Management of Hormone Refractory Prostate Cancer: Old Dog, New Tricks

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BC Cancer Agency
CARE & RESEARCH

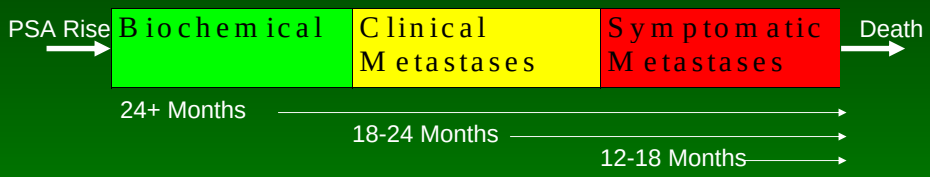
THE UNIVERSITY OF BRITISH COLUMBIA
PROSTATE CENTER

Agenda

- Defining the patient population
- Current management
  - Second line hormonal maneuvers
  - Chemotherapy
  - Bisphosphonates
- New tricks
  - Novel therapies

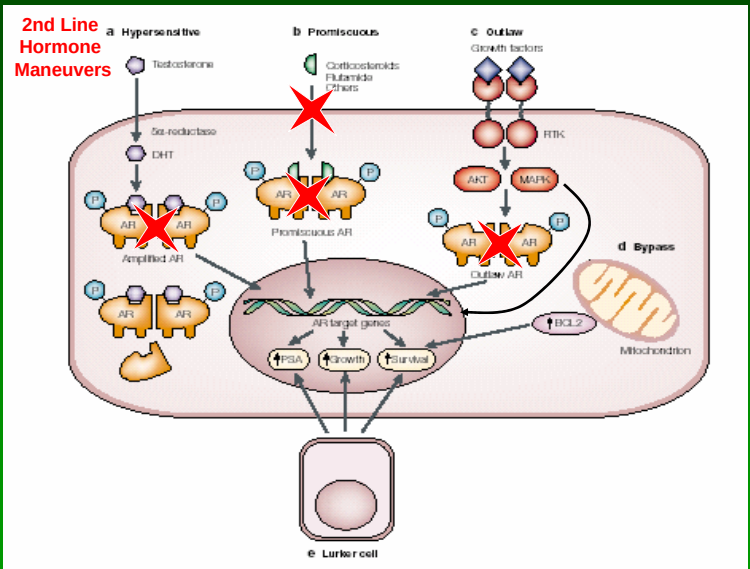
HRPC - Defining the Population: The Past

HRPC - Defining the Population: The Present



- Serial rise in PSA with castrate level testosterone
  - Heterogenous
    - Biochemical
    - Clinical metastases
      - Asymptomatic
      - Symptomatic
  - Larger population of patients demanding more effective treatment
  - Effects interpretation of single arm clinical trials

Mechanisms of Androgen Independence



Feldman and Feldman. Nature Reviews 2001

2nd Line Hormonal Maneuvers: RCT

- EORTC: Flutamide vs Prednisone
- N = 201, symptomatic patients
  - PSA Response Rate:
    - Prednisone: 21%
    - Flutamide: 23%
  - Palliative Response Rate
    - Prednisone: 56%
    - Flutamide: 45%

Fossa JCO 19:62 2001

Other NSAA

- Bicalutamide 150 mg: Phase II trial, no prior NSAA (SWOG 9235)
  - PSA RR = 20%
- Nilutamide: Retrospective, selected consecutive patients, all had prior NSAA
  - PSA RR: 50%

Kucuk Urology 58:53 2001; Vogelzang Urology 58:1016 2001

2nd Line Hormonal Maneuvers: RCT

- CALGB: AAWD Alone vs AAWD plus Keto/HC
  - PSA Response Rate

AAWD Alone	AAWD + Keto	AAWD -> Keto (Crossover)
11%	27%	30%

  - Objective Response Rate

AAWD Alone	AAWD + Keto	AAWD -> Keto (Crossover)
5%	14%	17%

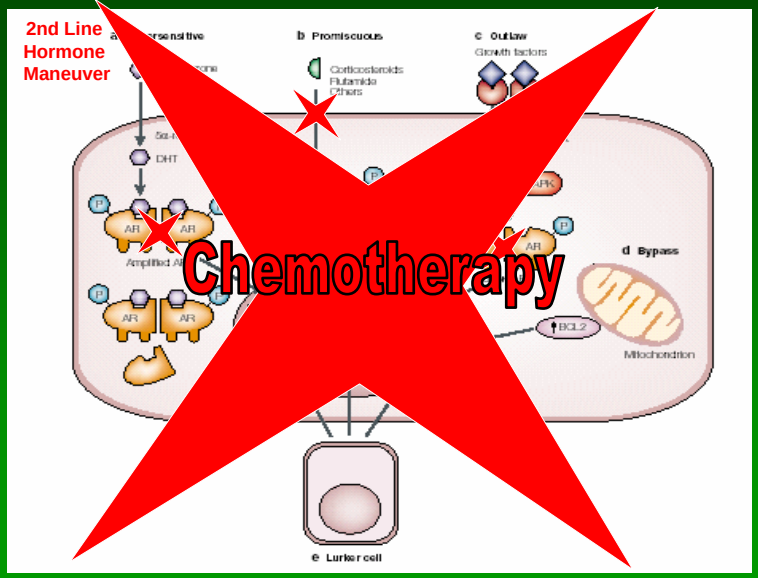
- Lower doses of ketoconazole may also be as effective (600 mg/day)
- Effect of corticosteroids alone?

Small, JCO 22: 1025, 2004; Harris, J Urol 168:542 2002

Summary: 2nd Line Hormonal Maneuvers

- Many options:
  - Initiate “maximum androgen blockade”
  - Corticosteroids
  - Antiandrogen withdrawal
  - Ketoconazole and hydrocortisone
  - Switching antiandrogens
- Clinical Impact?
  - Impact on survival has never been well defined for populations of patients - are we changing natural history?
  - But...
    - Well tolerated
    - Some very good biochemical and symptomatic responses
    - Appropriate for asymptomatic or chemotherapy ineligible patients

Mechanisms of Androgen Independence



Feldman and Feldman. Nature Reviews 2001

Chemotherapy in Prostate Cancer

Drug Class	Agents	Objective Response
Anthracyclines	Doxorubicin	10-20%
	Mitoxantrone	10-20%
	Epirubicin	10-20%
Alkylating Agents	Cyclophosphamide	10-20%
	CCNU	10-20%
	Ifosfamide	10-20%
Vinca Alkaloids	Vinblastine	10-20%
	Vincristine	<10%
Antibiotics	Mitomycin	10-20%
Antimicrotubule	Estramustine	10-20%
Agents	Paclitaxel	10-20%
Platinum	Cisplatin	10-20%
Complexes	Carboplatin	<10%
Antimetabolites	Methotrexate	10-20%
	5-FU	<10%
Topoisomerase	Etoposide	<10%
Inhibitors	Topotecan	<10%

