Award Number: DAMD17-02-1-0226

TITLE: A Phase I/II Study of Combination Neoadjuvant Hormone Therapy and Weekly OGX-011 Prior to Radical to Prostatectomy in Patients with Localized Prostate Cancer

PRINCIPAL INVESTIGATOR: Kim N. Chi, M.D.

CONTRACTING ORGANIZATION: University of British Columbia
Vancouver, British Columbia, Canada V6T 1Z3

REPORT DATE: August 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
**REPORT DOCUMENTATION PAGE**

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.

**PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

<table>
<thead>
<tr>
<th>1. REPORT DATE</th>
<th>2. REPORT TYPE</th>
<th>3. DATES COVERED</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-08-2005</td>
<td>Annual</td>
<td>1 Aug 2004 – 31 Jul 2005</td>
</tr>
</tbody>
</table>

**4. TITLE AND SUBTITLE**

A Phase II Study of Combination Neoadjuvant Hormone Therapy and Weekly OGX-O11 Prior to Radical to Prostatectomy in Patients with Localized Prostate Cancer

**6. AUTHOR(S)**

Kim N. Chi, M.D.

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

University of British Columbia
Vancouver, British Columbia, Canada
V6T 1Z3

**9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT –SEE ATTACHED PAGE**

**16. SUBJECT TERMS**

Prostate Cancer Clusterin, Antisense Oligonucleotide, Methoxyethyl Gapmer

**19a. NAME OF RESPONSIBLE PERSON**

USAMRMC

**19b. TELEPHONE NUMBER (include area code)**

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18
Abstract

The clusterin gene encodes a cytoprotective chaperone protein that promotes cell survival. Clusterin is expressed in a variety of cancers including prostate, increases in response to apoptotic stimuli, and confers a resistant phenotype. OGX-011 is a 2nd generation antisense complimentary to clusterin mRNA that inhibits expression of clusterin in xenograft models and thereby increases sensitivity to therapy. To evaluate OGX-011 as a potential treatment in humans, we have undertaken this Phase I/I1 study to evaluate the clinical, pathologic and biologic effects of OGX-011, in combination with neoadjuvant hormone therapy (NHT) in patients with prostate cancer and high risk features prior to radical prostatectomy. The primary objective of the phase I study was to determine phase II dose based on target regulation effect. The phase II component of this trial will assess the effects of combined NHT and OGX-011 on pathologic complete response. Progress: 25 patients were enrolled to 6 cohorts with doses of OGX-011 up to 640mg delivered. Toxicity was limited to grade 1/2, including fevers, rigors, fatigue and transient AST and ALT elevations and no dose-limiting toxicities. Plasma PK analysis showed dose proportional increases in AUC and Cmax with a t1/2 of approximately 2h. Prostate tissue concentrations of OGX-011 increased with dose, and tissue concentrations associated with preclinical effect could be achieved. Dose dependent decreases in prostate cancer cell clusterin expression were observed by QRT-PCR and immunohistochemistry (IHC). At 640mg dosing, clusterin mRNA was decreased to a mean of 8% (SD=4%) compared with lower dose levels and historical controls as assessed by QRT-PCR on laser captured microdissected cancer cells. By IHC, mean % cancer cells staining 0 intensity for clusterin protein at 640mg dosing was 54% (SD=24%). Dose-dependent changes in serum clusterin were also apparent. Conclusions: OGX-011 is well tolerated and can inhibit clusterin expression in prostate cancers. The recommended phase II dose for OGX-011 is 640mg based on target regulation results. The Phase II portion of this study, evaluating a 3-month neoadjuvant treatment with OGX-011 at the recommended phase II dose, enrolled the first patient in June 2004. To date 6 patients have been enrolled and 4 have commenced therapy.
Table of Contents

Cover...........................................................................
SF 298...........................................................................
Table of Contents..................................................
Introduction..........................................................  4
Body...........................................................................  4
Key Research accomplishments...............................  6
Reportable Outcomes..............................................  6
Conclusions ...........................................................  6
Tables and Figures...................................................  7
Figures.......................................................................  9
References.............................................................  13
Appendix................................................................... 14
INTRODUCTION

