New concepts in ADT
Agonists VS Antagonists
and All the Rest

Thomas E Keane MD.
Professor and Chair.
Department of Urology
Medical University of South Carolina.
Historical Timeline In Prostate Cancer Care

1867
First perineal prostatectomy

1904
First RP

1920
1940
1960
1980
2000
2020

1920s
Radium treatments

1938-Acid Phosphatase
1940
Huggins hormone control: orchiectomy and estrogen treatment

1867
First perineal prostatectomy

1970s
Steroidal and non-steroidal AAs available

1980s
LHRH agonists
• PSA use
• TRUS biopsy
• Radical prostatectomy

1995
Cryosurgery accepted option for recurrent cancer after RT

2003
First LHRH blocker (abarelix)

2004
Docetaxel/prednisone approved

2008
Degarelix approved in US
2010
Provenge immunotherapy
2011/2012
abiraterone/encealutamide

The Future
New androgen receptor-targeted drugs, immunotherapy biomarkers, genomic testing

Original Concept Courtesy Dr. David Crawford
Charles B. Huggins

Nobel Prize winner who established the fact that prostate cancer could be treated by hormonal treatment in the 1940’s

He also alluded to what we now call Castration Resistant Prostate Cancer (CRPC)........

“Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease.”

Nobel Lecture December 13, 1966
2016 CRPC Treatment Options

• Most only available since 2010
• Androgen pathway targeting
  − Abiraterone (androgen biosynthesis inhibitor)
  − Enzalutamide (anti-androgen)
• Radiopharmaceuticals
  − Radium 223
• Immunotherapy
  − Sipuleucel-T
• Chemotherapy
  − Docetaxel (1st line)
  − Cabazitaxel (2nd line)
ADT Options

- Orchiectomy/ Estrogens: not used often – very inexpensive
- LHRH agonists
  - Block T production at the pituitary level; brief T increase; can be given depot forms 1,3,4,6 months
- GNRH antagonists
  - Block T production at the hypothalamic level but no T increase; 28 day shots
- Anti-androgens: typically used with LHRH block- T receptor
  - Avoids brief T increase with LHRH agonists
- Secondary ADT: Ketoconazole, others
- Newer agents for mCRPC: Xtandi (enzalutamine), Zytiga (abiraterone)
ADT: mechanism of action in relation to CV risk

<table>
<thead>
<tr>
<th>Degarelix</th>
<th>LHRH agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid suppression of FSH, LH and testosterone</td>
<td>Initial surge in FSH, LH and testosterone</td>
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<td>No microsurges</td>
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<td>Inhibition of GnRH receptors</td>
<td>Stimulation of GnRH receptors</td>
</tr>
<tr>
<td>Prolonged suppression of FSH, LH and testosterone</td>
<td>FSH suppression not maintained long term</td>
</tr>
</tbody>
</table>

FSH, follicle-stimulating hormone
LH, luteinising hormone
Personalized ADT for the Specific Patient

• Cardiac
• Obesity and testosterone
• FSH
• High volume metastatic disease- Staging
• Docetaxol before or after or both
• New agents and their place
Cardiovascular Effects of Androgen Deprivation Therapy for the Treatment of Prostate Cancer
ABCDE Steps to Reduce Cardiovascular Disease in Patients With Prostate Cancer

Nirmanmoh Bhatia, MD; Marilia Santos, MD; Lee W. Jones, PhD; Joshua A. Beckman, MD; David F. Penson, MD, MPH; Alicia K. Morgans, MD, MPH; Javid Moslehi, MD
American Heart Association and observational studies link androgen deprivation therapy (ADT) to increased risk of cardiovascular events.

- ~50% of patients with locally advanced and metastatic prostate cancer receive ADT.

**ABCDE algorithm** - awareness, aspirin, blood pressure, cholesterol, cigarette cessation, diabetes, diet, exercise - may reduce cardiovascular disease (CVD) risks.

Study recommends initial CVD screening and quarterly monitoring appointments during the first year of therapy.

Preliminary trials show CVD event risk with GnRH antagonist treatment (degarelix) is 50% lower than with GnRH agonist treatment (leuprolide, goserelin, triptorelin, histrelin).

Figure 3. Algorithm to manage patients on androgen deprivation therapy (ADT) in the cardio-oncology clinic. ACC/AHA indicates American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; CHF, congestive heart failure; CV, cardiovascular; and HbA1c, hemoglobin A1c.
## ADT Medications

