Randomized Phase 2 Trial of Custirsen (OGX-011) in Combination with Docetaxel or Mitoxantrone as Second-line Therapy in Patients with Metastatic Castrate-Resistant Prostate Cancer Progressing after First-line Docetaxel: CUOG Trial P-06c

Fred Saad1, Sebastien Hotte2, Scott North3, Bernie Eigl4, Kim Chi5, Piotr Czaykowskki6, Lori Wood7, Michael Pollak8, Scott Berry9, Jean-Baptiste Lattouf1, Som D. Mukherjee2, Martin Gleave10, Eric Winquist11, for the Canadian Uro-Oncology Group

From the 1CRCUM-Université de Montréal, Montréal, QB; 2Juravinski Cancer Centre, Hamilton, ON; 3Cross Cancer Institute, Edmonton, AB; 4Tom Baker Cancer Centre, Calgary, AB; 5British Columbia Cancer Agency, Vancouver, BC; 6Cancer Care Manitoba, Winnipeg, Manitoba; 7Queen Elizabeth II Health Sciences Centre, Halifax, NS; 8Jewish General Hospital, Montreal, QB; 9Odette Cancer Centre, Toronto, ON; 10Vancouver Prostate Centre, Vancouver, BC; and 11London Health Sciences Centre, London, ON.

Corresponding author:
Fred Saad MD
1560 Sherbrooke East
Montreal, Quebec, Canada
H2L4M1.
Tel. 514-890-8000 ext 27466
e-mail: fred.saad.chum@ssss.gouv.qc.ca

Financial support: Grant in aid to CUOG from OncoGenex and Sanofi Aventis
STATEMENT OF TRANSLATIONAL RELEVANCE

Many strategies used to induce the apoptosis of cancer cells also induce stress-responses that activate survival pathways and promote emergence of a treatment resistant phenotype. Clusterin (CLU) is a stress-activated cytoprotective chaperone up-regulated by a variety of anti-cancer therapies that confers treatment resistance when over-expressed. Preclinical studies have shown that targeted knockdown of CLU enhances the effects of cytotoxic drugs, including docetaxel, in docetaxel-refractory cells. This clinical trial provides evidence that combining custirsen with chemotherapy is feasible in patients with progressive mCRPC following first-line docetaxel therapy and, as pain relief was higher than expected, provided some proof-of-principle of enhanced docetaxel activity. Moreover, it reaffirms that custirsen treatment significantly decreases levels of its target protein, CLU, and for the first time identifies correlations between serum CLU and survival that support further evaluation of serum CLU as a predictive biomarker. Two phase 3 trials evaluating custirsen plus docetaxel are currently ongoing.
ABSTRACT

**Purpose:** Clusterin (CLU) is an anti-apoptotic, stress-induced protein conferring treatment resistance when overexpressed. This study tested custirsen, a CLU inhibitor, in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing during or within six months of initial docetaxel therapy.

**Patients and Methods:** Men were randomized to receive either docetaxel+prednisone+custirsen (DPC) or mitoxantrone+prednisone+custirsen (MPC).

**Results:** Forty-two patients received study treatment. Toxicity was similar in both arms. Twenty patients treated with DPC received a median of eight cycles; overall survival was 15.8 months. Median time to pain progression (TTPP) was 10.0 months; 10 of 13 (77%) evaluable patients had pain responses. Three of 13 (23%) evaluable patients had objective partial responses. PSA declines of ≥90%, ≥50%, and ≥30% occurred in 4 (20%), 8 (40%) and 11 (55%) patients, respectively.

Twenty-two patients treated with MPC received a median of six cycles; overall survival was 11.5 months. The median TTPP was 5.2 months; 6 of 13 (46%) evaluable patients had pain responses. No objective responses were observed. PSA declines of ≥50% and ≥30% occurred in 6 (27%) and 7 (32%) patients, respectively.

Low serum CLU levels during treatment showed superior survival for patients using modeling with proportional hazard regression with a time-dependent covariate and different landmarks.

