

**A Randomized Phase II Study of OGX-011  
in Combination with Docetaxel and  
Prednisone or Docetaxel and Prednisone  
Alone in Patients with Metastatic  
Castration Resistant Prostate Cancer**

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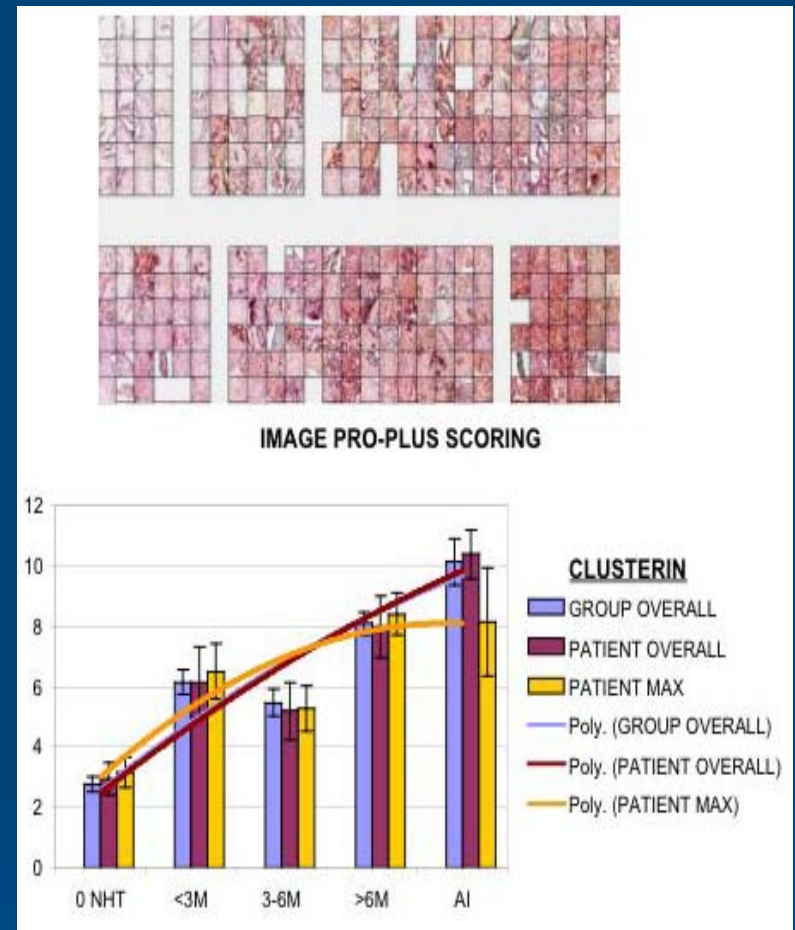
# Background: Clusterin

- Heterodimeric glycoprotein highly conserved across species
- Transcriptionally regulated by HSF-1
- Chaperone protein function similar to heat shock proteins
- Secretory and nuclear forms
  - sCLU - Anti-apoptotic
    - Prevents protein aggregation
    - Inhibits activated Bax
    - Increases NF-kB activity through I-kB degradation
  - nCLU - Pro-apoptotic

# Background: Clusterin

- Expressed in a number of cancers
- Expression induced by standard anti-cancer therapies
- Prostate Cancer
  - Increased expression correlates with higher Gleason Grade
  - Increases after castration therapy and in CRPC tissues
- Overexpression in pre-clinical models confers resistance to hormone, radiation and chemotherapy