The clusterin gene on chromosome 8 encodes a chaperone protein which has been implicated in a variety of physiologic processes. Also known as Testosterone repressed prostate message-2 (TRPM-2), or sulfated glycoprotein-2, clusterin is associated with numerous tumors including prostate [1], neuroblastoma [2], breast [3], lymphoma [4], urothelial [5] and renal cell carcinoma [6], and with various pathologic conditions including Alzheimer's [7] and nephrotoxic injury [8]. Clusterin levels increase dramatically during castration-induced apoptosis in rat prostate epithelial cells [9], in androgen dependent Shionogi tumors [10], and human prostate cancer CRW22 [11] and PC82 [12] xenografts. In human prostate cancer, clusterin levels are low or absent in most untreated hormone-naive tissues, but increase significantly within weeks after neoadjuvant hormone therapy [13]. Because clusterin binds to a wide variety of biological ligands [14,15], and is regulated by transcription factor HSF1 (heat shock factor 1) [16], the emerging view suggests that clusterin functions similarly to heat shock protein to chaperone and stabilize conformations of proteins at time of cell stress. Indeed, clusterin is substantially more potent than other HSP's at inhibiting stress-induced protein precipitation [17]. Significant differences exist, however, in amino acid sequence analysis which suggests that clusterin is a unique protein without any closely related family members yet identified.

Experimental and clinical studies in prostate cancer implicate clusterin with AI progression and with playing a protective role against apoptotic cell death from androgen withdrawal, chemotherapy and radiation [10,18,19,20]. OGX-011 is an ASO complementary to the clusterin mRNA. OGX-011 incorporates a phosphorothioate backbone with second-generation chemistry in the form of 2'-O-Methoxymethyl modifications to the 4 bases on either end of the 21-mer molecule. Such “gap-mer” modifications maintain the improved tissue pharmacokinetic profile of the second-generation chemistry but preserves high affinity for target mRNA and recruitment of RNase H necessary for activity. In pre-clinical models, OGX-011 improves the efficacy of chemotherapy, radiation, and androgen withdrawal by inhibiting expression of clusterin and enhancing the apoptotic response [10,19,20,21]. Furthermore, because of the second-generation chemistry and enhanced tissue half-life of OGX-011, more relaxed dosing schedules are possible while maintaining biologic efficacy of target inhibition. Rather than the prolonged continuous infusions of first generation phosphorothioate molecules that are usually employed, pre-clinical studies suggest that only weekly infusional dosing or less is required to maintain tissue levels of OGX-011 and target inhibition of clusterin [21], which is much more acceptable for patients in terms of tolerance and repeated administration.
Patients having localized prostate cancer with high-risk features and candidates for prostatectomy were enrolled to this dose escalation trial. OGX-011 was given by IV infusion over 2 hrs at a starting dose of 40mg on days 1, 3, 5, 8, 15, 22, and 29. Buserelin and flutamide were started on day 1. Prostatectomy was performed day 30-36. OGX-011 plasma PK and prostate tissue concentrations were determined. Prostate tissues, lymph nodes, and serial samples of peripheral blood mononuclear cells and serum were assessed for clusterin expression. The first patient was accrued December 2002, as soon as regulatory and ethical approval had been obtained. Twenty-five patients were enrolled to 6 dose levels on the phase I component of this trial and completed their 3 months of follow-up post radical prostatectomy. Patient characteristics are listed in Table 1.

Treatment was well tolerated with no unexpected toxicities, no serious adverse events and no dose limiting toxicities. The most usual toxicity was that of a flu-like syndrome occurring after the infusion of the OGX-011 with patients experiencing fevers, chills and myalgias, which was transient and resolved spontaneously. These usually occurred during the day 1 and 3 infusions only and did not re-occur. Other side effects including transient elevations in hepatic transaminases, again during the first week of treatment, and then resolving despite continued therapy with the OGX-011. Table 2 lists the Hematologic and non-Hematologic adverse events (graded according to NCI CTCAE v2.0 criteria) that were considered possibly, probably or definitely associated with OGX-011 therapy.