**Conclusion:** Custirsen plus either docetaxel or mitoxantrone was feasible in patients with progressive mCRPC following first-line docetaxel therapy. Pain relief was higher than expected, with interesting correlations between serum CLU and survival. A phase 3 trial evaluating the pain palliation benefit of custirsen with taxane therapy is ongoing.
INTRODUCTION

Docetaxel is standard first-line chemotherapy for men with metastatic castration-resistant prostate cancer (mCRPC) (1, 2). With progression, survival is less than one year (3-6). Second-line treatment with mitoxantrone and retreatment with docetaxel are commonly used despite limited data on safety and efficacy. A pressing need exists for novel therapeutics that target the molecular basis of treatment resistance in mCRPC. Experimental and clinical studies have associated elevated clusterin (CLU) levels with development of treatment resistance in prostate, lung, breast, ovarian and other cancers (7-12). CLU is a stress-induced, cytoprotective chaperone (8-13) up-regulated to inhibit cell death that confers broad-spectrum resistance by inhibiting protein aggregation and proteotoxic stress, cytochrome C release, and Bax and caspase activation (13-18). CLU is an attractive candidate for inhibition at the mRNA level.

Custirsen, a second-generation antisense oligonucleotide (ASO), has high affinity for CLU RNA, with increased potency, and a prolonged tissue half-life compared to first-generation ASOs. Custirsen potently suppresses CLU levels both in vitro and in vivo (19, 20). In preclinical CRPC prostate cancer models, treatment with custirsen increased tumor cell death and improved chemosensitivity to multiple drugs, including docetaxel and mitoxantrone (19, 21-25). A phase I study used a novel neo-adjuvant designed to identify the optimal biologic dose for custirsen in prostate cancer tissue (26). CLU levels decreased in a dose-dependent manner, with 92% knockdown of CLU protein and mRNA at the 640 mg dose; the mean apoptotic indices increased three-fold. The primary objective of the current study was to evaluate the safety of treating patients with mCRPC who progressed after first-line docetaxel chemotherapy with custirsen and prednisone in combination with either docetaxel (DPC) or mitoxantrone (MPC). The DPC arm of the study was motivated by preclinical data that custirsen re-sensitizes docetaxel-refractory prostate cancer cells to docetaxel (25).
PATIENTS AND METHODS

Study Design

This was an open-label, non-comparative, randomized study at 10 Canadian sites to evaluate the safety and efficacy of two second-line treatments for mCRPC. The primary endpoint was safety. Exploratory endpoints analyzed included measures of efficacy [pain response and time to pain progression (TTPP); prostate-specific antigen (PSA) response; measurable disease response; progression-free survival (PFS); and overall survival (OS)] and the relationship between serum CLU levels and survival.

Eligibility Criteria

Patients had a histological diagnosis of adenocarcinoma of the prostate, metastatic disease by imaging and ≥2 cycles of first-line docetaxel-based chemotherapy, with disease progression documented within six months of discontinuing treatment. Patients had a Karnofsky performance status ≥60%, adequate organ function and had recovered from prior therapy-related toxicity to ≤grade 2. Documentation and maintenance of a castrate serum testosterone level was required. Exclusion criteria included other active malignancies, congestive heart failure and central nervous system metastases. No change in current bisphosphonate usage was permitted. All patients provided written informed consent, and the study was approved by local Research Ethics Boards.

Treatment Plan

Custirsen, 640 mg, (supplied by OncoGenex Technologies Inc, Vancouver, BC, Canada) was administered intravenously (IV) three times during a nine-day loading-dose period followed by once weekly administration. Premedication included ibuprofen or acetaminophen. Either docetaxel 75mg/m² IV over 60 minutes or mitoxantrone 12 mg/m² IV over 30 minutes was administered on Day 1 of each 21-day cycle. Patients were pre-medicated with corticosteroids and received 5 mg of prednisone orally twice daily unless they were intolerant of steroids. Study treatment was continued until completion of nine cycles; disease or prostate-cancer pain progression; need for radiation therapy; deterioration of performance status (PS); unacceptable toxicity; or
more than a three-week delay in treatment. Patients did not discontinue study therapy for PSA progression. Patients were followed every two months for survival. Growth factor administration and blood transfusions were at the discretion of the investigator. Bone and CT scans were obtained at baseline, every three cycles, and with symptoms of disease progression. Responses were confirmed ≥3 weeks after the initial scan. Blood tests and pain assessment data were collected prior to the first loading dose, on Day 1 of each cycle until progression and at an End-of-Treatment Visit.