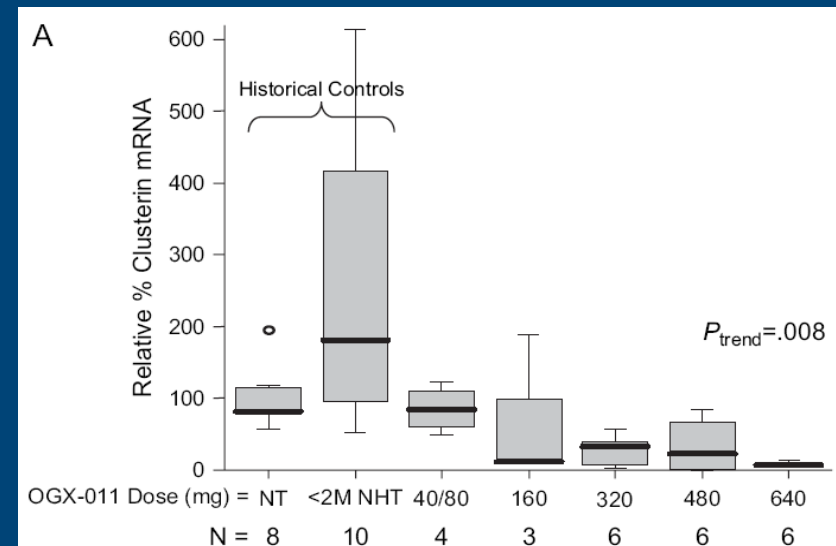
Clusterin increases after Androgen Ablation and in CRPC



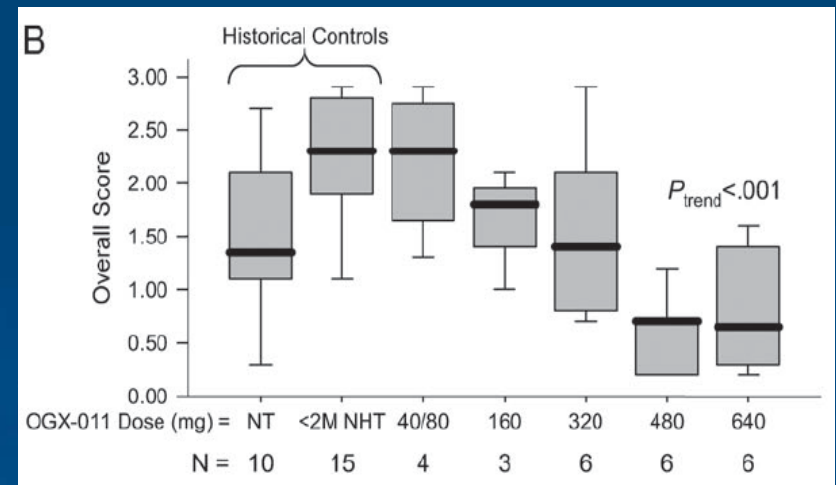
# OGX-011 (Custirsen)

- Antisense complementary to clusterin mRNA translation initiation site with 2<sup>nd</sup> generation chemistry
- *in vitro* and *in vivo* studies
  - Potent inhibition of sCLU expression
  - Increases nCLU by alternate splicing
  - Enhances activity of hormone, radiation and chemotherapy
- Phase I clinical trials
  - Decreases clusterin in tissues
  - Safely combined with chemotherapy

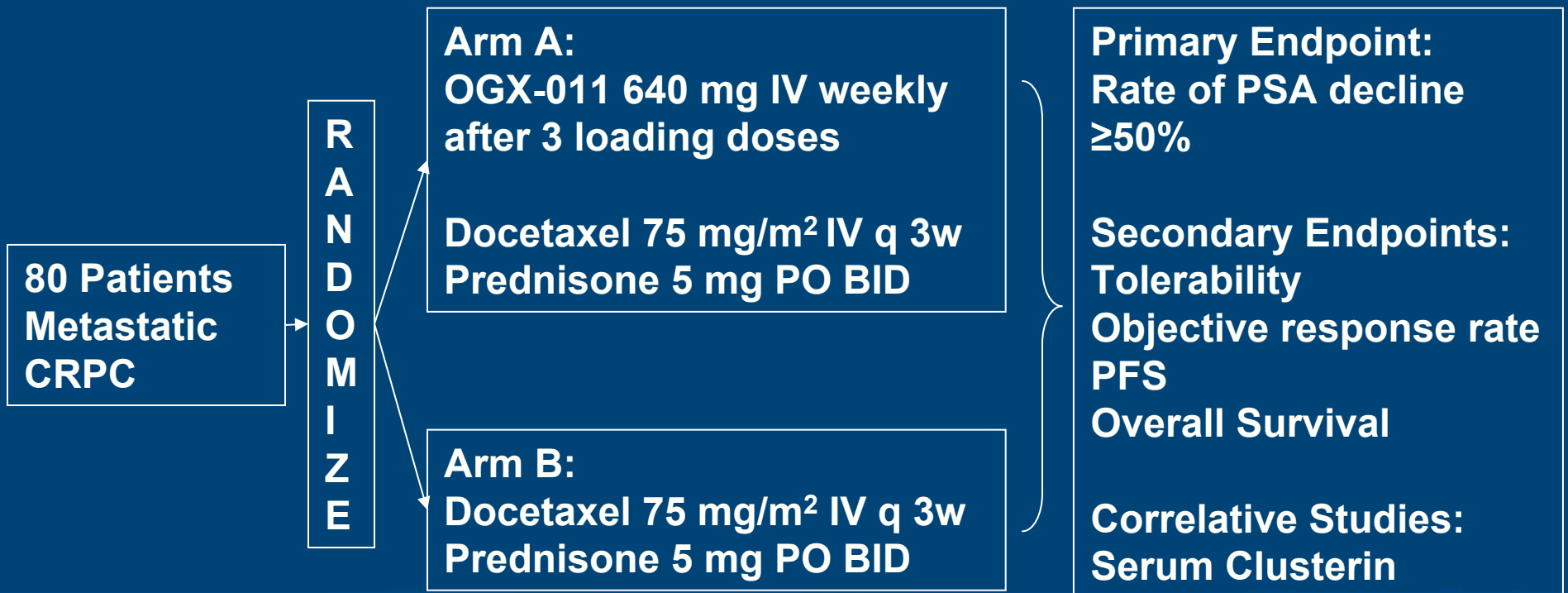
Phase I: OGX-011 Inhibition of Clusterin mRNA