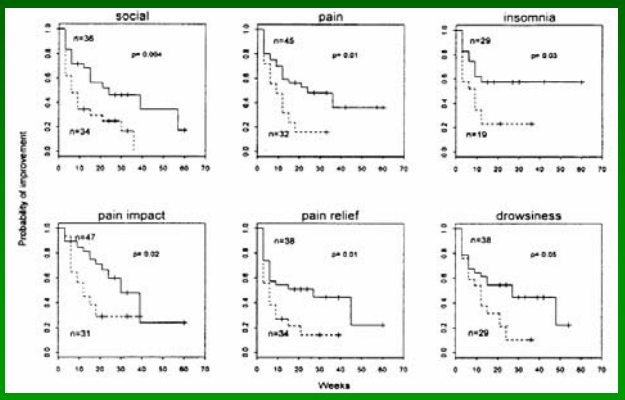
Chemotherapy as a Palliative Treatment

- Mitoxantrone as First Line Chemotherapy for Metastatic Prostate Cancer: Phase II results
- 13 patients
  - 3/13 PR (2 objective disease, 1 with >75% in PAP)
  - 5/13 symptomatic response: pain, PS, wt

N. Murray, C. Coppin, T MacDermaid, Proc of the 14th Int Congress of Chemo, Kyoto, 1985

Chemotherapy: Mitoxantrone as Standard

	M+P N=80		P N=81	
	No.	%	No.	%
Palliative Response	23	29	10	12



Tannock, J Clin Oncol, 14:1756, 1996; Osoba, J Clin Oncol, 17:1654, 1999

Mitoxantrone

Table 3. Greater Than 50% and 80% Reduction in PSA From Baseline by Arm

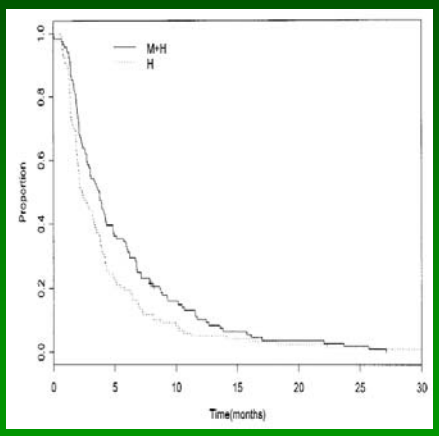
PSA Response (%)	Treatment Arm: M + H No.	M + H %	Hydrocordisone Alone No.	Hydrocordisone Alone %	Total No.	Total %
< 50	70	62.5	91	78.5	161	70.6
≥ 50*	42	37.5	25	21.5	67	29.4
≥ 80*	22	19.6	11	9.5	33	14.5

*The rows > 50% and ≥ 80% are not mutually exclusive; therefore, the number of patients with a PSA response > 50% includes those whose response was ≥ 80%.

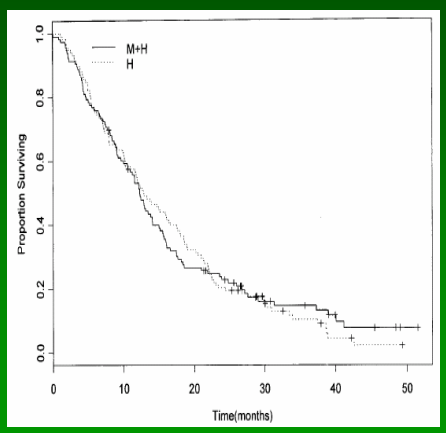
Kantoff, J Clin Oncol, 17:2506, 1999

Mitoxantrone

Time to Progression



Overall Survival



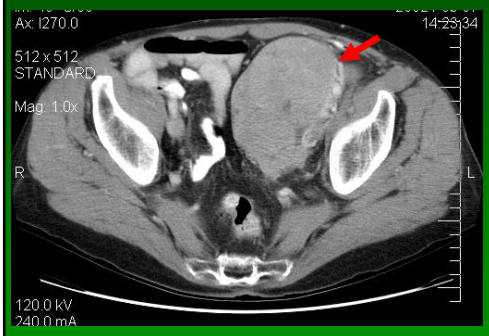
Kantoff, J Clin Oncol, 17:2506, 1999

Docetaxel

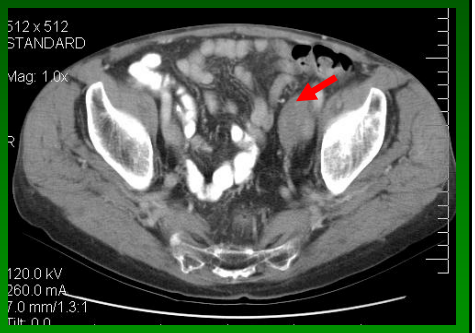
N	Regimen	PSA RR	ORR
35	75 mg/m^2 q3w	46%	28%
21	75 mg/m^2 q3w	38%	60%
60	36 mg/m^2/wk q6/8w	34%	33%
25	36 mg/m^2/wk q6/8w	43%	NR

Picus, Semin Oncol 1999; Friedland, Semin Oncol 1999; Beer, Proc ASCO 2000; Berry, Proc ASCO 1999

Mr. T.G.



Pre-Docetaxel



Post-Docetaxel

Docetaxel: The New Standard?