<table>
<thead>
<tr>
<th>TYPE OF DRUG</th>
<th>COMMON BRAND NAME</th>
<th>GENERIC NAME</th>
<th>HOW IT IS GIVEN</th>
<th>HOW OFTEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHRH AGONIST</td>
<td>Lupron Depot</td>
<td>leuprolide</td>
<td>Intramuscular injection</td>
<td>Every 1, 3, 4, or 6 months</td>
</tr>
<tr>
<td></td>
<td>Eligard</td>
<td>leuprolide</td>
<td>Subcutaneous injection</td>
<td>Every 1, 3, 4 or 6 months</td>
</tr>
<tr>
<td></td>
<td>Zoladex</td>
<td>goserelin</td>
<td>Subcutaneous injection (absorbable implant)</td>
<td>Every month or every 3 months</td>
</tr>
<tr>
<td></td>
<td>Telstar</td>
<td>triptorelin</td>
<td>Intramuscular injection</td>
<td>Every 1, 3 or 6 months</td>
</tr>
<tr>
<td></td>
<td>Vantas</td>
<td>histrelin</td>
<td>Subcutaneous implant (inner aspect upper arm)</td>
<td>Every 12 months</td>
</tr>
<tr>
<td>LHRH ANTAGONIST</td>
<td>Firmagon</td>
<td>degarelix</td>
<td>Subcutaneous injection</td>
<td>Two initial injections then monthly injections</td>
</tr>
<tr>
<td>ANTI-ANDROGEN</td>
<td>Eulexin</td>
<td>flutamide</td>
<td>Oral Pill</td>
<td>3 times daily</td>
</tr>
<tr>
<td></td>
<td>Casodex</td>
<td>bicalutamide</td>
<td>Oral Pill</td>
<td>Once Daily</td>
</tr>
<tr>
<td></td>
<td>Nilandron</td>
<td>nilutamide</td>
<td>Oral Pill</td>
<td>Once Daily</td>
</tr>
<tr>
<td>ANDROGEN PATHWAY INHIBITOR FOR CRPC</td>
<td>Xtandi</td>
<td>enzalutamide</td>
<td>Oral Pills</td>
<td>Once Daily</td>
</tr>
<tr>
<td>ANDROGEN PATHWAY INHIBITOR FOR CRPC</td>
<td>Zytiga</td>
<td>abiraterone</td>
<td>Oral Pills</td>
<td>Daily with oral prednisone twice a day</td>
</tr>
</tbody>
</table>
Cardiovascular risk profile and ADT

Is there a difference?
Degarelix belongs to a class of synthetic drug, GnRH antagonist (blocker)

GnRH belongs to a class of synthetic drug, GnRH antagonist (blocker).

Leuprolide

Goserelin

Triptorelin

Buserelin

Degarelix

Abarelix

Cetrorelix

Ganirelix

Most acute CVD events are caused by rupture of a vulnerable atherosclerotic plaque.
The vulnerable plaque – thin cap with inflammation
Plaque instability is at the heart of cardiovascular disease

<table>
<thead>
<tr>
<th>Thick</th>
<th>Cap</th>
<th>Thin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rich in SMC and matrix</td>
<td>Composition</td>
<td>Rich in inflammatory cells: proteolytic activity</td>
</tr>
<tr>
<td>Poor</td>
<td>Lipid</td>
<td>Rich</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Inflammatory state</td>
<td>Highly inflammatory</td>
</tr>
</tbody>
</table>

Libby P. Circulation 1995;91:2844-2850
Incidence of both prostate cancer and CV events is highest in older men

Prostate cancer

CV events

CV, cardiovascular
Major CV events = myocardial infarction, stroke, or death due to CV disease
All CV disease = major CV events + self-reported angina or revascularisation procedures

Men with prostate cancer and pre-existing CVD have an increased risk of death

<table>
<thead>
<tr>
<th>Population</th>
<th>n (%)</th>
<th>Cumulative survival (%)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>30,721 (100)</td>
<td>84.4</td>
<td>41.7</td>
</tr>
<tr>
<td>No IHD or stroke</td>
<td>25,114 (82)</td>
<td>85.4</td>
<td>43.5</td>
</tr>
<tr>
<td>IHD</td>
<td>4,276 (14)</td>
<td>80.5</td>
<td>36.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1,331 (4)</td>
<td>77.6</td>
<td>26.5</td>
</tr>
</tbody>
</table>

*HR adjusted for age, stage, calendar period and comorbidity (excluding IHD and stroke)

Influence of prostate cancer therapy on mortality rates not assessed

CVD, cardiovascular disease
IHD, ischaemic heart disease
Cardiovascular Disease is the Second Most Common Cause of Death in Men with Prostate Cancer

EORTC 30891\(^1\)

- CVD: 34%
- Prostate cancer: 36%
- Other: 30%

SEUG 9401\(^2\)

- CVD: 27%
- Prostate cancer: 41%
- Other: 32%

Cause of Death

CVD, cardiovascular disease; EORTC, European organisation for research and treatment of cancer; SEUG, South European ur oncological group

This association has been confirmed with other types of ADT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incident CHD</th>
<th>Myocardial infarction</th>
<th>Sudden cardiac death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>No ADT</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>GnRH agonist</td>
<td>1.19* (1.10–1.28)</td>
<td>1.28* (1.08–1.52)</td>
<td>1.35* (1.18–1.54)</td>
<td>1.21* (1.05–1.40)</td>
</tr>
<tr>
<td>Orchietomy</td>
<td>1.40* (1.04–1.87)</td>
<td>2.11* (1.27–3.50)</td>
<td>1.29 (0.76–2.18)</td>
<td>1.49 (0.92–2.43)</td>
</tr>
<tr>
<td>CAB</td>
<td>1.27* (1.05–1.53)</td>
<td>1.03 (0.62–1.71)</td>
<td>1.22 (0.85–1.73)</td>
<td>0.93 (0.61–1.42)</td>
</tr>
<tr>
<td>Antiandrogen</td>
<td>1.10 (0.80–1.53)</td>
<td>1.05 (0.47–2.35)</td>
<td>1.06 (0.57–1.99)</td>
<td>0.86 (0.43–1.73)</td>
</tr>
</tbody>
</table>

