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Phase I Trial of the Combination of Docetaxel, Prednisone, and Pasireotide in Metastatic Castrate-Resistant Prostate Cancer

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Abstract

The safety and efficacy of the additional use of the novel agent pasireotide with the standard regimen of docetaxel and prednisone was explored in patients with metastatic prostate cancer. The results showed tolerability and preliminary efficacy. The combination is worthy of future investigation in patients with metastatic castrate resistant prostate cancer with neuroendocrine features.

Background: Pasireotide (SOM230; Novartis Inc, Basel, Switzerland) is a multitargeted somatostatin receptor analogue likely to treat the neuroendocrine, and docetaxel resistant components within metastatic castrate-resistant prostate cancer (mCRPC). This phase I trial tested the combination of pasireotide, docetaxel, and prednisone in pretreated mCRPC.

Patients and Methods: Chemotherapy naive mCRPC patients received docetaxel 75 mg/m² intravenously every 21 days and pasireotide intramuscularly every 28 days at escalating dose levels of 40, 60, and 80 mg. Maximum tolerated dose and recommended phase II dose (RP2D) were assessed.

Results: Eighteen patients were enrolled with a median age of 65 (range, 49–75) years, and pretherapy prostate-specific antigen of 259.9 ng/mL. The dose-limiting toxicities were Grade 4 hyperglycemia unresponsive to therapy and Grade 4 neutropenia lasting for > 7 days in 1 patient each occurring at the 80-mg dose level of pasireotide. The RP2D was determined at 60 mg every 28 days. Four patients at the 60 mg dose had Grade 3 or 4 hyperglycemia, which responded adequately to therapy. Median time to progression and survival were 7.2 and 18.3 months, respectively. Three of 6 patients with circulating tumor cells > 5 converted to circulating tumor cells < 5 post therapy. The insulin like growth factor-1 levels revealed a median 51% decrease after therapy. The neuron-specific enolase and chromogranin did not show any marked change.

Conclusion: The addition of pasireotide to docetaxel and prednisone is clinically feasible at a dose level of 60 mg every 28 days. The combination showed potential for clinical efficacy but needs to be compared with the standard docetaxel and prednisone regimen.

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Disclosure

The authors have stated that they have no conflicts of interest.

Keywords

Clinical trial; Neuroendocrine; Pasireotide; SOM230

Introduction

Prostate cancer is the most common cancer in men with an estimated 180,890 new cases in 2016 in the United States.¹ Although most cases are treated in the localized stages, others present as disseminated disease or become metastatic after definitive treatment. Androgen deprivation therapy (ADT) is the initial standard therapy in the hormone-naïve population.² In the castrateresistant population, various agents like sipuleucel T, docetaxel, abiraterone, enzalutamide, cabazitaxel, and radium-223 have shown survival benefit.³ Docetaxel and prednisone remains the standard first-line chemotherapy in metastatic prostate cancer.⁴ The median overall survival (OS) of patients treated with docetaxel and prednisone in the castrate-resistant setting was reported to be within the range of 17 to 19 months on the basis of dosing schedule.^{5,6} Various agents have been used in addition to this combination in an attempt to increase tolerability as well as prolong benefit but none of the combination therapies have shown efficacy improved over the docetaxel and prednisone regimen.^{7–9}

Development of neuroendocrine features is a common resistance pathway noted in pretreated metastatic prostate cancer. Pasireotide (or SOM230; Novartis Inc, Basel, Switzerland) is a multitargeted somatostatin (sst) receptor analogue that binds to 4 of the 5 receptors (sst1, 2, 3, and 5).¹⁰ The binding occurs with extremely high affinity compared to the currently Food and Drug Administration-approved sst receptor analogue, octreotide. The binding results in dissociation of growth proteins and subsequent downstream effects of apoptosis, and inhibition of trophic factor secretion, angiogenesis, and proliferation. Cytokine release is also inhibited, hence inhibiting interleukin-6 and tumor necrosis factor- α secretion. Sst 1, 2, and 5 are expressed on prostate cancer cells and SOM230 showed 44% inhibition in xenograft models of human prostate cancer cell line (PC3) tumors.¹¹ When hormone and chemotherapy-refractory human prostate cancer cell lines, PC3 and DU145 were treated with SOM230, it resulted in synergistic cytotoxic activity and apoptosis. It also reduced secretion of stem cell factor and platelet-derived growth factor in PC3 cells, and decreased transforming growth factor- β and basic fibroblast growth factor in DU145 cells.^{12,13} The preclinical activity created a strong rationale for exploring the safety and activity of the combination of SOM230 and docetaxel in metastatic castrate-resistant prostate cancer (mCRPC). Hence we designed a phase I/II trial to ascertain safety and preliminary efficacy of the additional use of SOM230 with docetaxel and prednisone.

