Personalized ADT

Thomas Keane MD
Conflicts

- Ferring
- Tolemar
- Bayer
- Astellas
- myriad
Personalized ADT for the Specific Patient

• Cardiac
• Obesity and testosterone
• Fsh
• High volume metastatic disease
• Docetaxol
• Significant LUTS
Cardiovascular risk profile and ADT

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

![Diagram of GnRH agonists and antagonists]

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

Age-specific incidence per 100,000 person-years

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></td>
<td></td>
<td>1-year</td>
<td>5-years</td>
</tr>
<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

Oestrogen therapy increases risk of CV-related side effects

- 2,052 patients with stage I–IV prostate cancer treated using radical prostatectomy or orchiecetomy with or without oestrogen
  - Survival significantly shorter in patients with stage I–III prostate cancer receiving oestrogens, but incidence of prostate cancer-related death reduced
  - Significant increase in deaths due to CV disease in patients treated with oestrogen

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No oestrogen therapy (n=1,035)</th>
<th>Received oestrogen therapy (1,017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>149 (14.4%)</td>
<td>107 (10.5%)</td>
</tr>
<tr>
<td>CV</td>
<td>90 (8.7%)</td>
<td>149 (14.7%)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>10 (1%)</td>
<td>11 (1.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>85 (8%)</td>
<td>91 (9.0%)</td>
</tr>
</tbody>
</table>

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>Orchiectomy</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

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)\(^1\)

- Patients with moderate or severe comorbidities* had a greater risk of a fatal myocardial infarction when receiving RT + ADT compared with RT alone\(^2\)

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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 (orchiectomy, 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%

CVD is the second most common cause of death in men with prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>Prostate cancer n (%)</th>
<th>CVD n (%)</th>
<th>Other n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC 30891</strong>¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate ADT</td>
<td>94 (37)</td>
<td>88 (34)</td>
<td>75 (29)</td>
</tr>
<tr>
<td>Delayed ADT</td>
<td>99 (35)</td>
<td>97 (34)</td>
<td>88 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>193 (36)</td>
<td>185 (34)</td>
<td>163 (30)</td>
</tr>
<tr>
<td><strong>SEUG 9401</strong>²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent ADT</td>
<td>74 (44)</td>
<td>41 (24)</td>
<td>55 (32)</td>
</tr>
<tr>
<td>Continuous ADT</td>
<td>65 (39)</td>
<td>52 (31)</td>
<td>52 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>139 (41)</td>
<td>93 (27)</td>
<td>107 (32)</td>
</tr>
</tbody>
</table>

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%)

CVD history

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</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>334 (22)</td>
<td>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>

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

*Data classified according to the MedDRA system

Tombal B, et al. EAU 2013;Poster 677
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

HR=0.60 (95% CI 0.41-0.87)
p=0.008
Lower risk of CV event or death with degarelix in men with baseline CVD

There is a >60% lower risk of serious CV event for men with CVD history receiving degarelix (HR=0.367, 95% CI 0.174-0.774, p=0.0086)

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
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
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
Plaque instability is at the heart of cardiovascular disease

Stable plaque

Vulnerable plaque

<table>
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<tr>
<td>Poor</td>
<td>Lipid</td>
<td>Rich</td>
</tr>
<tr>
<td>inflammatory</td>
<td>Inflammatory state</td>
<td>More</td>
</tr>
</tbody>
</table>

Libby P. Circulation 1995;91:2844-2850
GnRH receptors are expressed by smooth muscle cells in atherosclerotic plaques

Hultgårdh, Nilsson et al, unpublished
Atherosclerotic plaques induced by different types of shear stress

Unstable plaque (low shear)

Stable plaque (oscillatory shear)
Leuprolide induces necrosis in stable oscillatory shear stress-induced plaques

- 16 weeks
  - Cholesterol-rich diet

- 18 weeks
  - Shear stress-modifier

- 26 weeks
  - Degarelix
  - Leuprolide
  - Untreated

- 30 weeks
  - End point

% necrosis:

