

**A Phase 1 Study Evaluating a
Second Generation Antisense
Oligonucleotide
(OGX-427) That Inhibits
Heat Shock Protein 27 (Hsp27)**

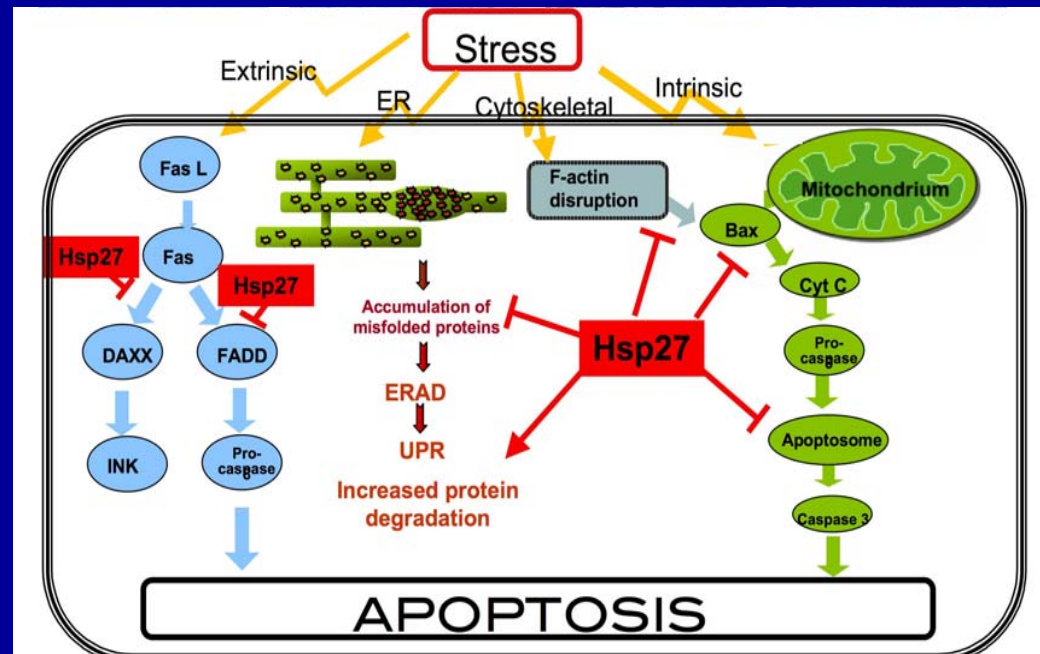
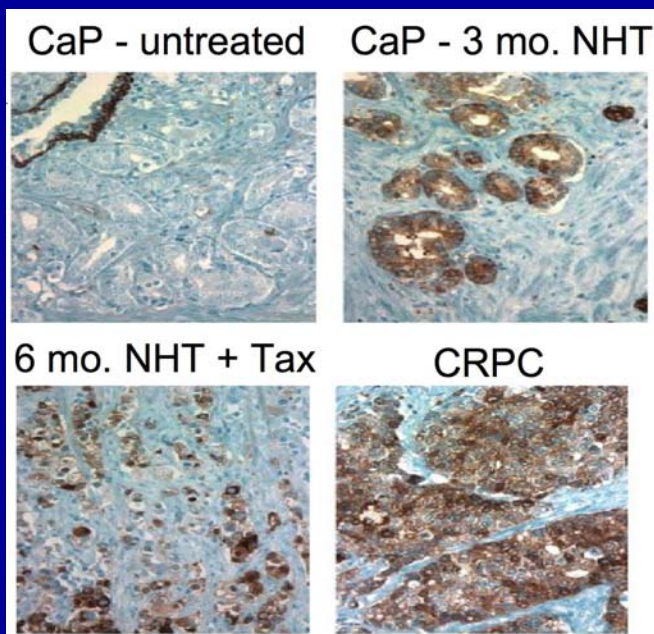
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Introduction and Background

Hsp27 is a stress-activated, ATP-independent Cytoprotective Chaperone that Mediates Treatment Resistance in Cancer