Plasma concentrations of OGX-011 were measured at various time points for pharmacokinetic profiling on Day 1 and repeated on Day 29 to evaluate possible repetitive dosing effects. Plasma pharmacokinetic profile of OGX-011 was as predicted from animal studies and clinical studies with other antisense oligonucleotides with no evidence of significant effect from the multiple dosing schedule (Table 4). Initial half life was approximately 2 hours, and peak concentration (C_MAX) (Figure 1, Panel A) and area under the curve (AUC) (Figure 1, Panel B) were proportional to dose. More importantly, and more interestingly, concentrations of full length OGX-011 associated with biologic effect in vitro, could be achieved in humans prostate tissue (Figure 2). Tissue concentrations increased proportionally to dose (P<0.001). Using an immunostain specific for the antisense, OGX-011 could be visualized within the cytoplasm of cancer cells (Figure 3)

Clusterin mRNA expression was measured from laser captured microdissected prostate cancer cells from the subjects prostatectomy specimens using quantitative real time PCR (Figure 4). Laser captured microdissected prostate cancer cells were taken from subjects prostatectomy specimens that had not been treated with any neoadjuvant therapy, or from subjects treated with less than 2 months of neoadjuvant hormone therapy served as historical controls. The first two columns in Figure 4 represent the historical controls with the first column representing clusterin mRNA expression in prostate cancer cells from subjects without prior neoadjuvant hormone therapy, and the second column representing clusterin mRNA expression in prostate cancer cells from subjects treated with less than 2 months of neoadjuvant hormone therapy, nicely showing the increase in clusterin that occurs in surviving cells after neoadjuvant hormone therapy. In the subjects treated with OGX-011 there was a dose-response relationship with the expression of Clusterin mRNA decreasing with higher dosing of OGX-011 (P<0.001) . The prostate cancer cells from subjects treated at the 640 mg dosing had 8% of the expression of Clusterin mRNA as compared to historical untreated controls.

Protein expression of Clusterin was evaluated using immunohistochemistry. Staining and scoring of prostate cancer cells from representative sections from the prostatectomy specimens were assessed by two pathologists blinded to treatment assignment. Overall score was a composite of staining intensity as well as percentage of prostate cancer cells with that staining (i.e. overall score = (% cells with visual score 1) x 1 + (% cells with visual score 2) x 2 + (% cells with visual score 3) x 3). Results for overall score are shown in Figure 5. A dose response effect is seen with decreased expression of clusterin in prostate cancer cells from patients treated with higher doses of OGX-011 (P<0.01). More revealing is the percentage of prostate cancer cells that had 0 intensity scoring (i.e. presumably no clusterin protein expression) as shown in Figure 6. Again, a dose-response effect is observed (P<0.001), with an increasing percentage of cells with suppressed clusterin protein expression and somewhat of a plateau in biological effect between the 480 mg and 640 mg dose levels. In addition, the percentage of cells that had suppressed clusterin expression (visual score 0) also increased from baseline (as assessed from the core biopsy specimens) to after treatment with OGX-011 in a dose dependent fashion (P<0.001) (Figure 7). It must be taken into consideration however, that the magnitude of the suppressive effect of OGX-011 on clusterin protein expression may be under-appreciated given the upregulation of clusterin that normally occurs with neoadjuvant hormone therapy which is not taken into account with this analysis (and hence the use of historical control populations in the previous analyses).

Normal lymph nodes have high expression of clusterin, especially in the germinal center. Similar to the tumor tissue, in normal lymph node tissues taken at the time of radical prostatectomy, there was also an OGX-011 dose dependent inhibition of clusterin mRNA expression (Figure 8) as assessed by QRT-PCR (P<0.001) and of protein expression as assessed by immunohistochemistry. The apoptotic index was also determined from the prostatectomy specimens post treatment. Apoptotic cells were identified using an antibody against ssDNA. As shown in Figure 9, there was a trend to an increasing number of apoptotic cells in the prostatectomy specimens with increasing dose of OGX-011 (P<0.001).

Expression of clusterin using QRT-PCR was performed in peripheral blood mononuclear cells however the results are uninterpretable due to widely fluctuating results at baseline (three baseline samples taken at different time points). Circulating clusterin in serum has been evaluated using an ELISA assay. Results suggest that a decrease in serum clusterin was evident in patients administered OGX-011 at the 640 mg dose level.