- Untreated
- Degarelix
- Leuprolide

Hultgårdh, Nilsson et al, unpublished
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 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

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
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
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 <em>subcutaneous</em> 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>

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

Personalized ADT for the Specific Patient

- Cardiac
- Obesity and testosterone
- **FSH**
- High volume metastatic disease
- Docetaxol
- Significant LUTS
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>
</tr>
<tr>
<td>No microsurges</td>
<td>Microsurges on repeat injection</td>
</tr>
<tr>
<td>Unlikely that testosterone suppression can explain differences in risk</td>
<td></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 stimulation</td>
<td></td>
</tr>
<tr>
<td>Prolonged suppression of FSH, LH and testosterone</td>
<td>FSH suppression not maintained long term</td>
</tr>
<tr>
<td>Increased potential for metabolic syndrome and atherogenesis with agonist therapy</td>
<td></td>
</tr>
</tbody>
</table>

FSH, follicle-stimulating hormone
LH, luteinising hormone
FSH and LUTS


LHRH Antagonist Cetrorelix Reduces Prostate Size and Gene Expression of Proinflammatory Cytokines and Growth Factors in a Rat Model of Benign Prostatic Hyperplasia

BACKGROUND. Recent findings suggest that BPH has an inflammatory component. Clinical trials have documented that therapy with LHRH antagonist Cetrorelix causes a marked and prolonged improvement in LUTS in men with symptomatic BPH. We investigated the mechanism of action and effect of Cetrorelix in a rat model of BPH.

METHODS. Adult male Wistar rats were used. BPH was induced in rats by subcutaneous injections of TE 2 mg/day for 4 weeks. Control animals received injections of corn oil. After induction of BPH, rats received depot Cetrorelix pamoate at the doses of 0.625, 1.25, and 12.5 mg/kg on days 1 and 22 and TE-control rats received vehicle injections. Whole prostates were weighed and processed for RNA and protein. Real-time RT-PCR assays for numerous inflammatory cytokines and growth factors were performed. Quantitative analyses of prostatic LHRH receptor, LHRH, androgen receptor (AR) and 5α-reductase 2 were done by real-time RT-PCR and immunoblotting; serum DHT, LH, PSA, and IGF-1 by immunoassays.

RESULTS. mRNA levels for inflammatory cytokines IFN-γ, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, IL-15, and IL-17 and for growth factors EGF, FGF-2, FGF-7, FGF-8, FGF-14, TGF-β1, and VEGF-A were significantly reduced by Cetrorelix 0.625 mg/kg ($P < 0.05$). Prostate weights were also significantly lowered by any dose of Cetrorelix.

CONCLUSIONS. This study suggests that Cetrorelix reduces various inflammatory cytokines and growth factors in rat prostate and, at doses which do not induce castration levels of testosterone, can lower prostate weights. Our findings shed light on the mechanism of action of LHRH antagonists in BPH. *Prostate* 71: 736–747, 2011. © 2010 Wiley-Liss, Inc.
Degarelix versus Goserelin plus Bicalutamide Therapy for Lower Urinary Tract Symptom Relief, Prostate Volume Reduction and Quality of Life Improvement in Men with Prostate Cancer: A Systematic Review and Meta-Analysis

Yuanshan Cui  Huantao Zong  Huilei Yan  Nan Li  Yong Zhang

Department of Urology, Beijing Tian-Tan Hospital, Capital Medical University, Beijing, China
• Literature review performed of all published RCTs that used degarelix vs. GnRH agonists + antiandrogens for treatment of Pca

• Degarelix vs. GnRH + Bicalutamide
  - Better IPSS reduction
  - Decreases in IPSS greater in patients with initial IPSS score >13
  - Prostate volume reduction similar for both groups
  - Quality of life related to urinary symptoms similar for both groups
52 articles were identified including:
MEDLINE: 40 articles
EMBASE: 12 articles
Cochrane Controlled Trials Register: 0 articles