Dose Modifications

Adverse events (AE) were graded according to the Common Terminology Criteria for Adverse Events v3.0. Dose modifications were made on Day 1 of each cycle. Patients were removed from therapy for recurrence of toxicity despite two dose-reductions or grade 4 life-threatening AEs. Docetaxel or mitoxantrone was held until recovery for a neutrophil count <1.5 x 10^9 cells/L or platelet count <100 x 10^9/L. The dose of either drug was reduced at the next cycle for grade 3/4 hematological toxicity lasting >7 days; febrile neutropenia or infection with neutropenia; and grade 4 thrombocytopenia or gross bleeding associated with a platelet count <50 x 10^9/L. Both drugs were held until recovery and subsequently dose-reduced or discontinued dependent on the level of increase in AST and/or bilirubin. Docetaxel or mitoxantrone was held and subsequently dose-modified for grade 4 non-life-threatening and any other grade 3 or prolonged grade 2 toxicity related to study treatment and considered to be clinically significant. Patients receiving mitoxantrone were removed from therapy for symptomatic congestive heart failure. Custirsen was dose-modified for hyponatremia.

Efficacy Analyses

Pain was assessed on an 11-point numeric rating worse pain scale (WPS) (27). Analgesics were coded according to the World Health Organization analgesic ladder which classifies analgesics into three levels: level 1: mild (non-opioids); level 2: moderate (codeine-class opioids); and level 3: strong (morphine class opioids) (28). Patients with a baseline WPS of ≥2 and/or receiving opioids were considered evaluable for pain response. Pain response was defined as ≥2-point reduction in the WPS from baseline without an increase in the analgesic level, or a reduction in the analgesic level from 3 to ≤2 or from 2 to ≤1, without an increase in the WPS, both maintained for ≥3
weeks. TTPP for all patients was defined as the time from start of study treatment to a ≥2-point increase from the average of all previous WPS scores; an increase in analgesic level from 0 or 1 to 2 or 3, or from level 2 to 3, both maintained for ≥3 week; or requirement for radiation therapy.

PSA response was defined as a decrease in PSA values of ≥50% relative to baseline on two or more consecutive measurements 4-6 weeks apart. Disease progression was defined as one or more of the following: measurable progression by RECIST, pain progression, and deterioration of performance status (PS), the latter two due to prostate cancer progression. Overall survival was defined as the time from the start of study treatment to the date of death. Overall survival time was censored at the date of the last follow-up for subjects who were still alive. Progression-free survival was defined as the time from the start of study treatment to the first documentation of disease progression or the date of death. Patients who failed to return for assessments or received new anti-cancer therapy were censored at the time of the last disease assessment.

**Serum Clusterin Analysis**

Serum CLU samples were collected at baseline and on Day 1 of each cycle. Samples were analyzed at Mayo Clinical Trial Services (Rochester, Minnesota) utilizing the BioVendor Clusterin ELISA kit, (Ann Arbor, Michigan), a solid-phase, enzyme-linked immunosorbent assay (ELISA) in microplate format designed for the quantitative measurement of human CLU in serum, plasma and CSF.

**Statistical Considerations**

The planned sample size was 20 patients per arm. With 20 patients, an AE with 10% probability of occurrence is highly likely to be observed at least once with 88% probability. Patients were centrally randomized in order to eliminate subjectivity in arm selection. The primary analysis set included patients who initiated both custirsen and chemotherapy. The primary endpoint was safety, reported as the percent of patients experiencing any serious or ≥grade 3 AE. Feasibility, reported as the median number of treatment cycles administered within treatment arms, was also of interest. Assessments for PSA response and TTPP were preplanned.
To evaluate the effect of custirsen on CLU, minimum CLU levels during treatment were compared to baseline levels using a two-sided paired t-test. In addition, exploratory analyses to assess the relationship between survival and serum CLU levels were performed using a proportional hazard regression procedure. A CLU response was defined as three successive CLU levels during therapy ≤ median baseline CLU for the population. Patients with <3 CLU levels during therapy were defined as non-responders. The starting survival model included the baseline CLU level (as above or below the baseline median), the chemotherapy arm, and a time-dependent variable indicating the start of response, and all interactions (three-way or below). The model reported is the most parsimonious hierarchical step-down model using a 0.1 criterion for exclusion of terms. Only patients with baseline and assessments through the Day 50 landmark (~Cycle 3 Day 1) were included in the analyses in order to reduce the bias related to censoring due to early deaths (29). Other patient selection criteria, including no landmark and a Day 30 landmark (~Cycle 2 Day 1), were evaluated in order to assess robustness of the conclusions.

