“Hormonal” Therapy in Advanced Prostate Cancer - Beyond Simple Castration

Martin Gleave MD, FRCSC, FACS

Distinguished Professor, UBC
B.C. Leadership Chair in Prostate Research
Director, The Prostate Centre at VGH
Chair, GU Tumour Group, BCCA
Chairman, NCIC GU Clinical Trials Group, & CUOG
Hormonal therapy for CaP: Beyond Simple Castration

History of Androgen Therapy

- Male sex hormones are collectively known as androgens, which is derived from the Greek andros, (man) and gennan (to produce).

- 1786: John Hunter described seasonal variations in the size of the testicles and prostate gland in animals. Later tested the effects of castration on secondary sex organs.


- 1935: Clyde Deming reported that castration decreased the size of the prostate in primates but had no effect on BPH.

Hormonal therapy for CaP: Beyond Simple Castration

- Charles Huggins
  - Canadian-born; Urologic-scientist at U of Chicago
  - Nobel Prize
    - Physiology & Medicine
    - Nobel Laureate, 1966

- Most men had incurable/metastatic disease
- Castration = surgical or estrogen
- Limited understanding of molecular basis of androgen action or resistance
Hormonal Therapy for CaP: Approaches and Issues

- Androgen Action
- Androgen Deprivation Therapy
  - Maximal androgen blockade
  - Timing
    - Immediate vs deferred
    - Intermittent vs continuous
- Androgen Resistance - CRPC
  - Targeted therapies

Androgen Axis and Hormonal Therapy

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
Androgen Action

Androgen Receptor: Interactions

http://www.androgendb.mcgill.ca/
Androgen Action: Genomic and Non-genomic AR Activity

- AR is a ligand dependent nuclear transcription factor, part of the steroid receptor super-family

<table>
<thead>
<tr>
<th>Ligand-dependent receptor activation</th>
<th>Ligand-independent receptor activation</th>
<th>Nonnuclear action through cell surface receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen</td>
<td>Cell membrane</td>
<td>Androgen Receptor</td>
</tr>
<tr>
<td>Nuclear Androgen Receptor</td>
<td></td>
<td>Increased secretory activity</td>
</tr>
<tr>
<td>Nuclear actions</td>
<td></td>
<td>mitogenic + anti-apoptotic effects</td>
</tr>
</tbody>
</table>

Increased secretory activity mitogenic + anti-apoptotic effects

Androgen Axis and Hormonal Therapy

Activation of Steroid Receptors

- Testosterone leads to DHT through 5αR.
- Steroid receptor diffusion into cells.
- HSP90 complex with transformation or activation.
- DNA binding dimerization.
Androgens rapidly phosphorylate Hsp27 in a dose and time dependent manner

**A**

Hsp27 is phosphorylated predominantly on Ser 78, and 82

**B**

The rapid time frame of androgen action is consistent with non genomic effect of androgen


Androgen receptor interacts and co-localizes with Hsp27 in LNCaP cells

Effects of Hsp27 Expression Levels and AR Transactivation

Hsp27 knockdown decreases AR and PSA levels

MM Hsp27 ASO

AR

Hsp27

Vinculin

Effect of hsp27 on AR Activity requires the AR since it is blocked by antiandrogen, Casodex


Effects of Hsp27-AR interactions on genomic and non-genomic activity of androgen/AR

Androgen Action:
Pro-survival and Mitogenic

Androgen-Induced Changes in Gene Expression

Clusterin is an AR-regulated Cytoprotective Gene

sCLU-2 - cytoprotective chaperone that interacts with and inhibits Bax, a proapoptotic Bcl-2 family member

miR 125b - AR regulated miRNA that negatively regulates expression levels of Bak1, a proapoptotic member of Bcl-2 family (Shi XB, PNAS, 2007)
Androgen Transcriptionally Regulate CLU Expression

Clusterin mRNA

Tubulin

Androgen Action: Pro-survival and Mitogenic

Apoptotic Rheostat

- T → DHT regulates transcriptional activity of AR
- AR has both genomic and non-genomic effects
- Potentiates IGF-1 responsiveness through increased IGF-1R levels (Kruekl et al, Cancer Res, 2004)
- Increases expression levels and/or activation of cytoprotective chaperones
  - eg: clusterin, phosho-Hsp27
- Increases expression miRNA that negatively regulates expression of pro-apoptotic genes
  - eg: Bak
Hormonal therapy for CaP: Approaches and Issues

