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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 complementary 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/II 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 and the phase II primary objective was to assess the effects on pathologic complete response. 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. The Phase II portion of this study evaluated a 3-month neoadjuvant treatment with OGX-011 at the recommended phase II dose of 640 mg. The first patient was enrolled in June 2005 with a total of 24 patients enrolled. Toxicity was predominantly grade 1/2 including fevers, rigors, fatigue and transient AST and ALT elevations. 4 patients did not complete protocol therapy: 2 for grade 3/4 AST/ALT toxicity, 2 for pre-existing cardiac reasons. Median nadir PSA pre-surgery=0.2 (range 0.1-1.4). OGX tissue concentrations associated with preclinical effect were achieved (>1ug/g). Compared to historical controls inhibition of clusterin expression was observed: by IHC (score 0-3), mean score was 1.1 (SD=0.6) for OGX treated and 2.1 (SD=0.5) for control (p<0.001), % of cancer cells with IHC score of 0 was 33.7% (SD=24.9) for OGX treated and 8.5% (SD=11.1) for control (p<0.001). Using laser capture microdissection and QRT-PCR, mean clusterin mRNA was decreased by 61% compared to control (p=0.009). Mean apoptotic index was 1.3% (SD=0.4) for OGX treated and 0.8% (SD=0.3) for control (p=0.003). There were no pathologic complete responses and the trial closed after the first stage. Because of this phase I/II study demonstrating biologic activity of OGX-011, additional studies of OGX-011 in combination with chemotherapy have been conducted in patients with lung, breast and prostate cancer, and a phase III trial is planned in patients with castration resistant prostate cancer.

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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. More recently, clusterin has been shown to inhibit the apoptosis inducing protein Bax, thus rendering cells more resistant to cell death [22].

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-Methoxyethyl 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.

To evaluate OGX-011 as a potential treatment in humans, we have undertaken this Phase I/II study to evaluate the clinical, pathologic and biologic effects of OGX-011, in combination with neoadjuvant hormone therapy in patients with prostate cancer and high risk features prior to radical prostatectomy. This primary objective of the phase I component of this trial was to define a recommended phase II dose of OGX-011 based on toxicity and maximal biologic effect. Secondary aims were to determine toxicity, the serum and tissue pharmacokinetic profile and measure evidence of OGX-011 effect on clusterin expression in tumor and peripheral blood mononuclear cells, and clusterin serum levels. The primary objective of the phase II component was to assess the effects of combined neoadjuvant hormone therapy and OGX-011 for 3 months prior to radical prostatectomy on pathologic complete response.

A significant difficulty in the development of targeted therapy agents like OGX-011 is the determination of a biologically effective dose. The biologically effective dose can often be significantly different from that of the maximally tolerated dose, the usual endpoint in classically designed phase I trials. This study's phase I design allowed for a determination of an optimal biologically effective dose based on the target of interest (i.e. clusterin) within target tissue itself (i.e. prostate cancer) which has allowed for confidence in moving forward in phase II trials of the agent. The phase II portion of this study confirmed in a larger group of patients the observations of biological activity of OGX-011 at the recommended phase II from the phase I trial (i.e. 640 mg) and further delineated toxicity. Although the pathologic complete response rate in the phase II trial did not meet the pre-defined criteria for continuation in this clinical setting, the demonstrated biologic activity of OGX-011 in these trials provided the rationale for further phase I and II clinical trials of OGX-011 in combination with chemotherapy [23] in patients with advanced lung [24], breast [25] and castration resistant prostate cancer [26, 27]. A phase III trial of docetaxel with or without OGX-011 is being planned in patients with castration resistant prostate cancer who have previously received docetaxel (PI: K. Chi).

BODY

TASK 1. STUDY INFRASTRUCTURE PREPARATION

- *Health Canada (Therapeutic Products Program) Investigational New Drug Submission*
- *Case Report Forms*
- *Medical and data monitoring*
- *Institutional Review Board*

All preparatory steps have been completed. Federal regulatory approval was given on 4 October 2002 (File Number 9427-N0711-98C). Initial University of British Columbia Research Ethics Board approval was granted October 24, 2002 (Number C02-0430), and HSRRB approval granted December 2002 (Number A-11279). Medical and Data monitoring and Case Report Form creation services were contracted with the National Cancer Institute of Canada - Clinical Trials Group.

