient population likely to benefit from platinum-based therapy would help guide the choice of agent and improve the efficiency of the chemotherapy. In our study, ERCC1 TT/CT genotype had a progression HR of 1.91, demonstrating a higher likelihood of benefit with the CC genotype. With careful selection based on ERCC1 status, the regimen of satraplatin and bevacizumab demonstrated a median TTP of 12.7 months for the CC patients. A number of lines of evidence have shown an association wherein the CC form of ERCC1 was predictive of improved outcomes with platinum-based (carboplatin or oxaliplatin) therapies [23,24]. ERCC is a nucleotide excision repair gene in which the variant alleles (CC) predict for an overall aggressive disease course and a better outcome with cisplatin-based chemotherapy, as compared with the TT (more frequent or wild-type allele within the population) [25]. ERCC1-variant expression has been shown to be associated with improved clinical response and benefit in other cancers (non-small cell lung and colorectal cancers) when treated with platinum-based therapies. Future clinical trial assessments of platinum-based chemotherapy in metastatic CRPC should be planned in docetaxel pretreated/refractory disease, with patient selection based on ERCC1 status. The findings of this study are hypothesis generating however validation in larger sample size would be needed.

CTC counts were studied in metastatic breast cancer and CTC of $<5/7.5$ ml vs. $5/7.5$ ml were established as the favorable and unfavorable risk groups, respectively [26]. In metastatic CRPC, baseline CTC and posttherapy change in CTC was superior to PSA kinetics in predicting OS [27]. The results of our trial reiterate the importance of CTC counts as a prognostic surrogate for OS, with CTC ≤ 5 posttherapy demonstrating a 3-fold better median OS as compared to the patients with CTC > 5 .

In conclusion, this phase II trial of combination of satraplatin and bevacizumab demonstrated some encouraging responses and durable remissions in metastatic CRPC. The study demonstrated that platinum-based chemotherapy could be a therapeutic consideration, especially in the ERCC1 (CC) genotype. Future investigations to develop effective tools to individualize therapy based on clinical and molecular markers, are likely to optimize the outcome in metastatic CRPC.

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References

1. Petrylak D, Tangen C, Hussain M, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004; 351:1513–20. [PubMed: 15470214]
2. Tannock IF, Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004; 351:1502–12. [PubMed: 15470213]
3. Oh W, Manola J, Babcic V, et al. Response to second-line chemotherapy in patients with hormone refractory prostate cancer receiving two sequences of mitoxantrone and taxanes. *Urology*. 2006; 67:1235–40. [PubMed: 16765185]
4. Jeske S, Tagawa ST, Olowokure O, et al. Carboplatin plus paclitaxel therapy after docetaxel in men with metastatic castrate resistant prostate cancer. *Urol Oncol*. 2011; 6:676–81. [PubMed: 20451413]
5. Bhargava A, Vaishampayan UN. Satraplatin: leading the new generation of oral platinum agents. *Expert Opin Investig Drugs*. 2009; 18:1787–97.
6. Sternberg CN, et al. Satraplatin in the treatment of hormone-refractory prostate cancer. *Br J Urol Int*. 2005; 96:990–4.
7. Sternberg CN, Whelan P, Hetherington J, et al. Phase III trial of satraplatin, an oral platinum plus prednisone vs prednisone alone in patients with hormone refractory prostate cancer. *Oncology*. 2005; 68:2–9. [PubMed: 15741753]
8. Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol*. 2009; 27(32):5431–8. [PubMed: 19805692]
9. Bok RA, Halabi S, Fei DT, et al. Vascular endothelial growth factor and basic fibroblast growth factor urine levels as predictors of outcome in hormone-refractory prostate cancer patients A cancer and leukemia group B study. *Cancer Res*. 2001; 61:2533–6. [PubMed: 11289126]
10. George DJ, Halabi S, Shepard TF, et al. Prognostic significance of plasma vascular endothelial growth factor levels in patients with hormone-refractory prostate cancer treated on Cancer and Leukemia Group B 9480. *Clin Cancer Res*. 2001; 7:1932–6. [PubMed: 11448906]
11. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*. 2005; 307:58–62. [PubMed: 15637262]

12. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol.* 2007; 25:1539–44. [PubMed: 17442997]
13. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006; 355:2542–50. [PubMed: 17167137]
14. Monzo M, Moreno I, Navarro A, et al. Single nucleotide polymorphisms in nucleotide excision repair genes XPA, XPD, XPG and ERCC1 in advanced colorectal cancer patients treated with first-line oxaliplatin/fluoropyrimidine. *Oncology.* 2007; 72:364–70. [PubMed: 18204222]
15. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92:205–16. [PubMed: 10655437]
16. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 1999; 17:3461–7. [PubMed: 10550143]
17. Lawless, JF. Statistical models and methods for lifetime data analysis. New York: Wiley; 1982. p. 108
18. Lee, E.; Wang, JW. Statistical methods for survival data analysis. 3. New York, NY: Wiley & Sons Inc; 2003. p. 76-91.
19. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011; 364:1995–2005. [PubMed: 21612468]
20. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012; 367:1187–97. [PubMed: 22894553]
21. Parker C, Heinrich D, O'Sullivan JM, et al. Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases. *J Clin Oncol.* 2012; (Suppl 5):30. [PubMed: 23169502]
22. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol.* 2012; 30:1534–40. [PubMed: 22454414]
23. Ryu JS, Hong YC, et al. Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. *Lung Cancer.* 2004; 44:311–6. [PubMed: 15140544]
24. Isla D, Sarries C, Rosell R, et al. Single nucleotide polymorphisms and outcome in docetaxel-cisplatin-treated advanced non-small-cell lung cancer. *Ann Oncol.* 2004; 15:1194–203. [PubMed: 15277258]
25. Bradbury PA, Kulke MH, Heist RS, et al. Cisplatin pharmacogenetics, DNA repair. polymorphisms, and esophageal cancer outcomes. *Pharmacogenet Genomics.* 2009; 19:613–25. [PubMed: 19620936]
26. Dawood S, Cristofanilli M. Integrating circulating tumor cell assays into the management of breast cancer. *Curr Treat Options Oncol.* 2007; 8:89–95. [PubMed: 17634836]
27. De Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2008; 14:6302–9. [PubMed: 18829513]

Fig. 1. Kaplan-Meier plot of time to progression (TTP) in 31 patients treated with satraplatin and bevacizumab. Median TTP was 7.0 months (90% CI: 4.7–8.5 mo). The 6-month progression-free rate was 55% (90% CI: 40%–70%). The 12-month progression-free rate was 32% (90% CI: 17%–47%).

Fig. 2. Kaplan-Meier plot of OS in 31 patients treated with satraplatin and bevacizumab. Median OS was 11.2 months (90% CI: 9.1–16.4 mo). The 6-month survival rate was 82% (90% CI: 70%–94%). The 12-month survival rate was 47% (90% CI: 3%–62%).

Fig. 3.
 Kaplan-Meier plot of OS in patients with CTC < 5 vs. CTC ≥ 5.

Fig. 4.
Kaplan-Meier plot of TTP in patients by ERCC status: CC vs. CT/TT genotype.

Table 1Patient characteristics (*N* = 31 enrolled patients)

Characteristic	No (%)
Median age	67 years (range 50–85 years)
Median pretherapy PSA	180.7 ng/ml (4.7–1,432.8 ng/ml)
Zubrod performance status	
0	6 (19)
1	25 (81)
Prostatectomy	
Yes	6 (19)
No	25 (81)
Bone pain	
Yes	21 (68)
No	10 (32)
Disease extent	
Minimal	4 (13)
Extensive	25 (81)
Superscan	2 (6)
Gleason score	
6	2(6)
7	8 (26)
8–10	20 (65)
Unknown	1 (3)
Race	
Caucasian	21 (68)
African American	10 (32)
Pretherapy PSA doubling time	
0	4 (13)
1 Month	4 (13)
1–2 Months	13 (43)
2–4 Months	7 (23)
>4 Months	2 (7)
Unknown	1 (3)
Prior chemotherapy cycles	
Docetaxel 4 cycles	6 (20)
Docetaxel > 4 cycles	24 (80)
Unknown	1 (3)
Type of progression/metastasis	
Measurable disease	12 (39)
Bone metastasis progression	17 (55)
PSA progression	26 (84)

