Agonists and antagonists: A Review of what is known and Recent data on disease-related outcomes from a pooled analysis

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Charleston, SC, USA
Contents

• Mechanism of action
  • How do GnRH antagonists and agonists differ?
• Pivotal phase III trial CS21 and extension CS21A
• Disease-control and cardiovascular outcomes from a pooled database of phase III clinical trials
• Conclusions
Mechanism of action of GnRH antagonists differs significantly from that of agonists

- Surge in FSH, LH and testosterone before suppression
- Microsurges in LH and testosterone on repeat injection
- FSH suppression, but not maintained long term

- Immediate suppression of FSH, LH and testosterone
- No microsurges
- Prolonged suppression of FSH, LH and testosterone

FSH, follicle-stimulating hormone; LH, luteinizing hormone
Combined Androgen Blockade

• Does not abrogate the initial testosterone surge intrinsic to LHRH agonists
• Marketed antiandrogens do not completely inhibit the cytoplasmic androgen receptor, thus allowing endogenous androgens to stimulate non-inhibited androgen receptors
• Mutations of the androgen receptor induced by antiandrogens are common and may result in the development of hormonal refractory state. Antiandrogens thus act as agonists of the androgen receptor.
• The initial standard treatment for managing CRPC in patients on CAB is to “withdraw” the antiandrogen
  • This maneuver results in a 25-30% response rate
• Antiandrogens have a spectrum of adverse events independent of testosterone suppression
• CAB does not cause complete suppression of FSH
• FSH may be involved in the development of prostate cancer and the transition to a hormonally refractory state
GNRH Antagonists

• Completely avoids the testosterone surge and causes more rapid medical castration
• Does not affect the androgen receptor
• Devoid of antiandrogen adverse events
• More profound suppression of FSH, acutely and chronically
Questions

• What is an appropriate castrate testosterone

• Do differences exist between the efficacy and benefits of GnRH agonists and antagonists
  • Time to castration onset and PSA suppression
  • PSA PFS (time to castration resistance), particularly in those at greater risk of progression
  • Overall survival

• Are there significant differences in the safety profile of GnRH agonists and antagonists
  • Control of skeletal metastases
  • Cardiovascular events
Clinical impact of low testosterone levels: two peer-reviewed articles

• Morote – Urology 2007

  Redefining Clinically Significant Castration Levels in Patients With Prostate Cancer Receiving Continuous Androgen Deprivation Therapy

  Juan Morote, Anna Orsola, Jacques Planas, Enrique Trilla, Carles X. Raventós, Lluis Cecchini and Roberto Catalán

  From the Department of Urology, Vall d’Hebron Hospital and Autonoma University of Barcelona School of Medicine, Barcelona, Spain

• Perachino – BJUI 2009

  Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: prognostic significance?

  Massimo Perachino, Valerio Cavalli and Fabio Bravi

  Department of Urology, Santo Spirito Hospital, Casale Monferrato, Alessandria, and *Department of Biometry, Ibis Informatica s.r.l., Milan, Italy

  Accepted for publication 5 June 2009
Time to hormonal resistance by median T in year 1 in continuous arm: Secondary analysis of NCIC CTG PR7

Median T based on ≥3 Ts in the first year, for each patient, segregated as to <20 (0.7), 20-50 (0.7-1.7), and >50 ng/mL (>1.7 nM)

N=626

P=0.009

HR 1.4

HR 1.9

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

Prostate Cancer Patient Populations Studied with ADT.

- Stage D1/D2 (asymptomatic)
- Rising PSA
- Neoadjuvant/adjuvant/salvage Hormonal Therapy,
- Intermittent Hormonal Therapy
  - Randomized, controlled (vs L, L+C, Z+C) Pivotal Studies
- Symptomatic, advanced patients
  - Spinal Cord Compression, Urinary Tract Obstruction, Hydronephrosis, Skeletal Pain requiring Narcotic Analgesics
- Others
  - Prostate Gland Volume Reduction, Androgen Independent Disease
Why GNRH antagonists for Hormonally Responsive Prostate Ca?

- Developed to avoid known complications of LHRH agonist induced testosterone surge and disease worsening
- Provide a superior therapy to Maximum Androgen Blockade (CAB, TAB, MAB) with one drug and avoid AE’s of antiandrogens -
- Avoid necessity for surgical castration

Why GNRH antagonists for Androgen Independent Prostate Ca?