Based on these data, dose escalation for the trial was halted, and the recommended phase II dose was declared 640 mg based on the demonstration of biologic effect on clusterin expression. Furthermore, given that dose-limiting toxicities of oligonucleotides are potentially related to peak concentration and that complement activation in pre-clinical studies was predicted to occur at peak doses of ≥100 µg/ml, extrapolating from the current pharmacokinetic data did not justify further dose escalation.
A manuscript of the results of this trial has been accepted for publication by the Journal of the National Cancer Institute, which has one of the highest impact factors for cancer journals.

**TASK 3. PHASE II TRIAL**

- Patient enrollment
- Phase II protocol treatment with OGX-011 (estimate 300g total drug)
- Efficacy determination
- Pathologic complete response rate
- Characterize clusterin expression
- PSA nadir and recurrence

All preparatory steps have been completed for the phase II trial. University of British Columbia – British Columbia Cancer Agency Research Ethics Board (UBC-BCCA REB) approval was granted 3 November, 2004 (Number R04-0092). Federal regulatory approval was given on 17 December 2004 (File Number 9427-B0877-32C). However, HSRRB final approval notification was not received until May 4, 2005 (Number A-11279.2) which was a longer approval process than initially anticipated. Medical and Data monitoring and Case Report Form creation services were contracted out to private groups.

The first patient was enrolled and received their first protocol treatment on 15 June 2005. To date, 6 patients have been enrolled and 4 have commenced protocol therapy. There has been 1 serious adverse event in 1 patient of increased liver enzyme test elevations (Grade 3-4) requiring holding of protocol therapy. Patient was otherwise asymptomatic with no other toxicities. After 1 week of withdrawal from protocol therapy, the patients liver enzyme elevation has resolved to a Grade 2-3 toxicity and the toxicity reported as a serious adverse event for expedited reporting to the HSRRB, the UBC-BCCA REB, and Federal Health Regulatory Authorities (Therapeutic Products Directorate). Protocol therapy continues in all other patients and no other incidences of > grade 1-2 liver enzyme toxicity have been noted.

Because of delays in start-up and approval for the phase I and II trials, a no-cost one-year time extension was requested and provided. Enrolment is expected to proceed at 1-2 patients per week and that rate the project should be able to finish on schedule in 2006.

**KEY RESEARCH ACCOMPLISHMENTS**

- Completion of the first clinical trial of a second generation phosphorothioate antisense oligonucleotide in patients with cancer
- Novel study design using neoadjuvant therapy prior to radical prostatectomy
- Proof of principal demonstration of biologic effect
- Determination of recommended phase II dose of OGX-011 based on biological efficacy
- Phase II neoadjuvant trial initiated

**REPORTABLE OUTCOMES**

**Manuscripts**


**Abstracts**


**Presentations**


**CONCLUSIONS**

This phase I trial provides proof of principal evidence that OGX-011 can inhibit expression of clusterin in prostate cancer cells in humans. This is the first demonstration of dose dependent inhibition of a target, within target tissue by an antisense targeted therapeutic. Because of the successful determination of the biologically effective dose, phase II clinical trials with OGX-011 can move forward with confidence in the dosing regimen and schedule.
### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (Range), y</td>
<td>63 (45–71)</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Gleason Score</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>8–10</td>
<td>6</td>
</tr>
<tr>
<td>Baseline PSA, ng/mL</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>16</td>
</tr>
<tr>
<td>&gt;10–20</td>
<td>6</td>
</tr>
<tr>
<td>&gt;20</td>
<td>3</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>12</td>
</tr>
<tr>
<td>2a</td>
<td>9</td>
</tr>
<tr>
<td>2b</td>
<td>3</td>
</tr>
<tr>
<td>3a</td>
<td>1</td>
</tr>
</tbody>
</table>

*PSA = prostate specific antigen. Clinical staging was according to UICC TNM 1997 classification.

