Androgen deprivation therapy: New concepts

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Faculty disclosure statement:  
Laurence Klotz, MD

Clinical Research funding:
1. Bayer/Algeta
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3. Abbott
4. GSK
5. EMD Serono

Advisory boards:
1. Dendreon
2. Amgen
3. Janssen
4. Ferring
5. GSK
6. Profound

Speaking/Honoraria:
1. GSK
2. Sanofi-Aventis
3. Amgen
4. Ferring
5. Janssen
6. Dendreon
7. Merck
8. Sanofi-Aventis
9. Profound

Stock Ownership:
None
Developments in last decade:

• Understanding of mechanisms of castration resistance (intracrine/autocrine synthesis of androgens, AR pathway alterations)
• Genomic vs non-genomic pathways of AR action
• Limitations of early ADT/timing
• Intermittent therapy: data from large RCTs
• Importance of testosterone levels
• Systemic/metabolic/CV effects of ADT
• LHRH antagonists
• Role of FSH, estrogen
• Survival benefit in CRPC with new AR pathway targeted agents
Enzymes mediating T/DHT synthesis upregulated in CRPCa
Androgen regulated genes
(N=1500)
A healthy 75-year-old male has a rising PSA 3 years after an RP for Gleason 4+3 pT2N0 PCa

**ADT options**

1. Early vs Delayed ADT
   - what PSA level?
2. LHRH agonist monotherapy
3. CAB with LHRH agonist & anti-androgen
4. Agonist/antagonist
5. 1/2/3/4/6 month depot
6. Anti-androgen monotherapy (Bicalutamide 150 mg)
7. Orchiectomy

**Other options**

1. Continuous vs intermittent ADT
   1. Duration of induction
   2. Trigger for re-treatment
2. CAB: flare blockade or continuous?
3. Monitor testosterone?
4. BMD assessment: When, how often
5. Bone-targeted agents for BMD protection
Intermittent therapy and on-treatment testosterone levels
Background

Intermittent androgen deprivation for prostate-specific antigen (PSA) elevation after radiotherapy may improve quality of life and delay hormone resistance. We assessed overall survival with intermittent versus continuous androgen deprivation in a noninferiority randomized trial.
Overall Survival (ITT)

Hazard Ratio 1.02 (95% CI = 0.86 – 1.21)

Test for non-inferiority of HR (IAS vs CAD) ≥ 1.25; p-value = 0.009

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Median (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous Androgen Deprivation (CAD)</td>
<td>9.1</td>
</tr>
<tr>
<td>Intermittent Androgen Suppression (IAS)</td>
<td>8.8</td>
</tr>
</tbody>
</table>

# At Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
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<tbody>
<tr>
<td>Continuous</td>
<td>696</td>
<td>652</td>
<td>561</td>
<td>319</td>
<td>125</td>
<td>35</td>
</tr>
<tr>
<td>Intermittent</td>
<td>690</td>
<td>651</td>
<td>571</td>
<td>327</td>
<td>140</td>
<td>34</td>
</tr>
</tbody>
</table>
Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., Stephen Prescott, M.D., Subramanian Kanaga Sundaram, M.D., Eric Jay Small, M.D., Nancy Ann Dawson, M.D., Bryan J. Donnelly, M.D., Peter M. Venner, M.D., Ulka N. Vaishampayan, M.D., Paul F. Schellhammer, M.D., David L. Quinn, M.D., Ph.D., Derek Raghavan, M.D., Ph.D., Benjamin Ely, M.S., Carol M. Moinpour, Ph.D., Nicholas J. Vogelzang, M.D., and Ian M. Thompson, Jr., M.D.

ABSTRACT

BACKGROUND
Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy. Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.

METHODS
Men with newly diagnosed, metastatic, hormone-sensitive prostate cancer, a per-

N ~ 1500  M+
Non-inferiority design; pre-defined Δ = 1.2
SWOG 9346 Survival: ‘Results inconclusive’

HR 1.09 (.95-1.24)
Possible outcomes of a non-inferiority trial
### PR.8: Survival by Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extent of disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>743</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Minimal</td>
<td>792</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bone pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>415</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>No</td>
<td>1120</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.2 ng/ml</td>
<td>995</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>&gt; 0.2–4.0 ng/ml</td>
<td>540</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>189</td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>Not black</td>
<td>1066</td>
<td></td>
<td></td>
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<td><strong>Performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>1476</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous hormone therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>186</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>No</td>
<td>1349</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>280</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>North America</td>
<td>1255</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1535</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PSA, prostate specific antigen*  
PSA Response is Predictive of Outcome