• Observational study of 37,443 men with prostate cancer
• 39% received some form of ADT during follow-up, primarily GnRH agonists (37.5%)
  – Few were treated with orchiectomy (0.8%) or oral antiandrogen monotherapy (3.3%) at any time or CAB (4.9%) for >6 weeks at the start of GnRH agonist therapy

ADT, androgen deprivation therapy
CAB, combined androgen blockade
CHD, coronary heart disease; ref, reference

Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer

Swedish PCa database (n=41,362 PCa ADT+ vs 187,785 aged match PCa ADT-)

CVD-related events highest within 6 months of ADT initiation in men with pre-existing CVD
Move by FDA Based on the Agency’s Review of Seven Published Studies and an AHA/ACS/AUA Science Advisory


GnRH Agonists: Regulatory Warnings

- October 2010: US FDA asks manufacturers of GnRH agonists to add extra safety information to drug labels
  - Increased risk of diabetes and certain CV diseases (heart attack, sudden cardiac death, stroke) in men with prostate cancer
- EMA prompted a label change for GnRH agonists and GnRH antagonists
  - ‘Cardiovascular disease such as stroke and myocardial infarction has been reported in the medical literature in patients with androgen deprivation therapy. Therefore, all cardiovascular risk factors should be taken into account.’

The risk has been shown to be increased in older men and those with comorbidities

- Men aged ≥65 years receiving 6 months of ADT had shorter times to fatal myocardial infarction compared with RT alone (p=0.017)

- Patients with moderate or severe comorbidities* had a greater risk of a fatal myocardial infarction when receiving RT + ADT compared with RT alone

ADT, androgen deprivation therapy
RT, radiotherapy

*Based on Adult Comorbidity Evaluation 27 (ACE-27)

... as well as those with pre-existing cardiac disease

- Significant increase in CV morbidity during oestrogen treatment in patients with a history of CVD (p<0.001)
  - 33% of these patients had a CV event during PEP treatment

- Oestrogen treatment was the greatest risk factor for CV events in a multivariate analysis (p=0.029)
Based on the studies shown...

- **The increase in risk of CV disease** in men treated with ADT (orchiectionomy, oestrogen or GnRH agonist) **appears to be 20–25%**

- In comparison, known major risk factors for CV disease increase lifetime risk as follows:
  - **Smoking vs no smoking:** 22%
  - Hypertension vs no hypertension: 20-93%
  - Low vs not low HDL cholesterol: 44%
  - High vs low total cholesterol: 73%
  - Diabetes vs no diabetes: 122%
  - No randomized controlled trial has been performed assessing the risk of one form of ADT vs another.

Pooled data from randomized phase III/IIIb trials of degarelix vs GnRH agonists

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (months)</th>
<th>Comparator</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS21</td>
<td>12</td>
<td>Leuprolide</td>
<td>Klotz et al. BJU Int 2008</td>
</tr>
<tr>
<td>CS35</td>
<td>12</td>
<td>Goserelin</td>
<td>Shore et al. SIU 2012</td>
</tr>
<tr>
<td>CS37</td>
<td>7-12</td>
<td>Leuprolide</td>
<td>Crawford et al. SUO 2013</td>
</tr>
<tr>
<td>CS28</td>
<td>3</td>
<td>Goserelin*</td>
<td>Anderson et al. Urol Int 2012</td>
</tr>
<tr>
<td>CS30</td>
<td>3</td>
<td>Goserelin*</td>
<td>Mason et al. Clin Oncol 2013</td>
</tr>
<tr>
<td>CS31</td>
<td>3</td>
<td>Goserelin*</td>
<td>Axcona et al. BJU Int 2012</td>
</tr>
</tbody>
</table>

*All patients on goserelin also received antiandrogen flare protection

LUTS, lower urinary tract symptoms
RT, radiotherapy
TPV, total prostate volume
Pooled analysis: Treatment groups

2328 Patients

1491 Degarelix

463 (31%)

837 GnRH agonist

245 (29%)

458 Goserelin

379 Leuprolide

CVD, cardiovascular disease

### Selected baseline demographics relating to CV risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>Degarelix n=1491</th>
<th>GnRH agonist n=837</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>71.7</td>
<td>71.6</td>
</tr>
<tr>
<td>Body mass index &gt;30, n (%)</td>
<td>27.2 334 (22)</td>
<td>27.5 200 (24)</td>
</tr>
<tr>
<td>History of CVD, n (%)</td>
<td>463 (31)</td>
<td>245 (29)</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>707 (47)</td>
<td>432 (52)</td>
</tr>
<tr>
<td>History of alcohol use, n (%)</td>
<td>889 (60)</td>
<td>475 (57)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>1117 (75)</td>
<td>615 (74)</td>
</tr>
<tr>
<td>Serum cholesterol &gt;6.2 mmol/L, n (%)</td>
<td>399 (27)</td>
<td>247 (30)</td>
</tr>
<tr>
<td>Statin medication use, n (%)</td>
<td>400 (27)</td>
<td>234 (28)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>221 (15)</td>
<td>128 (15)</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease

Results: Overall incidence of CV events*

<table>
<thead>
<tr>
<th></th>
<th>Degarelix, n (%) n=1491</th>
<th>GnRH agonist, n (%) n=837</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV event</td>
<td>37 (2.5)</td>
<td>40 (4.7)</td>
</tr>
<tr>
<td>Serious CV event</td>
<td>25 (1.7)</td>
<td>24 (2.9)</td>
</tr>
</tbody>
</table>

*Data classified according to the MedDRA system

- A serious CV event was an event considered life-threatening or that required hospitalization
Overall survival

Prostate cancer was not the cause of death in the majority of these patients.

HR=0.47 (95% CI 0.25–0.90)  
p=0.022

CVD, cardiovascular disease

Miller K, et al. EAU 2013; Poster 678
Lower risk of CV event or death with degarelix (all patients)

HR adjusted for common CV risk factors including age, statin use, hypertension and serum cholesterol by Cox regression

Tombal B, et al. EAU 2013;Poster 677
Lower risk of CV event or death with degarelix in men with baseline CVD

HR adjusted for common CV risk factors including age, statin use, hypertension and serum cholesterol by Cox regression

CVD, cardiovascular disease

Tombal B, et al. EAU 2013;Poster 677
Effect of degarelix remains when adjusted for common CVD variables

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degarelix treatment</td>
<td>0.44</td>
<td>0.26–0.74</td>
<td>0.002</td>
</tr>
<tr>
<td>Statin medication use</td>
<td>0.54</td>
<td>0.28–1.03</td>
<td>0.061</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.43</td>
<td>0.24–0.77</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>2.09</td>
<td>1.08–4.06</td>
<td>0.030</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.26</td>
<td>0.72–2.19</td>
<td>0.417</td>
</tr>
<tr>
<td>Serum cholesterol &gt;6.2 mmol/L</td>
<td>1.14</td>
<td>0.62–2.08</td>
<td>0.681</td>
</tr>
<tr>
<td>Treated type 2 diabetes</td>
<td>0.83</td>
<td>0.34–2.00</td>
<td>0.669</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>0.63</td>
<td>0.32–1.24</td>
<td>0.182</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>1.03</td>
<td>0.99–1.07</td>
<td>0.152</td>
</tr>
<tr>
<td>Baseline testosterone</td>
<td>0.79</td>
<td>0.66–0.94</td>
<td>0.009</td>
</tr>
<tr>
<td>Baseline body mass index</td>
<td>0.97</td>
<td>0.91–1.04</td>
<td>0.357</td>
</tr>
</tbody>
</table>

*Diastolic >90 or systolic >140 mmHg
CVD, cardiovascular disease

Pooled analysis: Summary

• When treated with degarelix compared with a GnRH agonist, patients with pre-existing CVD:
  – Had significantly fewer CV events during the first year of treatment
  – Had a relative risk reduction of >50% (absolute risk reduction 8.2%)

CVD, cardiovascular disease
GnRH receptors are expressed by smooth muscle cells in atherosclerotic plaques

Hultgårdh, Nilsson et al, unpublished
Leuprolide induces necrosis in stable oscillatory shear stress-induced plaques

<table>
<thead>
<tr>
<th>Time</th>
<th>Diet/Modifier</th>
<th>End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 weeks</td>
<td>Cholesterol-rich diet</td>
<td>26 weeks Degarelix Leuprolide Untreated</td>
</tr>
<tr>
<td>18 weeks</td>
<td>Shear stress-modifier</td>
<td>30 weeks End point</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>22.5</td>
</tr>
<tr>
<td>20.0</td>
</tr>
<tr>
<td>17.5</td>
</tr>
<tr>
<td>15.0</td>
</tr>
<tr>
<td>12.5</td>
</tr>
<tr>
<td>10.0</td>
</tr>
<tr>
<td>7.5</td>
</tr>
<tr>
<td>5.0</td>
</tr>
<tr>
<td>2.5</td>
</tr>
</tbody>
</table>

Hultgårdh, Nilsson et al, unpublished
Potential mechanisms for differences in CV risk with different forms of ADT

Differences in CV risk could be due to differences in the effect of different ADTs on:

1. Metabolic changes
2. GnRH receptor activation
3. FSH levels
T cells express GnRH receptors: Agonists and antagonists have different effects

GnRH or GnRH agonist

- Increased proliferation and activity
- Fibrotic cap disruption and plaque instability

GnRH antagonist

- Complete blockade of receptors with no signal transduction
- Inhibition of stimulated responses

**T lymphocytes are key drivers of collagen metabolism in atherosclerotic plaques**

Disruption of the fibrotic cap

Plaque instability

Increased risk of thrombo-embolic complications and cardiovascular disease

Libby P J. Lipid Res 2009;50:S352-S357
T lymphocytes may be key drivers of collagen metabolism in atherosclerotic plaques

- **T lymphocyte**
  - IFN-γ secretion
    - Inhibition of collagen synthesis
  - CD40L
    - Upregulation of collagenases

**Fibrotic cap disruption and plaque instability**

**Increased risk of thrombo-embolic complications**

Does the distinct mechanism of action of GnRH antagonists alter the risk of a CV event?