- Assess the potential importance of FSH differential effects compared to LHRH agonists
CS21: A randomised phase III trial comparing degarelix with leuprolide

Day 0
Starter dose

Degarelix 240 mg
Leuprolide 7.5 mg

Day 28–364
Maintenance dose

Degarelix 80 mg (n=207)
Degarelix 160 mg (n=202)
Leuprolide 7.5 mg (n=201)

• Previous or current hormonal treatment not allowed, except as neoadjuvant or adjuvant to curative intent (≤6 months treatment, discontinued for >6 months)
• Antiandrogen flare protection in agonist arm at investigator discretion
• Primary endpoint: Testosterone ≤50 ng/dL at any monthly measurement

Study endpoints

• Primary endpoint
  • Cumulative probability of testosterone ≤50 ng/dL at all monthly measurements from day 28 through day 364 – Non inferior

• Secondary endpoints
  • Proportion of patients with testosterone surge - Significantly different
  • Proportion of patients with testosterone ≤50 ng/dL at day 3 (testosterone microsurges) - Significantly different
  • Percentage change in PSA from baseline to day 28 and time to PSA failure – Significantly different
  • Frequency and severity of adverse events – no difference except ISR
  • Frequency of PSA progression – Significantly different
Degarelix significantly reduces the risk of PSA progression (castration resistance) or death

- Also, significantly more men with baseline PSA >20 ng/mL have PSA progression when treated with leuprolide vs degarelix (p=0.0436)
S-ALP: Metastatic disease*

* Retrospective analysis from non-inferiority design pivotal trial

CS21A extension study: Up to 5 years of degarelix treatment

Day 0
Starter dose

Degarelix 240 mg
Leuprolide 7.5 mg

Day 28-364
Maintenance dose

Degarelix 80 mg (n=207)
Degarelix 160 mg (n=202)
Leuprolide 7.5 mg (n=201)

Months 13 to 60
Extension study*

Degarelix 240 mg
Degarelix 240 mg
Degarelix 240 mg
Degarelix 80 mg
Degarelix 160 mg

Starter
dose

Maintenance
dose

CS21
CS21a

*Cross-over at 12 months was preplanned and not due to failure of leuprolide treatment

Further FSH suppression after crossover from leuprolide to degarelix

Median (quartiles) percentage change from baseline

CS21: degarelix or leuprolide

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

Human prostate tumor section labeled for FSH receptor and vascular endothelial cell marker

Red = FSH-R immunostaining
Green = Vascular endothelial cell marker
Yellow = Colocalization of markers

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

FSH, follicle-stimulating hormone; PCa, prostate cancer
PSA PFS is improved after crossover from leuprolide to degarelix

Crossover was preplanned; patients were not switched to degarelix because of agonist failure
PFS, progression-free survival

CS21/21A: Overall summary

• Compared with LHRH agonist therapy, degarelix offers:
  • Faster castration onset and PSA suppression, with no risk of clinical flare\(^1\)
  • Longer PSA PFS, especially in those at greatest risk of progression (PSA>20 ng/mL)\(^2\)

• For up to 5 years of degarelix treatment:
  • PSA PFS is improved after crossover from leuprolide to degarelix\(^3,4\)
  • Therapy was well tolerated\(^3,4\)

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• Disease-control and cardiovascular outcomes from a pooled database of phase III clinical trials
  • How does the control of disease outcomes with degarelix and LHRH agonists compare?
• Conclusions
Data from six randomized phase III/IIIb trials of degarelix vs LHRH agonists were pooled

<table>
<thead>
<tr>
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</tr>
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</tr>
<tr>
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<td>3</td>
<td>Goserelinb</td>
<td>Mason et al. Clin Oncol 2013</td>
</tr>
<tr>
<td>CS31</td>
<td>3</td>
<td>Goserelinb</td>
<td>Axcona et al. BJU Int 2012</td>
</tr>
</tbody>
</table>

- Efficacy data was collected from the degarelix clinical trials database
- Safety data was patient reported and categorised by MedDRA criteria

