Clinical and Correlative Results of SWOG S0354: a Phase II Trial of CNTO328 (siltuximab), a Monoclonal Antibody against Interleukin-6 (IL-6), in Chemotherapy Pre-treated Patients with Castration-Resistant Prostate Cancer (CRPC)

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Abstract

Purpose—IL-6 facilitates cancer cell survival via pleotrophic effects. We conducted a multicenter phase II study of CNTO328 (siltuximab) as second-line therapy for men with CRPC.

Experimental Design—Eligible men had CRPC treated with one prior chemotherapy. Subjects were treated with CNTO328 6 mg/kg IV every 2 weeks for 12 cycles. Response was assessed after every 3 cycles. Primary endpoint was PSA response rate (RR) defined as a 50% reduction. Accrual was planned in 2 stages, with 20 eligible patients in the first stage and 40 overall. Plasma cytokines and growth factors were measured by Luminex.

Results—53 eligible subjects had all received prior taxane therapy. Two (3.8%; 95% CI: 0.5%, 13.0%) had PSA response. None of the 31 patients with measurable disease had a RECIST response but 7 (23%) had stable disease (SD). With median follow-up of 14.8 months, median progression-free survival is 1.6 months (95% CI: 1.6, 1.7) and median overall survival was 11.6 months (95% CI: 7.5, 19.0). Grade 3/4 toxicities included DIC (1), CNS ischemia (1), elevated AST (1), gastritis/

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esophagitis (2), thrombocytopenia (2), pain (2), leukopenia (1), and neuropathy (2). Median baseline IL-6 levels were 12.5 pg/ml (IQR 2.5, 41.5). Patients with IL-6 >12.5 pg/mL had worse survival than those with levels < 12.5 pg/mL (53% vs 94%, p=.02). After treatment, IL-6 levels were > 250-fold higher. Thirty-two of 38 patients had a decline in C-reactive protein (CRP) plasma levels at 6 weeks.

Conclusions—CNTO328 resulted in a PSA RR of 3.8% and RECIST SD rate of 23%. Declining CRP levels during treatment may reflect biologic activity. Despite evidence of CNTOmediated IL-6 inhibition, elevated baseline IL-6 levels portended a poor prognosis.

INTRODUCTION

Background

Castration-resistant prostate cancer (CRPC) results in approximately 27,000 deaths annually in the United States (1). Although docetaxel plus prednisone has been shown to prolong survival (2,3) and provide palliation of symptoms (4), there is no standard treatment after failure of docetaxel. Clinical trials of standard chemotherapy agents in the second-line setting have yielded disappointing response rates, on the order of 20%, and overall survival remains poor (5,6). The development of novel therapies targeted at the unique biology of CRPC is an important priority.

Even after progression to castration resistance, signaling through the androgen receptor (AR) continues to drive prostate cancer (7). Interleukin-6 (IL-6) is one of many cytokines which can stimulate AR activity (8-10). In addition, IL-6 has been shown to affect prostate cancer cell proliferation, apoptosis, differentiation, and therapy resistance (11-13). It has been implicated in the unique interaction between prostate cancer cells and the bone marrow stroma (14). Higher levels of serum IL-6 have been associated with larger tumor burden, especially bone metastases, and inferior survival (15,16). In xenograft models, blocking IL-6 was found to increase apoptosis and induce tumor responses (17,18). Inhibition of IL-6 is a rational therapeutic concept for metastatic CRPC.

CNTO328 (siltuximab) is a chimeric (murine-human) IgG1 monoclonal antibody against IL-6. The Southwest Oncology Group completed an open-label phase II trial (ClinicalTrials.govIdentifier: NCT 00433446) to determine the response rate of CNTO328 as second-line therapy for metastatic CRPC. Molecular correlates included IL-6 and soluble gp130 (sgp130), since IL-6 signaling may occur via homodimerization of gp130 in the absence of IL-6 binding to cell-surface IL-6 receptors(19). C-reactive protein, a marker of systemic inflammation, as well as neuroendocrine markers chromogranin A (ChrA) and neuron-specific enolase (NSE), were assessed before and after treatment due to known effects of IL-6 on inflammation and promotion of neuroendocrine differentiation in prostate cancer cells (20). The final results of the clinical trial and correlative findings are presented herein.