- Androgen Action
  - Anti-apoptotic, effects on chemosensitivity

- ADT - (Dosing and Scheduling Issues)
  - Maximal androgen blockade - Relevance today?
  - Timing
    - Immediate vs deferred
    - Intermittent vs continuous

- Androgen Resistance - CRPC

Rationale for Combined Androgen Blockade

[Diagram showing the hypothalamus, pituitary gland, adrenal glands, and testes with hormonal interactions and feedback control.]

**10-Year Survival: Randomized Trials of MAB vs AS Alone**

- PCTCG meta analyses of MAB vs monotherapy
- 27 trials: 8,275 men
- 1.8% improvement in 5 year survival for MAB compared with monotherapy
  - 25.4% vs 23.6%
  - HR 0.96 (p=0.026)

Meta-analyses:
4 month survival advantage with LHRH-A + NSAA (eg. Bicalutamide, flutamide)

New RCT data - Overall survival improved in MAB arm - 0.78 HR:

Hormonal therapy for CaP: Approaches and Issues

- Androgen Axis and Action
  - Anti-apoptotic, chemo- and radio-sensitization

- Maximal androgen blockade
  - Relevance today?
  - Implications for ↑↑ T suppression, AR blockade
  - We are now recommending LHRH + bicalutamide at BCCA

- AR remains an important and relevant target
  - Inhibition of intracrine T production (eg. abiraterone)
  - Super AR antagonists
  - AR disruptors (eg. Hsp27, Hsp90, HDAC inhibitors)

Hormonal therapy for CaP: Approaches and Issues

- Androgen Axis and Action
  - Anti-apoptotic, effects on chemosensitivity

- Maximal androgen blockade
  - Relevance today? - implications for > T suppression, AR blockade

- Timing
  - Immediate vs deferred
  - Intermittent vs continuous
  - Neoadjuvant, adjuvant, combination regimens

- Androgen Resistance - HRPC
Effects of Timing of Androgen Ablation on Time to AI Progression in Shionogi Tumour Model

- Time to androgen-independent recurrence is directly proportional to tumor burden at time of castration

So et al, BJU Int. 2004 Apr;93(6):845-50

Optimal Timing of ADT - Immediate vs Delayed?

Evidence Supporting Immediate Therapy

1. Xenografts: improved survival when castrated at low tumour volume
2. EORTC: improved survival with immediate HT post-RT (Bolla et al, NEJM 1995)
3. ECOG: 2% vs 30% PCa mortality with immediate vs delayed HT in N+ disease post-RP (Messing et al, NEJM 2000)
4. EPC Data (Casodex monotherapy trial)
   - prolongs time to radiographic and biochemical progression (predictable)
   - overall survival reduced in Casodex arm in low risk CaP! (HR 1.47)
   - overall survival improved in Casodex arm in high risk CaP! (HR 0.68)

> emphasizes need for careful selection
(use life expectancy, risk factors, PSAdt as guide)
Immediate vs Delayed Androgen Ablation?

Evidence Supporting Immediate Therapy

1. Xenografts: improved survival when castrated at low tumour volume
2. EORTC: improved survival with adjuvant therapy post-radiotherapy
3. MRC: Delayed time to progression and improved survival M0 CaP
4. ECOG: 2% vs 30% PCa mortality with immediate vs delayed HT in
   - N+ disease post-RP (NEJM 2000)
5. EPC Data (Casodex monotherapy trial)
   - reduces radiographic and biochemical time to progression (predictable)
   - OS adversely affected in Casodex arm in low risk CaP! (HR 1.47)
   - OS improved in Casodex arm in high risk CaP! (HR 0.68)

➢ No supporting evidence that delayed therapy equivalent to immediate in other tumours, but EPC emphasizes need for careful selection

Immediate vs Delayed Androgen Ablation + RT

Radiotherapy Plus Adjuvant HT

- Bolla et al, EORTC
- Phase III; Tx, high grade or T3-T4, n=415
- randomized to RT alone vs RT + adj Zoladex X 3 yrs.

