Phase I Trial of OGX-427, a 2'methoxyethyl Antisense Oligonucleotide (ASO), Against Heat Shock Protein 27 (Hsp27)

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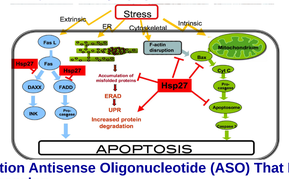
BACKGROUND

Hsp27: a Stress-activated, ATP-independent Cytoprotective Chaperone that Mediates Treatment Resistance in Cancer by Inhibiting Apoptosis.



OGX-427: a Second Generation Antisense Oligonucleotide (ASO) That Induces Apoptosis by Inhibiting Hsp27 Expression.

- **Decreases Hsp27 mRNA, inhibits cell growth, & induces apoptosis in many human cancer cell lines.**
- **Inhibits several survival signaling pathways associated with treatment resistance.**
- **Demonstrates single agent and chemo-sensitizing activity in combination with several cytotoxic drugs, including docetaxel, in many preclinical cancer models.**

OBJECTIVES

- **OGX-427 Therapy as a Single Agent & in Combination with docetaxel.**
  - **Primary:**
    - **Assess the safety profile.**
    - **Determine the MTD (up to a maximum of 1000 mg).**
  - **Secondary:**
    - **Determine the PK profile.**
    - **Determine whether OGX-427 alters cardiac repolarization (QTcF interval duration).**
    - **Document disease response & stabilization.**
    - **Assess for a biologically effective dose of OGX-427 that inhibits serum Hsp27 & reduces serum PSA levels in patients with CRPC.**
    - **Measure CTC expression of Hsp27 pre- and post- therapy.**
    - **Estimate a biological dose, with acceptable toxicity, for further evaluation in Phase 2 studies.**

METHODS

- **OGX-427 was escalated from 200 to 1000 mg in 5 cohorts.**
- **Cohorts 6 & 7 added docetaxel at one dose below the MTD and at the MTD determined for OGX-427 as monotherapy.**
- **Planned sample size/cohort: 6**
- **Patient were replaced if they did not have complete safety assessments through Cycle 1.**

STUDY DESIGN

Three Loading Doses OGX-427 (Day -9 to -1)

↓

Cycle 1 (Day 1) OGX-427 (plus docetaxel for Cohorts 6+7)

(Day 8) OGX-427

(Day 15) OGX-427

↓

Individual Patient Safety Review Prior to Initiating Cycle 2

No DLT: Continue Study Treatment up to 10 cycles

DLT: Stopping Rules

INCLUSION/EXCLUSION CRITERIA

- **Histologically or cytologically confirmed cancer diagnosis of breast, ovary, prostate, bladder or lung (NSCLC)**
- **Metastatic disease**
- **≤ 3 chemotherapy regimens; (breast and ovarian, ≤ 6 regimens)**
- **Karnofsky score ≥ 60%**
- **No documented CNS metastasis**
- **Appropriate laboratory requirements**
- **Normal ECG & not on drugs know to increase QTc interval**

RESULTS

- **Study initiated in June 2007**
- **46 patients enrolled and treated**
- **Results presented as of May 3, 2010**
- **Median number of cycles received:**
  - **OGX-427 monotherapy: 2 (0-8)**
  - **OGX-427 combined with docetaxel: 6 (1-10)**
- **Reasons for discontinuation of therapy (3 remain on therapy)**
  - **Disease progression: 58%**
  - **Global deterioration: 23%**
  - **Toxicity: 12%**
  - **Other 7%**
- **MTD not met**
  - **1 DLT : cerebral hemorrhage in patient with undiagnosed brain metastasis**
- **No evidence of prolongation of cardiac repolarization.**

OGX-427 DOSE LEVELS PER COHORT

Cohort	OGX-427 Dose Level	# Patients Accrued	DLT
1 (OGX-427)	200 mg	6	
2 (OGX-427)	400 mg	7	
3 (OGX-427)	600 mg	7	1
4 (OGX-427)	800 mg	8	
5 (OGX-427)	1000 mg	6	
6 (OGX-427 + docetaxel)	800 mg	6	
7 (OGX-427 + docetaxel)	1000 mg	6	

DEMOGRAPHICS

Characteristics	All Patients (N=46)
Age (yrs): median (range)	64 (33-86)
Sex: Male/Female (%)	63/37
Karnofsky Score (%): median (range)	80 (70-100)
# Prior Chemotherapy Regimens: median (range)	3 (0-6)
# Metastatic Sites: median (range)	3 (1-9)
Disease Sites	
Prostate	25 (54%)
Breast	11 (24%)
Lung	5 (11%)
Ovary	5 (11%)