METHODS

Eligibility

Men were eligible for participation in SWOG study S0354 if they had metastatic CRPC with disease progression and absolute PSA ≥ 5 ng/mL after one chemotherapy regimen. Prior radiation therapy and surgery were allowed. Prior flutamide or ketoconazole must have been stopped at least 28 days before registration; prior bicalutamide or nilutamide must have been stopped at least 42 days before registration. Patients were required to have adequate hematologic, renal, and hepatic function, and Zubrod performance status 0-2. All patients gave oral and written informed consent in accordance with institutional and federal guidelines. The protocol was approved by the Institutional Review Boards at participating institutions, and was monitored by the Data and Safety Monitoring Committee of the Southwest Oncology Group.

Treatment Plan

Subjects received CNTO328 6 mg/kg intravenously every 2 weeks, without premedication, for a maximum of 12 doses. Disease assessment with PSA was performed at each cycle; and radiographic restaging was performed after every 3 cycles (6 weeks). Treatment with CNTO328 was continued until completion of 12 cycles, progression of disease, symptomatic deterioration, unacceptable toxicity, or withdrawal of consent.

Statistical Methods

The primary endpoint was confirmed PSA response rate, defined as a 50% reduction in accordance with the recommendations of the original PSA Working Group(21). Confirmed PSA response was defined as PSA response at two or more time points at least 4 weeks apart, without objective disease progression or symptomatic deterioration. Secondary objectives were overall survival, progression-free survival, and RECIST response (among patients with measurable disease). Progression-free survival was defined as either tumor progression by RECIST criteria, PSA progression by PSA Working Group criteria, or symptomatic deterioration.

It was judged that this therapy would be of further interest if the confirmed PSA response rate were 20% or greater, while further testing would not be pursued if the confirmed PSA response rate were 5% or lower. A two-stage design for patient accrual was used. Twenty patients were to be accrued in the first stage. If at least 1 confirmed PSA response was observed among these patients, an additional 20 would be accrued. Among these 40 patients, if a confirmed PSA response rate of at least 13% were observed, the null hypothesis would be rejected, and this regimen would be considered for further study. This design has a significance level of 4.7% and a power of 92%. Because of a surge in accrual just before study closure, in order to maintain the same significance level the threshold for rejection of the null hypothesis was revised down to an observed confirmed PSA response rate of 11%. The power of this test based on the actual accrual was 96%. Overall and progression-free survival curves were plotted using the Kaplan-Meier method(22).

Correlative Studies

CRP levels were measured at baseline and after 3 cycles; other correlative markers were drawn at baseline and after 2 cycles. All plasma cytokine, chemokine, soluble receptor and growth factor measurements were performed using the Luminex Multi-Analyte Profiling (MAP) [Luminex Corp., Austin, TX]. This system is based on unique populations of micro beads, with each bead set containing a capture antibody to a specific soluble factor. The following multiplex kits were used: 39-plex human cytokine/chemokine panel (Cat# MPXHCYTO-60K) and 14-plex soluble receptor panel (Cat# HSCR-32K) [Millipore Corporation, Billerica, Massachusetts]. Analysis was conducted as previously described (23). Due to sample size limitations, the prognostic effect of any marker was explored by dividing the patient population into high and low expression groups, using the median baseline expression level as the threshold value. Associations between the baseline expression levels of these markers and OS were evaluated by Kaplan-Meier plots and the log-rank test.