Tax 327

1003 Patients
HRPC with
Metastases

RANDOMIZATION

→ Docetaxel 75 mg/m^2 q3w

→ Docetaxel 30 mg/m^2 q1w

→ Mitoxantrone 12 mg/m^2 q3w

Plenary session at ASCO 2004

Docetaxel and Estramustine

N	Regimen	PSA RR	ORR
46	D 70 mg/m^2 d2 E 10 mg/kg/d d1-5 q3w	68%	50%
37	D 70 mg/m^2 d2 E 280 mg tid d1-5 q3w	68%	55%
17	*Arm A: D* 20-30 mg/m^2/wk E 420 mg tid d1-4 q6/8w	82%	71%
	Arm B: D 30-40 mg/m^2 d2,9 + E tid (420 mg × 4;280 mg × 5) d1-3, d8-10; q3w		
21	D 43 mg/m^2 d2 E 140 mg/d d1-5 q3/4w	71%	11%

Savarese, JCO 2001; Petrylak, Proc ASCO, 2000; Natale, Proc ASCO 1999; Kosty, Proc ASCO 2001

SWOG 9916

620 Patients
HRPC with
Metastases

RANDOMIZATION

→ Docetaxel 60 mg/m^2
Estramustine 280 mg TID d1-5
q3w

→ Mitoxantrone 12 mg/m^2 q3w

Plenary session at ASCO 2004

Summary: Chemotherapy

- Mitoxantrone
  - Demonstrated palliative patient benefit
  - Well tolerated
  - Still useful
- Docetaxel
  - Single agent q 3 weekly current standard for appropriate patients with HRPC at BCCA
  - Basis for future trials in HRPC

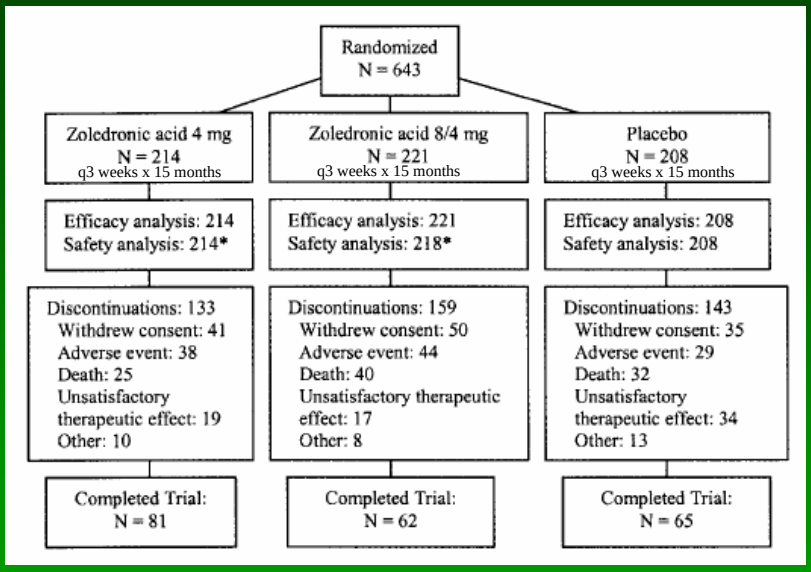
Bisphosphonates

- Stable analogues of Pyrophosphate
- Decrease depth and rate of formation of bone remodeling units
  - Inhibit bone resorption by osteoclasts
  - Promote apoptosis of osteoclasts
- A number of bisphosphonates are active in other cancers
- Rationale in prostate cancer
  - Increased activity of BRU
  - Osteoporosis from androgen withdrawal therapy
- Trials with bisphosphonates have all been negative
  - except for the one trial which used skeletal related event as the primary endpoint...

Zoledronic Acid vs Placebo in Prostate Cancer Patients with Hormone-refractory Metastatic Bone Lesions

- Primary endpoint: skeletal related events
  - Pathological fractures
  - Spinal cord compression
  - Radiation for bone pain or to treat or prevent pathologic fractures or spinal cord compression
  - Surgery to bone
  - Change of antineoplastic therapy for bone pain
  - Hypercalcemia of malignancy (HCM)

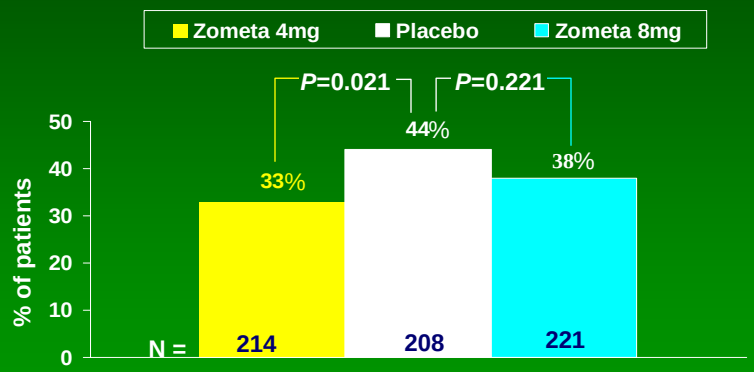
Saad, JNCI, 94:1458, 2002



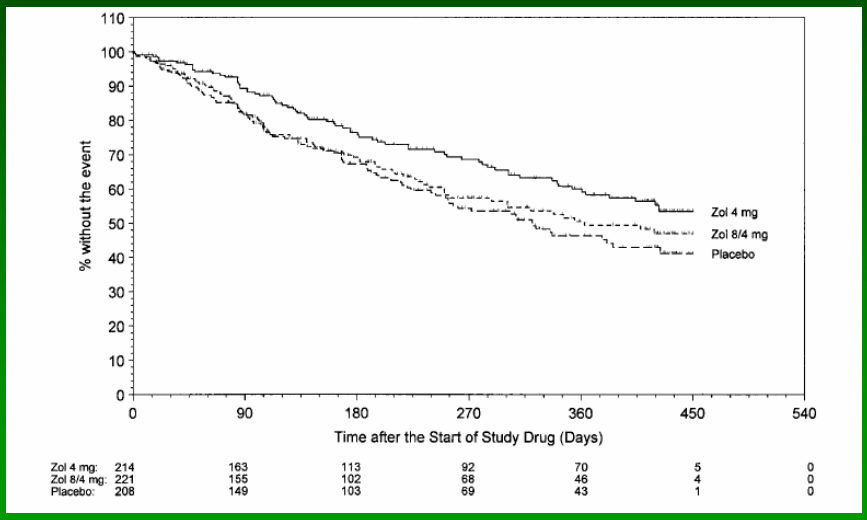
Toxicity

Adverse event*	No. of patients with adverse events in treatment group (%)		
	Zoledronic acid		
	4 mg (N = 214)	8/4 mg (N = 218)	Placebo (N = 208)
Bone pain	108 (50.5)	133 (61.0)	127 (61.1)
Nausea	77 (36.0)	115 (52.8)	77 (37.0)
Constipation	72 (33.6)	85 (39.0)	72 (34.6)
Fatigue	70 (32.7)	67 (30.7)	53 (25.5)
Anemia	57 (26.6)	60 (27.5)	37 (17.8)
Myalgia	53 (24.8)	53 (24.3)	37 (17.8)
Vomiting	46 (21.5)	64 (29.4)	43 (20.7)
Weakness	45 (21.0)	50 (22.9)	40 (19.2)
Anorexia	43 (20.1)	55 (25.2)	36 (17.3)
Fever	43 (20.1)	48 (22.0)	27 (13.0)
Edema, lower limb	41 (19.2)	48 (22.0)	27 (13.0)
Dizziness	38 (17.8)	22 (10.1)	24 (11.5)
Diarrhea	36 (16.8)	35 (16.1)	32 (15.4)
Weight decrease	36 (16.8)	38 (17.4)	26 (12.5)

