Clinical and Correlative Results of SWOG S0354: A Phase II Trial of CNTO328 (Siltuximab), a Monoclonal Antibody against Interleukin-6, in Chemotherapy-Pretreated Patients with Castration-Resistant Prostate Cancer

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Abstract

Purpose: Interleukin-6 (IL-6) facilitates cancer cell survival via pleiotrophic effects. We conducted a multicenter phase II study of CNTO328 (siltuximab) as second-line therapy for men with castration-resistant prostate cancer.

Experimental Design: Eligible men had castration-resistant prostate cancer treated with one prior chemotherapy. Subjects were treated with 6 mg/kg CNTO328 i.v. every 2 weeks for 12 cycles. Response was assessed after every three cycles. Primary end point was prostate-specific antigen (PSA) response rate defined as a 50% reduction. Accrual was planned in two stages, with 20 eligible patients in the first stage and 40 overall. Plasma cytokines and growth factors were measured by Luminex.

Results: Fifty-three 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 Evaluation Criteria in Solid Tumors) response but 7 (23%) had stable disease. With median follow-up of 14.8 months, median progression-free survival was 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 disseminated intravascular coagulation (1), central nervous system ischemia (1), elevated aspartate aminotransferase (1), gastritis/esophagitis (2), thrombocytopenia (2), pain (2), leukopenia (1), and neuropathy (2). Median baseline IL-6 levels were 12.5 pg/mL (interquartile range, 2.5-41.5). Patients with IL-6 >12.5 pg/mL had worse survival than those with levels <12.5 pg/mL (53% versus 94%; P = 0.02). After treatment, IL-6 levels were >250-fold higher. Thirty-two of 38 patients had a decline in C-reactive protein plasma levels at 6 weeks.

Conclusions: CNTO328 resulted in a PSA response rate of 3.8% and a RECIST stable disease rate of 23%. Declining C-reactive protein levels during treatment may reflect biological activity. Despite evidence of CNTO-mediated IL-6 inhibition, elevated baseline IL-6 levels portended a poor prognosis.

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 symptomatic (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 continues to drive prostate cancer (7). Interleukin-6 (IL-6) is one of many cytokines that can stimulate androgen receptor 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

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Translational Relevance

Interleukin-6 (IL-6) is a target of particular interest in prostate cancer due to its pleiotrophic effects on proliferation, differentiation, and therapy resistance. This phase II clinical trial of CNTO328, an antibody against IL-6, in men with taxane-refractory castration-resistant prostate cancer, documents biological activity with reduced C-reactive protein but no significant clinical activity. The toxicity profile of the agent is described. Correlative studies show a dramatic increase in plasma IL-6 after treatment and confirm the poor prognosis associated with elevated IL-6 at baseline. Insights gained from this trial will influence the design of future trials targeting this pathway.

Materials and Methods

Eligibility

Men were eligible for participation in SWOG study S0354 if they had metastatic CRPC with disease progression and absolute prostate-specific antigen (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 functions and a Zubrod performance status of 0 to 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 SWOG.

Table 1. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (range)</td>
<td>71 (46-92)</td>
</tr>
<tr>
<td>Baseline PSA (ng/dL), median (range)</td>
<td>75.1 (6.3-10,181)</td>
</tr>
<tr>
<td>Performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (36)</td>
</tr>
<tr>
<td>1</td>
<td>28 (53)</td>
</tr>
<tr>
<td>2</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Measurable disease, n (%)</td>
<td>48 (91)</td>
</tr>
<tr>
<td>Prior taxane therapy, n (%)</td>
<td>53 (100)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>49 (92)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

Treatment plan

Subjects received 6 mg/kg CNTO328 i.v. every 2 weeks, without premedication, for a maximum of 12 doses. Disease assessment with PSA was done at each cycle, and radiographic restaging was done after every three 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 end point 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 Evaluation Criteria in Solid Tumors) response (among patients with measurable disease). Progression-free survival was defined as 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, whereas 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 one 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, to maintain the same significance level, the threshold for rejection of the null hypothesis was revised.

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 (SWOG) completed an open-label phase II trial (ClinicalTrials.gov identifier: 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), as 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 (CRP), a marker of systemic inflammation, and neuroendocrine markers chromogranin A and neuron-specific enolase 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.
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 three cycles; other correlative markers were drawn at baseline and after two cycles. All plasma cytokine, chemokine, soluble receptor, and growth factor measurements were done using the Luminex Multi-Analyte Profiling (Luminex Corp.). This system is based on unique populations of microbeads, 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 and 14-plex soluble receptor panel (Millipore Corporation). 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 overall survival 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 overaccrual 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 disseminated intravascular coagulation and one episode of cerebral ischemia. Grade 3 toxicities included elevated aspartate aminotransferase/alanine aminotransferase (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, 1.6-5.3 months). Kaplan-Meier curves of progression-free and overall survival are shown in Figs. 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 posttreatment change in selected correlative markers are presented in Table 3. Among the 31 patients with posttreatment measurements, IL-6 levels increased dramatically after two cycles of treatment. A modest increase in IFN-inducible protein 10 (IP10) levels was also observed, whereas sgp130 levels did not change appreciably. Median CRP levels declined after treatment. Among the 11 patients with posttreatment measurements, no appreciable changes in chromogranin