### Table 2. Selected adverse effects of the phosphothionate oligonucleotide OGX-011 by dose level*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose level, mg/mL</td>
</tr>
<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>N = 3</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>AST</td>
<td>1</td>
</tr>
<tr>
<td>ALT</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
</tr>
<tr>
<td>Rigors</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
</tr>
<tr>
<td>Rigors</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>0</td>
</tr>
<tr>
<td>Myalgias</td>
<td>0</td>
</tr>
</tbody>
</table>

*AST = aspartate aminotransferase; ALT = alanine aminotransferase. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.
Table 3. Plasma Pharmacokinetic Parameters of OGX-011

<table>
<thead>
<tr>
<th>Dose level (mg)</th>
<th>No. Of Patients</th>
<th>Treatment Day</th>
<th>C_{MAX} μg/mL*</th>
<th>T_{1/2, h}**</th>
<th>AUC_{0-∞, h}*μg·h/mL‡</th>
<th>V_{z, L}*§</th>
<th>CL, L/h*</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>1</td>
<td>1</td>
<td>4.0</td>
<td>0.5</td>
<td>9.5</td>
<td>3.3</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>3.6</td>
<td>0.5</td>
<td>8.1</td>
<td>3.4</td>
<td>4.9</td>
</tr>
<tr>
<td>80</td>
<td>3</td>
<td>1</td>
<td>12.3 (9.2-23.7)</td>
<td>0.8 (0.5-1.2)</td>
<td>34.0 (4.3-63.7)</td>
<td>3.2 (0.5-6.8)</td>
<td>2.6 (0.1-2.5)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>11.2 (5.0-22.9)</td>
<td>0.8 (0.3-1.3)</td>
<td>23.1 (-74.1-120.4)</td>
<td>4.4 (-13.8-22.7)</td>
<td>3.9 (-12.5-20.3)</td>
</tr>
<tr>
<td>160</td>
<td>3</td>
<td>1</td>
<td>23.1 (16.4-29.9)</td>
<td>1.1 (0.7-1.5)</td>
<td>72.6 (25.7-119.4)</td>
<td>3.7 (1.2-6.2)</td>
<td>2.3 (1.0-3.6)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>22.6 (7.9-37.2)</td>
<td>2.2 (-1.4-5.7)</td>
<td>70.5 (-107.0-248.0)</td>
<td>7.6 (-23.2-38.5)</td>
<td>2.4 (-3.6-8.3)</td>
</tr>
<tr>
<td>320</td>
<td>6</td>
<td>1</td>
<td>39.5 (28.3-50.7)</td>
<td>2.0 (1.5-2.5)</td>
<td>138.4 (117.1-159.7)</td>
<td>6.6 (5.9-7.4)</td>
<td>2.4 (2.0-2.7)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>30.4 (22.8-38.1)</td>
<td>2.7 (2.3-3.1)</td>
<td>116.8 (85.2-148.4)</td>
<td>11.5 (7.5-15.5)</td>
<td>2.9 (2.2-3.6)</td>
</tr>
<tr>
<td>480</td>
<td>6</td>
<td>1</td>
<td>55.4 (37.9-72.9)</td>
<td>2.1 (1.4-2.8)</td>
<td>217.6 (147.8-287.5)</td>
<td>7.0 (3.7-10.3)</td>
<td>2.3 (1.7-2.9)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>48.0 (30.8-65.2)</td>
<td>3.2 (2.8-3.7)</td>
<td>199.7 (128.3-271.1)</td>
<td>12.2 (8.1-16.4)</td>
<td>2.6 (1.9-3.3)</td>
</tr>
<tr>
<td>640</td>
<td>6</td>
<td>1</td>
<td>61.1 (55.3-66.9)</td>
<td>2.4 (1.8-2.9)</td>
<td>251.9 (225.9-278.0)</td>
<td>8.8 (6.8-10.7)</td>
<td>2.6 (2.3-2.9)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td></td>
<td>69.9 (64.8-74.9)</td>
<td>3.3 (2.9-3.8)</td>
<td>284.3 (221.1-347.4)</td>
<td>11.0 (9.4-12.6)</td>
<td>2.3 (1.8-2.8)</td>
</tr>
</tbody>
</table>

*Values represent mean (95% confidence interval). T_{MAX} - time to reach peak plasma concentration. C_{MAX} - observed peak plasma concentration.
**T_{1/2} - plasma distribution half-life.
‡AUC = area under the plasma concentration versus time curve.
§V_{z} = apparent volume of distribution.
‖CL = total clearance from plasma.
FIGURES