*aExcluded from efficacy-related outcomes analysis as recruited population comprised patients with early disease with biochemical failure after primary definitive therapy; bAll patients on goserelin also received antiandrogen flare protection.
LUTS, lower urinary tract symptoms; TPV, total prostate volume; RT, radiotherapy*
Baseline patient characteristics were comparable across treatment groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Degarelix n=1263</th>
<th>LHRH agonist n=657</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>71.7 (8.0)</td>
<td>71.8 (7.9)</td>
</tr>
<tr>
<td>Median testosterone, ng/mL (25-75 percentile)</td>
<td>4.2 (3.1–5.4)</td>
<td>4.3 (3.3–5.4)</td>
</tr>
<tr>
<td>Median PSA, ng/mL (25-75 percentile)</td>
<td>17.3 (8.6–53.7)</td>
<td>16.7 (7.7–51.1)</td>
</tr>
<tr>
<td>Disease stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>432 (34)</td>
<td>226 (34)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>375 (30)</td>
<td>170 (26)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>282 (22)</td>
<td>153 (23)</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>174 (14)</td>
<td>108 (16)</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>91 (7)</td>
<td>41 (6)</td>
</tr>
<tr>
<td>5-6</td>
<td>381 (30)</td>
<td>179 (27)</td>
</tr>
<tr>
<td>7-10</td>
<td>784 (62)</td>
<td>436 (66)</td>
</tr>
<tr>
<td>PSA category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 10</td>
<td>391 (31)</td>
<td>224 (34)</td>
</tr>
<tr>
<td>10 – 20</td>
<td>283 (23)</td>
<td>140 (21)</td>
</tr>
<tr>
<td>20 – 50</td>
<td>250 (20)</td>
<td>124 (19)</td>
</tr>
<tr>
<td>50+</td>
<td>328 (26)</td>
<td>165 (25)</td>
</tr>
</tbody>
</table>

Data on file
Superior overall survival with degarelix vs LHRH agonists (all patients)\textsuperscript{1}

- Very few patients died of prostate cancer over the year of the study
- Most men with prostate cancer die of other causes such as CVD\textsuperscript{2,3}


CVD, cardiovascular disease
Lower probability of musculoskeletal events with degarelix vs LHRH agonists (all patients)

Lower probability of a urinary tract event with degarelix vs LHRH agonists (all patients)

LUTS control: Degarelix vs. goserelin + bicalutamide

Mean change in IPSS at Week 12 (full analysis set)

<table>
<thead>
<tr>
<th>Study</th>
<th>Degarelix</th>
<th>Goserelin + bicalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS28¹</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>CS30²</td>
<td>174</td>
<td>60</td>
</tr>
<tr>
<td>CS31³</td>
<td>81</td>
<td>93</td>
</tr>
</tbody>
</table>

- CS28¹: p=0.044
- CS30²: p=0.06
- CS31³: p<0.05

Data are not directly comparable between studies

Contents

• Mechanism of action
• Pivotal phase III trial CS21 and extension CS21A
• Disease-control and cardiovascular outcomes from a pooled database of phase III clinical trials
  • Is the risk of cardiovascular events increased with LHRH agonists compared with degarelix?
• Conclusions
ADT and risk of CVD

• ADT is associated with an increased risk of CV events
  • LHRH agonists linked to increased CV morbidity compared to orchiectomy\(^1\)
  • Men with history of CVD most at risk\(^2,3\)
• Degarelix has a distinct mechanism of action to LHRH agonists
  • Risk of CV events may also be different
• The risk of CV events in men receiving LHRH agonists or degarelix was assessed in a pooled analysis of 6 randomized phase III trials

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ADT, androgen deprivation therapy
CVD, cardiovascular disease

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
Oestrogen therapy increases risk of CV-related side effects