PSA at end of 7-month induction period and OS

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>At Risk</th>
<th>Deaths</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ≤ 0.2</td>
<td>602</td>
<td>199</td>
<td>75</td>
</tr>
<tr>
<td>0.2 &lt; PSA ≤ 4.0</td>
<td>360</td>
<td>166</td>
<td>44</td>
</tr>
<tr>
<td>PSA &gt; 4.0</td>
<td>383</td>
<td>322</td>
<td>13</td>
</tr>
</tbody>
</table>

P < .0001

PSA, prostate specific antigen; IAD, intermittent androgen deprivation; OS, overall survival; SWOG, Southwest Oncology Group

Testosterone levels after orchiectomy

Testosterone breakthrough

Pickles et al\(^1\) (N=2368)

Casey et al\(^2\) (N=62)

Niazi et al\(^3\) (N=542)

**Breakthrough rate (%)**

- **BUSERELIN**
  - >=1.7nmol/L: 29.1%
  - 1.1-1.7nmol/L: 2.4%
  - 0.7-1.1nmol/L: 23.6%

- **ELIGARD**
  - >=1.7nmol/L: 35.8%
  - 1.1-1.7nmol/L: 4.7%
  - 0.7-1.1nmol/L: 23.3%

- **GOSERELIN**
  - >=1.7nmol/L: 25.7%
  - 1.1-1.7nmol/L: 3.6%
  - 0.7-1.1nmol/L: 19.3%

- **LUPRON**
  - >=1.7nmol/L: 24.6%
  - 1.1-1.7nmol/L: 3.6%
  - 0.7-1.1nmol/L: 18.4%

**Agonists**

2. Pickles T et al. 2010 CARO Annual Scientific Meeting, Vancouver
Does the T level on ADT matter?

• 3 retrospective studies suggested yes
  – Morote J Urol 2007: N=79
  – Parachino Euro Urol 2009: N=129
  – Bertaglia Euro Urol 2013: 153
Survival free of AIP according to serum testosterone behaviour

Testosterone Increases
Group 1   20 ng/dL
Group 2   20–50 ng/dL
Group 3   >50 ng/dL

AIP, Androgen independent progression

20 ng/dL = 0.7 nmol/L
50 ng/dL = 1.7 nmol/L
Testosterone Levels After 6 Months of ADT predicts PFS and OS in men with Pca


N=153 men, 54 with bone mets

Whole group

99 with PSA failure
Relationship between serum T, CAB vs monotherapy with LHRH, and PFS. Morote et al. J Urol 2007; 178: 1290-1295

Group 1: CAB
Group 2: LHRH monotherapy

T > 1.7 nM

T < 1.7 nM
Conundrum: If intermittent therapy (with rising T in off treatment interval) non-inferior, how could T be important?

- Intracrine synthesis of androgens through back door pathway
- Mutations and amplification of AR, splice ligands, alteration of chaperone proteins, etc., etc.
PR7 Sub-analysis: serum T on ADT in continuous arm and outcome. Klotz L et al, JCO 2015

- Analysis of the 626 patients on continuous ADT in the PR-7 trial
- Serum Testosterone measured 3 times in first year of treatment
- Examined median T and maximum T as predictor for time to CRPCa
### Testosterone in first year of ADT: PR7

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>≤0.7 (20)</th>
<th>0.7-1.7 (20-50)</th>
<th>≥ 1.7 (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum T</td>
<td>79%</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>Median</td>
<td>53%</td>
<td>42%</td>
<td>5%</td>
</tr>
<tr>
<td>Maximum</td>
<td>27%</td>
<td>50%</td>
<td>23%</td>
</tr>
</tbody>
</table>
NCIC CTG PR.7 Sub Analysis

HR event SURVIVAL: Based on Median of 1st Year Testosterone Levels

P = 0.009

HR 1.4

HR 1.9

Time from randomization (years)
NCIC CTG PR.7 Sub Analysis

HR SURVIVAL: Based on Minimum of 1st Year Testosterone Levels

HR 1.3

HR 2.8
Time from hormone resistance to death by minimum T value
How to reconcile the conundrum

• Heterogeneity of prostate cancer cells response to T in vivo (demonstrated in vitro)

• Concept: Advantageous to hit cells hard in induction phase, targeting androgen sensitive and less sensitive cells