To assess the consistency of the results, in addition to the hazard regression analysis, Kaplan-Meier estimates for three classifications of patients were plotted based on: median baseline CLU (≤ median vs > median); median minimum CLU (≤ median vs > median) for the population during treatment; and a threshold minimum CLU level ≤45 µg/mL (≤ vs >45 µg/mL) during treatment. Although several threshold minimum CLU levels were evaluated, 45 µg/mL was chosen as a value between the median baseline CLU level of 54 µg/mL and the median minimum CLU level of the population during treatment of 34 µg/mL. Survival by the above described classifications was compared using a median estimate and log-rank test.
RESULTS

Patient Characteristics and Demographics at Study Entry

Between July 2006 and April 2007, 45 patients were randomized (21 to the DPC arm and 24 to the MPC arm). Three patients (one in the DPC arm and two in the MPC arm) did not initiate both components of the study (custirsen and chemotherapy) and, therefore, were not included in the primary analysis set. Baseline characteristics of the 20 remaining patients in the DPC arm and 22 in the MPC arm are presented in Table 1. For the entire population, the median age was 66 (range: 48-81) years and median PSA was 130 (range: 5-3570) ng/mL. Forty-three percent were on opioids for pain. The median time from the end of first-line therapy to study treatment was 4.2 (range: 0.6-11) months.

First-line Docetaxel Therapy Prior to Study Entry

Patients had received a median of 10 (range: 2-22) cycles of docetaxel. Twenty-two of 42 patients (52%) progressed while on first-line therapy. More patients on the MPC arm progressed while on first-line therapy (64%) than patients on the DPC arm (40%). The median time from the end of first-line therapy to progression for the remaining patients was 3.0 (1.1-6.4) months. Three patients received 1-2 “chemotherapy holidays” during first-line therapy. Thirty of 35 patients (86%) with available PSA data had ≥30% declines in PSA. Disease progression following first-line therapy was based on radiographic evidence in half the patients. Table 2 summarizes first-line therapy.

Protocol Therapy Received

A median of eight (range: 1-9) cycles of DPC and six (range: 1-9) of MPC were administered. Treatment with DPC was discontinued early in ten patients: six for disease progression, three for toxicity (fatigue, bronchiolitis, and weakness) and one for withdrawal of consent. Treatment with MPC was discontinued early in 14 patients: ten for disease progression, three for toxicity (dyspnea, weakness, and increased AST) and one at the investigator’s discretion.
Toxicity

The most common toxicities felt to be related to either custirsen or docetaxel included: fatigue (64%), chills (50%), nausea (50%), pyrexia (40%), anorexia (38%), diarrhea (36%) and vomiting (31%). Over 90% of the AEs were grades 1 and 2. In general, toxicities were similar between the arms. Thirty percent of patients on the DPC arm and 27% on the MPC arm had a documented serious adverse event. Sixty percent of patients on the DPC arm and 73% on the MCP arm had a grade 3 or higher AE. Grade 3/4 AEs are listed in Table 3. The most common grade 3/4 AEs on either arm were fatigue and lymphopenia, the latter of which was seen in 31% of all patients. Grade 3/4 neutropenia was low, occurring in 10% and 18% of patients treated with DPC and MPC, respectively. There was no grade 3/4 neuropathy. Two patients on the MPC arm had neutropenic fever, one patient died from pneumonia with septicemia and one further patient died of heart failure following Cycle 8.