TASK 2. PHASE I TRIAL

- *Patient enrollment*
- *Protocol treatment and dose escalation with OGX-011*
- *Define recommend phase II dose based on toxicity, serum and tissue pharmacokinetic and pharmacodynamic data*

TASK 4. SUPPORTING AND TRANSLATIONAL STUDIES

- *Serum pharmacokinetics*
- *Tissue pharmacokinetics*
- *Clusterin expression – prostate/tumor, mononuclear cells, serum*
- *Comparative molecular marker analysis in pathologic specimens*

As previously described in the 2005 Annual Report, these tasks have been completed for the phase I trial. To summarize, subjects ($n = 25$) with localized prostate cancer with high-risk features who were candidates for prostatectomy were treated with OGX-011 by 2-hour intravenous infusion on days 1, 3, and 5 and then weekly from days 8 – 29 combined with androgen blockade starting on day 1; prostatectomy was performed on days 30 – 36. Six different doses were tested, from 40 to 640 mg. OGX-011 plasma and prostate tissue concentrations were measured by an enzyme-linked immunosorbent assay method, and the pharmacokinetics of OGX-011 were determined from these data. Prostate cancer tissue, lymph nodes, and serial samples of peripheral blood mononuclear cells were assessed for clusterin expression using quantitative real-time polymerase chain reaction and immunohistochemistry. All statistical tests were two-sided. Only grade 1 and 2 toxicities were observed. The plasma half-life of OGX-011 was approximately 2 – 3 hours, and the area under the concentration versus time curve and C MAX (peak plasma concentration) increased proportionally with dose ($P_{\text{trend}} < .001$). OGX-011 in prostate tissue increased with dose ($P_{\text{trend}} < .001$). Dose-dependent decreases in prostate cancer and lymph node clusterin expression were observed by polymerase chain reaction of greater than 90% ($P_{\text{trend}} = .008$ and $< .001$, respectively) and by immunohistochemistry ($P_{\text{trend}} < .001$ and $= .01$, respectively). We concluded that OGX-011 was well tolerated and reduces clusterin expression in primary prostate tumors and that the optimal biologic dose for OGX-011 at the schedule used was 640 mg.

The manuscript was published in the Journal of the National Cancer Institute (2005;97:1287–96) 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). HSRRB final approval notification was received May 4, 2005 (Number A-11279.2). Medical and Data monitoring and Case Report Form creation services were contracted out to private groups.

The first subject was enrolled and received their first protocol treatment on 15 June 2005. Eleven subjects were initially enrolled at a rate of 4-5 per month. However, in this first set of subjects, there were 2 subjects who experienced serious adverse events in the form of increased liver enzyme test elevations (Grade 3-4) requiring holding of protocol therapy. The subjects were otherwise asymptomatic with no other toxicities. After withdrawal from protocol therapy, the subjects liver enzyme elevations had resolved and both patients went on to have a prostatectomy without complications. The elevated liver enzymes were most likely related to OGX-011, however a non-steroidal anti-androgen effect could not be ruled out. The protocol was amended in the following manner:

- 1) Flutamide was replaced with bicalutamide, given its lower incidence of toxicity and the phase I experience of successfully changing from flutamide to bicalutamide in the face of Grade 1 or 2 elevated liver enzymes.
- 2) Patients that developed AST, ALT or bilirubin elevations were to have OGX-011 dose modifications and be prescribed a short course of dexamethasone.
- 3) Biochemistry lab testing was to be performed on a weekly basis in cycle 1, 2 and 3 (instead of every 2 weeks during cycle 2 and 3) to more closely monitor liver enzymes and other lab tests.

Approval was granted by Health Canada and the local REB by January 2006. Approval from the HSRRB was granted in June of 2006. With these changes, no further severe toxicities were observed and the trial completed accrual to the first stage. No pathologic complete responses were observed in this cohort and the trial accrual was held.