Phase I: OGX-011 Inhibition of Clusterin Protein



# Study Design



# Endpoint Definitions

- Primary
  - Rate of  $\geq 50\%$  PSA decline from baseline (minimum 5 ng/ml) confirmed  $\geq 3$  weeks later
- Secondary
  - Objective response rate by RECIST
  - Progression
    - Objective progression by RECIST
    - PSA progression
      - Non-responders:  $\geq 25\%$  increase from nadir (confirmed)
      - Responder:  $\geq 50\%$  increase from nadir (confirmed)
  - Survival
    - From date of randomization to progression or death

# Study Design

- Non-comparative, single stage randomized phase II with internal control
  - $H_0 < 40\%$ ,  $H_1 > 60\%$ ,  $\alpha = 0.1$ ,  $\beta = 0.1$
  - Further evaluation warranted if  $>20/40$  patients had a PSA  $\geq 50\%$  decline in arm A

# Key Eligibility Criteria

- Pathologic diagnosis of prostate adenocarcinoma
- Castrate resistance:
  - Rising PSA
  - New metastatic lesions
- PSA  $\geq 5$
- ECOG PS = 0-2
- No prior chemotherapy
- Adequate hematologic, renal and hepatic function
  - ANC  $\geq 1.5 \times 10^9/L$ , Platelets  $\geq 100 \times 10^9/L$
  - Bilirubin  $\leq$  ULN, AST/ALT  $\leq 1.5 \times$  ULN
  - Creatinine  $\leq 1.5 \times$  ULN