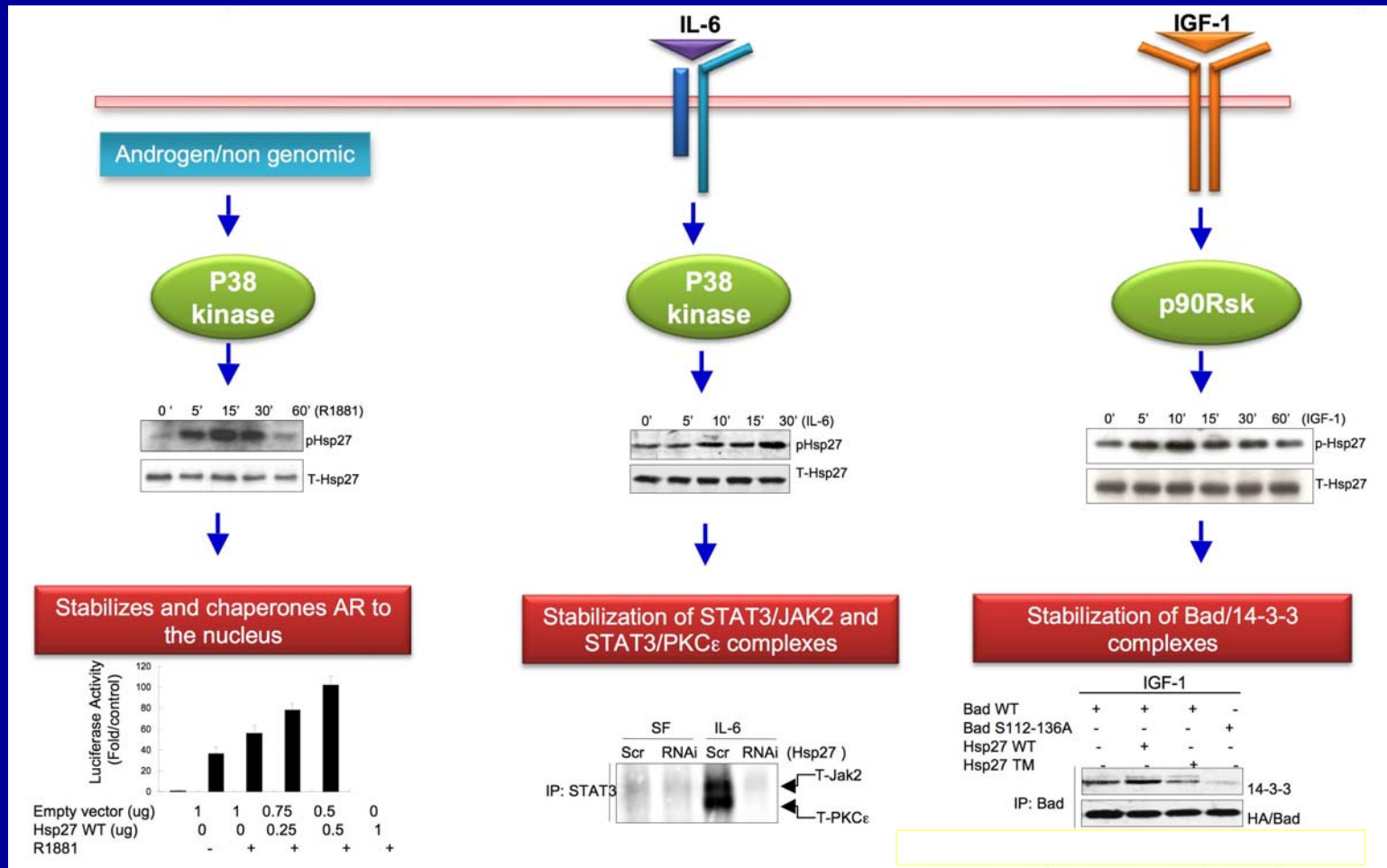
Phospho-activated on ser 78 & 82 to form chaperoning oligomer

- Inhibits apoptosis at several points along both intrinsic and extrinsic pathways
- Inhibits ER stress, enhances ubiquitin-proteasomal pathway activity
- Facilitates normal protein folding and function (signaling, transcription), including AR, IGF-1, IL-6