Patients and Methods

Study Design

This was a single-arm, single institution, phase I study of the combination of docetaxel, prednisone, and pasireotide in patients with mCRPC. The primary objective of the study was to establish the maximum tolerated dose (MTD) and recommended phase II dose of pasireotide in the combination. Secondary objectives were to evaluate preliminary efficacy

defined according to response rate (RR) time to progression (TTP), OS, pharmacokinetics (PK), and to assess changes in pre- and post-therapy insulin like growth factor-1 (IGF-1), serum chromogranin A, neuron-specific enolase (NSE), and their association with TTP and OS and to assess change in circulating tumor cells (CTCs) and its association with TTP and OS. The study was approved by the institutional review board and written signed informed consent was obtained from all patients before registration.

Patient Selection

Patients age 18 years or older and with histologically confirmed mCRPC and objective progression or rising prostate-specific antigen (PSA) level despite ADT therapy and antiandrogen withdrawal were included. Patients with rising PSA level had to show a rising trend with 2 successive elevations at a minimum interval of 1 week. A minimum PSA of 5 ng/mL or new areas of bony metastases on bone scan was required for patients with no measurable disease. No minimum PSA was required for patients with measurable disease. All patients had to be documented to be castrate with a testosterone level 0.5 ng/mL. Luteinizing hormone releasing hormone agonist therapy was continued, if required to maintain castrate levels of testosterone. Patients had to be not taking antiandrogens for a minimum of 4 weeks for flutamide and 6 weeks for bicalutamide or nilutamide. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 and life expectancy of 12 weeks or more were eligible. Patients were required to have adequate bone marrow, liver, and renal function. Patients who had received any previous chemotherapy for metastatic disease were excluded. Previous therapy with abiraterone or enzalutamide or both was permitted. Other key exclusion criteria included uncontrolled brain or leptomeningeal metastases, uncontrolled diabetes mellitus, congestive heart failure (New York Heart Association class III or IV), significant cardiac arrhythmias, baseline QTc $\geq$ 470 ms, known hypersensitivity to sst analogues, or previous exposure to any component of the SOM230 or octreotide long-acting release formulations. Any other significant comorbidities, that in the investigator's judgement would render the subject inappropriate for entry into this study were also considered exclusion criteria.

Treatment Plan

Docetaxel was given at a dose of 75 mg/m² intravenously every 21 days along with prednisone 5 mg orally twice daily. Pasireotide was given as a long-acting intramuscular injection every 28 days. Starting dose (level 1) was 40 mg. The dose levels 2 and 3 were 60 mg and 80 mg, respectively. A cohort of 3 patients each was treated for 56 days with escalating doses of SOM230 according to the dose levels defined (Table 1) until dose-limiting toxicity (DLT) was observed. The MTD was defined as the dose level at which 0 or 1 of 6 patients experienced DLT with at least 2 patients experiencing DLT at the next higher dose level. If the initial 3 patients in each dose level did not demonstrate DLT then therapy was escalated to the next dose level. If 1 of 3 patients demonstrated DLT then 3 additional patients were treated at the same dose level. If 2 or more patients had DLT at a given dose level, then this was considered the maximum administered dose and patients were then treated at 1 dose level lower, which was considered the MTD. The time period for DLT monitoring was 56 days because this was the time required to establish steady state of SOM230. Toxicities requiring dose modifications of prednisone were not considered DLT.

Toxicities were evaluated weekly for the first 8 weeks and subsequently, on days of administration of docetaxel or pasireotide therapy. Radiologic evaluation was performed every 12 weeks with scans, and PSA levels were checked every 21 days.