<table>
<thead>
<tr>
<th><strong>GnRH Antagonist</strong></th>
<th><strong>GnRH/LHRH agonists</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid suppression of FSH, LH and testosterone</td>
<td>Initial surge in FSH, LH and testosterone</td>
</tr>
<tr>
<td>No microsurges</td>
<td>Microsurges on repeat injection</td>
</tr>
<tr>
<td>Inhibition of GnRH receptors</td>
<td>Stimulation of GnRH receptors</td>
</tr>
<tr>
<td>Potential for agonists to have a plaque destabilising effect due to induction of necrosis and T cell and macrophage stimulation</td>
<td></td>
</tr>
<tr>
<td>Prolonged suppression of FSH, LH and testosterone</td>
<td>FSH suppression not maintained long term</td>
</tr>
</tbody>
</table>

Unlikely that long-term castration effect can explain differences in risk

Increased potential for metabolic syndrome and atherogenesis with agonist therapy

CV, cardiovascular; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone
Personalized ADT for the Specific Patient

- Cardiac
- **Obesity and testosterone**
- FSH
- High volume metastatic disease
- Docetaxol
- Significant LUTS
ADT has been associated with metabolic changes

• Metabolic syndrome is a disorder of energy utilisation and storage, diagnosed by co-occurrence of any 3 of:
  – Abdominal (central) obesity
  – Elevated blood pressure
  – Elevated fasting plasma glucose
  – High serum triglycerides
  – Low high-density (HDL) cholesterol levels

• Metabolic syndrome increases the risk of developing CVD

• ADT leads to:
  – Insulin resistance
  – Accumulation of subcutaneous fat and decreased lean body mass
  – Increased glucose levels
  – Abnormalities in lipid levels

Kelly DM, Jones TH. J Endocrinol 2013;217:R25-45
Metabolic syndrome and metabolic changes induced by ADT are different

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>Metabolic changes with ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased triglycerides</td>
<td>Increased triglycerides</td>
</tr>
<tr>
<td>Increased visceral fat</td>
<td>Increased subcutaneous fat</td>
</tr>
<tr>
<td>Reduced HDL</td>
<td>Increased HDL</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased fasting glucose</td>
<td>Increased fasting glucose</td>
</tr>
<tr>
<td>Decreased adiponectin</td>
<td>Increased adiponectin</td>
</tr>
<tr>
<td>Increased C-reactive protein</td>
<td>Normal C-reactive protein</td>
</tr>
</tbody>
</table>
Personalized ADT for the Specific Patient

- Cardiac
- Obesity and testosterone
- **FSH**
- High volume metastatic disease
- Docetaxol
- Significant LUTS
FSH and adipogenesis

• Stimulation of FSH receptors possibly alters endothelial cell function, lipid metabolism and fat accumulation

• Preclinical studies have shown:\(^1\)
  – Mice treated with degarelix have lower FSH levels than those treated with LHRH agonist or orchiectomy
  – Degarelix-treated mice gain less weight and visceral fat than mice treated with LHRH agonists

Overall survival

HR=0.47 (95% CI 0.25–0.90)
p=0.022

Prostate cancer was not the cause of death in the majority of these patients.

CVD, cardiovascular disease  
Miller K, et al. EAU 2013; Poster 678
PSA Progression-Free Survival Beyond 1 Year

- Time to PSA failure* or death = all patients

<table>
<thead>
<tr>
<th>All patients (ITT)</th>
<th>Hazard rates</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS21</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Degarelix 240/80 mg</td>
<td>0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>Leuprolide 7.5 mg</td>
<td>0.20</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*PSA increase ≥50% from nadir and ≥5 ng/mL on 2 consecutive occasions ≥2 weeks apart.