Introduction and Background

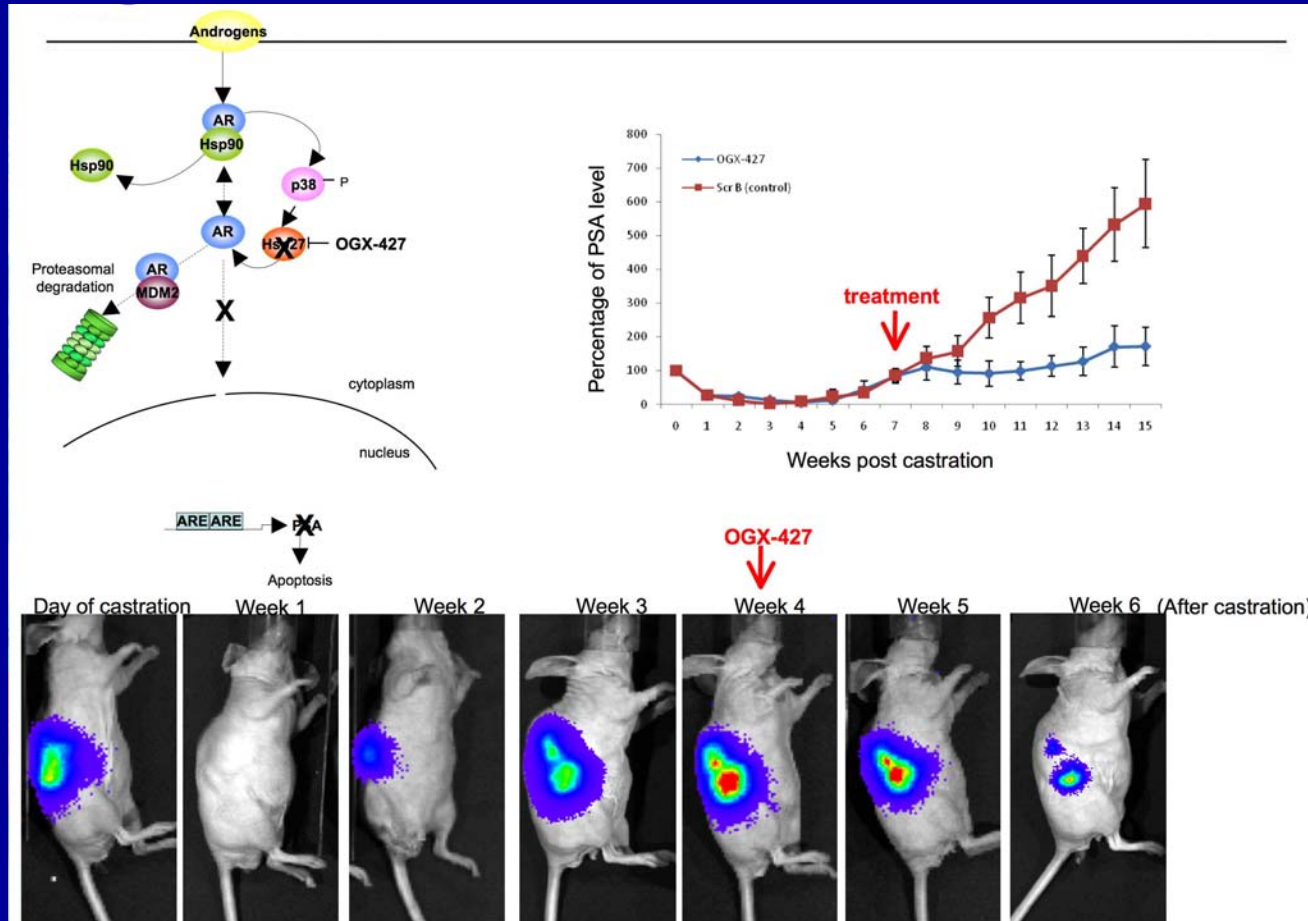
Hsp27 Mediates Castrate Resistance in Prostate Cancer via Several Survival Pathways



Rocchi et al Cancer Res 2004, 2005
Zubeidi et al Cancer Res 2007

Introduction and Background

Hsp27 Knockdown induces apoptosis and Delays Progression in Human Prostate LNCaP Cancer



[Increased Hsp27 after androgen ablation facilitates androgen-independent progression in prostate cancer via signal transducers and activators of transcription 3-mediated suppression of apoptosis.](#) Rocchi P, Beraldi E, Ettinger S, Fazli L, Vessella RL, Nelson C, Gleave M. *Cancer Res.* 2005 Dec 1;65(23):11083-93

[Cooperative interactions between androgen receptor \(AR\) and heat-shock protein 27 facilitate AR transcriptional activity.](#) Zoubeidi A, Zardan A, Beraldi E, Fazli L, Sowery R, Rennie P, Nelson C, Gleave M. *Cancer Res.* 2007 Nov 1;67(21):10455-65

Introduction and Background

OGX-427

- **Second generation antisense oligonucleotide (ASO) that inhibits 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**

[Heat Shock Protein 27 as a New Therapeutic Target for Radiation Sensitization of Head and Neck Squamous Cell Carcinoma.](#) Hadchity E, Aloy MT, Paulin C, Armandy E, Watkin E, Rousson R, Gleave M, Chapet O, Rodriguez-Lafrasse C. Mol Ther. 2009 May 12

[Hsp27 knockdown using nucleotide-based therapies inhibit tumor growth and enhance chemotherapy in human bladder cancer cells.](#) Kamada M, So A, Muramaki M, Rocchi P, Beraldi E, Gleave M. Mol Cancer Ther. 2007 Jan;6(1):299-308.

[Small interference RNA targeting heat-shock protein 27 inhibits the growth of prostatic cell lines and induces apoptosis via caspase-3 activation in vitro.](#) Rocchi P, Jugpal P, So A, Sinneman S, Ettinger S, Fazli L, Nelson C, Gleave M. BJU Int. 2006 Nov;98(5):1082-9.