Baseline characteristics of the patients were as follows: median age=62, Gleason Score ≥ 8 in 39%, median PSA=7.9 (range 2.7-28), clinical T2 in 83% (Table 1). Toxicity was predominantly grade 1/2 including fevers, rigors, fatigue and transient AST and ALT elevations (see Table 2: Adverse Events). 4 patients did not complete protocol therapy: 2 for grade 3/4 AST/ALT toxicity, 2 for pre-existing cardiac reasons. Median nadir PSA pre-surgery=0.2 (range 0.1-1.4). OGX tissue concentrations associated with preclinical effect were achieved ($>1\mu\text{g/g}$) and sustained for up to 7 days after the last dose of OGX-011 (Figure 1). Compared to historical controls (NHT alone), inhibition of clusterin expression was observed. By immunohistochemistry (score 0-3), mean score was 1.1 (SD=0.6) for OGX treated and 2.1 (SD=0.5) for control ($p<0.001$), % of cancer cells with IHC score of 0 was 33.7% (SD=24.9) for OGX treated and 8.5% (SD=11.1) for control ($p<0.001$) (Figure 2). Using laser capture microdissection and QRT-PCR, mean clusterin mRNA was decreased by 61% compared to control ($p=0.009$) (Figure 3). Mean apoptotic index (TUNEL) was 1.3% (SD=0.4) for OGX treated and 0.8% (SD=0.3) for control ($p=0.003$) (Figure 4). A manuscript for publication is in preparation.

Table 1: Baseline Characteristics

Characteristic	Median (Range)	No. of Patients
Median Age (Range)	62 (48-71)	
Gleason Score		
6		1
7		14
8-9		9
Baseline PSA		
<10		11
10-20		12
>20		1
Clinical Stage		
1c		4
2a		9
2b		10
3a		1

Table 2: Adverse Events (Adverse events listed by worst by patient and include those that were considered possibly, probably or definitely related in >1 patient)

Adverse Event	Number of Patients				
	GRADE	1	2	3	4
Any		7	10	1	3
AST Increased		3	2	0	2
ALT Increased		3	1	0	2
Neutropenia					1
Hyperglycemia				1	
Hypoglycemia				1	
Fatigue		12	3		
Fever		10	3		
Chills		16	2		
Hyperhidrosis		7	2		
Diarrhea		4	2		
Myalgia		3	1		
Arthralgia		2	1		
Bilirubin			1		
Infection - Viral			1		
Hypertension			1		
Hot Flush		13			
Nausea		4			
Rash		4			
Anorexia		3			
Vomiting		2			
GGT Increased		2			

Figure 1: OGX-011 Concentrations in Tissues

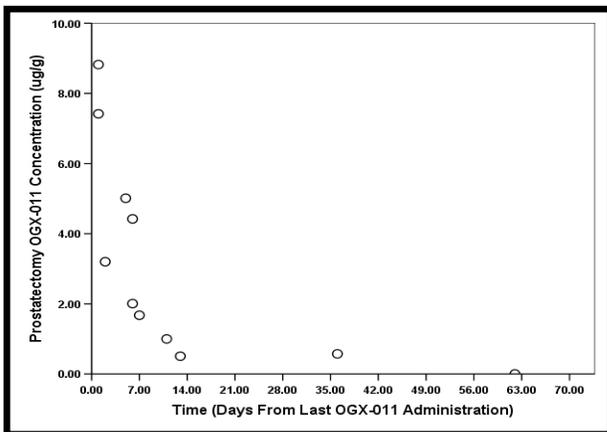


Figure 2: Clusterin Expression by Immunohistochemistry

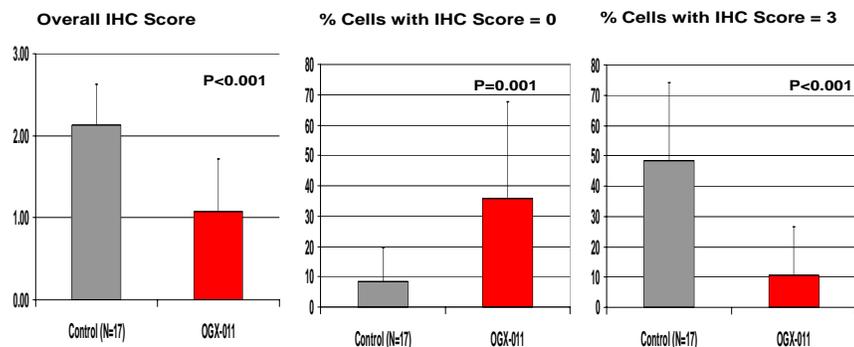


Figure 3: Clusterin mRNA Expression (QRT-PCR) in Laser Captured Microdissected Prostate Cancer Cells (A) and Lymph Nodes (B)