Further FSH suppression after crossover from leuprolide to degarelix

CS21: degarelix or leuprolide

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>0</th>
<th>28</th>
<th>56</th>
<th>84</th>
<th>112</th>
<th>140</th>
<th>168</th>
<th>196</th>
<th>224</th>
<th>252</th>
<th>280</th>
<th>308</th>
<th>336</th>
<th>364</th>
<th>392</th>
<th>420</th>
<th>448</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients by time point (Degarelix)</td>
<td>206</td>
<td>206</td>
<td>201</td>
<td>195</td>
<td>193</td>
<td>186</td>
<td>187</td>
<td>188</td>
<td>183</td>
<td>179</td>
<td>173</td>
<td>172</td>
<td>166</td>
<td>167</td>
<td>40</td>
<td>13</td>
<td>112</td>
</tr>
<tr>
<td>Number of patients by time point (Leuprolide)</td>
<td>199</td>
<td>196</td>
<td>195</td>
<td>191</td>
<td>190</td>
<td>190</td>
<td>185</td>
<td>188</td>
<td>183</td>
<td>181</td>
<td>178</td>
<td>179</td>
<td>172</td>
<td>171</td>
<td>124</td>
<td>120</td>
<td>113</td>
</tr>
</tbody>
</table>

*Median (quartiles) percentage change from baseline
FSH, follicle-stimulating hormone

Median Concentration of FSH after Abarelix and after GnRH-agonist with Antiandrogen

FSH receptor is strongly expressed by human prostate tumor blood vessels

Analysis of samples from 773 patients with PCa; all samples expressed FSH receptor, whereas normal tissue had no receptor expression

FSH, follicle-stimulating hormone; PCa, prostate cancer

Conclusion

• Data indicate clinical benefits with degarelix including a significant improvement in
• PSA progression free survival
• Overall Survival
• Reduced incidence of joint, and musculoskeletal events compared with LHRH agonists.
Personalized ADT for the Specific Patient

- Cardiac
- Obesity and testosterone
- Fsh
- **High volume metastatic disease**
- Docetaxol
- Significant LUTS
High Volume Metastatic Disease

- Rapidity of Castration and PSA suppression
- Lack of flare and miniflare
- Better FSH suppression
- Better suppression of S-ALP
- Less SRE
- Longer duration of HSPCa state
- Differences were more apparent in pts with higher PSAs and more advanced disease.
Sources of Androgen Production

- Androgens are produced at 3 sites:
  - Testes
  - Adrenal gland
  - Prostate tumor cells (NEW DISCOVERY!)
Abiraterone

- Androgen synthesis inhibitor (CYP17 inhibitor)
  - Approved by the FDA: April 2011 post chemo, December 2012 pre chemo
  - Interferes with steroidal hormone biosynthesis pathway

- Indications
  - Combination with prednisone for the treatment of mCRPC who have received prior chemotherapy w/docetaxel
  - Combination with prednisone for the treatment of mCRPC who had not received prior cytotoxic chemotherapy
Abiraterone
Phase 3 Trial: COU-AA-301

- Initiated in April 2008

- Post-docetaxel mCRPC
- Up to 2 prior therapies
- ECOG PS 0-1
- Medical or surgical castration, testosterone < 50 ng/dL
- n = 1158

R 2:1

Abiraterone acetate
1000 mg/day (4 x 250 mg tablets)
PO;
5 mg prednisone/prednisolone BID

Placebo plus
5 mg prednisone/prednisolone BID

Primary endpoint: Overall survival

Secondary endpoints: Progression-free survival (PFS), Proportion achieving 50% PSA reduction, time to PSA progression, QOL

Abiraterone Phase 3 Trial
COU-AA-302

• Initiated in April 2009

- Asymptomatic or mildly symptomatic mCRPC
- Progression after previous anti-androgen withdrawal
- ECOG PS 0-1
- Medical or surgical castration, testosterone < 50 ng/dL
- n = 1000

R 1:1

Abiraterone acetate
1000 mg/day (4 x 250 mg tablets)
PO;
5 mg prednisone/prednisolone BID

Placebo plus 5 mg prednisone/prednisolone BID

Primary endpoints: OS and PFS

Secondary endpoints: Time to opiate use, time to chemo, time to first ECOG PS deterioration, time to PSA progression

Enzalutamide

- Androgen receptor blocker
  - FDA Approved: Post August 2012; Pre September 2014

- Indications
  - mCRPC with recurrence or metastasis
  - mCRPC in patients who had received prior docetaxel
  - May be used in men who are not candidates for chemotherapy

- Trials:
  - AFFIRM (post-docetaxel) Post approval study
  - PREVAIL (pre-docetaxel) Pre approval study
  - STRIVE (vs. bicalutamide with CRPC) completed
Prevail – extended analysis

- Reduced risk of radiographic progression by 68% or death by 23%
- rPFS was 20 months vs 5.4 for placebo
- Median OS -35.3 vs 31.3 for placebo.

- Evaluated longer term efficacy/safety up to the prespecified number of deaths in the final analysis. 20 m for rPFS, 9 m for OS, 4 m for safety

- A/E back pain, constipation, fatigue and arthralgia
STRIVE

- Enzalutamide vs Bicalutamide in men with Pca progressing on ADT. 198pts in each arm.