- 2,052 patients with stage I–IV prostate cancer treated using radical prostatectomy or orchiectomy 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</td>
<td>Adjusted HR</td>
<td>Adjusted HR</td>
<td>Adjusted HR</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(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*</td>
<td>1.28*</td>
<td>1.35*</td>
<td>1.21*</td>
</tr>
<tr>
<td></td>
<td>(1.10–1.28)</td>
<td>(1.08–1.52)</td>
<td>(1.18–1.54)</td>
<td>(1.05–1.40)</td>
</tr>
<tr>
<td>Orchiectomy</td>
<td>1.40*</td>
<td>2.11*</td>
<td>1.29</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>(1.04–1.87)</td>
<td>(1.27–3.50)</td>
<td>(0.76–2.18)</td>
<td>(0.92–2.43)</td>
</tr>
<tr>
<td>CAB</td>
<td>1.27*</td>
<td>1.03</td>
<td>1.22</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>(1.05–1.53)</td>
<td>(0.62–1.71)</td>
<td>(0.85–1.73)</td>
<td>(0.61–1.42)</td>
</tr>
<tr>
<td>Antiandrogen</td>
<td>1.10</td>
<td>1.05</td>
<td>1.06</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>(0.80–1.53)</td>
<td>(0.47–2.35)</td>
<td>(0.57–1.99)</td>
<td>(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\(^2\)

\(\text{ADT, androgen deprivation therapy} \)
\(\text{RT, radiotherapy} \)
\(\text{*Based on Adult Comorbidity Evaluation 27 (ACE-27)} \)

... 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)

CVD, cardiovascular disease
PEP, polyestradiol phosphate

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%

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

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*All patients on goserelin also received antiandrogen flare protection

LUTS, lower urinary tract symptoms
RT, radiotherapy
TPV, total prostate volume
Pooled database: Treatment groups and CVD history

CVD history was defined as an event of myocardial ischaemia, coronary artery disease, myocardial infarction, cerebrovascular accident, angina pectoris or coronary artery bypass at baseline.

Baseline demographics relating to CV risk were balanced

<table>
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<th>Variable</th>
<th>Degarelix n=1491</th>
<th>LHRH agonist n=837</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>71.7 (46–94)</td>
<td>71.6 (51–98)</td>
</tr>
<tr>
<td>Body mass index &gt;30, n (%)</td>
<td>27.2 334 (22.4)</td>
<td>27.5 200 (23.9)</td>
</tr>
<tr>
<td>History of CVD, n (%)</td>
<td>463 (31.1)</td>
<td>245 (29.3)</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>707 (47.4)</td>
<td>432 (51.6)</td>
</tr>
<tr>
<td>History of alcohol use, n (%)</td>
<td>889 (59.6)</td>
<td>475 (56.8)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>1117 (74.9)</td>
<td>615 (73.5)</td>
</tr>
<tr>
<td>Serum cholesterol &gt;6.2 mmol/L, n (%)</td>
<td>399 (26.8)</td>
<td>247 (29.5)</td>
</tr>
<tr>
<td>Statin medication use, n (%)</td>
<td>400 (26.8)</td>
<td>234 (28.0)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>221 (14.8)</td>
<td>128 (15.3)</td>
</tr>
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Higher incidence of CV events with LHRH agonists than degarelix (all patients)*

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<th>LHRH agonist, n (%) n=837</th>
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<tr>
<td>Any CV event</td>
<td>42 (2.8)</td>
<td>37 (4.4)</td>
</tr>
<tr>
<td>Death</td>
<td>20 (1.3)</td>
<td>22 (2.6)</td>
</tr>
</tbody>
</table>

*Data classified according to the MedDRA system
Lower risk of CV event or death with degarelix (all patients)

HR=0.60 (95% CI 0.41–0.87)  
p=0.008

Higher incidence of CV events with LHRH agonists than degarelix (patients with CV history)*

<table>
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<tr>
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<th>Degarelix, n (%) n=463</th>
<th>LHRH agonist, n (%) n=245</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV event</td>
<td>21 (4.5)</td>
<td>23 (9.4)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (1.9)</td>
<td>13 (5.3)</td>
</tr>
</tbody>
</table>

*Data classified according to the MedDRA system
Lower risk of CV event or death with degarelix (patients with CV history)

HR=0.44 (95% CI 0.26–0.74)

p=0.002

## 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

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
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>

Plaque instability is at the heart of cardiovascular disease.

Stable plaque:
- Thick
- Rich in SMC and matrix
- Composition:
- Poor
- Lipid
- Inflammatory state

Vulnerable plaque:
- Thin
- Rich in inflammatory cells: proteolytic activity
- More

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

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


IFN, interferon
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

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>
What does this mean for our patient?