Dose-Limiting Toxicity

Dose-limiting toxicity was defined as any 1 of the following occurrences if they were considered at least possibly related per treating physician, to either docetaxel or SOM230 during the first 56 days of therapy:

- (1) Absolute neutrophil count nadir $< 500/\text{mm}^3$ for > 7 -day duration or occurrence of febrile neutropenia.
- (2) Platelet count $< 50,000$ for > 7 -day duration or platelet count $< 50,000$ of any duration with clinically significant bleeding.
- (3) Persistent fasting hyperglycemia of Grade > 3 , despite optimal therapy.
- (4) Other Grade ≥ 3 nonhematologic toxicities attributable to therapy, except alopecia, fatigue, nausea, and emesis, except for Grade ≥ 3 fatigue (unrelieved by rest and limiting self-care activities of daily living) lasting > 7 days or Grade ≥ 3 emesis that lasted > 5 days despite optimal medical therapy.

Pharmacodynamic Correlative Studies

Prostate-specific antigen, CTC count, IGF-1 chromogranin A, and NSE were assessed at baseline (day 1), day 22, and day 43.

Pharmacokinetics

Pharmacokinetic evaluations for docetaxel as well as pasireotide were performed. Samples or standards were incubated with I-125 tracer for pasireotide and antiserum. After incubation, the immunological complexes were captured by the addition of antirabbit coated magnetic beads. After elimination of unbound fraction by washing, the bound radioactivity was determined in a gamma counter. A radioimmunoassay on the basis of the competition between I-125-pasireotide and pasireotide for a fixed number of antibody binding sites was determined.

Statistical Methods.—Descriptive statistics were calculated to summarize the demographic, clinical, correlative, and outcome variables. Multiple box plots were used to display the summary statistics and outliers of the correlates. Point estimates of RRs and Wilson type (2-sided) confidence intervals (CIs) were calculated using Stata 14 software (StataCorp, College Station, TX). The 90% CI was used for the full study population (approximately 18 patients), and the 80% CI was used for the small subsets (eg, by neuroendocrine status) of 8–10 patients each. All other statistical analyses were performed and statistical graphics generated using SAS 9.4 software (SAS Institute Inc, Cary, NC). Proportions of patients with visceral disease were compared according to neuroendocrine status using Fisher exact test (2-sided).

Response and progression was assessed per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria for patients with measurable disease and PSA response was assessed per PSA working group 2 guidelines.¹⁴ TTP was measured from treatment start date to the first date of documented progression, whether according to PSA level or imaging. Patients not experiencing progression were censored for TTP as of the date of their last PSA or imaging result. OS was measured from treatment start date to the date of death from any cause. Patients were censored for OS as of the last date on which they were confirmed to be still alive. Patients were followed for progression and survival every 3 months, for a maximum of 24 months after discontinuing protocol therapy. Standard KaplanMeier (K-M) estimates of the censored TTP and OS distributions were computed, with the error in those distributions expressed graphically using the HalleWellner confidence band, with the 90% CI. Because of the small sample size, TTP and OS summary statistics (eg, median) were estimated more conservatively using linear interpolation among successive event times on the K-M curves.¹⁵ TTP and OS distributions were compared according to neuroendocrine status and dichotomized correlative biomarkers using the generalized Wilcoxon test. Biomarker multiple comparisons adjustment was performed using the false discovery rate of Benjamini and Hochberg.

A purely exploratory analysis of the association of each of the correlates with clinical outcome (TTP and OS) was performed using all of the patients via univariable Cox regression models. Point and 90% CI estimates of the hazard ratio (HR) were calculated. When subsets (eg, according to neuroendocrine status) were examined, the 80% CI was used for CI estimates of the HR. The proportional hazards assumption was examined for each of the dichotomized correlates by inspection of log(-log) survival time plots, and inspection of smoothed hazard functions estimated with the Epanechnikov kernel smoother. When the association of change (from day 1 to day 43) in correlates was analyzed in relationship to duration of TTP or duration of OS, the landmark method was used (with a landmark time of 43 days) to ensure that the putative cause and effect sequence was preserved. This restriction resulted in negligible loss of effective sample size for those 10 Cox models of change in levels of the correlative biomarkers. Only 1 patient had to be excluded from the landmark method Cox model analysis of TTP, and none for OS. Absolute change (in number of cells) was computed for CTC count. Relative change (ie, percentage) was computed for the other 4 correlates. Change in a correlative can be either negative or positive, and the resulting dichotomizing cut points were negative for all 5 change distributions.