# Accrual and Follow-Up

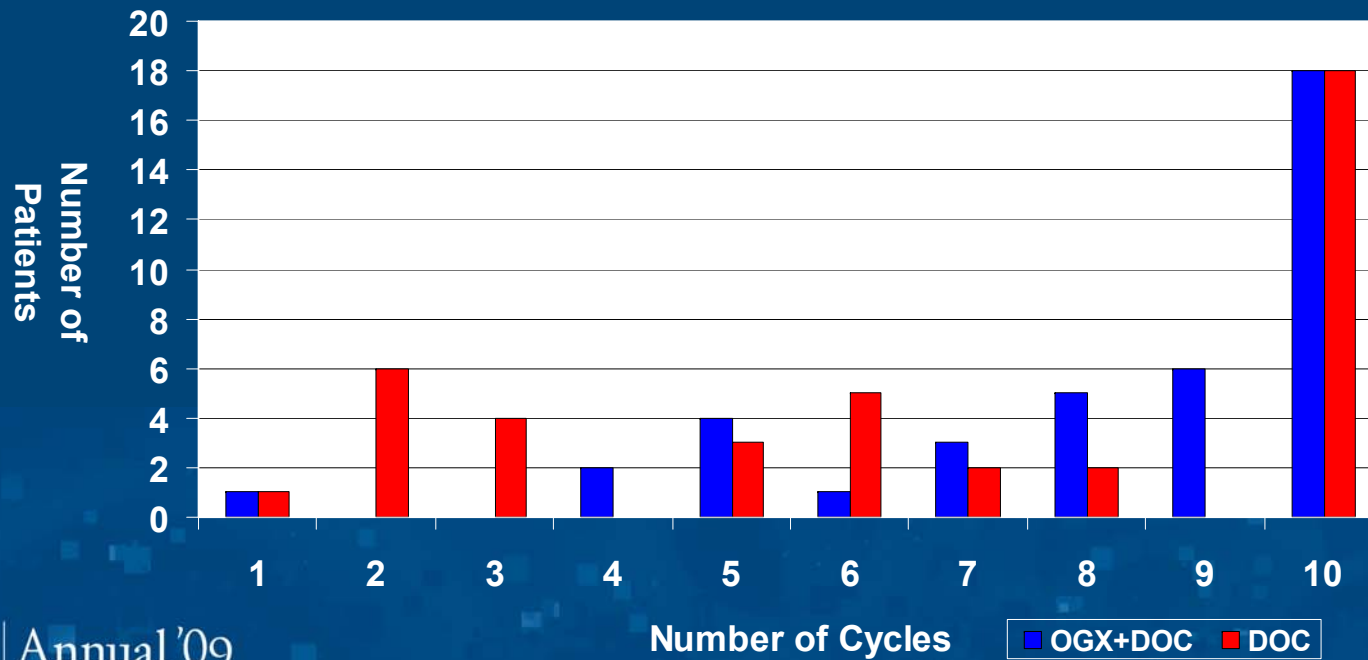
- 82 patients from 12 sites in Canada and USA were accrued from September 2005 to December 2006
- All patients are now off study treatment
- Median follow-up = 32 months
- 58 deaths

# Baseline Characteristics

		<i>OGX + DOC</i> <i>N=40*</i>	<i>DOC</i> <i>N=41</i>
Median age (range)		68 (54-84)	69 (49-87)
ECOG PS	0 : 1	21 : 19	20 : 21
Measurable disease	No : Yes	14 : 26	17 : 24
Bone/nodal metastases only	Yes : No	27 : 13	24 : 17
PSA	≤100 : >100	20 : 20	20 : 21
LDH	≤ULN : >ULN	24 : 16	28 : 13
Alk Phos	≤ULN : >ULN	23 : 17	22 : 19
Hemoglobin	<100 : ≥100	2 : 38	0 : 41
Gleason Score	≤7 : 8-9 : UNK	13 : 26: 1	18 : 22 : 1
Progression at randomization	Objective : PSA	5 : 35	9 : 32
Halabi nomogram predicted median OS		12.7 m (3.6-28.0)	11.1 m (3.5-30.1)

# Cycles Administered

	<i>Median Cycles (Range)</i>	<i>Receiving &gt; 90% Planned DOC Dose Intensity</i>
OGX + DOC	9 (1-10)	66.7
DOC	7 (1-10)	70.7



# Reasons for Protocol Therapy Discontinuation

	<i>OGX + DOC</i> <i>N (%)</i>	<i>DOC</i> <i>N (%)</i>
Treatment complete (10 cycles)	18	16
Adverse event	9	5
Progression		
Total	7	16
Objective	3	7
PSA	2	6
Objective and PSA	2	3
Symptomatic progression	1	0
Death	0	1
Intercurrent illness	0	1
Refused treatment	3	0
Other	2	2