Survival and Disease Progression

All patients were followed until death or a minimum of 39 months. No patient was lost to follow-up. Median OS from the start of study therapy was 15.8 months (95% CI: 9.9, 23.3) for DPC, with four patients alive at 39-44 months, and 11.5 months (95% CI: 6.1, 15.2) for MPC, with one alive at 43 months. Two-year survival was 25% (95% CI: 9.1, 44.9) for DPC and 14% (95% CI: 3.4, 30.9) for MPC. Median PFS was 7.2 months (95% CI: 4.4, 9.3) for DPC and 3.4 months (95% CI: 1.6, 5.2) for MPC. KM estimates for median OS from the start of first-line therapy was 30.2 months (95% CI: 19.9, 36.4) for patients receiving DPC and 23.5 months (95% CI: 13.8, 32.0) for those receiving MPC. Eight patients on the DPC arm and 14 on the MPC arm progressed while receiving first-line therapy. The median survival of this group, irrespective of arm, was 9.9 months. For the remaining patients who progressed after discontinuing first-line therapy (median of 3.0 months), the overall survival was 17.9 months (21.4 and 12.8 months for the DCP and the MCP arms, respectively).
PSA Response

A PSA response, defined as a confirmed decrease in PSA of ≥50% relative to baseline, was documented in 8 of 20 (40%) patients on the DPC arm and 4 of 22 (18%) on the MPC arm.

As illustrated in the Waterfall Plot in Figure 1, of the 20 patients treated with DPC, 4 (20%), 8 (40%), and 11 (55%) had a PSA best percent change of ≥90%, ≥50%, and ≥30%, respectively. Of the 22 patients treated with MPC, 6 (27%) and 7 (32%) had a PSA best percent change of ≥50% and ≥30%, respectively.

Measurable Disease Response

Patient evaluability for response was defined as having measurable disease and at least one follow-up assessment. In the DPC arm, a confirmed PR occurred in 3 (15%) of 13 evaluable patients for 4.6, 6.7, and 34.7 months. Nine had stable disease for 1.8 to 12.0 (median of 5.6) months. In the MPC arm, 5 (71%) of 7 evaluable patients had stable disease for 4.5 to 17.2 (median of 6.9) months.

Time to Pain Progression and Pain Response

The median TTPP for all patients was 10.0 months in the DPC arm and 5.2 in the MPC arm. Twenty-six patients, with a median baseline WPS of three (range: 0-7), were evaluable for pain response. Forty-three percent of evaluable patients were on opioids at baseline. Ten of 13 (77%) evaluable patients in the DCP retreatment arm responded, with discontinuation of opioids in six. Six of 13 (46%) evaluable patients in the MPC arm responded, with discontinuation of opioids in three. All responses but one occurred within two cycles. Overall, the pain response was durable (i.e. ≥3 months) in 14 of the 16 (88%) patients.

Effect of Custirsen Treatment on Serum Clusterin Levels

Of the 42 patients, 40 had both baseline and at least one serum CLU value during treatment and are included in the serum clusterin analyses. The mean and median CLU levels at baseline for the 40 patients were 55.0 and 54 µg/mL (SD: 21.5), respectively. Custirsen treatment significantly reduced the mean average CLU level during treatment by 16.4 µg/mL (26%) compared to baseline (p <0.0001). Thirty-five of
40 evaluable patients (88%) had a reduction in CLU during treatment and 31 of 40 (78%) reached a targeted minimum level of $\leq 45 \, \mu g/mL$. Twenty-eight (70%) patients were classified as serum CLU responders. The median time to CLU response was approximately 30 days. The mean and median CLU levels at baseline, reduction of mean average CLU levels during treatment, and median time to CLU response were similar in both arms.

**Association of Serum Clusterin Levels and Survival**

The classification of baseline serum CLU, chemotherapy type and the interactions were not associated with survival. The most parsimonious 50-day landmark proportional hazard regression model included only the time-dependent serum CLU response indicator and was based on 36 patients. This model failed to show a between-arm difference. A CLU response was defined as three successive CLU levels during therapy $\leq$ median baseline CLU for the population. The estimated death hazard ratio (CLU response over no response) was 0.3 (95% CI: 0.1 – 0.6), representing a 70% reduction in the hazard of death at the start of the serum CLU response. The results from the models with no landmark (40 patients) and a 30-day landmark (39 patients) were consistent, with hazard ratio estimates of 0.2 and 0.2.