[Increased Hsp27 after androgen ablation facilitates androgen-independent progression in prostate cancer via signal transducers and activators of transcription 3-mediated suppression of apoptosis.](#) Rocchi P, Beraldi E, Ettinger S, Fazli L, Vessella RL, Nelson C, Gleave M. Cancer Res. 2005 Dec 1;65(23):11083-93

Objectives

- **Primary: as a single agent & in combination with docetaxel**
 - **Assess the safety profile of OGX-427**
 - **Determine the MTD of OGX-427 up to a maximum dose of 1000 mg**

Objectives

- **Secondary: as a single agent & in combination with docetaxel**
 - **Determine the PK profile of OGX-427**
 - **Determine whether OGX-427 alters cardiac repolarization (QTcF interval)**
 - **Document any disease response or stabilization to OGX- 427**
 - **Assess for a biologically effective dose of OGX-427 that inhibits Hsp27 & reduces serum PSA levels**
 - **Measure Hsp27 expression in CTC post OGX- 427**

OGX-427 Dosing Levels

Cohort	OGX-427 Dose Level	Target Number of Patients
1	200 mg	6
2	400 mg	6
3	600 mg	6
4	800 mg	6
5	1000 mg	6
Established MTD	TBD	Additional 6
6 + Docetaxel	Dose below MTD determined for OGX-427 as a single agent in Cohorts 1-5	6
7 + Docetaxel	MTD determined for OGX-427 as a single agent in Cohorts 1-5	6
Established MTD + docetaxel	TBD	Additional 6

Study Design

Cycle 1

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

(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

Definition of DLT

- **An AE occurring during the Loading Dose Period or Cycle 1**
 - Any grade 5 AE
 - Any grade 4 AE (except: alopecia, anemia, pain, fatigue, insomnia, arthralgias, myalgias, or nail changes)
 - Any grade 3 AE felt by the investigator to be clinically relevant which does not resolve to \leq grade 2 within 48 hours of therapy (e.g. antiemetic for nausea)
 - Grade 4 neutropenia or thrombocytopenia lasting ≥ 7 days
 - Grade 3/4 thrombocytopenia requiring platelet transfusion or associated with overt bleeding
 - Febrile neutropenia or documented infection with $\text{ANC} < 1000 \text{ cells/mm}^3$

Inclusion/Exclusion Criteria

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

Preliminary Results (Cohorts 1-6)

- **Study initiated in June 2007**
- **41 patients enrolled and treated in the first 6 cohorts**
 - **1 patient (Cohort 1) deteriorated prior to any therapy and is not included in the analysis**
- **Results presented are as of April 22, 2009**
- **No evidence of prolongation of cardiac repolarization observed in any cohort**

Demographics

Characteristic	All Patients (N=40)
Age (yrs): median (range)	62 (33-86)
Sex: Male/Female (%)	60/40
Karnofsky Score (%): Median (range)	80 (70-100)
# Prior Chemotherapy Regimens: Median (range)	3 (0-6)
# Metastatic Sites: Median (range)	2 (1-9)
Disease Sites	
Breast	11 (28%)
Lung	3 (8%)
Ovary	5 (13%)
Prostate	21 (53%)

Number of Cycles Received by Dose Cohort

OGX-427	Cohort 1 200 mg (n=7)	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)*
Loading Dose Only				2		
Cycles: Median (range)	2 (1-5)	2 (1-8)	1 (1-6)	3 (1-6)	2 (2-7)	3 (2-4)

***Preliminary data: 6 patients (2 in Cohort 5 and 4 in Cohort 6) remain on study treatment**

Patient Disposition and Reasons for Therapy Discontinuation

OGX-427	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)
Enrolled	6	7	7	8	6	6
Discontinued	6	7	7	8	4	2
Reason for Discontinuation						
Disease Progression	6 (100%)	7 (100%)	6 (86%)	5 (63%)	4 (67%)	2(33%)
Adverse event			1 (14%)	2 (26%)		
Voluntary withdrawal				1 (13%)		

Safety Analysis

- **One DLT (Cohort 3): cerebral hemorrhage in patient with undiagnosed brain metastasis**
- **Majority of AEs were Grade 1 or 2**
- **Most common non-laboratory AEs**
 - **chills (55%)**
 - **pruritus (40%)**
 - **fatigue (38%)**
 - **dyspnea (28%)**
 - **flushing (25%)**
 - **diarrhea (25%)**
 - **arthralgias (25%)**

Adverse Events Related to Infusions

- Documented in 55% of patients
 - infusion interrupted: 5/40 patients (1 each in Cohorts 3, 4, and 5 and 2 in Cohort 6)
 - infusion discontinued: 2/40 patients (1 each in Cohorts 3 & 4)
- Majority of AEs were Grade 1 or 2
- Mainly seen during the loading dose period
- Trend for increasing incidence with increasing dose
 - 33% at the 200 mg dose vs 67% at the 1000 mg dose)

Grade 3/4 Non-laboratory AEs Related to Study Treatment

Preferred Term	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)
Chills			1	1	1	
Fatigue			1			1
Bleed into brain met			1			
Cytokine release syndrome				1		
Infusion reaction					1	