<table>
<thead>
<tr>
<th></th>
<th>LC</th>
<th>cNED</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT alone</td>
<td>75%</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>RT + HT</td>
<td>95%</td>
<td>85%</td>
<td>78%</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Bolla et al NEJM, 1998
Survival Benefit of Earlier Hormone Therapy in Nonmetastatic Disease

Medical Research Council Prostate Cancer Working Party Investigators Group.


- reduces radiographic and biochemical time to progression (predictable)
- OS adversely affected in Casodex arm in low risk CaP! (HR ~1.4)
- OS improved in Casodex arm in high risk CaP! (HR ~1.4)

EPC Survival — Trial 25
Localized vs Locally Advanced Patients

HR=1.47 (1.06, 2.03)
Casodex events = 90 (25.6%)
placebo events = 64 (17.8%)

HR=0.68 (0.50, 0.92)
Casodex events = 73 (28.6%)
placebo events = 94 (37.6%)

ECOG 7887: Disease-free and Overall Survival

Immediate HT Versus Observation After RP and Pelvic Lymphadenectomy in Node-positive Patients

Prostate cancer is not the only cause of death in men

- delayed progression
- decreased local complications
- improved survival
- psychological benefits

Balancing the Benefits of Early Hormone Therapy

- IAS offers opportunity to improve quality of life
  - balances benefits of immediate androgen ablation
  - reduces treatment-related side effects and expense

short-term side effects
- expense
- long-term metabolic effects
  - decreased muscle mass
  - osteoporosis
  - anemia
  - lipid profile
  - immune surveillance
  - cardiovascular risk
  - Cognition/mood
IAS Prolongs Time to Non-Androgen Regulated PSA Gene Expression in the LNCaP model


Clinical Experience with IAS

Urology 45:839, 1995
Mol Urol. 3:287, 1999
Clinical Studies of IAS

   • Mean time on 9 months; 50% off therapy; up to 5 cycles
   • median f/u 22 months, 2 completed cycles, 38% of time off therapy
   • median f/u 24 months, 3 completed cycles, 50% of time off therapy
   • up to 5 completed cycles, 8 months on; 50% of time off therapy
5. Bruchovsky et al: 100 pts, Multicentre Phase II, Post-XRT Failures
   • median f/u 24 months, 1 completed cycle, 50% of time off therapy
   • improved Q of L off treatment

Phase III Studies of Intermittent vs Continuous ADT

1. SWOG/NCIC PR-8: 1300 accrued - closed aug 2008
   • Hormone naïve M1 disease; 9 months on, restart PSA > 10-20
2. NCIC PR-7/SWOG 1300 accrued; closed 2007
   • M0, post-RT failures; 9 months on, restart PSA 6-15
   • Problem - low CaP death rate

German and Portuguese IAS Trials

• Locally advanced, metastatic; 800 pts enrolled
• no difference in time to AI progression or survival (AUA, 2006, 2007)
Hormonal therapy for CaP: Approaches and Issues

- Androgen Axis and Action
  - Anti-apoptotic, effects on chemosensitivity
- Maximal androgen blockade
  - Relevance today?
- Timing
  - Immediate vs deferred
  - Intermittent vs continuous
  - Neoadjuvant, adjuvant, combination regimens
- Androgen Resistance - HRPC

Hormonal Therapy in Advanced Prostate cancer:
Neoadjuvant and Adjuvant Strategies

Theoretical Pros & Cons of NHT Prior to RT

<table>
<thead>
<tr>
<th>Cons</th>
<th>Pros</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell cycle arrest</td>
<td>Shionogi model data</td>
</tr>
<tr>
<td>Increased Bcl-2 &amp; clusterin</td>
<td>Lower tumor volume</td>
</tr>
<tr>
<td>Affects PSA as marker of RT response</td>
<td>Androgens are anti-apoptotic</td>
</tr>
<tr>
<td></td>
<td>Reduced hypoxia</td>
</tr>
</tbody>
</table>
Theoretical Pros & Cons of NHT Prior to RT

Pros

- Shionogi model data
- Lower tumor volume
- Androgens are anti-apoptotic
- Reduced hypoxia

% hypoxic cells decreases after castration

Yapp et al, Radiation Research, 2004,

Combined Hormone Therapy + RT for Localized Prostate Cancer

5 randomized studies

High recurrence rate with radiation monotherapy
- RTOG 85-31
- RTOG 86-10
- RTOG 92-02
- EORTC 22863 - Bolla et al
- Laverdiere et al

Combined HT + XRT:
- reduced local recurrence
- decreased PSA recurrence
- improved survival in high risk disease & longer term HT
Does RT Add anything above and beyond HT in High Risk Localized CaP?