On the basis of titles and abstracts, 39 articles were excluded

13 relevant articles were included

9 articles were not RCTs

4 articles were included

1 article lacked useful data

3 RCTs included in the final analysis compared degarelix with goserelin plus bicalutamide over 12 weeks

Fig. 1. Flow diagram of the study selection process.
Forest plots showing changes in IPSS, IPSS >= 13, TPC and QoL related to urinary symptoms in the treatment studies. SD = standard deviation; IV = inverse variance

- No heterogeneity among trials, pooled estimate of standardized mean difference is -1.85, 95% CI (-2.97 to -0.72) (p=0.001). Results suggest decreases in IPSS greater in degarelix.
- Patients with baseline IPSS >= 13 larger benefit in degarelix group
Forest plots showing changes in treatment-emergent adverse events, injection site reaction, and hot flushes in the treatment studies. M-H = Mantel-Haenszel
<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>Therapy in experimental group</th>
<th>Therapy in control group</th>
<th>Country</th>
<th>Sample size</th>
<th>Inclusion population</th>
<th>Exclusion population</th>
<th>Duration of therapy</th>
<th>Form of experiment and dosing</th>
<th>Form of control and dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axcrona [11], 2012</td>
<td>degarelix</td>
<td>goserelin plus bicalutamide</td>
<td>Denmark</td>
<td>82 97</td>
<td>PCa (all stages), patients with PSA &gt;2 ng/ml, TPV &gt;30 ml, bone scan in the past 12 weeks</td>
<td>previous use of a urinary bladder catheter, treatment with a 5α-reductase inhibitor or botulinum toxin in the past 6 months, treatment with α-blocker in the past 4 weeks</td>
<td>12 weeks</td>
<td>I 240/80 mg</td>
<td>O 3.6 mg + 50 mg</td>
</tr>
<tr>
<td>Anderson [12], 2013</td>
<td>degarelix</td>
<td>goserelin plus bicalutamide</td>
<td>Switzerland</td>
<td>27 13</td>
<td>PCa (all stages), PSA &gt;10 ng/ml, IPSS ≥12, Q(_{max}) ≤12 ml/s, prostate size &gt;30 ml</td>
<td>treatment with a 5α-reductase inhibitor ≥6 months, treatment with α-blocker ≥8 weeks, prior transurethral resection of the prostate</td>
<td>12 weeks</td>
<td>I 240/80 mg</td>
<td>O 3.6 mg + 50 mg</td>
</tr>
<tr>
<td>Mason [13], 2013</td>
<td>degarelix</td>
<td>goserelin plus bicalutamide</td>
<td>UK</td>
<td>180 64</td>
<td>PCa TNM category T2b–T4, N0, M0, Gleason score ≥7, or PSA ≥10 ng/ml; TPV &gt;30 ml</td>
<td>transurethral resection of the prostate; use of a urethral catheter; treatment with a 5α-reductase inhibitor or α-blocker in the past 12, 16 and 4 weeks, respectively</td>
<td>12 weeks</td>
<td>I 240/80 mg</td>
<td>O 3.6 mg + 50 mg</td>
</tr>
</tbody>
</table>

\(Q_{max}\) = Peak urinary flow; I = injection; O = oral.
Table 2. Baseline values of TPV, IPSS, QoL, PSA and testosterone