Figure 1. OGX-011 Maximum Concentrations ($C_{\text{max}}$) (Panel A) and Area Under The Curve (AUC) (Panel B) Vs. Dose Curves

PANEL A

PANEL B

Figure 2. Scatter Plot of OGX-011 Tissue Concentrations Vs. Dose
Figure 3. Immunostain of OGX-011 in Prostate Cancer Tissue Showing Intracellular Location

Control

640 mg Dose

Figure 4. Clusterin mRNA Expression in Microdissected Prostate Cancer Cells (Quantitative Real Time-PCR)

Historical Controls

Columns represent mean ± standard error
Figure 5. Clusterin Protein Expression in Prostate Cancer Cells (Immunohistochemistry - Overall Visual Score)

Figure 6. Box Plot of Clusterin Protein Expression in Prostate Cancer Cells (Immunohistochemistry - Percentage of Cells with a Visual Score 0)

Figure 7. Change in Clusterin Protein Expression in Prostate Cancer Cells from Baseline to Prostatectomy (Immunohistochemistry - Percentage of Cells with a Visual Score 0)
Figure 8. Box Plot Clusterin mRNA Expression in Normal Lymph Nodes (Quantitative Real Time-PCR)

Figure 9. Box Plot of Apoptotic Index (Immunohistochemistry of ssDNA)
REFERENCES


A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of OGX-011, a 2’methoxyethyl phosphorothioate antisense to clusterin, in patients with prostate cancer prior to radical prostatectomy

Kim N. Chi, Elizabeth Eisenhauer, Ladan Fazli, Edward C. Jones, Jean Powers, Antonio Hurtado-Coll, Larry Goldenberg, Martin E. Gleave

Background: The clusterin gene encodes a cytoprotective chaperone protein that promotes cell survival. Clusterin is expressed in a variety of cancers including prostate, increases in response to apoptotic stimuli, and in pre-clinical models confers a resistant phenotype. OGX-011 (Oncogenex Technologies Inc) is a 2nd generation antisense complimentary to clusterin mRNA that inhibits expression of clusterin in xenograft models and thereby increases sensitivity to therapy. The objective of this first-in-man study was to determine phase II dose based on target regulation effect in addition to standard toxicity parameters.

Methods: Patients having localized prostate cancer with high-risk features and candidates for prostatectomy were enrolled to this dose escalation trial. OGX-011 was given by IV infusion over 2 hrs at a starting dose of 40mg on days 1, 3, 5, 8, 15, 22, and 29. Buserelin and flutamide were started on day 1. Prostatectomy was performed day 30-36. OGX-011 plasma PK and prostate tissue concentrations were determined. Prostate tissues, lymph nodes, and serial samples of peripheral blood mononuclear cells and serum were assessed for clusterin expression.

Results: 25 patients were enrolled to 6 cohorts with doses of OGX-011 up to 640mg delivered. Toxicity was limited to grade 1 or 2, including fevers, rigors, fatigue and transient AST and ALT elevations. Plasma PK analysis showed linear increases in AUC and Cmax with a t1/2 of approximately 2 hrs. Prostate tissue concentrations of OGX-011 increased with dose, and tissue concentrations associated with preclinical effect could be achieved. Dose dependent decreases in prostate cancer cell clusterin expression were observed by rtPCR, in situ hybridization and immunohistochemistry (IHC). At 640mg dosing, clusterin mRNA was decreased to a mean of 8% (SD=4%) compared with lower dose levels and historical controls as assessed by rtPCR on laser captured microdissected cancer cells. By IHC, mean % cancer cells staining 0 intensity for clusterin protein at 640mg dosing was 54% (SD=24%) compared with 2-15% for lower dose levels and historical controls.

Conclusions: OGX-011 is well tolerated and can inhibit clusterin expression in primary prostate cancers. The recommended phase II dose for OGX-011 is 640mg based on pharmacokinetic parameters and target regulation results. Phase II studies of OGX-011 in combination with hormone and chemotherapy are planned in patients with prostate, breast and lung cancers. Supported by a grant from the U.S. Department of Defense and coordinated by the NCIC-CTG.