A Randomized Phase II Study of OGX-427 + Prednisone vs. Prednisone Alone in Patients with Chemotherapy-Naive Metastatic Castration Resistant Prostate Cancer

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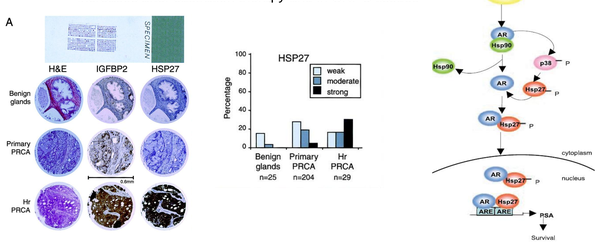
BACKGROUND

- Heat Shock Protein 27 (Hsp27)
  - Stress activated, ATP-independent member of the small heat shock protein group
  - Phospho-activated to form chaperoning oligomer which regulates multiple cell signaling and survival pathways
    - Inhibits apoptosis along intrinsic and extrinsic pathways
    - Involved in proteasome mediated degradation
    - Facilitates normal protein folding and function
      - Steroid receptors: AR, ER
      - Growth factor: IGF-1, VEGF-1, FGF
      - Cytokine: IL-6, TGF-beta
  - Highly expressed in many cancers including prostate cancer
    - High expression associated with poorer prognosis
    - Increases after castration therapy and in CRPC tissues



Bubendorf et al, J Natl Cancer Inst, 91:1758, 1999; Rocci et al, Cancer Res, 64:6595, 2004; Rocci et al, Cancer Res, 65:11083, 2005; Zoubeidi et al, Cancer Res, 67:10455, 2007

- OGX-427 (OncoGenex Technologies Inc.)
  - Second generation phosphorothioate antisense oligonucleotide with 2'-MOE modifications
    - Prolonged tissue half life ~10 days
    - Inhibits Hsp27 expression *in vitro* and *in vivo* with single agent anti-tumour activity
    - Enhances efficacy of hormone and chemotherapy
    - Disrupts AR function and enhances AR degradation
  - Phase I Studies (*Hotte et al, J Clin Oncol 28:15s, 2010 (abstr 3077)*)
    - Dose-dependent grade 1-2 infusion reactions
    - Reductions in tumor markers in patients with prostate and ovarian cancer
    - Declines in circulating tumour cells (CTC) observed
    - ≥15% decrease in measurable disease in 27% of patients

Figure 1. OGX-427 suppresses Pb-Luc Bioluminescence, AR, Hsp90 and Hsp27 *in vivo* (LNCaP)

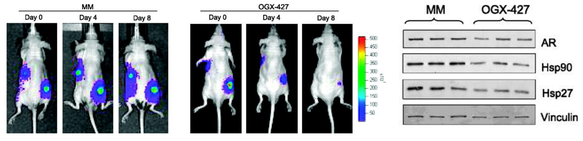
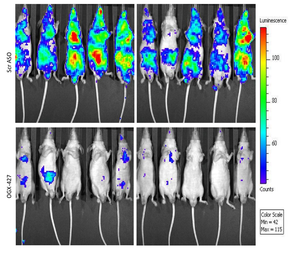


Figure 2. OGX-427 prevents metastases (PC-3M)

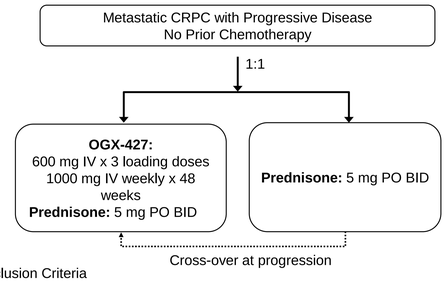


Zoubeidi et al, Cancer Res, 67:10455, 2007

OBJECTIVES

- Primary
  - To evaluate the proportion of patients without disease progression at the 12-week evaluation
    - Disease progression is defined by any one of the following:
      - PSA: confirmed increase of ≥ 25% and ≥ 2 ng/mL
      - Measurable disease: progression per RECIST 1.1 by CT
      - Bone scan: ≥ 2 new lesions confirmed
      - Disease related deterioration of health status
      - Need for palliative radiation therapy
- Secondary
  - Assess the proportion of patients who have a PSA decline
  - Determine measurable disease response
  - Estimate PFS and time to disease progression
  - Evaluate CTC (Veridex™) pre- and post-study treatment
  - Assess safety and tolerability