<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>TPV, ml</th>
<th>IPSS</th>
<th>QoL</th>
<th>PSA, ng/ml</th>
<th>Testosterone, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
<td>G+B</td>
<td>D</td>
<td>G+B</td>
<td>D</td>
</tr>
<tr>
<td>Axcrorna [11], 2012</td>
<td>54.8</td>
<td>49.9</td>
<td>14.3</td>
<td>13.4</td>
<td>2.85</td>
</tr>
<tr>
<td></td>
<td>(26)</td>
<td>(15.5)</td>
<td></td>
<td>(7.36)</td>
<td>(1.62)</td>
</tr>
<tr>
<td>Anderson [12], 2013</td>
<td>53.5</td>
<td>50.3</td>
<td>20.1</td>
<td>21.1</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>(14.0)</td>
<td>(14.0)</td>
<td></td>
<td>(6.9)</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Mason [13], 2013</td>
<td>50.9</td>
<td>52.5</td>
<td>9.5</td>
<td>8.5</td>
<td>2.27</td>
</tr>
<tr>
<td></td>
<td>(20.3)</td>
<td>(18.8)</td>
<td></td>
<td>(6.30)</td>
<td>(1.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) or median with range (minimum–maximum). D = Degarelix; G+B = goserelin plus bicalutamide.

Table 3. Quality assessment of individual studies

<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>Allocation sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Loss to follow-up</th>
<th>Calculation of sample size</th>
<th>Statistical analysis</th>
<th>Intention-to-treat analysis</th>
<th>Level of quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axcrorna [11], 2012</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>7</td>
<td>yes</td>
<td>analysis of covariance</td>
<td>yes</td>
<td>A</td>
</tr>
<tr>
<td>Anderson [12], 2013</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>0</td>
<td>yes</td>
<td>analysis of covariance</td>
<td>no</td>
<td>A</td>
</tr>
<tr>
<td>Mason [13], 2013</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>7</td>
<td>yes</td>
<td>analysis of covariance</td>
<td>yes</td>
<td>A</td>
</tr>
</tbody>
</table>

A = All quality criteria met (adequate) – low risk of bias; B = one or more of the quality criteria only partly met (unclear) – moderate risk of bias; C = one or more criteria not met (inadequate or not used) – high risk of bias.

No evidence of bias was found
Conclusion

• Meta-analysis indicates that compared to goserelin plus bicalutamide, degarelix has significantly more pronounced effects on LUTS
Prostate Cancer

Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists
Randomized comparative phase 3 trials of degarelix and luteinizing hormone-releasing hormone agonists included in the pooled analysis (safety analysis set)

<table>
<thead>
<tr>
<th>Authors/trial</th>
<th>Study arms (dose*, mg)</th>
<th>Patients, no.</th>
<th>Follow-up, mo</th>
<th>Main PCa inclusion criteria</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz et al. [1]/CS21</td>
<td>Degarelix (240/80)</td>
<td>207</td>
<td>12</td>
<td>• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy</td>
<td>Probability of testosterone ≤0.5 ng/ml from days 28–364</td>
</tr>
<tr>
<td></td>
<td>Degarelix (240/160)</td>
<td>202</td>
<td></td>
<td>• Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leuprolide (7.5)</td>
<td>201</td>
<td></td>
<td>• PSA level at screening &gt;2 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Anderson et al. [4]/CS28</td>
<td>Degarelix (240/80)</td>
<td>27</td>
<td>3</td>
<td>• PSA level at screening &gt;10 ng/ml</td>
<td>Change from baseline in total IPSS at week 12 using the last observation carried forward approach</td>
</tr>
<tr>
<td></td>
<td>Goserelin (3.6)</td>
<td>13</td>
<td></td>
<td>• TNM staging at baseline: T3/4, any N, any M</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• IPSS ≥12</td>
<td></td>
</tr>
<tr>
<td>Mason et al. [5]/CS30</td>
<td>Degarelix (240/80)</td>
<td>181</td>
<td>3</td>
<td>• Planned for radical radiotherapy treatment and in whom neoadjuvant is indicated</td>
<td>Mean percentage reduction in prostate volume at 12 wk as compared to baseline</td>
</tr>
<tr>
<td></td>
<td>Goserelin (3.6)</td>
<td>64</td>
<td></td>
<td>• TNM stage: T2 (b or c)/T3/T4, N0, M0; or Gleason score ≥7 or PSA level ≥10 ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PSA level at screening ≥2 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Axcrona et al. [3]/CS31</td>
<td>Degarelix (240/80)</td>
<td>84</td>
<td>3</td>
<td>• TNM stage: any T, any N, any M</td>
<td>Mean percentage reduction in prostate volume measured with TRUS at 12 wk compared to baseline</td>
</tr>
<tr>
<td></td>
<td>Goserelin (3.6)</td>
<td>98</td>
<td></td>
<td>• PSA level at screening &gt;2 ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Prostate &gt;30 ml</td>
<td></td>
</tr>
<tr>
<td>Shore et al. [6]/CS35</td>
<td>Degarelix (240/480)</td>
<td>565</td>
<td>12</td>
<td>• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy</td>
<td>Cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from days 28–364 with degarelix</td>
</tr>
<tr>
<td></td>
<td>Goserelin (3.6/10.8)</td>
<td>283</td>
<td></td>
<td>• Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PSA level at screening &gt;2 ng/ml</td>
<td>Difference in cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from days 3–364 between degarelix and goserelin</td>
</tr>
</tbody>
</table>

