A Phase II Neoadjuvant Study Of OGX-011, a 2'-Methoxyethyl Phosphorothioate Antisense Oligonucleotide To *Clusterin,* In Patients With Prostate Cancer Prior To Radical Prostatectomy

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BACKGROUND AND RATIONALE

Enhancing Apoptosis: Targeting Clusterin

- **Clusterin is a stress induced cytoprotective chaperone protein with anti-apoptotic function through a variety of mechanisms including inhibition of activated Bax** *(Michel, Biochem J, 1997; Humphreys, JBC, 1999; Zhang, Nat Cell Biol, 2005)*
- **In prostate cancer: increased expression correlates with higher Gleason Grade and expression increases after neoadjuvant hormone therapy** *(Steinberg, Clin Cancer Res, 1997 July, Prostate, 2002)*
- **Increased expression and poor prognosis factor in renal, bladder, ovary, lung and breast cancers** *(Redondo, Am J Path, 2000; Miyake, Urology, 2000; Parczyk, J Can Res Clin Oncol, 1994; July, Mol Can Thera, 2004; Redondo, Am J Path, 2000)*
- **Overexpression in pre-clinical models confers resistance to hormone therapy, chemotherapy and radiation** *(Miyake, Can Res, 2000; Miyake Clin Can Res, 2000; Zellweger, Clin Can Res, 2002)*

OGX-011 (OncoGenex Technologies Inc.)

- **Co-development with Isis Pharmaceuticals**
- **Phosphorothioate antisense oligonucleotide complimentary to the translation initiation site of *clusterin* mRNA**
- **Potently inhibits expression of clusterin in pre-clinical models and enhances apoptosis induced by hormone therapy, chemotherapy and radiation**
- **Incorporates second-generation chemistry in the form of 2'-O-methoxyethyl modifications to the 4 bases on either end of the 21-mer molecule which in pre-clinical models results in:**
  - **Increased tissue half-life to ~ 7 days**
  - **Decreased non-specific toxicity**
- **Phase I single-agent study in patients with localized prostate cancer prior to radical prostatectomy** *(Chi, JNCI, 2005)*:
  - **Dose-dependent increases in OGX-011 tissue concentrations**
  - **Dose dependent decreases in clusterin expression in prostate cancer tissue to <10%**
  - **Grade 1 or 2 toxicity only**
  - **Recommended phase II dose of 640 mg IV once weekly based on biologic activity and tolerability**

STUDY DESIGN

Primary Objective

- **To assess the pathologic complete response (pCR) rate of combined treatment with neoadjuvant hormone therapy (NHT) and OGX-011 in men with localized prostate cancer and high risk features**

Secondary Objectives

- **To determine the prostate tissue concentration of OGX-011**
- **To measure evidence of OGX-011 effect on clusterin expression in post-radical prostatectomy specimens**
- **To measure evidence of OGX-011 effect on clusterin expression in patient serum**

Design

- **Open label, single center, phase II study**
- **Simon's 2-stage design: 21 eligible patients in first stage and if 2 or more pCR then an additional 20 patients enrolled (H0:5%, Ha:20%, α = 0.05, β=0.10)**

Patients

- **Candidates for prostatectomy and having localized prostate cancer with high risk clinical features (PSA > 10, Gleason 7-10, T3, or Gleason 6 and >3+ biopsies)**
- **Adequate marrow, hepatic and renal function**

Protocol Therapy

- **OGX-011 640 mg IV over 2-hours weekly x 4 x 3 cycles (12 weeks total) after loading doses on days 1,3,5**
- **LHRH agonist 3-month depot on day 1**
- **Flutamide 250 mg PO TID or bicalutamide 50 mg OD days 1-28**
- **Radical prostatectomy within 14 days of last dose**

RESULTS

Patient Characteristics (N=24)

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

Adverse Events (N=24)

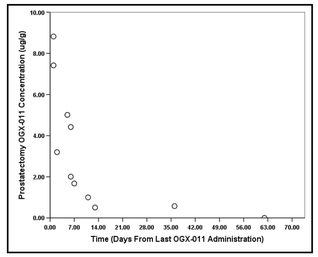
Adverse Event	GRADE			
	1	2	3	4
Any	7	10	1	3
AST Increased	3	2	0	2
ALT Increased	3	1	0	2
Neutropenia				1
Hyperglycemia			1	
Hypoglycemia			1	
Fatigue	12	3		
Fever	10	3		
Chills	16	2		
Hyperhidrosis	7	2		
Diarrhea	4	2		
Myalgia	3	1		
Arthralgia	2	1		
Bilirubin		1		
Infection - Viral		1		
Hypertension		1		
Hot Flush	13			
Nausea	4			
Rash	4			
Anorexia	3			
Vomiting	2			
GGT Increased	2			
Pruritis	1			
Urticaria	1			
Vasoconstriction	1			
Asthenia	1			
Pain – Abdomen	1			
Cheilitis	1			
Constipation	1			
LDH Increased	1			
Pain – Extremity	1			
Dizziness	1			
Headache	1			
Hypoaesthesia	1			
Parasthesia	1			
Thrombocytopenia	1			
Insomnia	1			
Sinus Congestion	1			