- PFS-Overall- (PSA, Radiographic or death)
  - 19.4 vs 5.7m  p<0.0001

- Time to PSA progression – NA vs 8.3 m  p<0.0001
- % -PSA response> 50%  81.3 vs 31.35
- Duration of RPFS- Na vs 8.3m
- Best overall soft tissue response %  60 vs 14

AEs and QOL no difference
Before 2010, the last agent approved for the treatment of CRPC was docetaxel.
New concept

• Should these advances be applied to Hormone Sensitive Prostate Cancer and if so:
  • Which agents and when
Discussion Topics

• E3805 (CHAARTED) data review
• Comparison with GETUG-AFU 15
• Who really should receive docetaxel? The high vs. low volume/risk disease debate
• Safety and toxicity considerations
E3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Metastatic Prostate Cancer

**Stratification**
- extent of mets (high vs low)
- age ≥70 vs < 70yo
- ECOG PS (0-1 vs 2)
- CAB > 30 days (yes vs no)
- SRE prevention (yes vs no)
- prior adjuvant ADT (≤12 vs > 12 months)

**Randomize**

**Arm A:**
- ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles

**Arm B:**
- ADT (androgen deprivation therapy alone)

**Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks**

**Follow for time to progression and overall survival**

- Chemotherapy at investigator’s discretion at progression

- Original design n=568 for high volume disease
- Adjustments for allowance of low volume disease and projected OS based on S9346 data n=780

- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but NO DAILY PREDNISONE

Sweeney C et al. ASCO 2014; Abstract LBA2.
E3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Metastatic Prostate Cancer

- **N=790** men accrued 07/28/06 - 11/21/12
- Planned interim analysis at 53% information met 10/13
- 01/16/14 median followup 29 months
  - 136 (110 high volume) deaths ADT alone vs. 101 (82 high volume) deaths ADT+D
  - 83.6% vs. 83.2% of deaths from prostate cancer

Sweeney C et al. ASCO 2014; Abstract LBA2.
E3805 CHAARTED: ChemoHormonal Therapy vs. Androgen Ablation for Metastatic Prostate Cancer

OS by extent of metastatic disease at start of ADT

>4 bone lesions and
>1 lesion in any bony structure beyond the spine/pelvis
OR
visceral disease

High volume

OS by extent of metastatic disease at start of ADT

p=0.0006
HR=0.60 (0.45-0.81)
Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months

Low volume

p=0.1398
HR=0.63 (0.34-1.17)
Median OS:
ADT + D: Not reached
ADT alone: Not reached

Sweeney C et al. ASCO 2014; Abstract LBA2.
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaelle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzef, Remy Delva, Ivan Krakowski, Brigitte Laguerre, Frédéric Rolland, Christine Théodore, Gael Deplanque, Jean Marc Ferrero, Damien Poussel, Loïc Mourey, Philippe Beuzeboc, Sylvie Zanetta, Muriel Habibian, Jean François Berdah, Jerome Dauba, Marjorie Bacuchka, Christian Platini, Claude Linassier, Jean Luc Laboure, Jean Pascal Machiels, Claude El Kouri, Alain Ravaud, Etienne Suc, Jean Christophe Eymard, Ali Hasbini, Guilhem Bousquet, Michel Soulie

Overall Survival

Biochemical PFS

HR=1.01 (0.75-1.36)
p=0.955
Median OS:
ADT + D: 58.9 months
ADT alone: 54.2 months

HR=0.72 (0.57-0.91)
p=0.005
Median OS:
ADT + D: 22.9 months
ADT alone: 12.9 months

# Key Differences between GETUG-AFU 15 and CHAARTED

<table>
<thead>
<tr>
<th></th>
<th>GETUG-15</th>
<th>CHAARTED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>385</td>
<td>790</td>
</tr>
<tr>
<td><strong>Docetaxel cycles</strong></td>
<td>Up to 9 (median 8)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Gleason 8-10</strong></td>
<td>56.1%</td>
<td>68.6%</td>
</tr>
<tr>
<td><strong>PSA median (ng/mL)</strong></td>
<td>ADT 25.8; ADT+D 26.7</td>
<td>ADT 50.5; ADT+D 56.0</td>
</tr>
<tr>
<td><strong>High volume/risk</strong></td>
<td>21.6%(^1)</td>
<td>65.1%(^2,3)</td>
</tr>
<tr>
<td><strong>Discontinuations early for toxicity</strong></td>
<td>20.3%</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Treatment related deaths</strong></td>
<td>4 (2.1%)</td>
<td>1 (0.3%) but 8 (2%) unknown</td>
</tr>
<tr>
<td><strong>Median followup</strong></td>
<td>50 months (data cutoff July 31, 2011)</td>
<td>29 months</td>
</tr>
<tr>
<td><strong>Subsequent docetaxel with CRPC (%)</strong></td>
<td>ADT (62); ADT+D (28)</td>
<td>ADT 129/174 (74.1); ADT+D 49/145 (33.8)</td>
</tr>
<tr>
<td><strong>Subsequent potent AR therapy with CRPC (%)</strong></td>
<td>ADT (&lt;15); ADT+D (&lt;16)</td>
<td>ADT 79/174 (45.5); ADT+D 92/145 (62.8)</td>
</tr>
</tbody>
</table>

---

Summary of Factors that may have Contributed to Different Results between GETUG-AFU 15 and CHAARTEDED

• Study size/statistical power
• Prognosis and staging definitions and disease risk/volume were different
• ? Toxicity e.g. deaths and early discontinuations and the use of other subsequent therapies were different
Grade 3-5 Hematologic Toxicity from TAX327 in mCRPC vs. GETUG-AFU 15 vs. CHAARTED