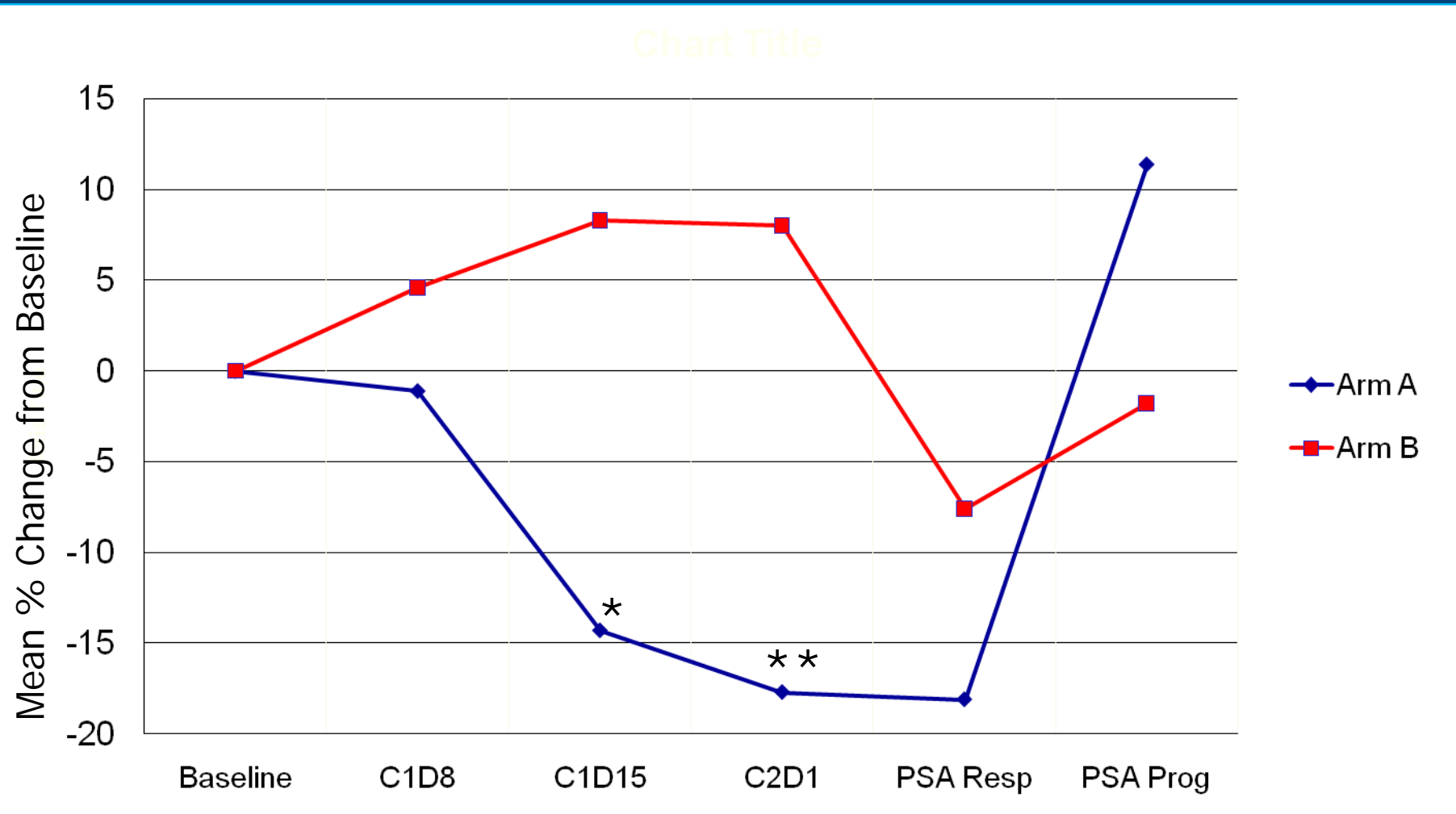
## Grade 3-4 Hematologic Adverse Events

	<i>OGX + DOC</i> (N=40)	<i>DOC</i> (N=41)
Granulocytes	29	26
Leukocytes	18	22
<b>Lymphocytes</b>	<b>21</b>	<b>9</b>
Hemoglobin	0	3
Platelets	1	0