NCIC CTG- PR.3

High Risk Loc CaP prostate cancer

Continuous androgen ablation
Continuous androgen ablation with radiation therapy

PI: P. Warde; Intergroup participation (NCIC, MRC UK, SWOG)
Primary Endpoint: Survival
Sample Size: 1200
Accrual: 1200 (study now closed)
Analysis: 2006

NHT Prior to Surgery: Randomized Studies of 0 vs 3 Months NHT

- 7 Phase 3 trials conducted during 1990’s compared 0 vs 3 months NHT prior to RP
- All powered for change in pos. margin rates as primary endpoint
- All studies show ~50% decrease in pos. margin rates
- No studies show improved bNED rates!
CUOG P95A: Randomized 3 vs 8 Months NHT Study

N = 549

Surrogates of Treatment Response
Changes in Serum PSA and Path Stage

Mean pre-surgery PSA significantly lower in 8 month group
0.056 vs 0.12 µg/L (p<0.0001)

Positive margin rates significantly lower in 8 month group
12% vs 23% (p=0.0106)

Gleave et al, J Urol. 166(2):500-6, 2001

CUOG P95A 3 vs 8 Months NHT Study:
PSA-Free Survival

7 Year Follow-up
Overall Survival = 93%
Overall PSA Relapse Rate - 31%
## PSA Recurrence by Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>n</th>
<th>PSA Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>177</td>
<td>32% vs 25%</td>
</tr>
<tr>
<td>Low Risk</td>
<td>229</td>
<td>25% vs 22%</td>
</tr>
<tr>
<td>High Risk</td>
<td>97</td>
<td>52% vs 59%</td>
</tr>
</tbody>
</table>

**CUOG P95A 3 vs 8 Months NHT Study:**

**High vs Low Volume Centres**

### K-M PSA Relapse Rate

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>39%</td>
</tr>
</tbody>
</table>
CUOG P95A: 3 vs 8 Months NHT Study Summary

- Overall Survival = 93% with Overall PSA relapse - 31%
- Despite improved biochemical and pathologic surrogates, no significant difference in PSA recurrence rates at 5 years post surgery
  - Path response rates not predictive of improved bNED
- Subgroup analyses revealed significant site-to-site differences in PSA relapse rates that were independent of prognostic risk factors.
  - Illustrate effects of surgical technique on study endpoints, highlighting a need to stratify for site of surgery in future randomized multimodal RP trials
  - Generates an interesting hypothesis that a benefit of prolonged NHT may exist when employed by more experienced/higher-volume surgeons.

Hormonal Therapy in Advanced Prostate Cancer: Future Directions

- Taxotere-based hormone naïve disease
  - M1 hormone naïve
  - Adjuvant post RP in high risk pts
  - Salvage in high risk PSA failures post RP
  - Neoadjuvant in high risk pts pre RP
  - Combined NHT + adj in high risk pts pre-RT

- Chemo-hormonal combination trials
  - Which order, simultaneous or sequential?
The Problem: 
Hormone Refractory Prostate Cancer

Chemoresistant disease:
- ~18 month median survival

Standard Therapy:
- Taxotere (docetaxel)
- Response rate - ~50%
- ~25% improvement OS, TTP, QoL

Future = Combination Strategies with novel biologics
- Bio-Logical, based on relevant targets

Castration Resistance and Prostate Cancer

- underlying basis for most cancer deaths, and result from multiple, stepwise changes in DNA structure and gene expression arising from selective pressures of treatment.