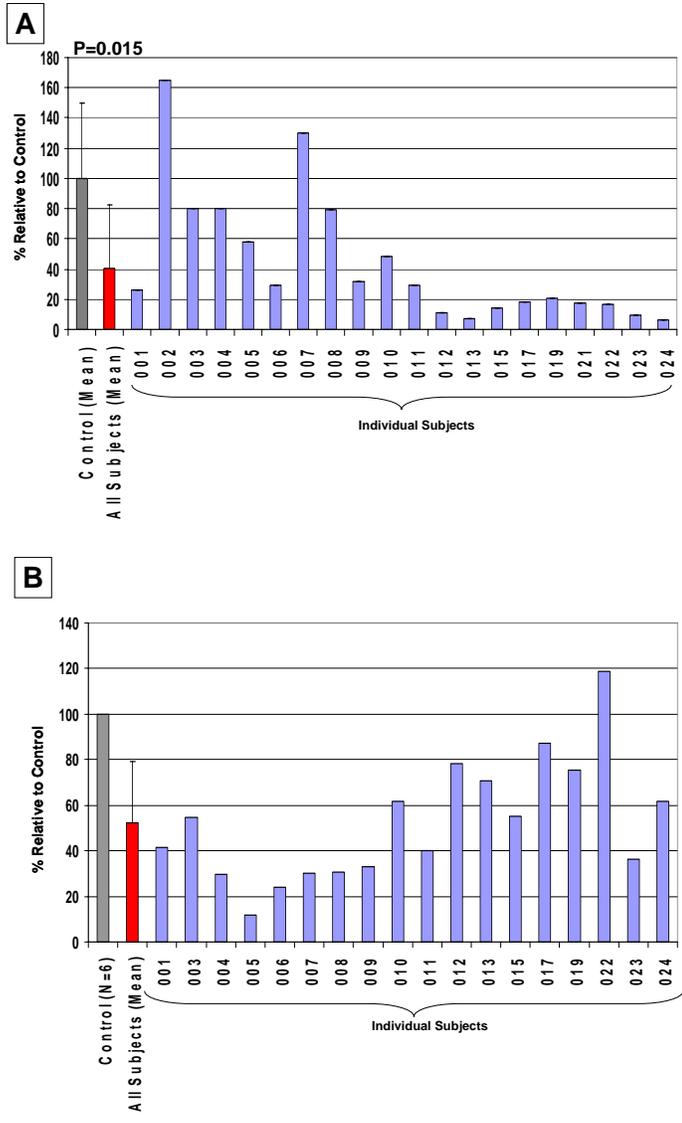
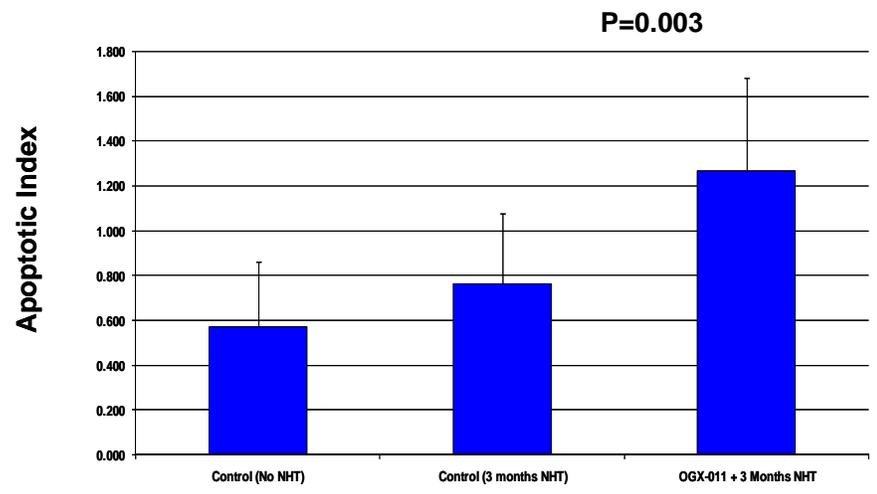