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**Table 2. Treatment-related adverse events**

<table>
<thead>
<tr>
<th>Toxicity category</th>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td>v</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Coagulation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation/diarrhea</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Gastritis/esophagitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Fig. 1.** The Kaplan-Meier curve for progression-free survival in chemotherapy-pretreated patients with CRPC treated with the monoclonal antibody CNT0328.
Elevated levels of IL-6 and IP10 at baseline were significantly associated with inferior survival (Fig. 3A). In addition, lower levels of sgp130 and soluble epidermal growth factor receptor (sEGFR) were associated with inferior survival (Fig. 3B). None of the other 48 markers analyzed by Luminex were significantly associated with overall survival.

**Discussion**

CNTO328 did not show significant activity as monotherapy in the treatment of CRPC after progression on taxane chemotherapy, yielding a low PSA response rate and a short progression-free survival of less than 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% to 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 preclinical experience. *In vitro* data suggest that IL-6 mediates resistance to docetaxel chemotherapy (26), and concurrent inhibition of IL-6 has been shown to sensitize prostate cancer cells to cytotoxic treatment (27). 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 antiandrogens (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 leukopenia. The grade 4 event of disseminated intravascular coagulation occurred during the third treatment cycle in a 71-year-old patient with bone metastases who developed grade 2 petechia/purpura during cycle 1, but whose baseline platelet count was robust, >300,000. He was taken off study with disease progression after the third 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. Although 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 IL-6 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

![Image](image1.png)

**Table 3.** Baseline and posttreatment correlative marker measurements

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sample Size</th>
<th>Median Baseline Level (Range)</th>
<th>Median Posttreatment Level (Range)*</th>
<th>Median Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dL)</td>
<td>38</td>
<td>1.3 (0.5-2.6)</td>
<td>0.2 (0.1-0.8)</td>
<td>−79</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>31</td>
<td>12.0 (1.6-33.0)</td>
<td>4,831 (3,450-8,637)</td>
<td>48,071</td>
</tr>
<tr>
<td>sgp130 (ng/mL)</td>
<td>31</td>
<td>136 (106-165)</td>
<td>158 (127-176)</td>
<td>9.4</td>
</tr>
<tr>
<td>sEGFR (ng/mL)</td>
<td>31</td>
<td>33.8 (27.1-42.5)</td>
<td>35.7 (27.3-42.8)</td>
<td>−0.1</td>
</tr>
<tr>
<td>IP10 (ng/mL)</td>
<td>31</td>
<td>0.6 (0.4-0.8)</td>
<td>0.9 (0.6-1.3)</td>
<td>48</td>
</tr>
<tr>
<td>NSE (μg/L)</td>
<td>11</td>
<td>4.8 (2.2-34.0)</td>
<td>4.5 (1.0-33.9)</td>
<td>−28</td>
</tr>
<tr>
<td>ChrA (units/L)</td>
<td>11</td>
<td>14.8 (12.2-15.9)</td>
<td>18.9 (11.9-23.4)</td>
<td>20</td>
</tr>
</tbody>
</table>

*Abbreviations: ChrA, chromogranin A; NSE, neuron-specific enolase.*

*Among the subset of patients with both baseline and posttreatment measurements.

†Posttreatment CRP was measured after three cycles (6 wk); all other markers were measured after two cycles (4 wk).
received CNTO328 to date, only 4 thromboembolic events (1.3%) have been noted, making a prothrombotic effect unlikely; the events seen in our trial were most likely related to underlying disease rather than protocol therapy.

The biological activity of CNTO328 was shown 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, is associated with similar dramatic increases of its target ligand and is thought to represent increased secretion compensating for decreased vascular endothelial growth factor signaling (30). Unfortunately, it is not currently possible to distinguish free and bound IL-6, and thus the underlying cause of the dramatic increase after treatment with CNTO328 cannot be determined. The reduction in CRP after treatment with CNTO328 may indicate biological activity because IL-6 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 confirmed 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 IL-6 signaling, as it inhibits proliferation induced by IL-6 complexed with soluble IL-6 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 and a prognostic role for any given biomarker. With these caveats in mind, sEGFR and IP10 emerged as markers that 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. IP10 is a chemokine (also known as CXCL10) that has an inhibitory effect on angiogenesis (38). In our study population, higher levels were associated with inferior survival, which is counterintuitive because overexpression 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 ibexap squirrel versus mitoxantrone trial (5) to 14 months in the satraplatin trial (24). Although it is impossible to compare patient populations across trials, in the satraplatin trial, the majority of subjects had an Eastern Cooperative Oncology Group 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-docolxetaxel for the first time, with cabazitaxel yielding a median survival of 15.1 months compared with 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 because IL-6 is thought to modulate nociception, as reviewed by De Jongh and colleagues (41).

In conclusion, CNTO328, a monoclonal antibody to IL-6, showed biological 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 under way.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Clinical Cancer Research

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