## Related Grade 3-4 and Non-Hematologic Adverse Events

AE	Arm A (OGX + DOC)			Arm B (DOC)		
	Grade 1-2	Grade 3-4	Total %	Grade 1-2	Grade 3-4	Total %
Fatigue	28	4	80	25	8	80
Neuropathy (sensory or motor)	22	2	60	18	0	44
Diarrhea	20	1	53	18	2	49
Nausea	14	1	38	18	3	51
Pain	12	2	36	12	1	33
Vomiting	6	0	15	10	1	27
Febrile neutropenia	0	4	10	0	5	12
Dehydration	4	0	10	2	3	12
<b>Rigors/chills</b>	<b>23</b>	<b>0</b>	<b>58</b>	<b>2</b>	<b>0</b>	<b>5</b>
<b>Fever</b>	<b>18</b>	<b>0</b>	<b>45</b>	<b>5</b>	<b>0</b>	<b>12</b>
<b>Elevated creatinine (normal baseline)</b>	<b>8</b>	<b>0</b>	<b>20</b>	<b>2</b>	<b>0</b>	<b>5</b>

# Results: Serum Clusterin (ELISA)



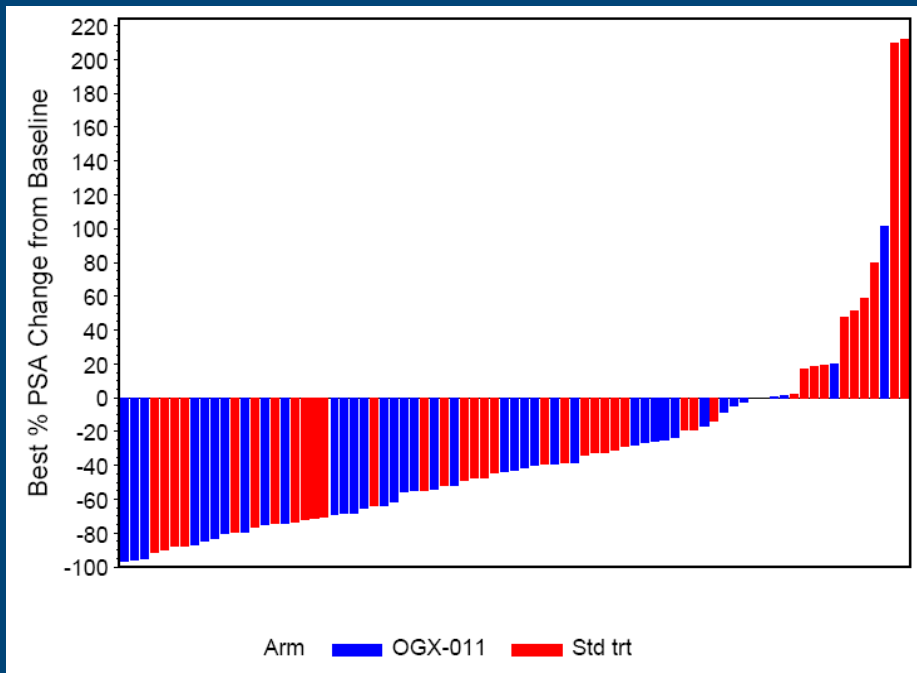
\*P=0.05 \*\*P=0.0005

# Post-Treatment PSA Changes

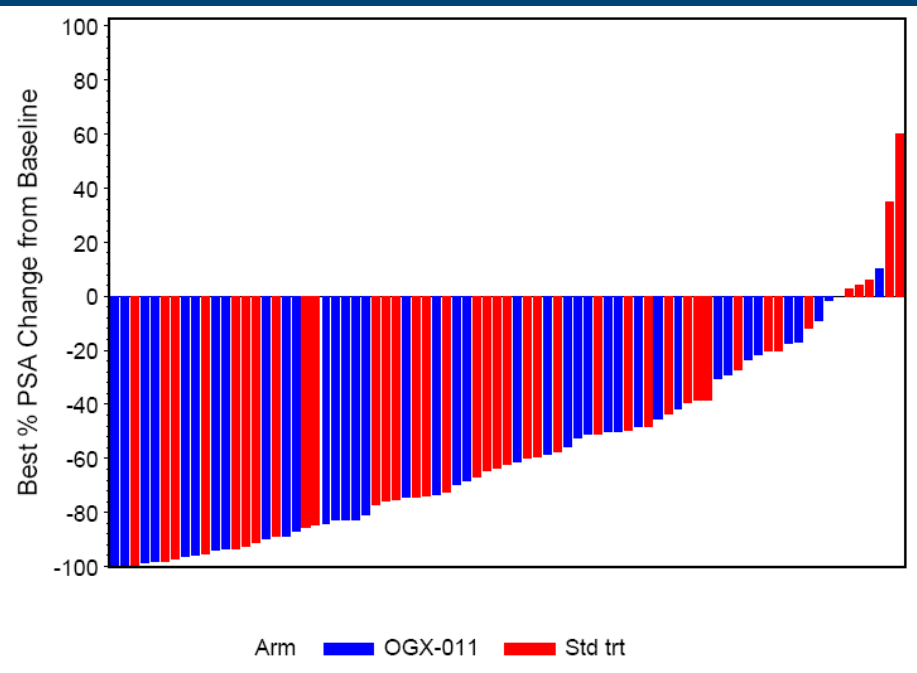
<i>PSA Decline Criteria</i>	<i>OGX + DOC N=40</i>	<i>DOC N=41</i>
≥ 50% decline (confirmed)	23 (58%)	22 (54%)
≥ 50% decline	26 (65%)	25 (61%)
≥ 30% decline at 12 weeks	26 (65%)	24 (59%)
≥ 30% decline	32 (80%)	31 (76%)
PSA progression	0 (0%)	3 (7%)
Inevaluable	1	1