STUDY DESIGN



- Key Inclusion Criteria
  - Metastatic CRPC
  - ECOG performance status 0-1
  - Evidence of progression by PSA, measurable disease or bone scan
  - No prior chemotherapy for metastatic disease
  - No or minimal pain symptoms (<30 mg morphine equivalent/day)
  - Prior prednisone/corticosteroid therapy permitted
  - Baseline laboratory values:
    - ANC ≥ 1.5 x 10^9 cells /L, platelet count ≥ 100 x 10^9 /L, and hemoglobin ≥ 9 g/dL
    - Creatinine ≤ 1.5 x ULN
    - Total bilirubin ≤ 1.1 x ULN, ALT and AST ≤ 2.5 x ULN
- H_0: 12-week progression free ≤ 5% vs. H_A: 12-week progression free ≥ 20%
- MinMax 2-stage design, α = 0.1, β = 0.1
  - Stage 1: 18 evaluable patients/arm if ≥1 has a response/stable disease at 12-weeks go to stage-2
  - Stage 2: An additional 14 evaluable patients/arm
- 70% power to detect the difference using a chi-square test at the 0.10 1-sided significance
- Accrual completed with a total of 73 patients enrolled
- Results of 65 patients with a minimum of 12 weeks on study are presented

BASELINE PATIENT CHARACTERISTICS

Parameter	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
Median Age, years (range)	66 (53-86)	73 (31-89)
Median PSA, ug/L (range)	57 (<1-638)	50 (<1-606)
Median Hemoglobin, g/L (range)	132 (98-157)	130 (104-167)
ECOG PS 0 : 1	22 (69%) : 10 (31%)	20 (61%) : 13 (39%)
Disease Sites		
Bone	23 (72%)	24 (73%)
Liver	1 (3%)	2 (6%)
Lung	3 (9%)	3 (9%)
Lymph Node	16 (50%)	21 (64%)
Gleason Score		
≤7	16 (50%)	14 (42%)
>7	14 (44%)	17 (52%)
Missing	2 (6%)	2 (6%)
Lactate Dehydrogenase >ULN	11 (34%)	6 (18%)
Alkaline Phosphatase >ULN	8 (25%)	4 (12%)
Prior Prednisone Therapy	6 (19%)	3 (9%)
CTC/7.5 ml		
Median (Range)	13 (1-72)	15 (3-273)
≥5	26 (81%)	29 (88%)

PATIENT DISPOSITION

Status	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
Median Treatment Duration, weeks (range)	17 (2-50)	14 (3-47)
Treatment Ongoing	13 (41%)	12 (36%)
Off Treatment		
Completed Therapy w/o Progression	2 (11%)	2 (10%)
Adverse Event	5 (26%)	0
Disease Progression	7 (37%)	15 (71%)
Withdrawal by Subject	3 (16%)	0
Treatment Delay > 3w	2 (11%)	0
Other/Missing	0	4 (19%)
Cross-over to OGX-427	N/A	15 (45%)

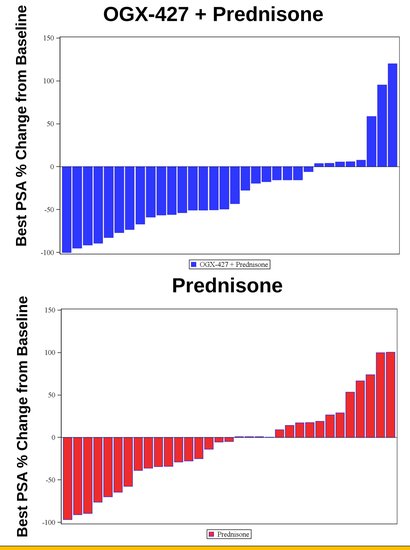
PRIMARY ENDPOINT: DISEASE PROGRESSION AT 12 WEEKS

	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
Non-evaluable	4 (13%)	4 (12%)
Evaluable	28	29
No Disease Progression	20 (71%) (95%CI: 0.513, 0.868)	14 (48%) (95% CI: 0.295, 0.675)
Disease Progression	8 (29%)	15 (52%)