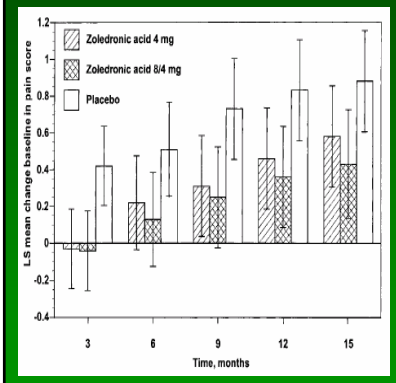
Skeletal Related Events



SRE Over Time



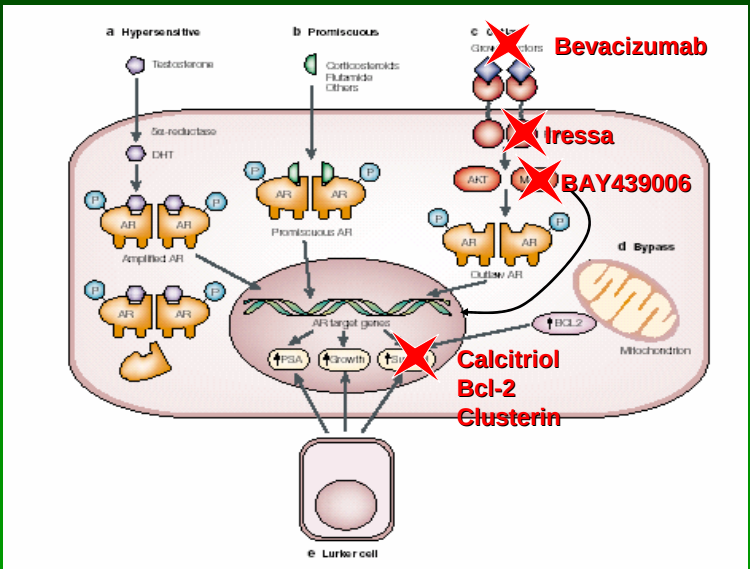
A Positive Trial



- Patient Benefit?
  - Pain Scale out of 10 - not a clinically significant difference
  - Analgesics and quality of life not different
  - Survival not different statistically
- Cost effectiveness
  - Number needed to treat = 1 in 9
  - An additional $32,000 per event avoided
  - An additional $59,000 for each man in whom an event is avoided
- PEC proposal under review
  - Available under the palliative drug benefit program

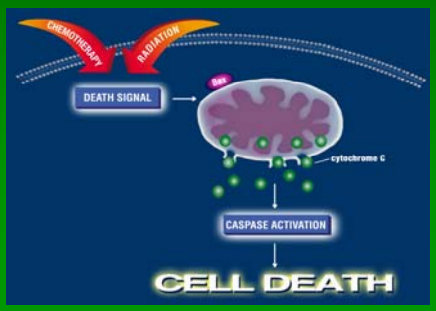
Reed, J Urology, 171:1537, 2004

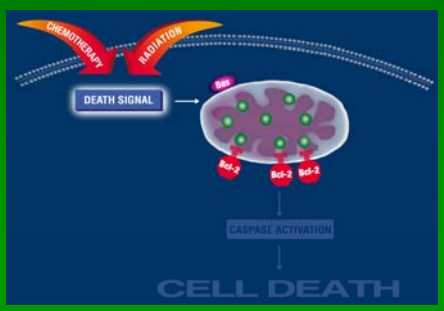
New Tricks: Targeted Therapy



Enhancing Apoptosis: Targeting Bcl-2

- B-cell lymphoma/leukemia associated gene 2
- Encodes a 26kd mitochondrial membrane associated protein with anti-apoptotic regulatory function
- First recognized member of a growing family of apoptosis regulatory gene products that function as death antagonists or agonists





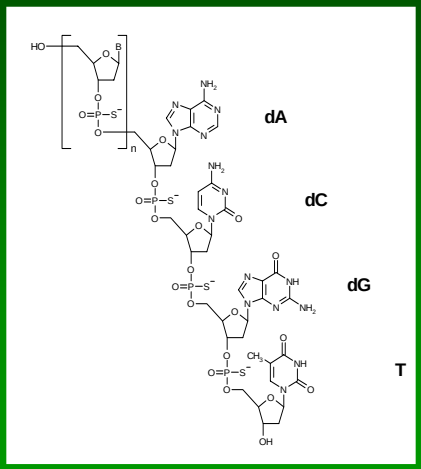
Bcl-2 in Prostate Cancer

- Localized Disease
  - correlated with high Gleason score, N+
  - independent negative predictive/prognostic factor
- Relapsed Disease
  - poorer response to androgen withdrawal therapy
- Hormone Refractory Disease
  - expression of Bcl-2
  - implicated in the development of androgen independence and mechanism of treatment resistance
  - taxanes phosphorylate Bcl-2 (D>P by 10^{2-3})

McDonnell, J Urol, 1997; Colombel, Am J Path, 1993; Bubendorf, Am J Path, 1996; Scherr, J Urol, 1999; Haldar, Cancer Res, 1997.

Targeting Bcl-2: G3139/Genasense (Genta Inc)

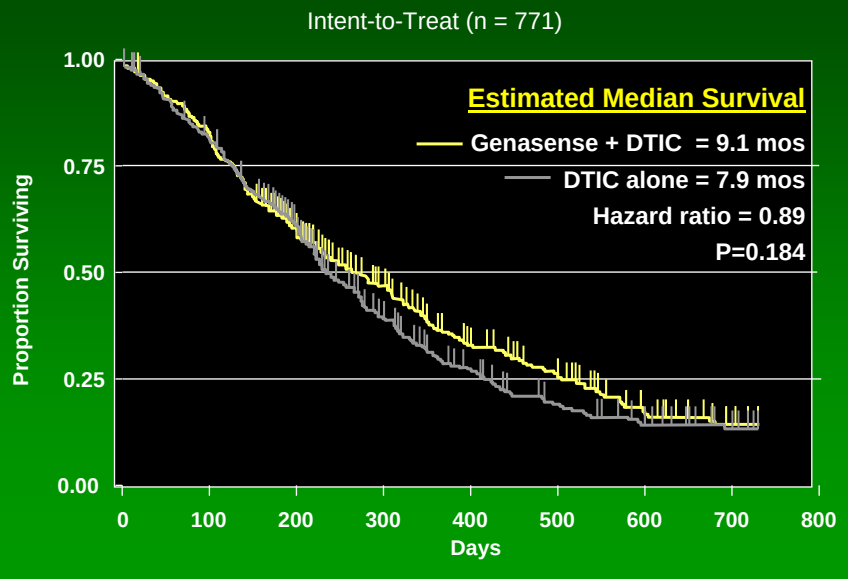
- 1st generation antisense oligonucleotide with a phosphorothioate backbone
- Complimentary to the first six codons of the human bcl-2 open reading frame
- Active in pre-clinical models in inhibiting expression of Bcl-2 and enhancing apoptosis
- In Phase I, II and III trials