RESULTS

Between July 2007 and January 2008, the initial cohort of 20 patients was accrued. A planned interim analysis revealed one confirmed PSA response, thereby opening the study to a second stage of accrual. Enrollment continued until May 2008, with a total of 62 patients registered; the over-accrual was due to rapid enrollment during the availability of the final slots for the trial. Nine men were ineligible due to prior treatments not allowed in the protocol (4), missing

baseline measurements (4), and inadequate renal function (1); these men did not receive study treatment, leaving 53 patients available for analysis.

The baseline and demographic characteristics of the study population are displayed in Table 1. All 53 eligible patients had received prior taxane therapy. The median number of cycles administered was 4 (range 2-12). Forty-four patients (83%) discontinued treatment due to disease progression; 4 (8%) discontinued due to toxicity and only 1 patient (2%) completed all 12 cycles of protocol therapy.

Toxicity is summarized in Table 2. Grade 4 toxicity included one case of DIC and one episode of cerebral ischemia. Grade 3 toxicities included elevated AST/ALT (1), gastritis/esophagitis (2), thrombocytopenia (2), pain (2), leukopenia (1) and neuropathy (2).

One subject had a confirmed PSA response and another patient had an unconfirmed PSA response, for an overall PSA response rate of 3.8% (95% CI: 0.5%, 13.0%). There were no RECIST responses, but 7 of 31 patients with measurable disease (23%) had stable disease for a median duration of 2.9 months (range 1.8-5.3 months). Kaplan-Meier curves of progression-free and overall survival are shown in Figures 1 and 2. All patients have progressed, with median progression-free survival of 1.6 months (95% CI 1.6, 1.7).Thirty-one patients have died, with median overall survival of 11.6 months (95% CI 7.5, 19.0). Median follow-up among the 22 surviving patients is 14.8 months.

Baseline levels and post-treatment change in selected correlative markers are presented in Table 3. Among the 31 patients with post-treatment measurements, IL6 levels increased dramatically after 2 cycles of treatment. A modest increase in IP10 levels was also observed, whereas sgp130 levels did not change appreciably. Median CRP levels declined after treatment. Among the 11 patients with post-treatment measurements, no appreciable changes in ChrA or NSE levels occurred. Elevated levels of IL-6 and IP10 at baseline were significantly associated with inferior survival (Figure 3a). In addition, lower levels of sgp130 and sEGFR were associated with inferior survival (Figure3b). None of the other 48 markers analyzed by Luminex were significantly associated with overall survival.

DISCUSSION

CNTO328 did not demonstrate significant activity as monotherapy in the treatment of CRPC after progression on taxane chemotherapy, yielding a low PSA response rate and short progression-free survival of under 7 weeks. For comparison, in the phase III trial of satraplatin in chemotherapy-refractory patients, of whom 51% had received prior Docetaxel and 20% had received mitoxantrone, the PSA response rate was 25% with a median progression free survival of 11.1 weeks(24). A randomized trial of ixabepilone or mitoxantrone for CRPC after progression on taxane chemotherapy documented PSA response rates of 17-20% with median time to progression of 2.3 months(5). Even combination chemotherapy has yielded modest response; a trial of ixabepilone plus mitoxantrone as second-line therapy for CRPC showed a PSA response rate of 31% (25). Studies of CNTO328 in combination with other agents may still be warranted, given its mild toxicity profile and drawing from the pre-clinical experience. In vitro data suggest that IL6 mediates resistance to Docetaxel chemotherapy(26) and concurrent inhibition of IL6 has been shown to sensitize prostate cancer cells to cytotoxic treatment (27). Specifically, in a mouse model of CRPC, treatment with CNTO328 enhanced the antitumor efficacy of Docetaxel at low and high doses (unpublished data, E. Keller, U Mich). Of note, 22 of 37 men (59%) treated with Docetaxel in combination with CNTO328 as part of an ongoing clinical trial have had a PSA response(28). In addition, laboratory data suggest that IL-6 increases androgen receptor expression(29) and may be involved in resistance

to anti-androgens(12), making it reasonable to assess the utility of CNTO328 in combination with androgen deprivation in future trials.