PSA DECLINE

Best PSA Decline from Baseline	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
≥90%	3 (9%)	2 (6%)
≥50%	15 (47%)	7 (21%)
≥30%	17 (53%)	11 (33%)
Any	24 (75%)	17 (52%)

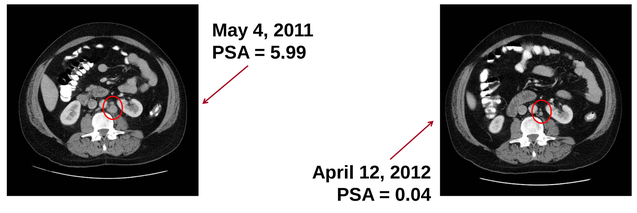
Waterfall Plots of PSA Declines



MEASURABLE DISEASE RESPONSE

Best Response Category	OGX-427 + Prednisone (N=16)	Prednisone (N=17)
Complete Response	1 (6%)	0
Partial Response	3 (19%)	2 (12%)
Stable Disease	6 (38%)	11 (65%)
Progressive Disease	0	3 (18%)
Not Evaluable	6 (38%)	1 (6%)

PATIENT WITH COMPLETE RESPONSE ON OGX-427/PREDNISONE



CTC CHANGES

Best CTC Change from Baseline	OGX-427 + Prednisone (N=29)	Prednisone (N=32)
≥ 5 to < 5	15 (52%)	13 (41%)
< 5 to < 5	3 (10%)	3 (9%)
≥ 5 to ≥ 5	11 (38%)	16 (50%)

ADVERSE EVENTS

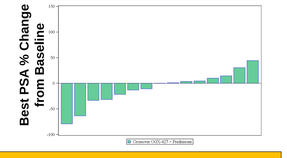
Incidence of Non-Laboratory Treatment Related Adverse Events*	OGX-427 + Prednisone (N=32)***	
Grade	1-2	3-4
Chills**	18 (56%)	1 (3%)
Diarrhea**	11 (34%)	
Fatigue**	10 (31%)	1 (3%)
Nausea**	10 (31%)	
Flushing**	6 (19%)	
Pyrexia**	5 (16%)	
Vomiting**	5 (16%)	
Dizziness	3 (9%)	1 (3%)
Hot flashes	4 (13%)	
Muscular Weakness	2 (6%)	1 (3%)
Hypertension	1 (3%)	2 (6%)
Presyncope		1 (3%)
Tachycardia		1 (3%)
Hemolytic Uremic Syndrome		1 (3%)
Hypoxia		1 (3%)
Pulmonary embolism		1 (3%)
Vasculitis Purpura (worsening)		1 (3%)

*All Grade 3-4 events and any AE occurring in >3 patients **Mainly related to OGX-427 infusion reactions
***93% were Grade 1-2

Incidence of Grade 3-4 Laboratory Treatment-Emergent Adverse Events	OGX-427 + Prednisone (N=32)	Prednisone (N=33)
Lymphopenia	4 (12%)	3 (9%)
Hyperglycemia	4 (12%)	1 (3%)
Elevated Creatinine	2 (6%)	1 (3%)
Hyponatremia	1 (3%)	0
Thrombocytopenia	1 (3%)	0
Anemia	1 (3%)	0

PRELIMINARY DATA ON CROSS OVER PATIENTS (N=15)

- Measurable Disease (N=10)
  - 1 patient with PR, 5 patients with stable disease, 4 patients not done/too early
- PSA Decline (N=15)



CONCLUSIONS

- These data provide clinical evidence for the role of Hsp27 as a therapeutic target for prostate cancer
- In this phase II study, OGX-427 demonstrated anti-tumour activity in patients with metastatic CRPC with objective responses, PSA declines and a delay in disease progression, which supports continued clinical evaluation
- OGX-427 treatment has been well tolerated with adverse events having been predominantly infusion related and grade 1-2
- Randomized phase II studies with OGX-427 are ongoing:
  - in combination with abiraterone acetate for patients with metastatic CRPC (ClinicalTrials.gov: NCT01681433)
  - in combination with gemcitabine-cisplatin for patients with bladder cancer (ClinicalTrials.gov: NCT01454089)

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