Does Antisense Bcl-2 Work in People?: Phase III Melanoma Trial

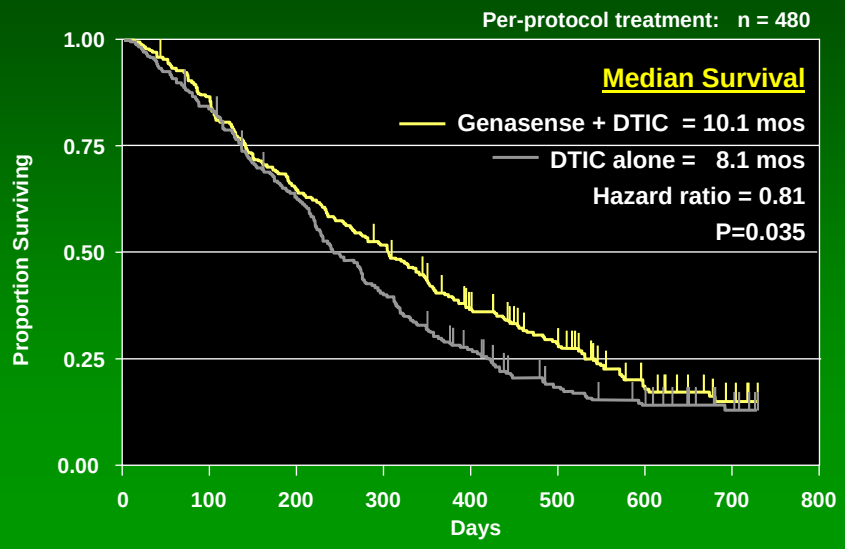
	Genasense + DTIC (N = 386)		DTIC (N = 385)		P value
Progression-free survival	78 d		49 d		0.0003
Time-to-progression	78 d		49 d		0.0003
Overall response (CR + PR)	45	(11.7%)	26	(6.8%)	0.0185
Complete response	5	(1.3%)	2	(0.5%)	
Partial response	40	(10.4%)	24	(6.2%)	
Stable disease	116	(30.1%)	106	(27.5%)	
Total	161	(41.7%)	132	(34.3%)	0.034
Progressive disease	152	(39.4%)	178	(46.2%)	
Durable response (6 mo.)	13	(3.4%)	5	(1.3%)	
Ongoing response	23	(6.0%)	14	(3.6%)	

Primary Endpoint: Overall Survival



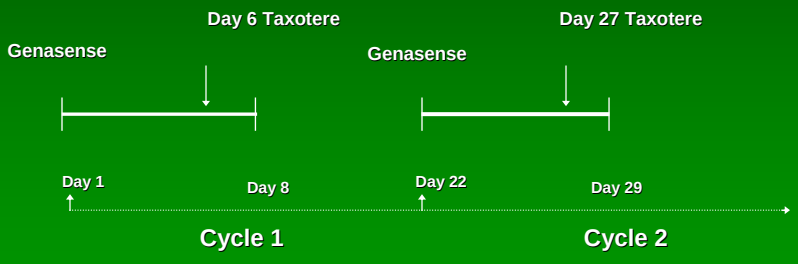
Overall Survival

Patients with ≥ 12 Months Follow-Up



A Phase II Pharmacokinetic and Biologic Correlative Study of G3139 and Docetaxel in Hormone-Refractory Prostate Carcinoma

Institute for Drug Development and BC Cancer Agency



Genasense – 7 mg/kg/24 hours CIVI D1-D8

Taxotere – 75 mg/m^2 IV on D6

Growth factors not used routinely

Chi, Proc of ASCO, 2003

Patient Characteristics

Characteristic	Median (Range)	No. of Patients (%) N=31
Age	66 (44-82)	
Years since diagnosis	5.9 (0.6-17.4)	
ECOG PS		
0		8 (26)
1		19 (61)
2		4 (13)
Baseline Fatigue		
Grade 1		11 (36)
Grade 2		4 (13)
Sites of Disease		
Bone		13 (42)
Lymph Node		9 (29)
Other		9 (29)
PSA	127.6 (0.12-3,717)	
Hemoglobin	12.7 (9.1-15.2)	
Alkaline Phosphatase	166 (63-3,738)	
Prior Therapy		
Orchiectomy		4 (13)
LHRH Agonist		27 (87)
Non-Steroidal Antiandrogen		30 (97)
Steroidal antiandrogen		13 (42)
Estrogen		8 (26)
Corticosteroids		13 (42)
Ketoconazole		3 (10)
Radiotherapy (prostate)		13 (42)
Radiotherapy (other sites)		17 (55)
Chemotherapy		6 (19)
Other		1 (3)