# PSA Waterfall Plots

12 weeks



At any time



# Measurable Disease Response

<b>RECIST</b>	<b>Arm A (OGX + DOC) N=26</b>	<b>Arm B (DOC) N=24</b>
Complete Response	0	0
Partial Response	5 (19%)	6 (25%)
Stable Disease	20 (77%)	12 (50%)
Progressive Disease	1 (4%)	4 (17%)
Inevaluable	0	2

# Progression Free Survival

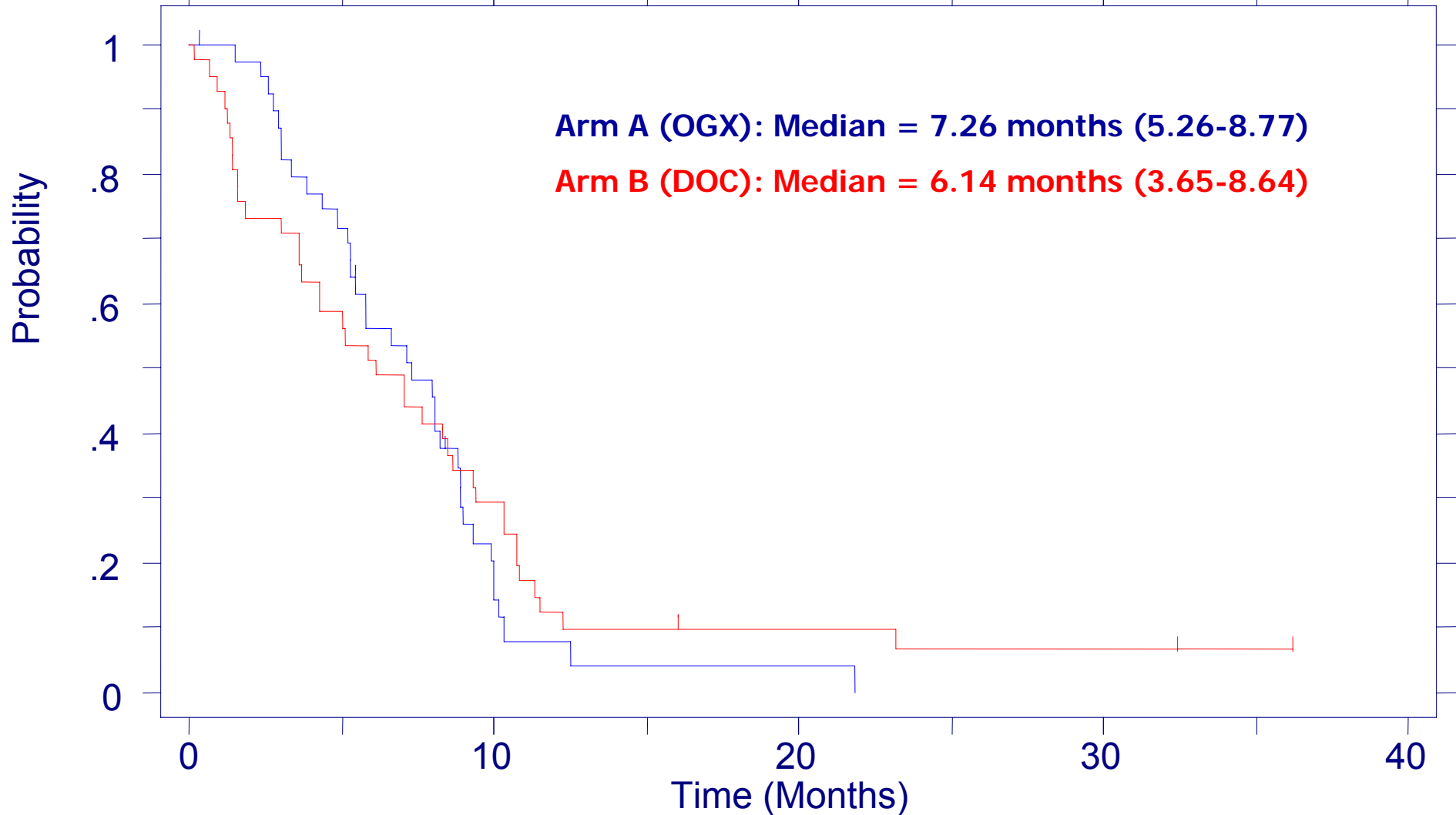
At Risk: 40  
At Risk: 41

6  
12

1  
3

0  
2

0  
0





# Cox Multivariate Analysis

<i>Variable</i>	<i>N</i>	<i>HR (95% CI)</i>	<i>P</i>
<b>OGX-DOC</b>	<b>41</b>	<b>0.49 (0.28-0.85)</b>	<b>0.012</b>
<b>DOC</b>	<b>41</b>		
<b>PS 0</b>	<b>41</b>	<b>0.28 (0.15-0.53)</b>	<b>&lt;0.0001</b>
<b>PS 1</b>	<b>41</b>		
<b>Other metastases</b>	<b>31</b>	<b>2.13 (1.20-3.77)</b>	<b>0.01</b>
<b>Bone/node only</b>	<b>51</b>		
HGB $\geq$ 100	29	0.52 (0.27-1.02)	0.06
HGB<100	52		
LDH $\leq$ ULN	52	0.63 (0.34-1.20)	0.16
LDH>ULN	29		
ALP $\leq$ 2.5xULN	45	1.14 (0.58-2.22)	0.70
ALP>2.5xULN	36		
Pain No	22	1.27 (0.63-2.58)	0.51
Pain Yes	60		
PSA $\leq$ 100	40	0.77 (0.44-1.33)	0.34
PSA>100	41		

# Exploratory Analysis: Number of Treatment Cycles and Overall Survival

<i>Number of Cycles</i>	<i>OGX + DOC N</i>	<i>DOC N</i>	<i>HR (95% CI)</i>