Results

Patient Characteristics

Between December 2011 and October 2014, 18 patients were enrolled in the study. Patient characteristics are outlined in Table 1. The mean age of the patients was 65 years, most of them were Caucasian (61%), with excellent ECOG PS (94% PS 1 and 6% PS 0). Six patients (33%) were African American. All of the patients were chemotherapy naive but had received multiple other treatments including novel therapies as well as clinical trial-based medications. Three patients received previous enzalutamide and 5 patients received previous abiraterone and prednisone. Ten patients had received previous radiation therapy to the

prostate and 7 had previous radical prostatectomy. Eight patients had neuroendocrine features defined as having any of the following: small cell histology or development of visceral metastasis in the presence of a PSA < 4 or a serum chromogranin A level > 5 times the upper limit of normal and/or NSE > 2 times the upper limit of normal. These criteria were used with the goal of assessing clinical outcomes with this therapy in mCRPC with small cell like clinical presentation also known as the anaplastic variant of prostate adenocarcinoma, and the mixed neuroendocrine carcinoma/acinar adenocarcinoma of the prostate per the morphologic classification of prostate cancer with neuroendocrine differentiation.¹⁶ Visceral disease was more frequent among the 7 neuroendocrine patients (63%) than among the 10 non-neuroendocrine patients (20%), but the difference was not statistically significant.

Toxicity

Two patients had dose-limiting toxicities at the 80-mg intramuscular dose of pasireotide. One patient had Grade 4 amylase elevation and the other had Grade 3 hyperglycemia requiring hospitalization. Twelve patients were evaluated at the 60 mg dose, and toxicities are summarized in Table 2. Grade 3 hyperglycemia was noted in 3 patients, hypertension in 2 patients, hypotension in 1, and hypophosphatemia in 3 patients, each of which was attributed to pasireotide. None of the patients experienced Grade 4 or 5 toxicities. Three hospitalizations because of hyperglycemia were deemed to be either probably or definitely related to SOM230. One hospitalization with urinary tract infection was attributed as probably related to docetaxel and prednisone.

Efficacy

Response was assessed in all 18 patients on the basis of PSA as well as measurable disease per RECIST criteria (Table 3). A partial RR of 43% was noted in 3 of 7 patients with measurable disease (Figure 1). PSA response for a nadir of $\geq 30\%$ was shown in 89% of the 18 patients (Figure 1). All patients were evaluable for TTP and OS (Figure 2). Median TTP was 7.2 months (90% CI, 3.8–8.2) and median OS was 18.3 months (90% CI, 15.0–29.7).

The 8 patients with neuroendocrine features had median TTP of 4.5 months (80% CI, 1.7–7.7) and median OS of 15.7 months (80% CI, 5.8–19.0 months). The 10 patients without neuroendocrine features had a median TTP of 8.3 months (80% CI, 4.0–8.6) and a median OS of 20.8 months (80% CI, 13.2–26.1; Figure 3).

Pharmacokinetic Results

Docetaxel clearance determined from the present study appeared to be 3- to 4-fold higher than the data reported in the literature. It is possible that coadministration of SOM230 changed the docetaxel PK, however, because single-agent docetaxel PK were not done, this finding cannot be confirmed. The SOM230 levels revealed that steady state was established in most patients by day 57. The median level at day 29 was 15.4 ng/mL (range, 4.75–46.1 ng/mL), at day 57 was 14.9 ng/mL (range, 5.15–34.2 ng/mL) and at day 85 was 14.5 ng/mL (range, 3.38–35.2 ng/mL).

Correlative Markers

The correlative markers tested on days 1, 22, and 43 consisted of PSA, CTC, IGF-1, NSE, and serum chromogranin A levels. Their summary statistics and outliers at each of the 3 time points are shown in Figure 4.