• From your perspective as urologists:
  • Consider which therapy will treat his prostate cancer effectively
  • Consider which therapy will control disease symptoms effectively
  • Consider minimising side effects
• In the absence of CV risk, probably little to choose between LHRH agonists and degarelix
• In the presence of CV risk (obesity, diabetes, prior MI), degarelix may be preferred
Summary

• ADT is associated with an increased risk of CV events, particularly in those with a history of CVD

• The GnRH antagonist, degarelix, may be associated with a lower incidence of CV events than LHRH agonists

• The difference in risk appears likely to be due to the differing mechanisms of actions of the types of ADT

• Risk of CVD should be carefully assessed prior to using ADT and risk minimised where possible
ADT and CVD: Conclusions

• When treated with degarelix rather than a LHRH agonist, patients with pre-existing CVD:
  • Had significantly fewer CV events during the first year of treatment
  • Had a relative risk reduction of >50%
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 year

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

Degarelix
• Better relief of LUTS

Degarelix or LHRH agonist

Abiraterone Clinical Summary

Mechanism of action
- Irreversible inhibitor of CYP17A
- Inhibits testosterone production in testis, adrenal glands and prostate
- Abi, 1000mg oral plus prednisone 5mg bid, non-fed state

Pre-docetaxel phase III trial (COU-302) asymptomatic or mildly symptomatic mCRPC\textsuperscript{3} co-primary endpoints-OS & rPFS
- Median rPFS not reached vs 8.28 months, respectively; HR=0.425; 95% CI 0.347–0.522; P<0.0001
- Median OS was longer for ZYTIGA\textsuperscript{®} plus prednisone compared with placebo plus prednisone
  - 35.3 months vs 30.1 months, respectively; HR=0.792; 95% CI 0.655–0.956; P=0.0151 (pre-specified value for statistical significance not reached)

Post-docetaxel phase III trial (COU-301) in mCRPC\textsuperscript{1} with primary endpoint OS
- Abiraterone plus prednisone improved OS in patients with (COU-301) mCRPC post-docetaxel\textsuperscript{1,2}
  - 3.9 month OS benefit(4.6 final...HR=0.74; 95% CI: 0.638, 0.859)\textsuperscript{2}
  - AEs of special interest - fluid retention hypokalemia, hypertension, and liver-function test abnormalities – abiraterone vs placebo (55% vs 43%, P<0.001)\textsuperscript{1}

---

CI, confidence interval
HR, hazard ratio
OS, overall survival

Enzalutamide Clinical Summary

Mechanism of action:
- Designed to have high affinity and selectivity for the androgen receptor
- An androgen receptor inhibitor that targets multiple steps in the androgen receptor signaling pathway in the tumor cell
- Enzalutamide, 160mg oral qd, no steroid or food requirement

Post-docetaxel phase III trial (AFFIRM) in mCRPC\(^1\) with primary endpoint OS
- Enzalutamide improved OS in patients with mCRPC post-docetaxel\(^1,2\)
  - 4.8 months OS benefit (HR = 0.631 (0.529, 0.752) P < 0.0001 37% Reduction in Risk of Death)\(^2\)
- AE’s of special interest: 0.9% seizure incidence, grade 1-4 neutropenia (15% vs. 6%), Grade 1 or 2 hallucinations (1.6%)
- Pre-CTX(PREVAIL) completed: improved OS in Pts with mCRPC.
- Benefit seen in pts with visceral disease and bony metastatic disease.