Figure 4: Apoptotic Index



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. This design is now being used to evaluate pharmacodynamic effect of a number of other targeted agents.
- Proof of principal demonstration of biologic effect of an antisense oligonucleotide
- Determination of recommended phase II dose of OGX-011 based on biological efficacy. This dose is the basis for other trials involving OGX-011 in patients with lung, breast and hormone refractory prostate cancer.
- Phase II neoadjuvant trial completed confirming biologic activity of OGX-011.

REPORTABLE OUTCOMES:

Manuscripts

1. Chi KN, Eisenhauer E, Fazil L, Jones EC, Goldenberg SL, Powers J, Tu D, Gleave ME. A Phase 1 Pharmacokinetic and Pharmacodynamic Study of OGX-011, a 2'-Methoxyethyl Antisense Oligonucleotide to Clusterin in Patients with Localized Prostate Cancer. *Journal of the National Cancer Institute*, 97(17):1287-96, 2005.
2. Gleave M, Chi KN. Knock-down of the cytoprotective gene, clusterin, to enhance hormone and chemosensitivity in prostate and other cancers. *Ann N Y Acad Sci*. 2005; 1058:1-15.
3. Gleave M, Miyake H, Chi K. Beyond simple castration: targeting the molecular basis of treatment resistance in advanced prostate cancer. *Cancer Chemother Pharmacol*. 2005; 56 Suppl 1:47-57.
4. K.N. Chi, E. Eisenhauer, L. Siu, H. Hirte, S.J. Hotte, S. Chia, J. Knox, E. Guns, J. Powers, ME Gleave. A Phase 1 study of a second generation antisense Oligonucleotide to Clusterin (OGX-011) in combination with Docetaxel: NCIC CTG IND 154. *Clinical Cancer Research*. 14: 833-839, 2008.
5. KN Chi, A Zoubeydi, ME Gleave. Custirsen (OGX-011): A Second-Generation Antisense Inhibitor of Clusterin for the Treatment of Cancer. *Expert Opinion on Investigational Drugs (In Press)*, 2008.

Abstracts

1. Chi KN, Eisenhauer E, Fazli L, Jones EC, Powers J, Hurtado-Coll A, Goldenberg SL, Gleave ME. 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. 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Oral Presentation at the Proffered Papers Plenary Session, Geneva, September 2004. *European Journal of Cancer Supplements*. Volume 2, No. 8, September 2004.
2. Kim N. Chi, Elizabeth Eisenhauer, Ladan Fazli, Ted Jones, Jean Powers, Debbie Ayers, Larry Goldenberg, Martin E. Gleave. A Phase I Pharmacokinetic and Pharmacodynamic Study of OGX-011, A 2'-methoxyethyl Phosphorothioate Gapmer Antisense To Clusterin, In Patients With Localized Prostate Cancer Prior To Radical Prostatectomy. *Proc of ASCO*, Abstract No. 3033, 2004. Poster Discussion Session, New Orleans, 2004.
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4. J.J. Laskin, K.N. Chi, B. Melosky, K. Sill, D. Hao, C.M. Canil, M. Gleave, N. Murray. Phase I study of OGX-011, a second generation antisense oligonucleotide (ASO) to clusterin, combined with cisplatin and gemcitabine as first-line treatment for patients with stage IIB/IV non-small cell lung cancer (NSCLC). *J Clin Oncol (Meeting Abstracts)* 2006 24:17078.
5. K. N. Chi, S. J. Hotte, E. Yu, B. J. Eigl, I. Tannock, F. Saad, S. North, J. Powers, E. Eisenhauer, National Cancer Institute of Canada - Clinical Trials Group. A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone refractory prostate cancer (HRPC). *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5069
6. K. N. Chi, L. Goldenberg, C. Kollmannsberger, N. Murray, L. Fazli, M. E. Gleave. A phase II neoadjuvant study of OGX-011, a 2'-methoxyethyl phosphorothioate antisense to clusterin, in patients with prostate cancer prior to prostatectomy. 2008 Genitourinary Cancers Symposium: A Multidisciplinary Approach (ASCO/ASTRO/SUO). Abstract 167, 2008.
7. F. Saad, S. J. Hotte, S. North, B. J. Eigl, K. Chi, P. Czaykowski, M. Pollak, L. A. Wood, E. Winquist. A phase II randomized study evaluating custirsen (OGX-011) in patients with hormone refractory prostate cancer (HRPC) who relapsed on or within 6 Months of first-line docetaxel therapy. 2008 Genitourinary Cancers Symposium: A Multidisciplinary Approach (ASCO/ASTRO/SUO). Abstract 151, 2008.
8. F. Saad, S. J. Hotte, S. A. North, B. J. Eigl, K. N. Chi, P. Czaykowski, M. Pollak, L. Wood, E. Winquist. A phase II randomized study of custirsen (OGX-011) combination therapy in patients with poor-risk hormone refractory prostate cancer (HRPC) who relapsed on or within six months of 1st-line docetaxel therapy. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 5002).