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TAX327 (%)</th>
<th>GETUG-AFU 15 (%)</th>
<th>CHAARTED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>32</td>
<td>32*</td>
<td>12</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>7*</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>0.3</td>
<td>2.1</td>
<td>0.3^</td>
</tr>
</tbody>
</table>

*After 56% accrual and 4 treatment-related deaths, DSMC recommended GCSF days 5-10 with Grade ¾ neutropenia rate decline from 41% to 15%, febrile neutropenia decline from 8% to 6% and no more deaths. ^2% of deaths were unknown

Key Conclusion: Tough to interpret toxicity data with incomplete information on growth factors and prophylactic antibiotics, but, is there some a sense that docetaxel may surprisingly be more toxic in mHSPC?

Docetaxel PK varies with Castration State

- 10 non-castrate and 20 castrate men with similar demographics
- Clearance of docetaxel in castrate men was 100% increased with 2 fold reduction in AUC
- Erythromycin breath test indicated hepatic CYP3A4 activity, for docetaxel metabolism, was not different
- Castrate rats have higher AUC of docetaxel in liver compared to intact animals

50% decrease in docetaxel clearance associated with >430% increase in odds of grade ≥ neutropenia*

What are the Implications of these PK Differences?

**Between Different Trials**

- May explain some of the greater hematologic toxicity but also survival benefit observed in castration-sensitive compared to castration-resistant trials
- Why was there greater hematologic toxicity in GETUG-AFU 15 compared to CHAARTED?
  - How many patients were non-castrate vs. castrate in each trial?
    - GETUG-AFU 15: 47% initiated ADT within 15 days of enrollment
    - CHAARTED: initiated ADT median 1.1 months to enrollment
  - How much GCSF was used in each trial?

**For the Practicing Clinician**

- Consider waiting until after 1-2 months of ADT or castrate testosterone levels have been reached before starting docetaxel?
- Use GCSF, at least for the first couple cycles, until castrate
STAMPEDE: Docetaxel and/or Zoledronic Acid in Hormone-Naive Metastatic PCa

First overall survival analysis of patients enrolled in the following 4 study arms:

- Standard of care (SOC; n = 1,184)
- Docetaxel (Doc) + SOC (n = 592)
- Zoledronic acid (ZDA) + SOC (n = 593)
- Doc + ZDA + SOC (n = 593)

<table>
<thead>
<tr>
<th></th>
<th>SoC</th>
<th>Doc + SoC</th>
<th>ZDA + SoC</th>
<th>Doc + ZDA + SoC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>67 mo</td>
<td>77 mo</td>
<td>80 mo</td>
<td>72 mo</td>
</tr>
<tr>
<td>Hazard ratio (p-value)</td>
<td>Ref*</td>
<td>0.76 (0.003)</td>
<td>0.93 (0.44)</td>
<td>0.81 (0.02)</td>
</tr>
<tr>
<td>Median failure-free survival</td>
<td>21 mo</td>
<td>37 mo</td>
<td>21 mo</td>
<td>37 mo</td>
</tr>
<tr>
<td>Hazard ratio (p-value)</td>
<td>Ref*</td>
<td>0.62 (&lt;0.1 x 10^{-10})</td>
<td>0.93 (0.26)</td>
<td>0.62 (&lt;0.1 x 10^{-10})</td>
</tr>
</tbody>
</table>

* Pairwise comparisons to control SOC study arm were calculated for each research arm.

- Docetaxel, and not ZDA, improves overall survival compared to SoC
- Docetaxel + ZDA improves survival but offers no obvious benefit over docetaxel alone

Question?

• If toxicity is greater with the use of Docetaxol in the pre-castrate state might not efficacy also be?

• We need a trial.
A PHASE II STUDY OF DOCETAXEL BEFORE MEDICAL CASTRATION WITH DEGARELIX IN PATIENTS WITH NEWLY DIAGNOSED METASTATIC PROSTATIC ADENOCARCINOMA.

N = 50 patients

Enrolling men with newly diagnosed treatment naïve metastatic prostate cancer of all volume statuses.

Primary Endpoint – Proportion of men who maintain a PSA ≤ 0.2 ng/ml at 40 weeks on study (7 months ADT)

Additional Endpoints – Toxicity, PSA response to Docetaxel alone, time to development of castration resistance, overall survival, correlating genomics with response.
Clinical considerations for the use of ADT: A hormonal therapy algorithm

History of CVD?
• Coronary artery disease
• Myocardial ischaemia and infarction
• Cerebrovascular accident
• Angina pectoris
• Coronary artery bypass

YES

Degarelix
• >50% lower CVD risk over one year

NO

PSA >20 ng/mL or metastases?

YES

Degarelix
• Longer PSA PFS
• No clinical flare
• Better S-ALP control
• Better bone pain control

NO

Patients with Met-HSPCA for Chemo/ADT

YES

Degarelix- Maybe Castrate in 48 hrs

NO

Either if none of above