Figure 2 shows the Kaplan-Meier estimates for no landmark and 30- and 50-day landmarks classified as to whether a patient had or did not have a CLU response during therapy. While these three graphs do not show the temporal relationship to CLU response, they do illustrate a consistent relationship between having a CLU response and survival for all three landmarks.

Figure 3 shows the Kaplan-Meier estimates for three classifications of patients based on: median baseline CLU ($\leq$ median vs > median); median minimum CLU ($\leq$ median vs > median) of the population during treatment and a threshold minimum CLU level $\leq 45 \, \mu g/mL$ ($\leq$ vs $> 45 \, \mu g/mL$) during treatment. Using the median baseline CLU level, survival estimates were similar for patients above or below the median. However, achieving a low serum CLU level during therapy improved survival for the other two classifications. The median OS for 22 patients with minimum CLU levels during treatment of less than or equal to the median minimum CLU of the population was 14.9 months compared to 9.9 month for 18 patients with CLU above the median (p=0.03).
Similarly, the median OS for 33 patients who achieved a CLU threshold minimum level of \( \leq 45 \, \mu g/mL \) during treatment was 15 months compared to 4.5 months for seven patients who did not (p<0.001).
DISCUSSION

This was a randomized study in patients with mCRPC designed to evaluate two second-line, custirsen-based combination regimens, DCP and MCP. Based on preclinical data (25), the protocol was enriched for patients who progressed while receiving or shortly after completing initial docetaxel treatment. Half of all patients progressed during initial docetaxel therapy and the median time from the end of first-line therapy to disease progression for patients who progressed after discontinuation of first-line therapy was 3.0 months. A PSA decline ≥30% with first-line docetaxel was not achieved in 14% of patients. At the time of study initiation, it was unknown whether such patients with docetaxel-recurrent/refractory disease could tolerate many additional cycles of chemotherapy.

The results of this study indicate that treatment with either combination was feasible and safe in the second-line setting, with a median of eight cycles of DCP and six of MPC delivered. Except for fatigue and lymphopenia, the incidence of grade 3/4 toxicity was the same or lower than seen in the TAX 327 study (1). Grade 3/4 lymphopenia, in part a class effect of ASOs, was seen in approximately one-third of patients, with no clinical sequelae. Grade 3/4 neutropenia was documented in 10% of patients on the DPC arm and 18% on the MPC arm. There was no grade 3/4 neuropathy. Although overall AEs, grade 3/4 AEs and SAEs did not differ substantially between arms, two patients on the MCP arm had febrile neutropenia, one died with pneumonia/septic shock, and another with cardiomyopathy. This may suggest a better safety profile of custirsen in combination with docetaxel retreatment.

Relief of bone pain is important in patients with mCRPC. Although studies have assessed pain response in first-line studies (30, 31), information about pain response in the second-line setting is limited. In the present study, 26 patients were evaluable for pain response. Sixteen (62%) experienced pain relief, with 88% having a durable response ≥3 months.

It is difficult to put the median survival of 15.8 months for docetaxel retreatment (21.4 months for patients who progressed after discontinuing first-line docetaxel) into perspective based on available literature. While PSA responses have been reported (32), reporting of survival from the start of second-line therapy is uncommon. In one
retrospective study, 25 patients were retreated with docetaxel following a PSA response of ≥30% and a median treatment interval of 12 months (33). The median OS from second-line docetaxel was 9.6 months. A recent letter to the editor by DiLorenzo discussed the need for prospective survival studies rechallenging patients with docetaxel after response to first-line docetaxel (34). Preliminary data were presented on a prospective study that enrolled patients who responded and progressed at least 5 months after discontinuation of first-line docetaxel therapy. The median survival was 13 months. The size of the study was not stated.