PCa = prostate cancer; PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; TRUS = transrectal ultrasound.
* Values indicate initial dose and, if relevant, maintenance dose monthly or every 3 mo.
### Treatment-emergent adverse events (>5% in either group)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Degarelix, no. (%)</th>
<th>LHRH agonist, no. (%)</th>
<th>( p ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety analysis set</td>
<td>1266 (100)</td>
<td>659 (100)</td>
<td>–</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>942 (74)</td>
<td>445 (68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hot flush</td>
<td>386 (30)</td>
<td>171 (26)</td>
<td>0.039</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>380 (30)</td>
<td>6 (&lt;1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythema</td>
<td>257 (20)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Swelling</td>
<td>76 (6)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Nodule</td>
<td>73 (6)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>59 (5)</td>
<td>35 (5)</td>
<td>0.578</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (4)</td>
<td>41 (6)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Urinary tract infection</strong></td>
<td><strong>43 (3)</strong></td>
<td><strong>37 (6)</strong></td>
<td><strong>0.023</strong></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>45 (4)</td>
<td>34 (5)</td>
<td>0.115</td>
</tr>
</tbody>
</table>

LHRH = luteinising hormone-releasing hormone.
* Two-sided Fisher exact test.
Probability of experiencing renal or urinary tract-related adverse event
Conclusion

• Data indicate clinical benefits with degarelix including a significant improvement in PSA PFS and OS as well as reduced incidence of joint, musculoskeletal and urinary tract events compared with LHRH agonists.
Normal prostate myofibroblast WPMY-1 and epithelial WPE1-NA22 cells, BPH-1 cells, androgen independent and dependent (PC-3 and LNCAP) cells and VCaP cells from (CRPC) patient were used

Discriminatory protein and lipid fingerprints of Normal, hyperplastic and Ca cells generated by matrix assisted laser desorption/ionization (MALDI) mass spec

Investigated cell lines express GNRHR1 and GNRHR2 and their endogenous ligands

Treatment with Degarelix reduced cell viability in all cell lines tested, except PC-3 cells, by increased apoptosis (increased caspase 3/7, 8 and 9 levels)

Cell viability was not affected by treatment with GnRH agonists Leuprolide and Goserelin

MALDI MS detected changes in m/z signals robust enough to create a complete discriminatory profile induced by Degarelix