Adverse events listed by worst by starting dose by patient and include those that were considered possibly, probably or definitely related

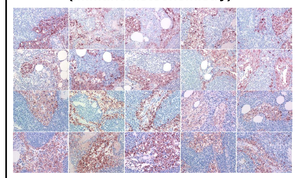
Treatments Administered

- **20 Patients completed protocol therapy as planned**
- **4 patients did not complete protocol therapy:**
  - **2 patients because of grade 4 AST/ALT increases in cycle 1**
    - **Protocol amended to substitute bicalutamide for flutamide and administration of corticosteroids for AST/ALT elevations with no further incidences of severe AST/ALT elevations**
  - **1 patient stopped because of angina (pre-existing) in cycle 1**
  - **1 patient did not undergo radical prostatectomy**
- **No pCR were observed and study stopped after the first stage**

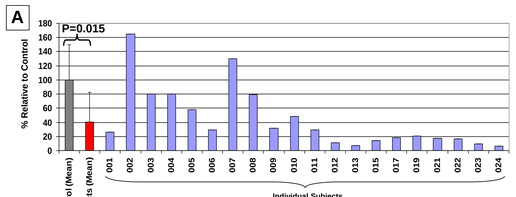
OGX-011 Concentration in Tissue (N=11)

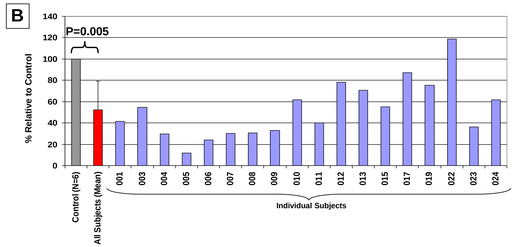


OGX-011 in Lymph Nodes (Immunohistochemistry)

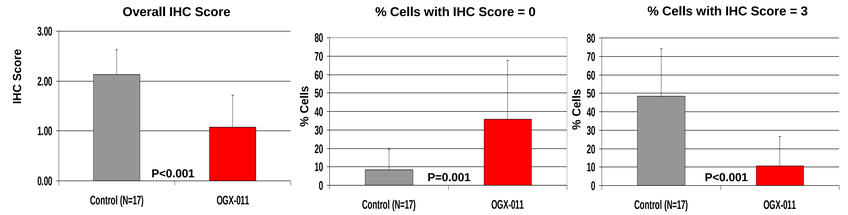


Clusterin mRNA Expression (QRT-PCR) in Laser Captured Microdissected Prostate Cancer Cells (A) and Lymph Nodes (B)

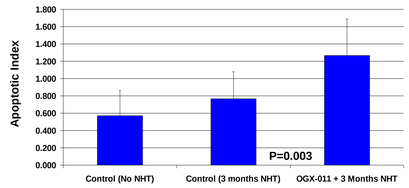




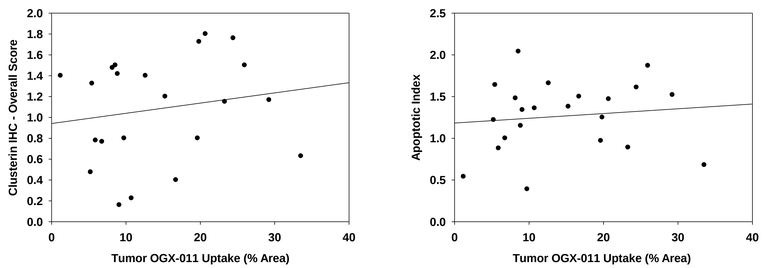
Clusterin Expression in Prostate Tumors - Immunohistochemistry



Prostate Tumor Apoptotic Index (TUNEL)



OGX-011 Uptake (ImagePro-Plus) vs. Clusterin IHC and Apoptotic Index



CONCLUSIONS

- **3 months of neoadjuvant OGX-011 and androgen withdrawal therapy was well tolerated**
- **Incidence of grade 3/4 liver enzymes elevation associated with OGX-011 was reduced after substitution of bicalutamide for flutamide and early institution of corticosteroids for abnormal liver enzymes**
- **OGX-011 concentrations associated with biologic activity were observed > 7 days post-infusion**
- **Decreased expression of clusterin and increase in apoptotic index was observed compared to historical control**
- **Neoadjuvant treatment was not associated with pathologic complete responses**

ACKNOWLEDGEMENTS

- **Funded by a grant from the Department of Defense - Prostate Cancer Research Program**
- **OGX-011 was provided by OncoGenex Inc.**
- **We thank Jenny Baybik for her technical assistance**