The results of exploratory Cox model analyses of baseline PSA and the baseline correlates are shown in Table 4. As an example for TTP, the first line indicates that a 100 ng/mL increase in baseline PSA was associated with a 16% increase in the risk of progression. An increase of only 10 units in baseline NSE was associated with a 56% increase in the risk of progression. The analogous results for OS are similar, and slightly stronger. All 10 of these exploratory Cox model results are only suggestive, although perhaps NSE is worthy of further investigation.

Baseline CTC count was dichotomized as: < 5 cells versus ≥ 5 cells (per 7.5 mL of blood) and was available on 15 patients. Baseline CTC was unfavorable (CTC ≥ 5) in 9 patients and favorable in 6 patients. Five of 9 (55%) converted to favorable CTC (< 5) post-therapy. Because of the small sample sizes, the other 4 baseline correlates (including PSA) were median dichotomized. For the 6 patients with baseline CTC count < 5 versus the 9 patients with baseline CTC count ≥ 5 we observed median OS estimates of 26.6 months and 14.6 months, respectively. Those results are similar to the findings of de Bono et al,¹⁷ who showed median OS in patients with CTC < 5 and ≥ 5 were 21.7 and 11.5 months, respectively. Table 5 summarizes the TTP and OS correlation with the 5 biomarkers; PSA, CTC, IGF-1, chromogranin A, and NSE, dichotomized at the median.

Discussion

Neuroendocrine or anaplastic prostate cancer remains a formidable challenge in the treatment of advanced prostate cancer. This component of prostate cancer is likely to be very aggressive and poorly differentiated and shows an explosive disease course and short life expectancy.¹⁵ Developing better regimens for the neuroendocrine component of prostate cancer to control it before the clinical manifestation was the goal of designing this combination. Combining pasireotide with docetaxel had shown preclinical therapeutic synergy and had the potential to control the lethal neuroendocrine component within prostate cancer.

This phase I trial showed that pasireotide can be safely combined with docetaxel and prednisone for the treatment of mCRPC. Although at the 80 mg dose, 2 patients did experience severe neutropenia and hyperglycemia, the combination was reasonably well tolerated at the 60 mg dose. Previously sst analogues have been studied with demonstrated clinical activity. Preclinical data revealed synergy of the combination of docetaxel and lanreotide in PC3 cell lines.¹³ Laboratory investigations have established a strong rationale for using sst receptor analogues in prostate cancer and have postulated multiple mechanisms for the synergy including IGF-1 blockade, modulating the sst receptors 2 and 5, overcoming P-glycoprotein mediated docetaxel resistance, and inducing proapoptotic proteins and inhibiting antiapoptotic proteins. A clinical trial was conducted randomizing patients with mCRPC to receive estramustine chemotherapy or a combination of lanreotide and steroids.¹⁸

The outcomes of pain control, PSA, and clinical response, and OS (18 months median OS) were no different between the 2 arms.

To our knowledge our study is the only clinical trial conducted in mCRPC to evaluate the efficacy of a combination of docetaxel, prednisone, and an sst receptor analogue. Our study established the tolerability of the combination and demonstrated relatively favorable outcomes within the neuroendocrine features subgroup. The PSA RR of 89% (30% decline) and measurable disease objective RR of 42% are noteworthy, especially because 8 of the 18 patients (44%) treated had neuroendocrine features. Unfortunately, the neuroendocrine markers were prognostic of worse OS outcome, but not predictive of a response to SOM230 therapy. This suggests that combination therapy should be considered earlier in the disease course to avert the clinical manifestations of neuroendocrine prostate cancer. The study has major limitations in determining efficacy. It is a phase I trial designed to evaluate the recommended phase II dose as the primary end point. The sample size is very limited and the study design is not conducive and adequately powered to determine efficacy. The omission of prednisone might have decreased the risk of hyperglycemia noted, however it was ethically concerning to deviate from an approved standard regimen of docetaxel and prednisone. The efficacy results could be entirely attributable to docetaxel and prednisone and the next step should be to compare the combination with a control arm of the standard docetaxel and prednisone regimen.