There were few adverse events above grade 2 during CNTO328 treatment; the most common toxicities were grade 1 or 2 fatigue, nausea, and leucopenia. The grade 4 event of disseminated intravascular coagulation (DIC) occurred during the 3rd treatment cycle in a 71-year old patient with bone metastases who developed grade 2 petechiae/purpura during cycle 1, but whose baseline platelet count was robust >300,000. He was taken off study with disease progression after the 3rd cycle, including development of a new bladder lesion. The second grade 4 adverse event was cerebrovascular ischemia, which occurred in a 77 year old man with diabetes and hypertension. His carotid arteries were not found to have significant atherosclerotic obstruction, and imaging revealed multiple areas of ischemia, which could indicate an embolic phenomenon. While malignancy itself increases the risk of thrombosis, we cannot exclude the possibility that these events were related to treatment with CNTO328. Nevertheless, it is difficult to draw a biological link between *inhibition* of IL6 and thrombosis, and in fact early phase studies of CNTO328 in multiple myeloma have been notable for fewer thrombotic events than were expected. In total, of 320 patients with malignancy who have received CNTO328 to date, only 4 thromboembolic events have been noted (1.3%) making a pro-thrombotic effect unlikely; the events seen in our trial were most likely related to underlying disease rather than protocol therapy.

Biologic activity of CNTO328 was demonstrated by our exploratory analysis of correlative markers. The significant elevation of IL-6 after treatment with CNTO328 is felt to represent the formation of antibody/analyte complexes, rather than a compensatory increase in secretion due to inhibition of the signal pathway. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), is associated with similar dramatic increases of its target ligand, and is thought to represent increased secretion compensating for decreased VEGF signaling (30). Unfortunately, it is not currently possible to distinguish free and bound IL6, so the underlying cause of the dramatic increase after treatment with CNTO328 cannot be determined. The reduction in CRP after treatment with CNTO328 may indicate biologic activity, since IL6 induces CRP secretion by hepatocytes (31). In previous studies of metastatic prostate cancer, elevated levels of CRP have been correlated with poor prognosis (32). However, baseline CRP levels were not correlated with survival in this small group of patients. Our study did confirm the significance of the IL-6 pathway in CRPC outcomes, as poor survival was predicted by both elevated baseline level of IL-6 and low level of sgp130. Soluble gp130 plays a key role in IL6 signaling, as it inhibits proliferation induced by IL-6 complexed with soluble IL6 receptor(19).

The analysis of a large panel of markers by Luminex has the limitation of yielding potentially false positive associations due to chance. Furthermore, in a single-arm study, it is not possible to distinguish between a predictive or prognostic role for any given biomarker. With these caveats in mind, soluble epidermal growth factor receptor (sEGFR) and IP10 emerged as markers which did not change over time, but whose baseline levels were associated with survival. Higher levels of sEGFR were associated with improved survival. This contrasts with prior reports that tissue levels of EGFR were not associated with clinical outcome in prostate cancer patients (33). Laboratory studies suggest a role for EGFR in prostate cancer progression, particularly in the bone (34), document cross-talk between the androgen receptor and EGFR (35,36), and suggest a positive relationship between prostate inflammation and EGFR expression (37), but provide no insight as to why elevated levels of sEGFR would correspond with improved survival. Interferon-inducible protein 10 (IP10) is a chemokine (also known as CXCL10) which has an inhibitory effect on angiogenesis (38). In our study population, higher levels were associated with inferior survival, which is counter-intuitive since over expression of IP10 was shown to reduce proliferation of LNCaP cells and decrease PSA production (39).

There was no clear relationship between baseline levels of sEGFR and IP10. These somewhat counterintuitive biomarker findings raise questions that need to be evaluated mechanistically, perhaps in preclinical models, and in other cohorts of men with CRPC.