1. Androgen receptor (AR) related
   - amplification (hypersensitive)
   - Mutations (promiscuous)
   - Intracrine T production
   - cross-talk - TK, AKT, STAT3 (phosphorylation, co-regulators)

2. Adaptation
   - Up-regulation of survival genes (Bcl-2, clusterin, Hsp27, YB-1)
   - Increased alternative GF pathways (her2/neu; IGF-1/IGFBP2&5; IL-6/STAT3)
**Mechanisms of Androgen Resistance**

1. Amplification of the AR Gene
2. Sensitivity of the AR
3. AR-Mutations
   - Progesterone and cortisol
   - Antagonists
   - Estrogens
   - Antiestrogens
4. Coactivators
   - SRC
   - MAPK
5. Activation of Alternate Growth Factor Pathways
   - IGF-1/IGF-1R
   - Her-2/neu
   - IL-6/stat-3
6. Upregulation of Survival Genes
   - Bcl-2, Bcl-xL
   - Clusterin
   - Hsp27
   - YB-1

**Intracrine Testosterone Production**

**Androgen Action:**

**Pro-survival and Mitogenic**

- TAB using non-steroidal anti-androgen like flutamide or bicalutamide has small benefit in prolonging survival

**BUT**

- AR remains present, activated and biologically relevant in acquisition of castrate resistance
- What are the mechanisms of AR transactivation after castration?
Residual Prostatic Androgens with ‘Castration’

The Adrenal Androgen Androstenediol Is Present in Prostate Cancer Tissue after Androgen Deprivation Therapy and Activates Mutated Androgen Receptor

Atsuhi Minagaki,1 Ettelo Koh,1 Hiroshi Fujita,1 Yoji Maeda,1 Masayuki Egawa,2 Kiyoshi Kohida,1 Seiiji Hanno,2 Evan T. Keller,2 and Miki Namioka1

1Department of Urology, Konan University, Kobe, Japan, 2Pharma Hormone, Inc., Konan, Japan, and 3Uni for Laboratory Animal Medicine and Department of Pathology, University of Michigan, Ann Arbor, Michigan

Vol. 33, Issue 4, January 15, 2004 Clinical Cancer Research

Featured Article

The Androgen Axis in Recurrent Prostate Cancer

James L. Mohler,1,3,8,9
Christopher W. Gregory,7,9 O. Harri Ford III,1,6
Dowd Kim,4 Catharina M. Weaver,5
Peter Pezzullo,7,8,9,11,12 and
Frank S. Field1

Department of Urology, Division of Urology; Pathology and Laboratory Medicine; Institute for Reproductive Biology; Critical (Developmental Biology and Biochemistry and Biophysics); and University of North Carolina-Chapel Hill, North Carolina; Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY; and Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY.

lower (Wilcoxon, P = 0.0000003, 0.00005, and 0.0009), respectively, in recurrent prostate cancer than in benign prostate, and mean dihydrotestosterone levels, although reduced, remained 1.5-fold in the recurrent prostate. Androgen receptor activation in recurrent prostate cancer was suggested by the androgens-regulated gene product A, protein-specific antigen, at 896 kDa, 8.80 MoV3 cell lines.

Conditioning, testosterone, and dihydrotestosterone occur in recurrent prostate cancer tissue at levels sufficient to activate androgen receptor. Novel therapies for recurrent prostate cancer should target androgen receptor directly and prevent the formation of androgens within prostate cancer tissues.

Intraprostatic Effects of Castration: Hormone Measurements

Tissue androgen levels in benign prostate (gray) and castrate recurrent prostate cancer (white) previously treated with androgen deprivation.


<table>
<thead>
<tr>
<th>Tissue androgen levels (pmol/g tissue)</th>
<th>SHBG</th>
<th>T</th>
<th>DHT</th>
<th>ASD</th>
<th>DHEA</th>
<th>DHEAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign prostate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
T, DHT, and Progesterone Levels Increase in Castrate Resistant LNCaP Tumors

- LNCaP xenograft androgens, like PSA, increase during progression post castration.
- Since mice synthesize scant adrenal androgens, we hypothesized that the tumors themselves are the source of increased androgens.