9. Kim N. Chi, Larry Goldenberg, Christian Kollmannsberger, Nevin Murray, Ladan Fazli, Martin E. Gleave. A phase II neoadjuvant study of OGX-011, a 2'methoxyethyl phosphorothioate antisense to clusterin, in patients with prostate cancer prior to prostatectomy. *Canadian Urological Association Journal* 2(3): 293 (abstr MP-8.14), 2008.

Presentations

1. "Clusterin Antisense". 4th International Congress on Targeted Therapies in Cancer. Washington, DC. August 26-28, 2005.
2. "Targeting the Cytoprotective Chaperone Protein Clusterin to Enhance Apoptosis in Patients with Prostate Cancer". US Department of Defense Prostate Cancer Research Program (PCRP) Innovative Minds in Prostate Cancer Today (IMPACT) meeting. Atlanta, GA. September 5-8, 2007.
3. "A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone refractory prostate cancer" (Oral Presentation). Prostate Cancer Conference 2007: Canadian Prostate Cancer Research Initiative/Canadian Prostate Cancer Network. Toronto, ON. September 28-10, 2007.
4. "A Randomized Phase II Study of OGX-011 (OGX) in Combination with Docetaxel (DOC) and Prednisone or Docetaxel and Prednisone Alone in Patients (Pts) with Metastatic Hormone Refractory Prostate Cancer (HRPC): NCIC CTG IND.165" (Oral Presentation). Making Connections: A Canadian Cancer Research Conference Celebrating the National Cancer Institute of Canada's 60th Anniversary. Toronto, ON. Nov 15-17, 2007.
5. "Antisense Therapeutics". 4th PacRim Breast and Prostate Cancer meeting. Whistler, BC. August 12-16, 2008.

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.

This trial has renewed interest in the antisense therapeutic platform, and several trials are moving forward with the second generation chemistry including antisense targeted against the cell survival proteins surviving, X-linked inhibitor of apoptosis and Heat Shock Protein 27 using the data from the phase I trial of OGX-011 to support dosing.

Phase II trials using the recommended phase II dose of OGX-011 are now proceeding. In addition to the neoadjuvant phase II trial discussed above, four other trials using OGX-011 are currently enrolling or have completed accrual: a randomized phase II trial of OGX-011 and docetaxel for patients with hormone refractory prostate cancer (grant funded by the National Cancer Institute of Canada), a randomized phase II trial of OGX-011 and mitoxantrone or docetaxel as second line therapy for patients with hormone refractory prostate cancer, a phase II trial of OGX-011 and docetaxel for patients with metastatic breast cancer, and a phase II trial of OGX-011 and Cisplatin-Gemciabine for patients with advanced lung cancer. A phase III trial is planned of Docetaxel with or without OGX-011 in patients with hormone refractory prostate cancer who have been previously treated with docetaxel.

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