Toxicity

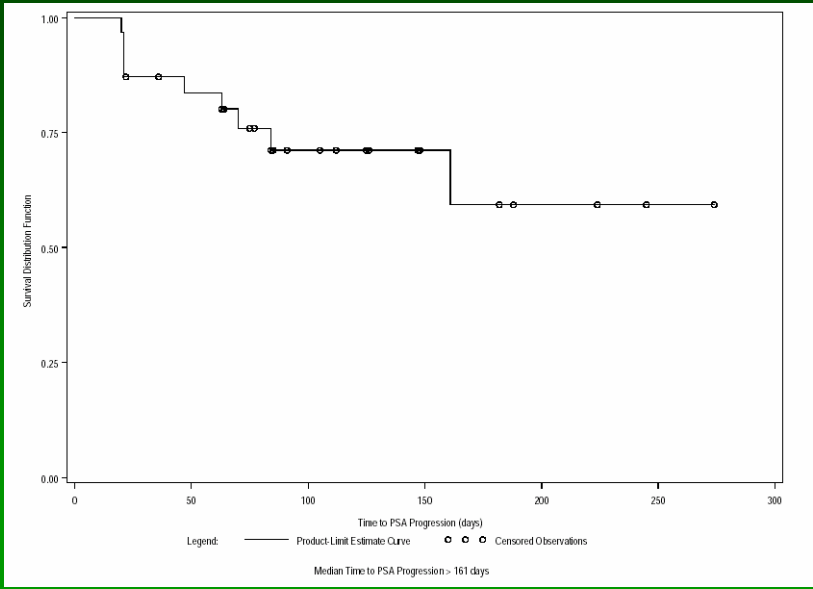
ADVERSE EVENTS	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*	*Total Patients*
HEMATOLOGICAL					
Neutropenia	0	1	7	20	**28**
Neutropenia (on day 6 pre-docetaxel)	3	1	0	0	**4**
Febrile Neutropenia	0	0	6	2	**8**
Anemia	3	3	1	0	**7**
Thrombocytopenia	0	1	1	0	**2**
NON-HEMATOLOGICAL					
Alopecia	15	8	0	0	**23**
Fatigue	6	11	5	0	**22**
Non-Neutropenic Fever	18	3	0	0	**21**
Diarrhea	12	4	5	0	**21**
Nausea	9	9	1	0	**19**
Vomiting	12	0	1	0	**13**
Myalgia	13	0	0	0	**13**
Arthralgia	5	5	0	0	**10**
Edema Peripheral	8	1	0	0	**9**
Hypotension	4	4	0	0	**8**
Hypophosphatemia	0	2	6	0	**8**
Dehydration	1	6	0	0	**7**
Hypoalbuminemia	1	1	2	0	**4**
G-CSF use: 6 pts/11 cycles					

Responses

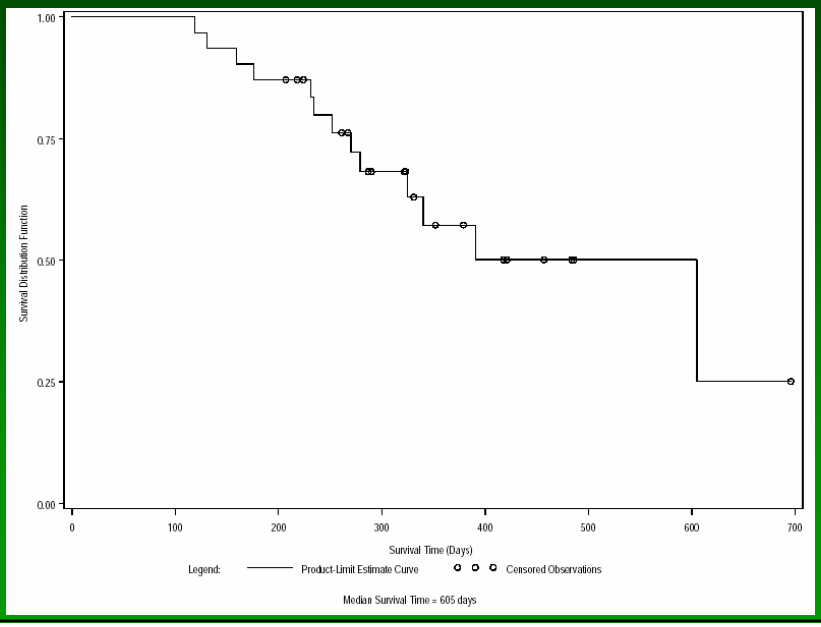
PSA Response	No. of Patients (%) N=29
≥ 50% reductions in PSA	14 (48)
≥ 75% reductions in PSA	6 (21)
≥ 90% reductions in PSA	2 (7)

Objective Response	No. of Patients (%) N=13
Complete Response (CR)	0
Partial Response (PR)	4 (31)
Stable/No Response (SD)	2 (15)
Progression of Disease (PD)	7 (54)

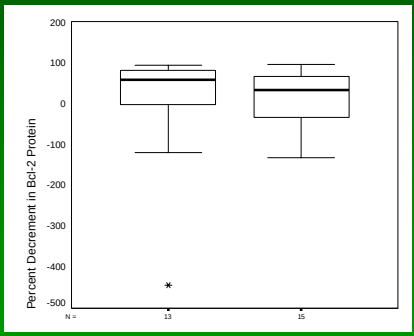
PSA Progression Free Survival

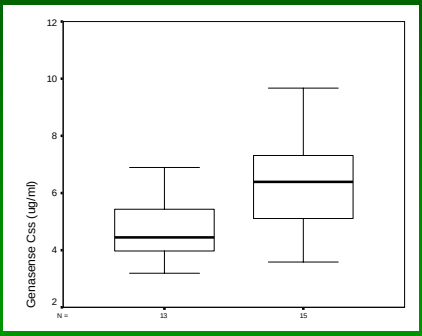


Overall Survival



Correlative Studies





Conclusions: Docetaxel + G3139 for HRPC

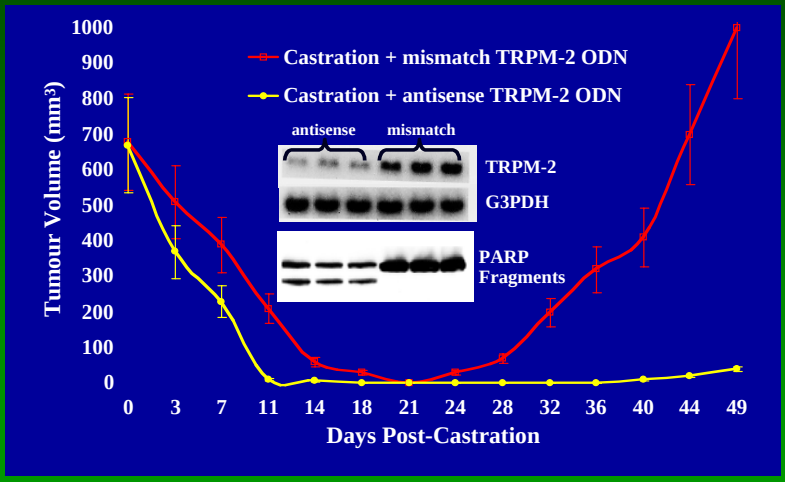
- "Interesting" activity
  - PSA response rate reasonable considering the patient population
    - Time to progression, overall survival
  - Not a "home run"
    - Drug - need more?
    - Target - not that important?
    - Population - Bcl-2 expression not assessed
- Phase III trial 3rd quarter 2004 by Aventis/Genta

Enhancing Apoptosis: Targeting Clusterin

- Clusterin associated processes
  - Tissue remodeling, lipid transport, membrane protection, complement defense and apoptosis
  - Anti-apoptotic
- In malignancy
  - Prostate
    - Low expression in normal prostatic tissue
    - Increased expression correlates with higher Gleason Grade
    - Increased expression after neo-adjuvant hormone therapy
  - Also expressed in renal, bladder, ovary, lung and breast cancers
  - Overexpression in pre-clinical models confers resistance to hormone, chemo and radiation therapy