De Novo Androgen Synthesis in Prostate Cancer Cells: Backdoor Pathway

- Classical pathway
  - Cholesterol → Pregnenolone → Progesterone → 17-OH progesterone → Androstenedione → Testosterone → Dihydrotestosterone
- Backdoor pathway
  - Cholesterol → Pregnenolone → Progesterone → Pregnan-3α-ol-20-one → Androstanediol
Intraprostatic Sources of Androgen: Backdoor Pathway:

$[^{14}C]$-acetic acid is converted to DHT in AI LNCaP tumor cells

<table>
<thead>
<tr>
<th>Identification</th>
<th>LC Radiometric RT (min)</th>
<th>$^{14}$C peak #</th>
<th>% of total $^{14}$C counts</th>
<th>LC MS Standard RT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>20.842</td>
<td>1</td>
<td>0.6</td>
<td>28.92</td>
</tr>
<tr>
<td>4-Pregnen-17-ol-3,20-dione</td>
<td>30.129</td>
<td>2</td>
<td>1.2</td>
<td>36.35</td>
</tr>
<tr>
<td>DHT</td>
<td>33.037</td>
<td>4</td>
<td>2.0</td>
<td>36.35</td>
</tr>
<tr>
<td>Progesterone</td>
<td>37.279</td>
<td>5</td>
<td>0.4</td>
<td>36.35</td>
</tr>
<tr>
<td>Unknown</td>
<td>41.709</td>
<td>6</td>
<td>3.6</td>
<td>36.35</td>
</tr>
<tr>
<td>Cholesterol and lipids</td>
<td>45.0-70.0</td>
<td></td>
<td>91.0</td>
<td></td>
</tr>
</tbody>
</table>

Locke et al, Cancer Res; 2008
Novel Agents In Clinical Trials for CRPC

Agents targeting critical pathways of progression such as AR, angiogenesis, growth factors, and apoptosis with potential to enhance docetaxel therapy

- Atrasentan (ZD 4054)
- Bevacizumab
- Abiraterone
- Sutent
- OGX-011
- MDV3100
- OGX-427
- Sorafenib
- Trastuzumab
- CP-751,871 (IGF-1R Ab)
- Celecoxib
- Thalidomide
- Strontium
- Imantinib
- GTI-2040
- Erlotinib
- RAD001
- ABT-751
- Failed
  - Bortezomib (Velcade)
  - GVAX
  - G3139 (Bcl-2 ASO)
  - DN101/calcitriol

Evolution of the Surgeon-Scientist

Applied Anatomist

↓

Applied Pathophysiologist
Evolution of the Surgeon-Scientist

Applied Anatomist

Applied Pathophysiologist

Applied Molecular Biologist

Evolution of the Surgeon-Scientist

Applied Anatomist

Applied Pathophysiologist

???
**Targeting Angiogenesis**

- BEVACIZUMAB, VEGF-trap
- VEGF
- VEGF-R

**Extracellular**

**Intracellular**

- Substrate
- Substrate
- Signaling molecules
- Proliferation
- Apoptosis
- Angiogenesis
- Metastases

**Atrasentan (& AZ4054) and the Endothelin Axis: Oncogenic Mechanisms**

- ET-1
- ETAR
- PLC
- G-protein
- Ras
- Raf
- MAPK
- Nucleus
- Plasma membrane

**ET-1 acting via ETAR Promotes:**
- Cell growth
- Inhibition of apoptosis
- Angiogenesis
- Osteoblastic remodeling

Endothelin in Prostate Cancer
Phase II Proof of Concept - ZD4054

Overall survival

ZD4054 15 mg vs placebo: HR=0.65 80%CI=(0.49, 0.86); P=0.052
ZD4054 10 mg vs placebo: HR=0.55 80%CI=(0.41, 0.73); P=0.008

Mechanisms of CRPC: Role of AR

- AR remains a functionally active in CRPC (Chen et al, Nat Med. 2004: 10(1):33-9)
- Prostate cancer cells can make DHT from cholesterol precursors (Locke et al, Cancer Res. 2008 1;68:6407-15)
- AR remains an important target in CRPC
  - Super AR antagonists (MDV3100, AZ, BMS)
  - Inhibition of intracrine T production (eg. abiraterone)
  - AR disruptors (eg. Hsp27, Hsp90, HDAC Inhibitors)
**Abiraterone Acetate (CB7630)**

- Irreversible inhibitor of CYP17 (P450c17)
- Reduces DHEA, Androstenedione and Testosterone by both the testis and adrenal glands
- Phase 1 and 2 studies:
  - Antitumor activity in CRPC
  - \( \sim 40\% \) PSA response, some with \( >90\% \) PSA declines
  - Objective RECIST responses
- Phase 3 trial - Aberaterone vs Placebo in 2nd line CRPC now underway