Table 2

Toxicity among 30 treated patients

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Venous thromboembolism	0	0	0	2
Fatigue	9	10	1	0
Neutropenia	9	2	3	0
Anemia	3	9	7	0
Thrombocytopenia	15	4	2	1
Nausea	9	7	0	0
Emesis	7	4	0	0
Diarrhea	8	2	2	0
Edema	3	0	0	0
Proteinuria	6	12	0	0
Dehydration	1	7	1	0
Hypertension	2	2	3	0
Hypokalemia and hyponatremia	5	0	1	0

Table 3

Response rate and time to progression (TTP) summary statistics

Endpoint	N	Events	Point estimate	90% Confidence interval
Time to progression	31	28		
Median			7.0 Months	4.7 Months 8.5 Months
6 Month rate			55%	40% 70%
12 Month rate			32%	17% 47%
ERCC1 = CC	9	9		
Median			12.7 Months	5.6 Months 16.7 Months
6 Month rate			76%	50% 100%
12 Month rate			57%	30% 84%
ERCC1 = TT/CT	5	5		
Median			6.7 Months	0.3 Months 13.6 Months
6 Month rate			54%	18% 90%
12 Month rate			28%	0% 64%

Table 4

Overall survival (OS) summary statistics

Endpoint	N	Events	Point estimate	90% Confidence interval
Overall survival	31	28		
Median			11.2 Months	9.1 Months 16.4 Months
6 Month rate			82%	70% 94%
12 Month rate			47%	33% 62%
CTC < 5	7	6		
Median			15.4 Months	0.0 Months 24.8 Months
6 Month rate			78%	50% 100%
12 Month rate			63%	32% 94%
CTC 5	10	8		
Median			5.7 Months	2.9 Months 19.6 Months
6 Month rate			48%	22% 74%
12 Month rate			35%	10% 61%
ERCC1 = CC	9	7		
Median			18.4 Months	11.3 Months 35.4 Months
6 Month rate			88%	65% 100%
12 Month rate			77%	51% 100%
ERCC1 = TT/CT	5	4		
Median			20.5 Months	3.2 Months ^a Months
6 Month rate			100%	^b 100%
12 Month rate			69%	33% 100%

For CTC analysis, OS is measured from the date of the blood drawn.

^a Cannot be calculated due to the small sample size and the censoring pattern.

^b This lower confidence limit cannot be calculated as no event occurred before the time point (but the upper limit will be 100%).

Table 5

Summary statistics of time-to-event (TTE) endpoints by extent of disease

TTE endpoint	N	Events	Point estimate	90% Confidence interval
Time to progression				
Extent of disease				
Minimal	4	4		
Median			12.8 Months	4.3 Months 14.7 Months
6 Month rate			72%	30% 100%
12 Month rate			53%	12% 94%
Extent of disease				
Extensive	25	22		
Median			7.0 Months	3.3 Months 8.5 Months
6 Month rate			57%	40% 73%
12 Month rate			27%	11% 43%
Overall Survival				
Extent of disease				
Minimal	4	4		
Median			18.9 Months	7.2 Months 24.5 Months
6 Month rate			100%	^a 100%
12 Month rate			70%	29% 100%
Extent of disease				
Extensive	25	22		
Median			11.2 Months	9.1 Months 16.4 Months
6 Month rate			82%	69% 96%
12 Month rate			47%	30% 63%

Extent of disease was missing for 2 of the 31 patients enrolled.

There were only 2 patients with superscan extent of disease, so they have been included with the 23 extensive disease patients for statistical analysis purposes.

^a Cannot be calculated as no event took place before 10 months.