• Recovery of androgen sensitive cells in off treatment interval
3 cell type model can explain conundrum

Stem cells, androgen insensitive

Partially insensitive

Androgen sensitive

On treatment

T < 20

Off treatment

Off treatment

T >> 20

Greater androgen dependence

Eventual adaptation/selection pressure

Less androgen dependence
ADT and cardiovascular risk

- Many studies, mostly population based, retrospective
- Results conflicting
- No prospective randomized studies with primary CV endpoint
- Larger trials support increased risk
- All studies suggest risk increased in men with pre-existing CV disease
- “ADT adversely affects CV risk factors, including serum lipoproteins, insulin sensitivity, and obesity. There is a relation between ADT and an increased risk of cardiovascular disease, although different studies have and have not reported an increased risk of cardiovascular death.”
Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist

Peter C. Albertsen\textsuperscript{a,*}, Laurence Klotz\textsuperscript{b}, Bertrand Tombal\textsuperscript{c}, James Grady\textsuperscript{a}, Tine K. Olesen\textsuperscript{d}, Jan Nilsson\textsuperscript{e}

\textsuperscript{a}University of Connecticut Health Center, Farmington, CT, USA; \textsuperscript{b}Division of Urology, University of Toronto, ON, Canada; \textsuperscript{c}University Clinics Saint Luc/ Catholic University of Louvain, Brussels, Belgium; \textsuperscript{d}Ferring Pharmaceuticals, Copenhagen, Denmark; \textsuperscript{e}Department of Clinical Sciences, Lund University, Sweden

Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists

Laurence Klotz\textsuperscript{a,*}, Kurt Miller\textsuperscript{b}, E. David Crawford\textsuperscript{c}, Neal Shore\textsuperscript{d}, Bertrand Tombal\textsuperscript{e}, Cathrina Karup\textsuperscript{f}, Anders Malmberg\textsuperscript{g}, Bo-Eric Persson\textsuperscript{h}

\textsuperscript{a}Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada; \textsuperscript{b}Charité Universitätsmedizin Berlin, Berlin, Germany; \textsuperscript{c}University of Colorado, Denver, CO, USA; \textsuperscript{d}Carolina Urologic Research Center, Myrtle Beach, SC, USA; \textsuperscript{e}Cliniques Universitaires Saint Luc/Université Catholique de Louvain, Brussels, Belgium; \textsuperscript{f}Ferring Pharmaceuticals, Copenhagen, Denmark; \textsuperscript{g}Ferring Pharmaceuticals, Saint-Prix, Switzerland
Pooled patient population (N=2328) 707 had pre-existing CV co-morbidity

<table>
<thead>
<tr>
<th>12-month phase III trials</th>
<th>3-month phase IIIB trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CS21</strong></td>
<td><strong>CS28</strong></td>
</tr>
<tr>
<td>Degarelix 240/80 mg; n=207</td>
<td>Degarelix 240/80 mg; n=27</td>
</tr>
<tr>
<td>Degarelix 240/160 mg; n=202</td>
<td></td>
</tr>
<tr>
<td>Leuprolide 3.6 mg; n=201</td>
<td></td>
</tr>
<tr>
<td><strong>CS35</strong></td>
<td><strong>CS30</strong></td>
</tr>
<tr>
<td>Degarelix 240/480 mg; n=565</td>
<td>Degarelix 240/80 mg; n=181</td>
</tr>
<tr>
<td>Goserelin 3.6/10.8 mg; n=283</td>
<td>Goserelin 3.6 mg; n=64</td>
</tr>
<tr>
<td><strong>CS37</strong></td>
<td><strong>CS31</strong></td>
</tr>
<tr>
<td>Degarelix 240/80 mg; n=175*</td>
<td>Degarelix 240/80 mg; n=83</td>
</tr>
<tr>
<td>Degarelix 240/80 mg; n=50</td>
<td></td>
</tr>
<tr>
<td>Leuprolide 3.6 mg; n=178</td>
<td></td>
</tr>
<tr>
<td>Goserelin 3.6 mg; n=98</td>
<td></td>
</tr>
</tbody>
</table>

*Patients received 7 months of treatment
Pooled Degarelix analysis

• **Strengths:**
  – Increased power to detect differences
  – More adverse events
  – All studies prospective, randomized, blinded
  – Detailed information about CV co-morbidity collected during trial

• **Limitations:**
  – Pooled analysis
  – Short term studies (3 and 12 months)
  – Post hoc analysis
  – Hypothesis generating
PSA progression: Pooled analysis

All patients

PSA > 20
Risk of CV event and OS

CV events

OS $P = .02$
Risk of CV event or death in men with and without baseline CVD

Relative risk reduction of 50%
Absolute risk reduction 7%
Degarelix - FSH

FIRMAGON rapidly decreased FSH and maintained lower levels than leuprolide during the 1-year study.