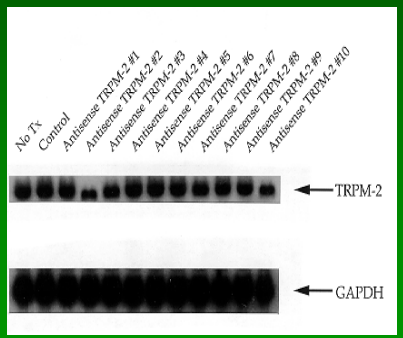
Poon, FEBS 2001; Lakins, Biochemistry 2002; Michel, Biochem J, 1997; Steinberg, Clin Cancer Res, 1997

Clusterin ASO Delay Androgen Independent Progression *In Vivo (Shionogi)*

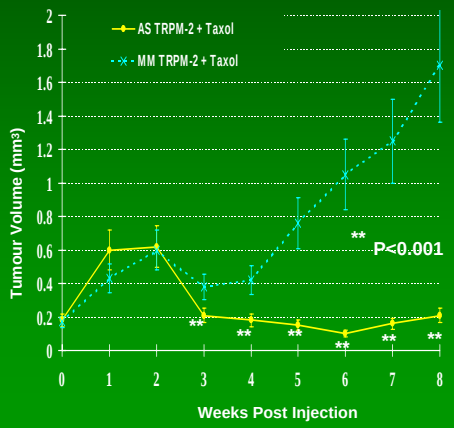


Clusterin ASO Enhance Chemosensitivity *In Vivo (PC3)*

A.

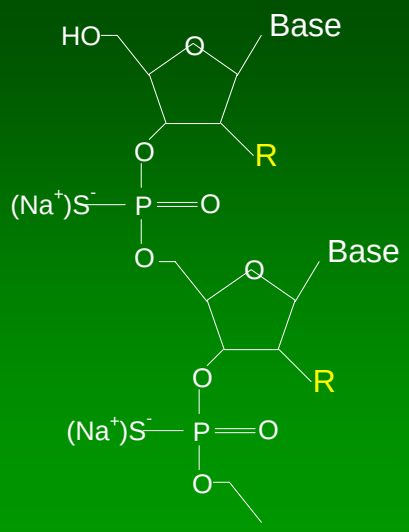


B.



OGX-011 (Oncogenex Technologies Inc)

- 21-mer complementary to the translation initiation site
- MOE-gapmer
  - Improved scheduling
    - Longer tissue t1/2
    - Longer suppression of target
  - Less non-specific toxicity



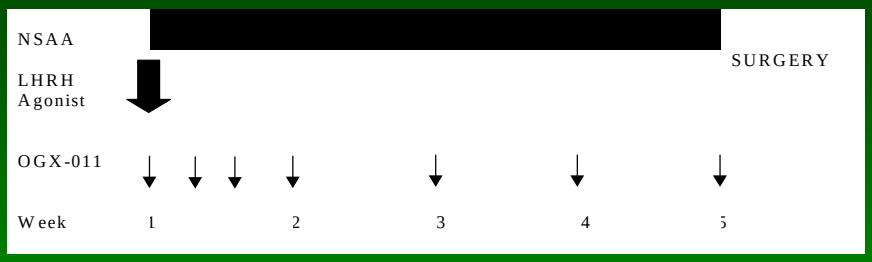
R = $-OCH_2CH_2OCH_3$

Difficulties in the Clinical Assessment of Targeted Therapies

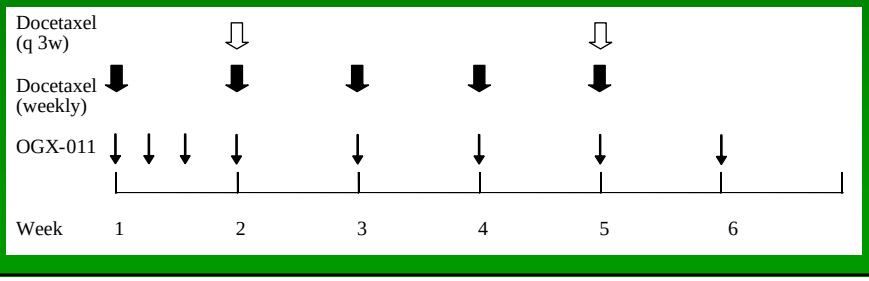
- What is the right dose?
  - Biologically Effective Dose vs Maximally Tolerated Dose
  - Assessment of biological effectiveness
    - Surrogate tissue vs tumour tissue
  - Antisense skepticism
- Single molecular target unlikely to be effectual in most solid tumour malignancies
  - Selection of the most appropriate patient population important
  - A combined approach will likely be required

OGX-011: Clinical Trials for 2003

NCIC.CTG. IND.153: Phase I trial of OGX-011 + NHT prior to Radical Prostatectomy



NCIC.CTG.IND154: Phase I trial of OGX-011 + Docetaxel



IND.153: Phase I Trial of OGX-011 + NHT Prior to Radical Prostatectomy

Human Neoadjuvant Model for Clinical Proof of Principal

Primary Objective

To determine the toxicity and define a recommended phase II dose *based on toxicity and biological effectiveness*

Secondary Objectives

1. Plasma pharmacokinetic profile.
2. Target tissue OGX-011 concentration.
3. Effect on clusterin expression in post-radical prostatectomy specimens (IHC, ISH, Western, rtPCR).
4. Effect on clusterin expression in patient peripheral blood mononuclear cells *(surrogate tissue)*.
5. Effect on patient clusterin serum levels *(surrogate tissue)*.
6. *Correlations* between plasma and prostate PK with toxicity and biological effectiveness

IND.153: Current Accrual

- Activated December 2002

Dose Level	OGX-011 (Days 1,3,5,8,15,22,29)	Planned # Patients	Patients Accrued
1	40 mg	1	1
2	80 mg	3	3
3	160 mg	3	3
4	320 mg	6	6
5	480 mg	6	6
6	640 mg	3-6	6
7	800 mg	3-6	-

Patient Characteristics

N=22

Median Age (Range)		64 (45-71)
Gleason Score	6 7 8-10	5 12 5
Baseline PSA	<10 10-20 >20	14 5 3
Clinical Stage	1c 2a 2b 3a	11 7 3 1