SAFETY

INCIDENCE OF NON-LABORATORY ADVERSE EVENTS RELATED TO STUDY TREATMENT

OGX-427 Monotherapy	% AE
Infusion Reactions/CRS	67
Chills	53
Pruritus	29
Flushing	21
Fatigue	15
Pyrexia	15
Elevated Creatinine	15
Arthralgia	15
Hypertension	12
Erythema	12

OGX-427 + Docetaxel	% AE
Infusion Reactions/CRS	83
Chills	75
Fatigue	75
Nausea	33
Back pain	33
Pruritus	33
Anorexia	33
Dyspnea	33
Diarrhea	25
Asthenia	25

INFUSION REACTIONS

- **Documented in 72% of patients**
- **Increasing incidence with increasing dose**
  - **33% at the 200 mg dose vs ~88% at the 800 & 1000 mg doses**
- **Grade 1 or 2 for 93% of patients**
- **Mainly seen during the Loading Dose Period and Cycle 1**
- **Few infusion alterations (mainly at 800 + 1000 mg doses) required for toxicity**
  - **Infusions delayed: 2.1%**
  - **Infusions modified: 1.1%**
  - **Infusion interrupted: 7.2%**
  - **Infusion discontinued: 0.8%**
- **Reactions at highest doses were successfully treated with steroids.**

GRADE 3/4 NON-LABORATORY ADVERSE EVENTS RELATED TO STUDY TREATMENT

Adverse Event	Cohorts						
	#1 200 mg (n=6)	#2 400 mg (n=7)	# 3 600 mg (n=7)	# 4 800 mg (n=8)	# 5 1000 mg (n=6)	#6 800 mg + docetaxel (n=6)	#7 1000 mg + docetaxel (n=6)
Chills			1	1	1		1
Fatigue			1			1	1
Infusion Reaction/CRS*			1	1	1		
Febrile Neutropenia							2
Cerebral Hemorrhage (DLT)			1				

* Cytokine Release Syndrome
The following adverse events were reported in only 1 patient:
Pruritus, urticaria, bronchospasm, chest pain, DVT, dyspnea, hypertension,, hypoxia, lymphorrhea, neuralgia & wheezing.

SAFETY (CONT.)

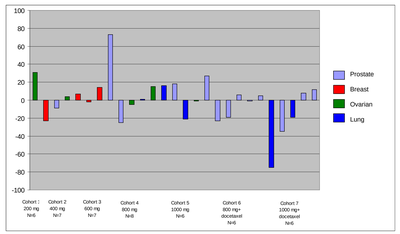
GRADE 3/4 LABORATORY ADVERSE EVENTS (IN DECREASING ORDER OF FREQUENCY)

Adverse Event	Cohort 1 200 mg (n=6)	Cohort 2 400 mg (n=7)	Cohort 3 600 mg (n=7)	Cohort 4 800 mg (n=8)	Cohort 5 1000 mg (n=6)	Cohort 6 800 mg + docetaxel (n=6)	Cohort 7 1000 mg + docetaxel (n=6)
Lymphopenia	2	2	2	5	2	4	5
Prolonged PTT	-	1	2	5	3	1	3
Neutropenia	-	-	1	-	-	5	6
Hyponatremia	1	1	1	2	1	1	3
Anemia	-	-	-	2	2	1	2
Elevated Creatinine	-	-	1	1	-	-	1
Thrombocytopenia	-	-	1	1	-	-	1

EFFICACY

- **OGX-427 Monotherapy**
  - **Tumor Markers:**
    - **CA-125: 2/4 evaluable patients with ovarian cancer had a ↓ ≥ 25%**
    - **PSA: 3/15 (20%) evaluable patients with prostate cancer had a ↓≥ 30%**
  - **Hsp27 CTC: ↓ seen at all dose levels and in all diseases**
  - **Reduction of serum Hsp27 protein levels by ≥ 30% from baseline in ~25% of patients treated at the 800 & 1000 mg doses**
    - **No dose-related or consistent reduction**
- **OGX-427 & Docetaxel**
  - **Tumor Markers:**
    - **PSA: 5/9 (55%) evaluable patients with prostate cancer had a ↓≥ 30%**
  - **Hsp27 CTC: ↓ seen in 71% of patients**
  - **Reduction of serum Hsp27 protein levels by ≥ 30% from baseline in ~35% of patients**
    - **Possible dose related effect and associated with length of treatment**