The overall survival of this cohort was within the range of previous study populations, ranging from 10 months in the ixabepilone versus mitoxantrone trial (5) to 14 months in the satraplatin trial (24). While it is impossible to compare patient populations across trials, in the satraplatin trial, the majority of subjects had an ECOG performance status of 0 or 1 and 43% had measurable disease by RECIST criteria, similar to our study participants. Data were recently presented documenting a survival advantage for chemotherapy in the treatment of CRPC post-docetaxel for the first time, with cabazitaxel yielding a median survival of 15.1 months compared to 12.1 months for mitoxantrone (40). The median survival of 11.6 months for men treated with CNTO328 in this study does not suggest an improvement over that which has been achieved with chemotherapy in this setting. Pain palliation is an important second goal of chemotherapy for CRPC; future trials of CNTO328 will benefit from incorporating pain assessments, particularly since IL6 is thought to modulate nociception, as reviewed by De Jongh and colleagues(41).

In conclusion CNTO328, a monoclonal antibody to IL-6, demonstrated biologic activity but minimal clinical activity as monotherapy in the treatment of men with CRPC whose disease has progressed after Docetaxel chemotherapy. Additional studies of CNTO328 in combination with chemotherapy are underway.

Acknowledgments

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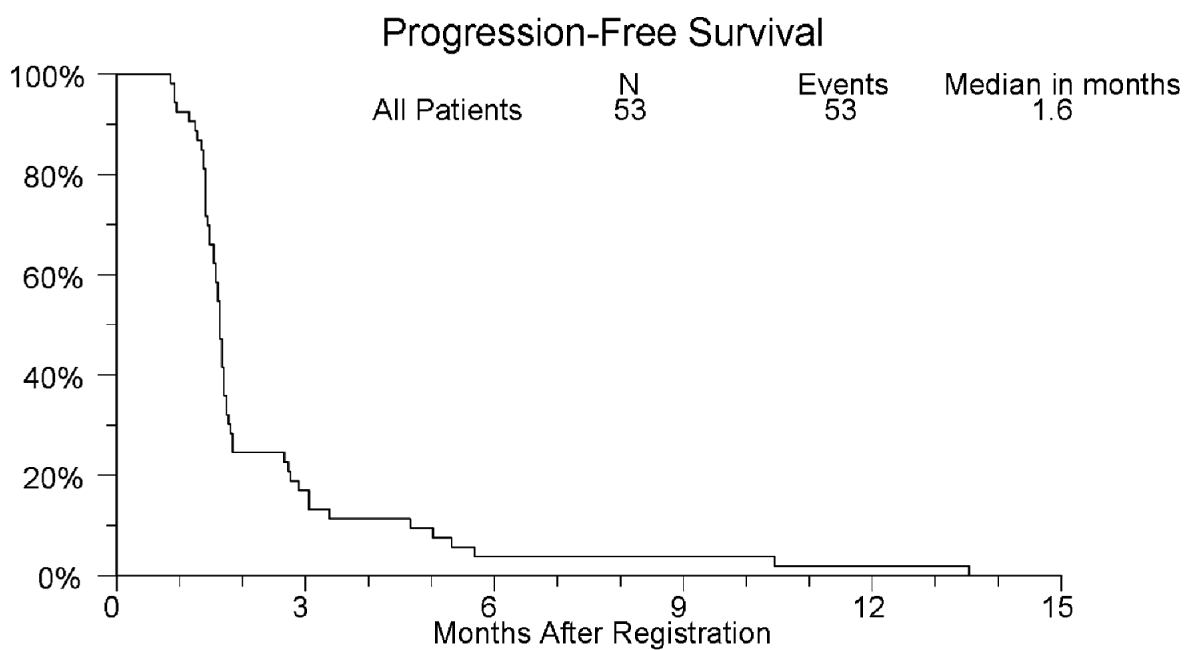
Progression-Free Survival