- AR remains an important target in CRPC
  - Super AR antagonists (MDV3100, AZ, BMS)
  - Inhibition of intracrine T production (eg. abiraterone)
  - AR disruptors (eg. Hsp27, Hsp90, HDAC inhibitors)

---

**Abiraterone - an Inhibitor of Androgen Synthesis: Effects on PSA in Men with Metastatic HRPC**

- **Testes, Adrenal, and Prostate Cancer:** Secrete Testosterone
- **Target Organ:** Testosterone to DHT

- **Adrenal Glands:** Secrete Androstenedione

- **% change PSA**
  - 38/54: PSA↓ 250% (70%)
  - 43/54: PSA↓ 130% (80%)

- **Graph:**
  - 0% to 100% change in PSA
  - Patient
MDV3100 - a 2nd generation anti-androgen

Percent PSA Change from Baseline at 12 Weeks for Chemo-naive Patients

- N=42 Chemo naïve
- ≥50% Decline: 23/42 (55%)
- 7 pt off study

Changes in Expression of Stress-Activated Molecular Chaperones After Castration and in CRPC

- Androgen-dependent
- Tumour regression
- Clonal selection
- Adaptive responses

- No NHT
- 3 Mo NHT
- HRPC

- clusterin
- Hsp27
sCLU-2 and Hsp27: Stress-induced Cytoprotective Chaperones

1. Transcriptionally activated by HSF-1
   a. Increased by diverse array of stress triggers (Heat shock, HT, CT, RT, valiade, herceptin)
   b. Increased by cell survival factors like androgen, IGF-1
   c. highly expressed in HRPC, other cancers, aggregapathies (eg Alzheimers, AMD, amyloid).

2. Over-expression confers broad spectrum treatment resistance
   - Inhibits protein aggregation, facilitates UPP activity
   - Interacts and inhibits activated Bax, prevents cytochrome C release
   - Activates NF-kB by facilitating proteasomal degradation of Ik-B

3. ASO or siRNA knockdown (OGX-011, OGX-427)
   - Enhances treatment-induced apoptosis in vitro and in vivo
   - Pre-clinical anti-cancer activity in many models

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

Cancer Research 65(23):11083-93, 2005

OGX-427

Phase 1 Study of OGX-427 in Solid Tumors:
Investigational New Drug Application

- OncoGenex sponsored; PI - K. Chi (SPORE funded)
- Solid Tumors (Prostate, Breast, Ovary, Lung, Bladder)
- Cohorts 1-5 - single agent OGX-427 in dose escalation design
  - 5 dose levels: 200mg up to 1000mg
- Cohort 6 & 7 evaluate OGX-427 in combination with docetaxel
- 3 pts with CaP had PSA declines of 43%, 58%, 62% and 3 pts with ovarian cancer had CA-125 declines of 27%, 28% and 41%.
- Declines in CTC and Hsp27+ CTC have been observed at all dose levels.

OGX-011 Clinical Program Chart

### Phase 1 Clinical Trials - Completed:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>OGX-011 with hormone ablation therapy</td>
<td>25 patients</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>OGX-011 with chemotherapy (docetaxel)</td>
<td>40 patients</td>
</tr>
</tbody>
</table>

### Phase 2 Clinical Trials – Follow Up Ongoing:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRPC</td>
<td>OGX-011 with 2nd line chemotherapy (docetaxel or mitoxantrone)</td>
<td>67 patients; Fully enrolled</td>
</tr>
<tr>
<td>HRPC</td>
<td>1st line chemotherapy (docetaxel) with and without OGX-011</td>
<td>81 patients; Fully enrolled</td>
</tr>
<tr>
<td>Advanced NSCLC</td>
<td>OGX-011 with 1st line chemotherapy (gemcitabine/cisplatin or carboplatin)</td>
<td>81 patients; Fully enrolled</td>
</tr>
<tr>
<td>Localized Prostate Cancer</td>
<td>OGX-011 with hormone ablation therapy</td>
<td>23 patients; Fully enrolled</td>
</tr>
<tr>
<td>Advanced Breast Cancer</td>
<td>OGX-011 with 2nd line chemotherapy (docetaxel)</td>
<td>15 patients; Fully enrolled</td>
</tr>
</tbody>
</table>