Laboratory AEs*

	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)
Hematology						
Lymphopenia	2 (33%)	2 (29%)	2 (29%)	5 (63%)	2 (33%)	4 (67%)
Neutropenia	-	-	1 (14%)	-	-	4 (67%)
Anemia	-	-	-	2 (25%)	2 (33%)	1 (17%)
Thrombocytopenia	-	-	1 (14%)	1 (13%)	-	-
Coagulation						
Prolonged PTT	-	1 (14.3%)	2 (29%)	5 (63%)	3 (50%)	1 (17%)
Serum Chemistry						
Elevated AST	-	-	1 (14%)	-	-	-
Elevated Creatinine	-	-	1 (14%)	1 (13%)	-	-
Hypokalemia	-	-	1 (14%)	-	1 (17%)	-
Hyponatremia	1 (17%)	1 (14%)	1 (14%)	2 (25%)	-	1 (17%)
Hyperbilirubinemia	-	-	1 (14%)	-	-	-

* Documented in more than 1 patient

Preliminary Efficacy: Measurable Disease

- **22/40 assessable for measurable disease response**
- **No patient met the definition for a partial response**
 - **breast cancer patient (Cohort 2):**
 - **23% reduction in measurable disease for 3 months & 19% reduction in CA15-3**
 - **prostate cancer patient (Cohort 2):**
 - **9% reduction in measurable disease for 5.7 months & 63% reduction in PSA**
 - **ovarian cancer patient (Cohort 4):**
 - **stable disease for 4.7 months & 28% reduction in CA-125**

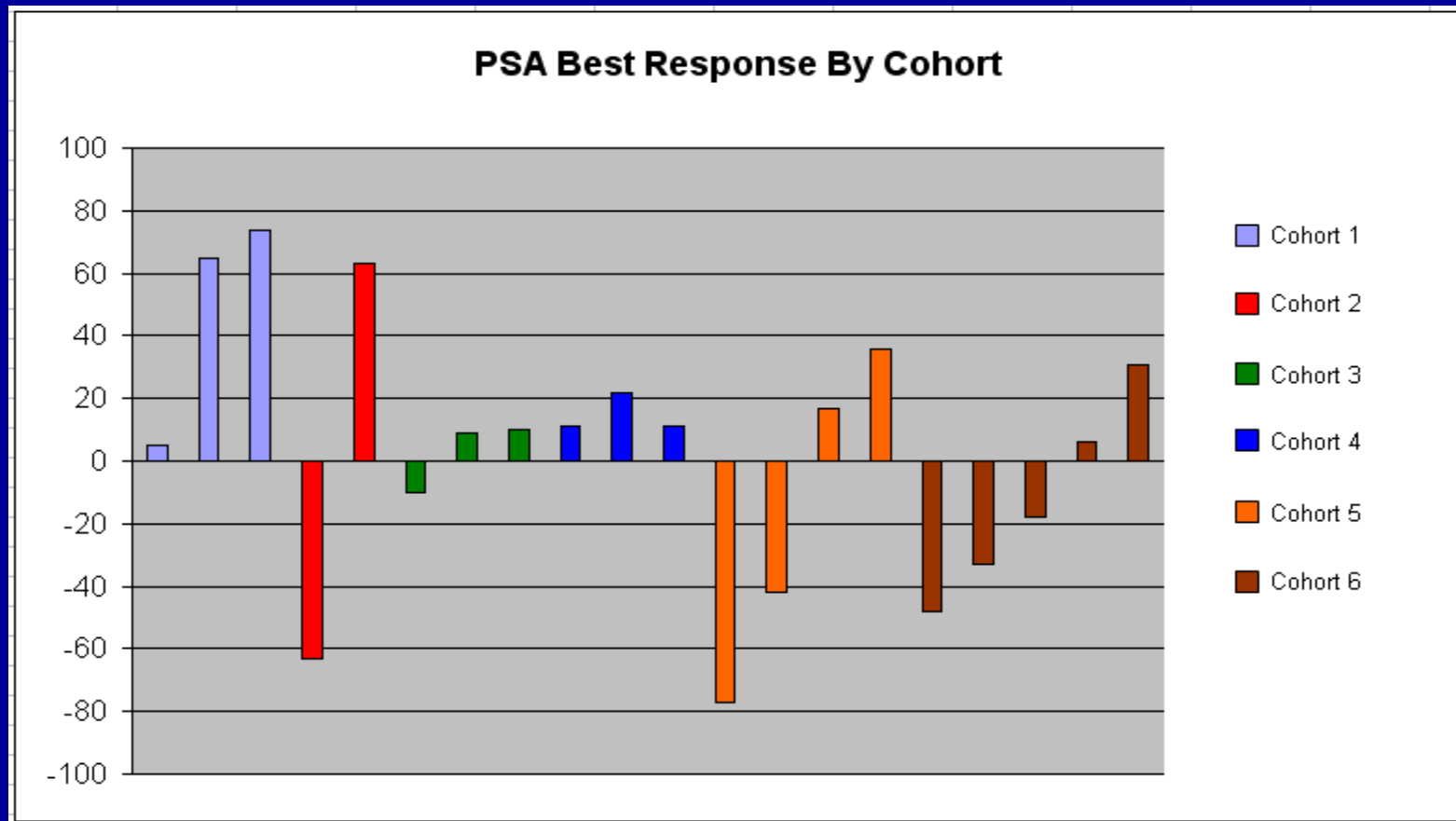
Preliminary Efficacy: Tumour Markers

CA-125

- 5/5 patients with ovarian cancer had serial CA-125
- 3/5 patients had a reduction of CA-125:
 - ↓27% (Cohort 1)
 - ↓ 28% (Cohort 4)
 - ↓ 63% (Cohort 5)