	N	Events	Median in months
All Patients	53	53	1.6

Figure 1.
The Kaplan-Meier curve for progression-free survival in chemotherapy pre-treated patients with castration-resistant prostate cancer treated with monoclonal antibody, CNTO328
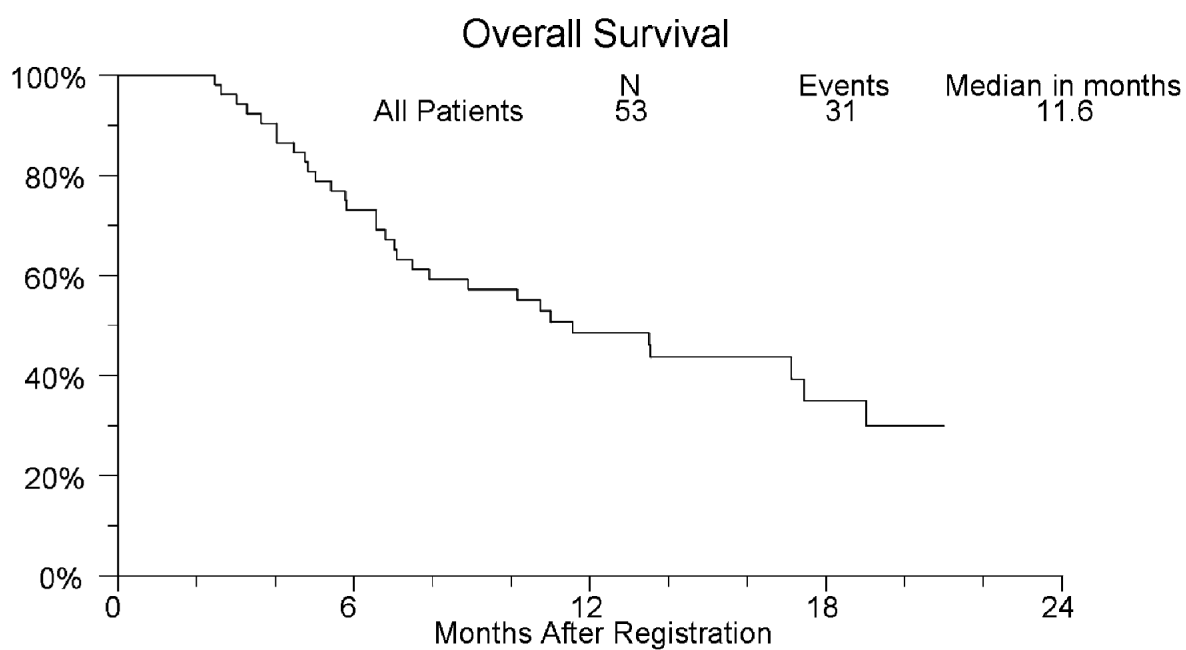
Figure 2.
The Kaplan-Meier curve for overall survival in chemotherapy pre-treated patients with castration-resistant prostate cancer treated with monoclonal antibody, CNTO328
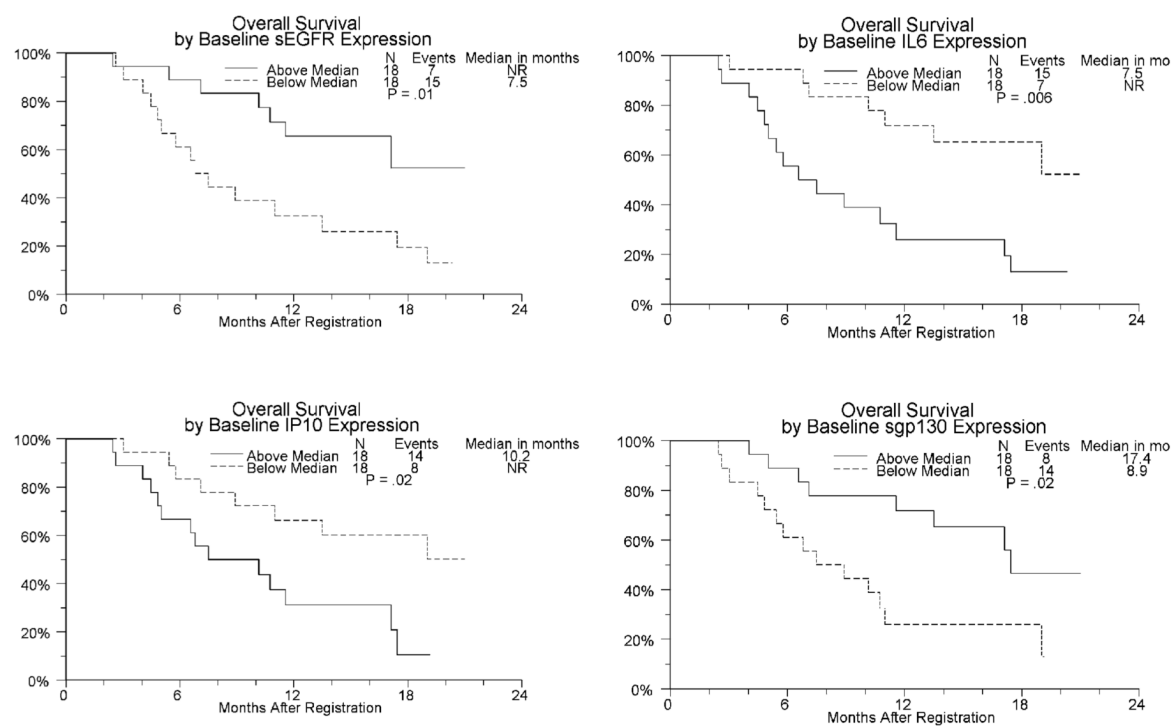
Figure 3.
Survival curves by baseline marker levels in chemotherapy pre-treated patients with castration-resistant prostate cancer treated with monoclonal antibody, CNTO328