Over 300 patients enrolled in OGX-011 clinical trials
**Clinical Proof-of-Concept - Phase I Pre-surgery trial:**
Dose-dependent Decreases in Clusterin Levels in RP Specimens using LCM and Real-Time PCR


**NCIC IND.165: Taxotere +/- OGX-011 in 1st Line Metastatic Castrate Resistant Prostate Cancer**
Time to Off Treatment & Progression Free Survival

Chi et al, ASCO, 2007

* 79% of patients are still alive

<table>
<thead>
<tr>
<th></th>
<th>OGX-011 + docetaxel</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>27.53 mo.</td>
<td>16.89 mo.</td>
</tr>
<tr>
<td>Number of Treatment Cycles</td>
<td>9 cycles</td>
<td>7 cycles</td>
</tr>
<tr>
<td>Early Discontinuation of Chemo</td>
<td>2.5%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Progressive Measurable Disease</td>
<td>4%</td>
<td>17%</td>
</tr>
<tr>
<td>Stable Measurable Disease</td>
<td>77%</td>
<td>50%</td>
</tr>
<tr>
<td>Primary PSA Progression</td>
<td>2.6%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

* 79% of patients are still alive

Chi et al, ASCO, 2007
Phase II Feasibility Trial of OGX-011 in 2nd Line Therapy in CRPC: CUOG P-06 (PI F. Saad, E. Winquist)

- More treatment cycles administered to patients with OGX-011.
  - Median of 7.5 cycles vs. 3-4 cycles reported for most 2nd-line studies
- PSA responses higher than anticipated
  - >50% decrease in PSA - 40% (compared to 30% contemporary controls)
  - >90% decrease in PSA - 20% (compared to 8% contemporary controls)
- Median survival > 13 months (compared to 9.6 months in historical controls)

CUOG 2nd Line Phase II Study of OGX-011 in CRPC Tumors:

Patient: 025-011

![Graph showing patient's response to treatment with OGX-011 over time.](image)
Hormonal therapy for CaP: Summary

- Androgen/AR signaling are important pro-survival growth factors in CaP
  - Early HT yields optimal prolongation in survival
    - BUT - Candidates require risk stratification
  - IAS allows early therapy while reducing cost and side effects
  - MAB (LHRH-A + NSAA) has yielded small clinically significant gains in survival

- Castrate Resistance remains critical hurdle
  - Understanding androgen action and mechanisms of CRPC yielding promising new targets
    - AR - super antagonists, AR disruptors, CYP17 inhibitors
    - Anti-angiogenesis agents
    - IGF-1, IL-6, ET-1a signaling inhibitors
    - molecular chaperones like sCLU-2, Hsp27

Future of Uro-Oncology - Leaders or Dancing Bears?

- Uro-oncologists must be trained to cover the spectrum of oncology
  - Clinical aspects of early & advanced disease
  - Tumor and translational biology
  - Clinical trials expertise
  - Epidemiology
Bio-Logical Therapy: Multi-Targeted and Biologically Rational Combination Therapy

Androgen Withdrawal

1. Apoptosis Enhancers -docetaxel
   - inhibitors of cytoprotective proteins eg. Bcl-2, AR, clusterin (OGX-011), Hsp90 (geldanamycin), Hsp27 (OGX-427)

2. Growth Inhibitors
   - signal transduction eg inhibitors of mTOR (CCI-779), VEGF (Avastin), ET1a (AZ4054); IGF-1R; IL-6

Hormonal therapy for CaP: Summary

- Androgen/AR signaling are important pro-survival growth factors in CaP
- Maximal androgen blockade has not yielded clinically significant gains in survival
- Early HT at time of minimal tumor burden yields optimal prolongation in survival
  - Candidate require risk stratification
  - Neoadjuvant/adjuvant combination strategies being evaluated
- Intermittent vs Continuous trials now completed
- Androgen Resistance remains critical hurdle
Hormonal therapy for CaP: Summary

- Androgen/AR signaling are important pro-survival growth factors in CaP

- Understanding of androgen action and mechanisms of AI progression yielding new targets
  - AR disruption a relevant goal in delaying AI progression
  - Cytoprotective chaperones like sCLU-2, Hsp27
  - Guides rationale combination, multi-modal therapies