BEST CHANGE IN MEASURABLE DISEASE BY CATEGORY & COHORT (in %)



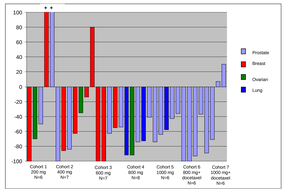
CTC AND HSP27^{+}CTC

- **Whole blood for circulating tumor cells was collected at screening, pretreatment and cycles 1, 2 ,3 & 5.**
- **CTC were enumerated using an immunomagnetic approach.**
- **Hsp27^{+} CTC were identified using an immunofluorescent method.**
  - **75% of the baseline total CTC were Hsp27^{+}.**
  - **No change in the % Hsp27^{+} CTC/ total CTC following treatment.**
  - **Median baseline Hsp27^{+}CTC (range): 15 (0-271)**

	# Patients (%) with > 5 Hsp27+CTC at Baseline*	# Patients (%) With Decrease to ≤ 5 Post Therapy	# Patients (%) With Any Decrease in Hsp27+CTC	Median Decrease (%)
OGX-427 Monotherapy*	28/32 (88%)	9/26 (35%)	24/26 (89%)	67%
OGX-427 & Docetaxel**	7/12 (58%)	4/7 (57%)	5/7 (71%)	89%

*2 patients did not have adequate Hsp27+ CTC data for analysis; 3 additional patients had ≤ 5 at baseline.
**3 patients did not have adequate Hsp27+ CTC data for analysis; 5 additional patients had ≤ 5 at baseline.

BEST CHANGE IN HSP27^{+}CTC BY CATEGORY & COHORT (in %)*



*patients who had a minimum of 5 CTCs at baseline

PHARMACOKINETICS

Dose [a]	N	Cmax [b]	AUC 0-inf [c]	t1/2 [d]	Cl [e]
200	6	21756	63558	2.91	3263
400	7	46986	163609	3.07	2558
600	6	102591	324396	2.75	2035
800	6	156127	586817	3.20	1595
1000	6	139624	551778	3.44	2004
800 + Docetaxel	6	113450	377146	3.21	2395
1000 + Docetaxel	6	163150	528687	3.40	2332

a: mg
b: ng/mL
c: ng*h/mL
d: h
e: mL/h,
D = docetaxel

- **Moderate non-proportional increases in AUC0-inf and Cmax with increasing dose**
- **Slight increase in the t1/2 over dosing range**
- **Moderate decrease in plasma clearance (Cl) with increasing dose**
- **No effect of docetaxel on PK parameters of OGX-427**

COMPLEMENT

- **Complement (C) split products (Bb, C3a and C5a) were drawn following the three loading doses and on Day 1 of each cycle.**
- **There was a significant correlation between the pre and post time-weighted ratios of all three C fragments and the dose of OGX-427.**
  - **Activation of the alternative pathway/amplification loop of C (C3a and Bb) was apparent at low doses of OGX-427, whereas activation of the terminal pathway (C5a) did not become apparent until highest doses.**
- **Cohorts where docetaxel was combined with OGX-427 appeared to generate lower levels of C, presumably due to the concomitant use of steroid prophylaxis for docetaxel.**
- **There was no apparent relationship between the time-weighted ratios of C and the incidence of infusion reactions.**

CONCLUSIONS

- **OGX-427 appeared safe at the highest dose of 1000 mg, both as a single agent and when combined with docetaxel.**
  - **MTD not reached at doses tested**
  - **Major toxicity was infusion reactions at 800-1000 mg doses**
    - **Majority were grade 1& 2 and were treatable with steroids.**
- **No evidence of alteration of cardiac repolarization**
- **Reduction in serum Hsp27 protein levels at 800 mg & 1000 mg doses**
- **OGX-427 as a single agent reduced tumor markers in patients with both prostate and ovarian cancer.**
- **Decline of ≥ 50% in both total CTCs & Hsp27^{+} CTCs observed in over half the patients**
  - **Observed in each of the 7 cohorts and each disease category (prostate, breast, lung, ovarian)**
- **Half-life increases slightly and there appears to be a non-proportional increase in C_{max} and AUC_{inf} & a decrease in Cl with increasing dose.**
- **Biological activity was demonstrated, with acceptable activity, at doses ≥ 600 mg.**
- **These results warrant study of OGX-427 in a Phase II trial.**

ACKNOWLEDGEMENTS

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