Recently, cabazitaxel was approved by the FDA in combination with prednisone for second-line treatment in patients previously treated with a docetaxel regimen based on a survival of 15.1 months compared with 12.7 months for patients randomized to mitoxantrone (HR, 0.72) (35). The pain response rate was 9%. The reported grade 3 or higher neutropenia rate following cabazitaxel treatment was 82%. Our data with docetaxel retreatment plus custirsen are from a similar but smaller population and compare favorably to cabazitaxel data. Our results are also consistent with a recently published randomized phase 2 study of first-line docetaxel and prednisone, with or without custirsen, in patients with mCRPC (36). Median survival was longer with the addition of custirsen (23.5 vs. 16.9 months), with a hazard ratio of 0.49.

Increased chemotherapy-induced cancer cell death resulting from custirsen treatment, with lowering of CLU levels, would be expected based on CLU’s multiple mechanisms of action that promote cell survival and confer broad-spectrum chemotherapy resistance (7-20, 37). This study reaffirmed that treatment with custirsen can significantly decrease its target protein, CLU, when compared to pretreatment baseline levels (p =0.0001, baseline vs minimum during treatment, paired t-test). A low serum CLU level during custirsen plus chemotherapy therapy was shown to be associated with a 70% reduction in the hazard of death at the start of the serum CLU response (p <0.001) (Figures 2 and 3). The effect of low serum CLU levels defined as median minimal or threshold minimal levels were analyzed based on several data parameters and showed similar results. Larger, randomized, controlled studies will be required to determine the value of serum CLU levels as a potential predictive biomarker.

The feasibility, safety, pain relief, PSA and disease response and median overall survival in this study, as well as an association of serum CLU response with longer
survival, provide a consistent signal that warrants further testing of docetaxel combined with custirsen. Two phase 3 studies, one with a primary endpoint of survival and one with pain palliation, and both evaluating serum CLU as a predictive marker of survival, are currently enrolling patients. As CLU expression is up-regulated in many other cancers, similar therapeutic approaches involving custirsen therapy is justified in other malignancies.
REFERENCES


TABLES

Table 1: Demographics at Study Baseline
Table 2: First-line Docetaxel Therapy Received Prior to Study Entry
Table 3: Number (%) of Patients with >5% Grade 3/4 Adverse Events in Either Arm

FIGURE LEGENDS

Figure 1: Best Percent PSA Change from Baseline At or After 12 Weeks.
Calculated from lowest PSA value at any time after baseline while on treatment by individual patients. One patient in the mitoxantrone group had >200% increase in PSA. The value was truncated at 100%.

Figure 2: Survival Analysis by Landmark.
Kaplan-Meier estimates for no landmark and 30- and 50-day landmarks classified as to whether a patient had or did not have a CLU response during therapy.

Figure 3: Clusterin at Baseline and Minimum Values During Treatment.
Kaplan-Meier estimates for three dichotomous classifications of patients based on: median baseline CLU (≤ median vs > median); median minimum CLU (≤ median vs > median) during treatment and threshold minimum CLU level ≤ 45 µg/mL (≤ vs > 45 µg/mL) during treatment.
<table>
<thead>
<tr>
<th></th>
<th>Docetaxel/Prednisone/Custirse</th>
<th>Mitoxantrone/Prednisone/Custirse</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (N=20)</td>
<td>n (N=22)</td>
<td>(N=42)</td>
</tr>
<tr>
<td>Median Age (Years) (Range)</td>
<td>68 years (48-80)</td>
<td>61 years (49-81)</td>
<td>66 years (48-81)</td>
</tr>
<tr>
<td>Median PSA (ng/mL) (Range)</td>
<td>154 (5-3570)</td>
<td>116 (20-2776)</td>
<td>130 (5-3570)</td>
</tr>
<tr>
<td>PSA ≥20 ng/mL (%)</td>
<td>90%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Median Hemoglobin (g/dL) (Range)</td>
<td>12.3 (9.0-13.7)</td>
<td>12.6 (8.5-14.3)</td>
<td>12.3 (8.5-14.3)</td>
</tr>
<tr>
<td>Median LDH (U/L) (Range)</td>
<td>231 (157-596)</td>
<td>291 (142-1088)</td>
<td>270 (142-1088)</td>
</tr>
<tr>
<td>Karnofsky Score (% of patients)</td>
<td>70-80%: (35%)</td>
<td>70-80%: (41%)</td>
<td>70-80%: (38%)</td>
</tr>
<tr>
<td>Receiving Bisphosphonates (%)</td>
<td>40%</td>
<td>36%</td>
<td>38%</td>
</tr>
<tr>
<td>Radiotherapy Since Progression (%)</td>
<td>50%</td>
<td>45%</td>
<td>48%</td>
</tr>
<tr>
<td>Worst Pain Score ≥2 at study entry (%)</td>
<td>40%</td>
<td>55%</td>
<td>48%</td>
</tr>
<tr>
<td>On Opioids at Study Entry (%)</td>
<td>45%</td>
<td>41%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Sites of Disease (% of patients)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bone</td>
<td>100%</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>- Node</td>
<td>65%</td>
<td>50%</td>
<td>57%</td>
</tr>
<tr>
<td>- Visceral</td>
<td>20%</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>Measurable Disease (% of patients)</td>
<td>65%</td>
<td>50%</td>
<td>57%</td>
</tr>
<tr>
<td>Median Time (Months) From End of First-line Docetaxel Therapy to Study Treatment (Range)</td>
<td>4.9 (0.9-7)</td>
<td>3.9 (0.6-11)</td>
<td>4.2 (0.6-11)</td>
</tr>
</tbody>
</table>
**Table 2: First-line Docetaxel Therapy Received Prior to Study Entry**