Transcriptomic analysis of BPH-1 cells provided a global map of genes affected by Degarelix, indicating the biological processes affected were related to cell growth, G-coupled receptors, the MAPK pathway, angiogenesis, and cell adhesion
Protein spectra of human prostate cells. (A) MALDI MS protein mass spectra showing differential expression of protein signals between the 3 cell types. (B) principal component analysis (PCA) score plot, and (C) comparison of the two most discriminant peaks across samples. These analysis identify unique protein signatures for each cell line.
Gene expression of prostate human cell lines for GnRH and its receptor subtypes 1 and 2. (A) GNRH1, (B) GNRHR1, (C) GNRH2, and (D) GNRHR2. The white bars show normal cells and the black bars show hyperplasia or cancer cells. Results are presented as a ratio between the target gene relative to the reference gene normalized to the levels of the control. Results shown are means +/- standard error from 3 independent experiments performed in triplicates. Results indicate significant differences between the various cell lines.
MTT assay showing the viability of prostate cell lines following treatment with the GnRH antagonist, degarelix. (A) WPMY-1, (B) WPE1-NA22, (C) BPH-1, (D) PC-3, and (E) LNCaP. Data are expressed as the percentage of the respective controls and the average +/- standard error. Each assay was done in triplicate in at least 3 independent experiments for each cell line. Two-way ANOVA indicated there was a significant difference overall for degarelix treatment (p<0.001), and the posttest indicated that there were differences against each control, as displayed in each graph (***p<0.001). For PC-3 cells only Time
MTT assay showing the viability of WPE1-NA22, BPH-1, and LNCaP cell lines following treatment with GnRH agonists. (A-C) Leuprolide and (D-E) goserelin. Note that the different cell lines are displayed in each column. The data are expressed in terms of the percentage of the respective control and the average +/- standard error. Each assay was done in triplicate with at least n=3 independent experiments for each cell line. Two-way ANOVA displayed p>0.05; there was no difference overall for the treatments.
MTT assay showing the viability of the VCaP cell line after treatment with the GnRH antagonist or agonists. (A) Degarelix, (B) leuprolide, and (C) goserelin. The data are expressed in terms of the percentage of the respective control and the average +/- standard error. Each assay was done in triplicate with at least n=3 independent experiments for each cell line. Two-way ANOVA indicates that there was a significant difference overall for degarelix treatment (p<0.001), and the posttest indicated that there were differences against each control, as displayed in each graph (*p<0.05). ANOVA displayed p>0.05; for the leuprolide and goserelin groups, there was no difference overall for the treatments.
Gene Ontology Classification (Based on Biological Processes) of Degarelix-deregulated Genes on BPH-1 Cells
Gene ontology classification (based on biological processes) of degarelix-deregulated genes on BPH-1 cells. (A-B) The number of genes deregulated by degarelix in various biological processes after 6 and 24h, respectively. The arrows point to potential interesting processes in the BPH and degarelix context. (C) Venn diagram illustrating the number of genes deregulated by degarelix at 6 and 24h.
These data demonstrate...

1. Degarelix exerts a direct effect on prostate cell growth through apoptosis

2. MALDI MS analysis provides a basis to fingerprint Degarelix-treated prostate cells

3. Clusters of genes affected by Degarelix suggest that in addition to use in prostate cancer, it may be efficacious in BPH
Conclusions

• Different types of human prostate cell lines (normal, hyperplasia and cancer) are sensitive to the antiproliferative effect of Degarelix.

• Prostate cell growth was directly inhibited possibly involving a cell cycle–related mechanism and leading to apoptosis.

• Gene Array results indicate a few interesting early molecular changes induced by degarelix that could have an impact in the prostate context, mainly controlling BPH growth.

• A maldi analysis provided the basis to discriminate between the specific proteins and lipids found following degarelix treatment.

• These findings suggest that GNRHR signaling within the prostate environment should be taken into consideration when designing therapies for the treatment of prostate diseases.
Further FSH suppression after crossover from leuprolide to degarelix

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

More FSH-R expressing vessels are present at or near the tumor border.

FSH, follicle-stimulating hormone; PCa, prostate cancer

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 SREs
- Longer duration of HSPCa state
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 ¾ 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.
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

**PSA >20 ng/mL or metastases?**

**Patients with LUTS: IPSS >12?**

**Degarelix**
- >50% lower CVD risk over one year¹

**Degarelix**
- Longer PSA PFS²
- No clinical flare³
- Better S-ALP control⁴
- Better bone pain control⁵

**Degarelix**
- Better relief of LUTS⁶⁻⁸

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