The combination of an sst receptor analogue-based combination therapy in mCRPC is worthy of further investigation. Treatment-related neuroendocrine-like prostate cancer has evolved into a well recognized entity.¹⁹ This condition has been reported typically after therapy with an androgen receptor axis targeted agent such as abiraterone or enzalutamide. This is an aggressive variant of prostate cancer that has a dismal prognosis with a reported median OS of < 6 months.¹⁹ The molecular features of amplification of MYCN and aurora kinase A expression have been well described, although clinical trials attacking these genomic targets have shown only modest efficacy.²⁰ Therapeutic strategies that would preempt or treat the clinical manifestation of neuroendocrine prostate cancer, represent a currently unmet need and the addition of pasireotide to chemotherapy is worthy of future exploration.

Conclusion

The combination of pasireotide and docetaxel was tolerable and showed preliminary efficacy. Future investigation of this regimen should be in comparison with docetaxel and prednisone with a focus on mCRPC with neuroendocrine features.

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Clinical Practice Points

- Pasireotide (SOM230) is an sst analogue that has shown clinical benefit in refractory neuroendocrine tumors.
- In prostate cancer, neuroendocrine differentiation is an aggressive form of disease with poor outcomes and lack of effective therapeutic options.
- Through this phase 1 trial we have shown the feasibility of combining pasireotide with docetaxel and prednisone with an acceptable toxicity profile.
- The combination showed preliminary efficacy and needs to be compared with docetaxel and prednisone.
- Future investigation of this regimen should be considered in metastatic prostate cancer with neuroendocrine features.

Figure 1. Waterfall Graph of Percent Prostate-Specific Antigen (PSA) Change and Percent Tumor Burden Change (Measurable Disease Patients Only) Per Response Evaluation Criteria in Solid Tumors version 1.1

Figure 2. Time to Progression and Overall Survival. (A) Kaplan-Meier Graph of Time to Progression of All 18 Study Patients. (B) Kaplan-Meier Graph of Overall Survival of All 18 Study Patients. All Patients Have Progressed; 5 Were Still Alive

Figure 3. Time to Event End Points According to Neuroendocrine Status. (A) Kaplan-Meier Graphs of Time to Progression. (B) Kaplan-Meier Graphs of Overall Survival. All Patients Have Progressed. Four Patients Without Neuroendocrine Disease and 1 Patient with Neuroendocrine Disease were Still Alive

Figure 4. Correlative Markers. (A) Log Base 10 of Circulating Tumor Cell (CTC) Count Plus 1. (B) Log Base 10 of Chromogranin A. (C) Insulin Like Growth Factor (IGF). (D) Log Base 10 of Neuron Specific Enolase (NSE)

Table 1

Baseline Patient Characteristics

Characteristic	Value
Median Age (Range)	65 years (49–75)
Race, n (%)	
Caucasian	11 (61)
African American	6 (33)
Other	1
Performance Status, n	
0	1
1	17
Median PSA (Range), ng/mL	259.9 (5.9–1119.0)
Neuroendocrine Features Present	8
Neuroendocrine Features Absent	10
Sites of Metastasis (All Patients Had Bone Metastasis)	
Bone only	6
Measurable disease	7
Visceral: lung/liver	6: 2 liver and 4 lung
Lymph nodes	7
Gleason Score^a	
8	11
7	6
Type of Progression	
Bone only	3
PSA only	7
Bone and PSA	8
Previous Treatment	
Radiation	10
Prostatectomy	7
Enzalutamide	3
Abiraterone	5

Data are presented as n except where otherwise noted.

Abbreviation: PSA = prostate-specific antigen.

^aGleason score not available for 1 patient.

Table 2

Toxicity of Pasireotide at MTD Dose Level of 60 mg

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Dehydration	0	0	1	0
Diarrhea	2	1	0	0
Dry Mouth	1	0	0	0
Electrocardiogram QT Corrected Interval Prolong	0	1	0	0
Hyperglycemia	0	0	3	0
Hyperkalemia	0	1	0	0
Hypertension	0	0	2	0
Hyponatremia	0	0	1	0
Hypophosphatemia	0	0	3	0
Hypotension	0	0	1	0
Injection Site Reaction	1	0	0	0
Rash Acneiform	1	0	0	0
Urinary Frequency	1	0	0	0

Data are presented as n.