Preliminary Efficacy: Tumour Markers

PSA



CTC and Hsp27⁺ CTC

- Whole blood for CTCs was collected at screening, pretreatment and Cycles 1, 2, 3, & 5
- CTCs were enumerated using an immunomagnetic approach
- Hsp27⁺ CTCs were identified using an immunofluorescent method
 - 75% of the baseline total CTCs were Hsp27⁺
 - No change in the % patients with Hsp27⁺ CTCs following treatment
- No dose-response effect

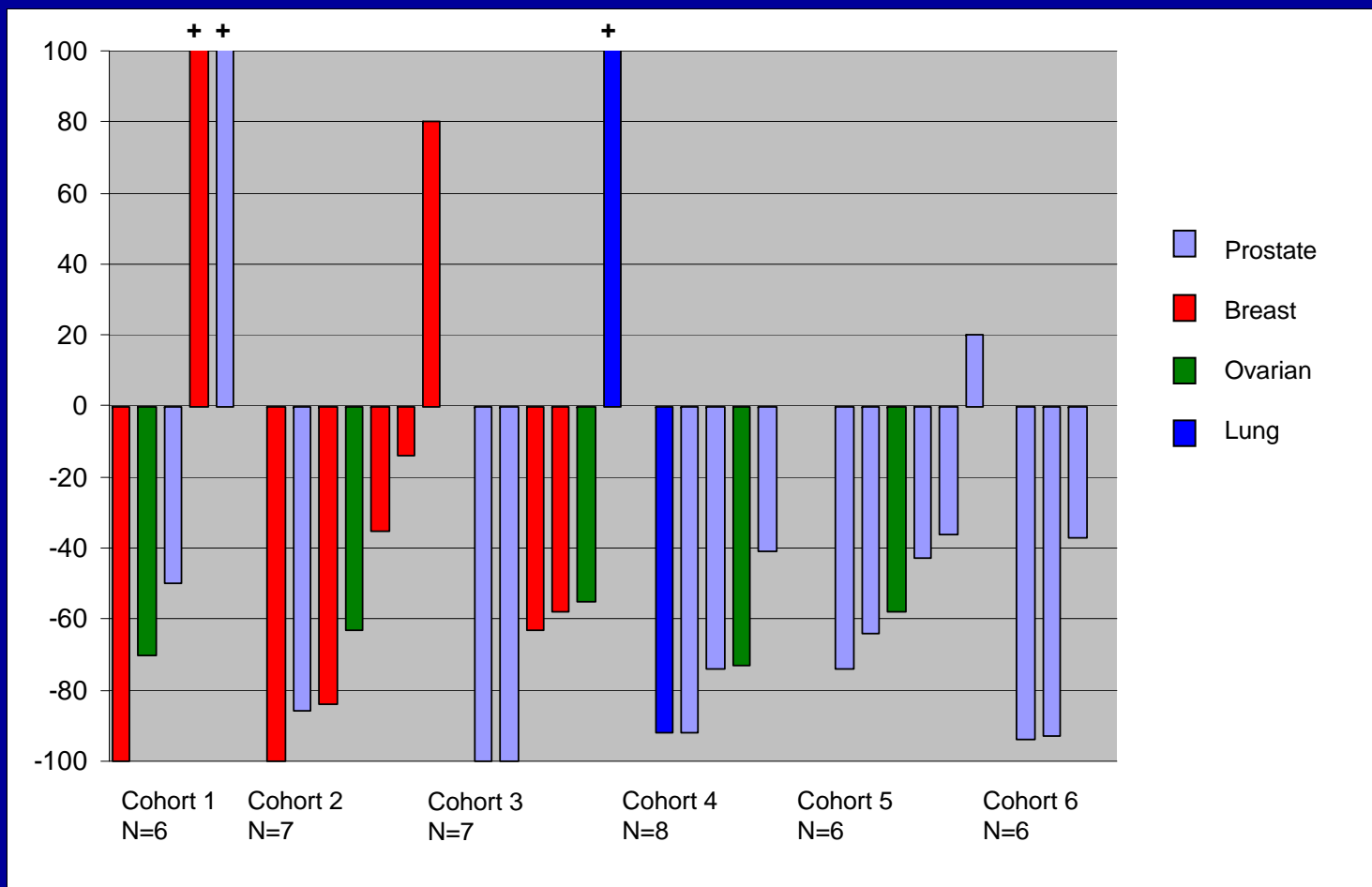
CTC and Hsp27⁺ CTC

	# Patients with > 5 at Baseline	# Patients (%) With Decrease to ≤ 5 Post Therapy	# Patients with ≤ 5 at Baseline	# Patients Who Remained ≤ 5 Post Therapy
CTCs*	34	9 (24%)	4	3
Hsp27⁺ CTCs**	33	10 (27%)	4	3