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel/Prednisone/Custirse (N=20)</th>
<th>Mitoxantrone/Prednisone/Custirse (N=22)</th>
<th>Total Population (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median # of Cycles of Treatment Administered (Range)</td>
<td>10 cycles (2-22)</td>
<td>10 cycles (2-22)</td>
<td>10 cycles (2-22)</td>
</tr>
<tr>
<td>≥30% Decline in PSA at Any Time (%) *</td>
<td>88%</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>Number of Patients (%) Relapsing While Receiving First-line Therapy</td>
<td>40%</td>
<td>64%</td>
<td>52%</td>
</tr>
<tr>
<td>Median Time (Months) From End of First-line Therapy to Disease Progression for Patients Progressing After First-line Therapy</td>
<td>2.5 months (1.1-5.1)</td>
<td>4.3 months (1.8-6.4)</td>
<td>3.0 (1.1-6.4)</td>
</tr>
</tbody>
</table>
| Basis of Progression:**
- Bone Scan | 20% | 27% | 24% |
- CT Scan | 20% | 27% | 24% |
- PSA only | 60% | 45% | 52% |

*PSA data available on 35 of 42 patients  
**Patients could have progressed by more than one method
Table 3: Number (%) of Patients with >5% Grade 3/4 Adverse Events in Either Arm

<table>
<thead>
<tr>
<th>Event</th>
<th>Docetaxel/ Prednisone/ Custirsen N=20</th>
<th>Mitoxantrone/ Prednisone/ Custirsen N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>6 (30%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (35%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (15%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (10%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (5%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1 (5%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1 (5%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td></td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Infections</td>
<td>2* (9%)</td>
<td>1** (5%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

*UTI and injection site infection
**pneumonia and septicemia
Figure 1: Best Percent PSA Change from Baseline At or After 12 Weeks.
Figure 2: Survival Analysis by Landmark.

No Landmark

- Non-responder: n = 12, median = 5.8 months
- Responder: n = 28, median = 15.1 months
- Log-rank Test P-value = <.001

Landmark = 30 Days

- Non-responder: n = 11, median = 6.1 months
- Responder: n = 28, median = 15.1 months
- Log-rank Test P-value = <.001

Landmark = 50 Days

- Non-responder: n = 9, median = 6.5 months
- Responder: n = 27, median = 15.2 months
- Log-rank Test P-value = <.001
Figure 3: Clusterin at Baseline and Minimum Values During Treatment.
Clinical Cancer Research

Randomized Phase 2 Trial of Custirsen (OGX-011) with Docetaxel or Mitoxantrone in Patients with Metastatic Castrate-Resistant Prostate Cancer: CUOG Trial P06c

Fred Saad, Sebastien Hotte, Scott North, et al.

Clin Cancer Res Published OnlineFirst July 25, 2011.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-0859

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.