Abbreviation: MTD = maximum tolerated dose.

Table 3

Response Rates for All Patients and Those With Neuroendocrine Features

Response Type	n	Response Rate, n (%)	90% Confidence Limits
All Patients			
Best response	18	8/18 (44)	0.27, 0.63
Best response, measurable disease	7	3/7 (43)	0.22, 0.64
PSA 30% ↓ at nadir	18	16/18 (89)	0.76, 0.95
PSA 50% ↓ at nadir	18	9/18 (50)	0.36, 0.64
PSA 90% ↓ at nadir	18	4/18 (22)	0.12, 0.37
Response Type	n	Response Rate, n (%)	80% Confidence Limits
Patients With Neuroendocrine Features			
Best response	8	2/8 (25)	0.11, 0.48
Best response, measurable disease	6	2/6 (33)	0.15, 0.59
PSA 30% ↓ at nadir	8	7/8 (88)	0.66, 0.96
PSA 50% ↓ at nadir	8	3/8 (38)	0.20, 0.60
PSA 90% ↓ at nadir	8	1/8 (13)	0.04, 0.34

Abbreviation: PSA = prostate-specific antigen.

Table 4

Hazard Ratios for Progression or for Death in Association With Specified Increases in Levels of Baseline (Day 1) Correlates

	n	Events, n	Increase in Correlate	Hazard Ratio	80% Confidence Limits
TTP					
PSA	18	18	100 ng/mL	1.16	1.06, 1.28
CTC	15	15	100 cells	1.05	0.97, 1.13
IGF	17	17	10 ng/mL	1.05	1.01, 1.10
Chromogranin A	17	17	100 ng/mL	1.04	0.99, 1.08
NSE	14	14	10 mcg/L	1.55	0.98, 2.45
OS					
PSA	18	13	100 ng/mL	1.17	1.04, 1.31
CTC	15	11	100 cells	1.21	1.09, 1.34
IGF	17	12	10 ng/mL	0.97	0.93, 1.02
Chromogranin A	17	12	100 ng/mL	1.07	1.02, 1.12
NSE	14	10	10 z-mcg/L	1.56	1.05, 2.34

Abbreviations: CTC = circulating tumor cells; IGF = insulin like growth factor; NSE = neuron-specific enolase; OS = overall survival; PSA = prostate-specific antigen; TTP = time to progression.

Table 5

Hazard Ratios for TTP and OS in Relation to Median Dichotomized Change (Day 43LDay 1) in Correlative Biomarkers

Biomarker (and Median Dichotomy)	TTP (Risk of Progression)				OS (Risk of Death)			
	n	Events, n	HR ^a	80% CI	n	Events, n	HR	80% CI
PSA (-26.44% vs. < -26.44%)	8	8	1.34	0.70–2.56	9	5	0.97	0.46–2.07
	9	9			9	7		
CTC (-29.5 cells vs. < -29.5 cells)	6	6	0.39 ^b	0.16–0.98	6	3	0.11 ^c	0.03–0.44
	6	6			6	5		
IGF (-65.64 % vs. < -65.64 %)	7	7	1.00	0.49–2.06	7	5	1.56	0.65–3.76
	8	8			8	5		
Chr (-21.43 % vs. < -21.43 %)	8	8	0.88	0.44–1.77	8	5	0.49	0.20–1.18
	7	7			7	5		
NSE (+8.00 % vs. < +8.00 %)	7	7	1.37	0.63–2.97	7	4	1.06	0.42–2.65
	6	6			6	5		

Abbreviations: Chr = chromogranin A; CTC = circulating tumor cells; CI = confidence interval for the hazard ratio; HR = hazard ratio; IGF = insulin like growth factor; NSE = neuron-specific enolase; OS = overall survival; PSA = prostate-specific antigen; TTP = time to progression.

^aHR = hazard ratio for patients in the upper half of the biomarker change distribution, compared with patients in the lower half of the biomarker change distribution.

^bHR significantly different from unity ($P = .1923$), without any adjustment for multiple comparisons.

^cHR significantly different from unity ($P = .0436$), without any adjustment for multiple comparisons.