*2 patients did not have adequate CTC data for analysis

**3 patients did not have adequate Hsp27⁺ CTC data for analysis

Best Change In Hsp27⁺ CTCs By Disease Category & Cohort (in %)



patients who had a minimum of 5 CTCs at baseline

Preliminary Pharmacokinetics

<u>Dose</u> ^a	<u>N</u>	<u>C_{max}</u> ^b	<u>AUC_{inf}</u> ^c	<u>t_{1/2}</u> ^d	<u>Cl</u> ^e
200	6	21756	63553	2.91	3264
400	7	46986	163609	3.07	2558
600	6	102591	328153	2.75	1967
800	4	175338	653055	3.15	1484

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

- Non-proportional increases in C_{\max} and AUC_{inf} with increasing dose
- Constant $t_{1/2}$ over dosing range
- Decrease in total body clearance (Cl) with increasing dose

Conclusions

- **OGX-427 appears safe up to a dose of 1000 mg as a single agent**
- **MTD was not reached when administered as a single agent**
- **OGX-427 appears safe at a dose of 800 mg when combined with docetaxel.**
- **Dose escalation of OGX-011 & docetaxel continues**
- **No evidence of alteration of cardiac repolarization**

Conclusions

- Reductions in tumor markers observed in patients with both prostate (PSA) and ovarian (CA-125) cancer
- Decline of 50% or greater in both total CTCs & Hsp27⁺ CTCs observed in over half the patients
 - Observed in each of the 6 cohorts and each disease category
- Although half-life remains constant, there appears to be a non-proportional increase in C_{\max} and AUC_{inf} & a decrease in Cl with increasing dose

**OGX-427 is being developed by OncoGenex
Technologies, Inc.**

**Funding for CTCs came in part from the Pacific
Northwest SPORE**

Extra Slides

Introduction and Background

OGX-427

- **Second generation 4-12-4 2' MOE gapmer ASO with phosphorothiolated internucleotide linkages chemically modified to optimize pharmacokinetic and safety profile**
- **Reduces Hsp27 mRNA & inhibits production of Hsp27 protein**
- **Inhibits cell growth & induces apoptosis in a number of human cancer cell lines**
- **Demonstrates chemosensitizing activity in combination with several cytotoxic drugs, including docetaxel**

Introduction and Background Hsp27

- **Over-expressed by many cancers**
- **Highly conserved heat shock protein whose expression is induced by cell stress (chemo-, radio-, and hormonal therapy)**
- **Interacts with key apoptosis-associated proteins**
- **Inhibits apoptotic cell death through multiple pathways by a variety of mechanisms**

Hsp27 is a stress-activated, ATP-independent Cytoprotective Chaperone that Mediates Treatment Resistance in Cancer

- 1. Heat shock response is a highly conserved adaptive response evolved to safeguard organisms & cells against stress - HSF-1 is a master regulator**
 - Hsp27 also increased by cell survival factors like androgen, IGF-1**
- 2. Hsp27 Protects proteome against oncogenic stress**
 - Chaperone activity regulated by its phosphorylation and oligomerization**
 - Facilitates normal protein folding and function (signaling, transcription)**
 - Inhibits protein aggregation, enhances UPP activity**
- 3. Hsp27 is anti-apoptotic, pro-proliferative by regulating many distinct signaling and transcriptional pathways and networks**

DLT Stopping Rules

Individual Patient

- **If an individual patient experienced a DLT prior to the completion of Cycle 1, therapy was discontinued**
- **Patients removed from study treatment were followed for safety for 30 days & response until disease progression**

Within a Cohort

- **If 2 or more patients within cohort experienced a DLT, treatment of patients within that cohort was discontinued**
- **Additional 6 patients enrolled at the MTD**
- **If a safety concern occurred in patient continuing treatment past cycle 1, the DSM could suspend treatment in that or a higher dose cohort or limit the number of continuing cycles**

DLT Stopping Rules

- If 2 or more patients within cohort experienced a DLT, treatment of patients within that cohort was discontinued; the MTD had been reached
- If a safety concern occurred in patient continuing treatment past cycle 1, the DSM could suspend treatment in that or a higher dose cohort or limit the number of continuing cycles

Escalating Dose Levels

- **Planned sample size each cohort: 6 patients**
- **Each cohort evaluated consecutively**
- **Patient were replaced if they withdrew consent or discontinued study for reasons other than toxicity**
- **All patients in cohort must have completed all Cycle 1 safety assessments**