≤ 6 cycles	9	19	0.30 (0.08-1.12)
≤ 9 cycles	23	23	0.35 (0.15-0.83)
10 cycles	18	18	0.20 (0.04-0.93)

# Conclusions

- OGX-011 is well tolerated in combination with docetaxel
- Evidence of biologic effect with serum clusterin decrease
- Primary endpoint: PSA decline rate with OGX-011/docetaxel therapy met protocol criteria for further study but control arm was similar
- Treatment with OGX-011/docetaxel combination was independently associated with improved overall survival in a pre-planned multivariate analysis (HR=0.49, P=0.012)
- Further evaluation of this combination in patients with CRPC is warranted

# Acknowledgements

- Patients and their families
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  - Dr. Martin Gleave
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  - Canadian Cancer Society
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# Post-Study Therapy

	<b>OGX + DOC</b> <b>N (%)</b>	<b>DOC</b> <b>N (%)</b>
Any	28 (70)	22 (54)
Mitoxantrone	13 (33)	7 (17)
Docetaxel	13 (33)	12 (29)
Targeted Therapy	10 (25)	2 (5)
Prednisone	10 (25)	4 (10)
Epothilone B	8 (20)	5 (12)
Blinded agent	5 (13)	5 (12)
OGX-011	0	6 (15)