Table 1

Baseline characteristics of study participants

	Median	Range
Age(years)	71	46-92
Baseline PSA(ng/dL)	75.1	6.3 – 10,181
	N	%
Performance Status		
0	19	36%
1	28	53%
2	6	11%
Measurable disease	48	91%
Prior Taxane therapy	53	100%
Race		
White	49	92%
Other	4	8%

Table 2

Treatment-related adverse events

Toxicity Category	Grade 1 / 2	Grade 3 / 4
Allergic reaction	2	0
Bone Marrow Anemia Leucopenia Thrombocytopenia	9 13 5	0 1 2
Coagulation	1	1
Fatigue	23	0
Dermatologic	7	0
GI Constipation/Diarrhea Nausea / Vomiting Gastritis / Esophagitis	6 15 3	0 0 1
Metabolic LFTs Electrolytes	9 3	2 0
Neurologic	11	2
Pain	6	2
Pulmonary	7	0

Table 3

Baseline and post-treatment correlative marker measurements

	N	**Median Baseline Level (range)**	**Median Post-Treatment Level (range)**[**]	**Median Change (%)**
CRP (mg/dL)	38	1.3 (0.5, 2.6)	0.2 (0.1, 0.8)	−79
IL-6 (pg/m L)	31	12.0 (1.6, 33.0)	4831 (3450, 8637)	48071
sgp130 (ng/m L)	31	136 (106, 165)	158 (127, 176)	9.4
sEGFR (ng/m L)	31	33.8 (27.1, 42.5)	35.7 (27.3, 42.8)	−0.1
IP10 (ng/m L)	31	0.6 (0.4, 0.8)	0.9 (0.6, 1.3)	48
NSE (μg/L)	11	4.8 (2.2, 34.0)	4.5 (1.0, 33.9)	−28
ChrA (μg/L)	11	14.8 (12.2, 15.9)	16.9 (11.9, 23.4)	20

[*] Among the subset of patients with both baseline and post-treatment measurements.

[**] Post-treatment CRP was measured after 3 cyc les (6 weeks); all other markers were measured after 2 cycles (4 weeks).