Pharmacokinetic & ECG Procedures: Day 1, Cycle 1

	Blood draw 2 mL/draw	Additional Action Required			ECGs	
Blood Sample #	Time	Record Time of Sample	Patient Supine for ECGs	Other	# of ECGs	Reference to Infusion
4	Pre-infusion	X	X	-	3	Pre-dose, prior to start of OGX-427 infusion
-	0 hr	-	-	Record actual start time of Infusion for OGX-427	-	Start of infusion for OGX-427 (no blood sample to be taken)
5	60 min	X	X	-	3	Mid-point of the 2hr OGX-427 infusion
6	120 min	X	X	-	3	Just prior to end of OGX-427 infusion
-	130 min	-	-	Record actual start time of Infusion for docetaxel (Cohorts 6+7)	-	Start of infusion for docetaxel (cohorts 6+7) (no blood sample to be taken)
7	150 min	X	X	-	3	Post SOI
8	190 min	X	X	-	3	Post SOI
9	5 hr	X	X	-	3	Post SOI
10	8 hr	X	X	-	3	Post SOI
11	10 hr	X	X	-	3	Post SOI
12	24 hr	X	X	-	3	Post SOI

Demographics

Characteristic	Monotherapy Cohorts 1-5 (N= 34)	800 mg + Docetaxel Cohort 6 (n=6)
Age (yrs): median (range)	62 (33-86)	63 (60-75)
Sex: Male/Female (%)	55/45	83/17
Karnofsky Score (%): Median (range)	80 (70-100)	70 (70-100)
# Prior Chemotherapy Regimens: Median (range)	3 (0-6)	2 (0-3)
# Metastatic Sites	2 (1-9)	2 (2-5)
Disease Sites		
Breast	10 (29%)	1(17%)
Lung	3 (9%)	-
Ovary	5 (15%)	-
Prostate	16 (47%)	5(83%)

Demographics (N=41)

Characteristic	Cohort 1 200 mg (n=7)	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)
Age (yrs)						
Median (range)	61 (53-69)	55 (33-60)	71(54-77)	73 (54-86)	62 (49-75)	63 (60-75)
Sex						
Male	4(57%)	2(29%)	3(43%)	6(75%)	5(83%)	5(83%)
Performance Status						
Karnofsky (median)	80	90	80	80	70	70
Prior chemotherapy regimens						
# (range)	3 (2-6)	3 (1-5)	3 (2-6)	3 (1-4)	2 (0-4)	2 (0-3)
# Metastatic Sites						
median (range)	2 (1-5)	4 (1-5)	3 (1-7)	2 (1-9)	3 (1-5)	2 (2-5)
Weight (kg)						
Median (range)	82 (55-104)	69 (58-130)	85 (54-93)	70 (66-93)	92 (50-134)	85 (78-89)
Disease Site						

Number of Cycles Received by Dose Cohort (N=41)

OGX-427	Cohort 1 200 mg (n=7)	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)*
No Dose Given	1 (14%)	-	-	-	-	-
Loading Dose Only	-	-	-	2 (25%)	-	-
1 cycle	2 (29%)	2 (29%)	4 (57%)	1 (13%)		
2 cycles	3 (43%)	2 (29%)	-	2 (25%)	4 (66.7%)	3 (50%)
3 cycles	-	-	-	1 (13%)	-	2 (33%)
4 cycles		1 (14%)	2 (29%)	1 (13%)	-	1 (17%)
5 cycles	1 (14%)-	-	-	-	-	-
6 cycles	-	1 (14%)	1 (14%)	1 (13%)	1 (17%)	-
7 cycles	-	-	-	-	1 (17%)	-
8 cycles	-	1 (14%)	-	-	-	-

*Data for Cohorts 5 and 6 preliminary: 6 patients (2 in Cohort 5 and 4 in Cohort 6) remain on study treatment

Preliminary Efficacy: Tumour Markers

PSA

- 20/22 patients had serial PSA
- 3/15 patients receiving OGX-427 alone had a reduction of PSA:
 - ↓63%(Cohort 2)
 - ↓ 77% (Cohort 5)
 - ↓ 42% (Cohort 5)
- 3/5 patients receiving 800 mg OGX-427 & docetaxel had a reduction of PSA:
 - ↓ 48% (Cohort 6)
 - ↓ 33% (Cohort 6)
 - ↓ 18% (Cohort 6)

CTC

- Whole blood for CTCs & Hsp27⁺ CTCs was collected at screening, pretreatment, and Cycles 1, 2, 3, & 5
- CTCs were enumerated using an immunomagnetic approach
 - 34/38 patients had baseline CTCs > 5 CTC
 - 9 (24%) ↓ to ≤ 5 CTCs
 - 4 patients had baseline CTC ≤ 5
 - 3 remained at ≤ 5 CTCs

Hsp27⁺ CTC

- Hsp27⁺ CTCs were identified using an immunofluorescent method
 - 33/37 patients had baseline Hsp27⁺ CTCs > 5
 - 10 (27%) ↓ to ≤ 5
 - 4 patients had baseline Hsp27⁺ CTCs ≤ 5
 - 3 remained ≤ 5
- 75% of the baseline total CTCs were Hsp27⁺
- No change in the % patients with Hsp27⁺ CTCs following treatment
- No dose response effect