Hem Toxicity

		Grade			
		1	2	3	4
40/80 mg (N=4)	WBC	1			
	Granulocytes				
	Hemoglobin	2			
	Platelets				
160 mg (N=3)	WBC				
	Granulocytes				
	Hemoglobin	3			
	Platelets				
320 mg (N=6)	WBC	4			
	Granulocytes	1	1		
	Hemoglobin	4			
	Platelets				
480 mg (N=6)	WBC	2			
	Granulocytes	1			
	Hemoglobin	5			
	Platelets				
640 mg (N=3)	WBC	1			
	Granulocytes	1			
	Hemoglobin	3			
	Platelets	1			

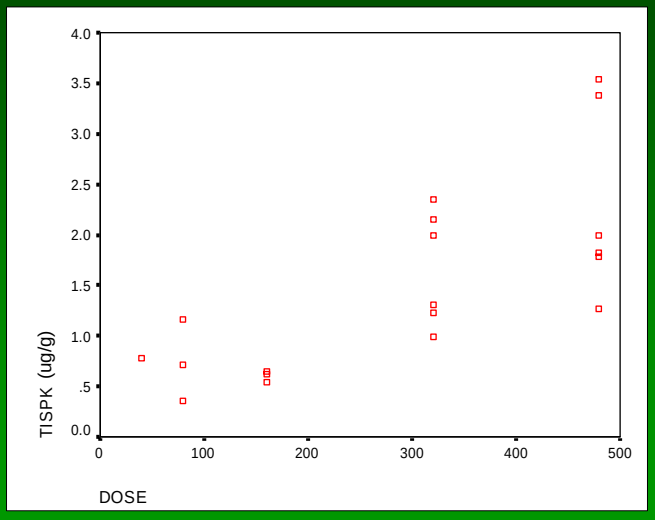
Non-Hem Toxicity

		Grade			
		1	2	3	4
40/80 mg (N=4)	Hot flashes	2			
	Arthralgias	1			
160 (N=3)	Fatigue	2			
	Hot Flashes	2			
	Rigors/Chills	1			
	Rhinitis	1			
	Headache	1			
320 mg (N=6)	Fatigue	5			
	Rigors/Chills	4			
	Fever	3			
	Nausea	2			
	Arthralgias	2			
	Myalgias	2			
480 mg (N=6)	Fatigue	2	1		
	Rigors/Chills	6			
	Fevers	4	1		
	Arthralgias	1			
640 mg (N=3)	Fatigue	2			
	Rigors/Chills	3			
	Fever	2			

Bch Toxicity

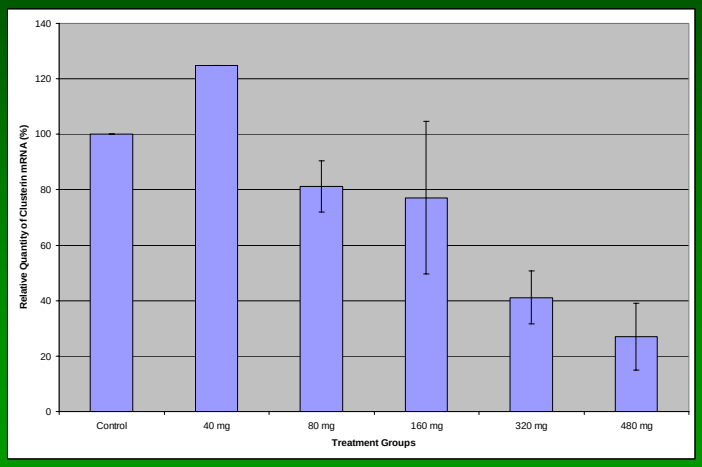
	Grade			
	1	2	3	4
40/80 mg (N=4)				
Cr				
AST	1	1		
ALT		1		
160 (N=3)				
Cr				
AST				
ALT				
320 mg (N=6)				
Cr				
AST	3			
ALT	3			
480 mg (N=6)				
Cr	1			
AST	3	1		
ALT	2			
640 mg (N=3)				
Cr				
AST	1	1		
ALT	2			

Prostate Tissue OGX-011 Concentrations



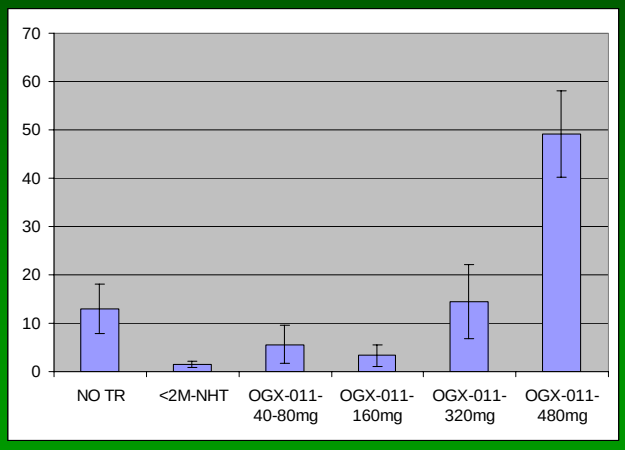
Clusterin Expression in Prostatectomy Specimens

rtPCR



Clusterin Expression in Prostatectomy Specimens

Immunohistochemistry: Visual Score 0



Conclusions: OGX-011

- Well tolerated and dose escalation continues
  - Single agent and in combination with docetaxel
- A phase II dose of OGX-011 based on toxicity and optimal biological effectiveness will be determined
  - First proof of principal demonstration of dose dependent target inhibition for an antisense molecule
- Phase II trials in neoadjuvant setting for prostate cancer, HRPC, breast and lung cancer planned for 2004

Summary: Management of HRPC

- No treatment for HRPC has (as yet) been shown in RCT to improve survival
  - Consider observation
  - Palliation of symptoms
    - Radiotherapy
    - Adequate analgesia
- Second line hormonal therapies
  - Benefit is not well defined but standard practice
  - Best suited for asymptomatic patients, chemo ineligible
- Bisphosphonates
  - Only Zoledronic Acid has been shown to be of benefit
    - SRE decreased
      - Patient benefit and cost-effectiveness debatable
  - More to come: osteoporosis, delay of progression

Summary: Management of HRPC

- Chemotherapy is active in HRPC
  - Mitoxantrone an accepted standard
    - Palliation of pain, delay in progression
  - Docetaxel +/- Estramustine and other combinations
    - Single agent Docetaxel a standard in Vancouver
    - Improved response rates
      - Landmark RCTs will report soon
      - Toxicity an issue
      - Overall benefit will likely be modest in HRPC
    - Active regimens as basis for further development
      - Combination with novel therapies
      - Earlier disease
        - » Adjuvant
        - » Neoadjuvant
        - » Androgen dependent recurrence
- Clinical trials of novel therapies

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