FSH results should be interpreted with caution because the clinical relevance has not been determined.

Biologically plausibility:

- Conventional wisdom: CV events related to metabolic syndrome and other effects of androgen deprivation

- But several other explanations:
  1. FSH receptor activity in prostate cancer, endothelium, adipocytes, bone mineral density
  2. LHRH receptors in endothelial plaque macrophages and T cells
FSH and FSH-receptors in prostate cancer

FSH and FSH-receptors expressed in

- Normal prostate +
- BPH ++
- Prostate cancer +++
- Androgen refractory prostate cancer ++++

ALSO:

- Adipocytes +++ + low prevalence; ++++ high prevalence
- Cardiac Myocytes +++

Mariani S et al. J Urol 2006; 175: 2072-2077
FSH stimulates growth of PC-3 human prostate cancer cells

PC-3 cell lines express the highest levels of FSH receptor protein

Serum FSH associated with extraprostatic extension of Pca Ide H et al, Prostate Int 2013;1(3):109-112

Factors predicting for ECE

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score</td>
<td>2.04 (0.75–5.54)</td>
<td>0.16</td>
</tr>
<tr>
<td>Log PSA</td>
<td>0.65 (0.13–3.29)</td>
<td>0.60</td>
</tr>
<tr>
<td>Log tumor size</td>
<td>23.93 (1.10–521.36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Log FSH</td>
<td>4.47 (1.09–18.31)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Factors prediction for tumour size

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score</td>
<td>1.51 (0.02–3.00)</td>
<td>0.050</td>
</tr>
<tr>
<td>No. of tumors</td>
<td>–0.17 (–0.91–0.58)</td>
<td>0.660</td>
</tr>
<tr>
<td>Log FSH</td>
<td>2.82 (0.72–4.92)</td>
<td>0.010</td>
</tr>
<tr>
<td>Log PSA</td>
<td>5.72 (3.40–8.02)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
FSH receptors identified on prostate tumour blood vessels

Tumour blood vessels become resistant to therapy

FSH receptor signalling may be associated with tumour cell proliferation

Lowering FSH levels decreases proliferation of PCa cells

FSH directly increases osteoclastogenesis and resorption.

Gi2a-coupled FSH receptors activate osteoclast NF-κB, and Akt resulting in enhanced osteoclast formation and function.

High circulating FSH causes hypogonadal bone loss.
How to explain difference in CV events: T cell activation by GnRH agonists

- Most acute CV events caused by rupture of atherosclerotic plaque
- Plaque degradation by infiltrating macrophages releasing matrix-degrading proteases
- Proinflammatory T-helper 1 (Th1) lymphocytes are macrophage activators; dominant in arterial plaques
- These express GnRH receptors
- GnRH activation stimulates T-cell expansion and Th1 differentiation
- GnRH agonists could promote plaque destabilization
Differential adiposity between different types of ADT. Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8):1126-34, 2014

control  castration  LHRH agonist  degarelix

Pink: adipose tissue
Blue: Lung tissue
Total body weight (g) at 4 months

Control
Castration
Enantone
Degarelix

BMI (g/cm²) at 4 months

Control
Castration
Enantone
Degarelix

*: significantly different from control
#: significantly different from enantone
Muriune hearts on different forms of ADT: Hopmans S, Klotz L, Pinthus J. Urol Oncol 32(8): 1126-34, 2014
(normal diet, at 5 µm depth)
Total plaque area and necrotic plaque area. Hopmans S et al, Urol Oncol 32(8): 1126-34, 2014
Conclusions re: ADT

- AR pathway complex
- Patients with pre-existing CV disease at increased risk for further events
  - Impact in healthy men less clear
  - Consider degarelix if patient has pre-existing CV disease
- Low nadir T important
  - Assay T along with PSA q 3 months
  - If consistently > 0.7, consider change in therapy
- Intermittent therapy for non-metastatic
- Hormone naïve metastatic:
  - Favorable risk: consider with excellent PSA response (< 1.0)
  - Unfavorable risk or poor PSA response: Chemotherapy