### Key Study Design Differences

<table>
<thead>
<tr>
<th>Category</th>
<th>PREVAIL</th>
<th>COU-AA-302</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control Group</strong></td>
<td><strong>Placebo</strong></td>
<td><strong>Prednisone</strong></td>
</tr>
<tr>
<td><strong>Eligibility Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral disease allowed</td>
<td></td>
<td>Visceral disease excluded</td>
</tr>
<tr>
<td>Blood pressure &lt;170/105 mmHg</td>
<td></td>
<td>Blood pressure &lt;160/95 mmHg</td>
</tr>
<tr>
<td>Excluded patients with NYHA class 3 or 4 CHF</td>
<td></td>
<td>Excluded patients with NYHA class 2, 3, or 4 CHF</td>
</tr>
<tr>
<td>Allowed patients with atrial fibrillation and other arrhythmias requiring therapy</td>
<td>Excluded patients with atrial fibrillation and any arrhythmia that requires therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Study Conduct</strong></td>
<td>Patients were allowed to continue study drug up until initiation of cytotoxic chemotherapy or an investigational agent</td>
<td>Patients needed to discontinue study drug if need for opiates to treat cancer pain, SRE, ECOG PS of 3 or higher</td>
</tr>
<tr>
<td>Provenge, systemic radiopharmaceuticals, allowed during treatment</td>
<td>Provenge, systemic radiopharmaceuticals excluded during treatment</td>
<td></td>
</tr>
</tbody>
</table>
# Selected Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographic/Baseline Characteristics</th>
<th>PREVAIL</th>
<th>302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enza (N=872)</td>
<td>Placebo (N=845)</td>
</tr>
<tr>
<td>Median age in yrs (range)</td>
<td>72 (43 – 93)</td>
<td>71 (42 – 93)</td>
</tr>
<tr>
<td>Median baseline PSA</td>
<td>54.1</td>
<td>44.2</td>
</tr>
<tr>
<td>Median baseline LDH (IU/L)</td>
<td>185</td>
<td>185</td>
</tr>
<tr>
<td>Presence of bone metastases at entry (%)</td>
<td>85.0%</td>
<td>81.7%</td>
</tr>
<tr>
<td>Presence of soft tissue disease at entry (%)</td>
<td>59.3%</td>
<td>59.6%</td>
</tr>
<tr>
<td>Presence of visceral disease at entry (%)</td>
<td>11.2%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Abiraterone data taken from Ryan et al NEJM 2013
### Exposure to Study Drug

<table>
<thead>
<tr>
<th></th>
<th>PREVAIL</th>
<th>Abiraterone 302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzalutamide (N=871)</td>
<td>Abi+pred (N=542)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=844)</td>
<td>Placebo+pred (N=540)</td>
</tr>
<tr>
<td>Treatment Duration (Months)</td>
<td>16.6</td>
<td>4.6</td>
</tr>
</tbody>
</table>
Subsequent Therapy

<table>
<thead>
<tr>
<th>Parameter (n%)</th>
<th>PREVAIL</th>
<th>Abiraterone 302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enza (N=872)</td>
<td>Abi + pred (N=546)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=845)</td>
<td>Placebo + Pred (N=542)</td>
</tr>
<tr>
<td>Median Follow-Up Time</td>
<td>22.3 months</td>
<td>22.3 months</td>
</tr>
<tr>
<td>Use of Subsequent Therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>32.8%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>56.7%</td>
<td>53%</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>5.8%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>13.0%</td>
<td>10%</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>20.5%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>45.6%</td>
<td>10%</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>1.0%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>4.4%</td>
<td>--</td>
</tr>
</tbody>
</table>

Abiraterone data taken from ASCO 2012 (presentation)/NEJM 2013/EPAR 2013
## Efficacy Data

<table>
<thead>
<tr>
<th></th>
<th>PREVAIL</th>
<th>Abiraterone 302</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td>HR = 0.706</td>
<td>HR = 0.792</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.0001</td>
<td>P = 0.0151 (Not significant)</td>
</tr>
<tr>
<td><strong>rPFS</strong></td>
<td>HR = 0.186</td>
<td>HR = 0.530</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td><strong>Time to Cytotoxic</strong></td>
<td>HR = 0.350</td>
<td>HR = 0.580</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td><strong>Time to PSA</strong></td>
<td>HR = 0.169</td>
<td>HR = 0.488</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td><strong>Degradation FACT-P</strong></td>
<td>HR = 0.625</td>
<td>HR = 0.778</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.0001</td>
<td>P = 0.0028</td>
</tr>
<tr>
<td><strong>Best Overall Soft</strong></td>
<td>Measurable disease: 45% vs. 45%</td>
<td>Measurable disease: 40% vs. 40%</td>
</tr>
<tr>
<td><strong>Tissue Response</strong></td>
<td>Responders: 59% vs. 5%, p&lt;0.0001</td>
<td>Responders: 36% vs. 16%, p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CR: 20% vs. 1%</td>
<td>CR: 11% vs. 4%</td>
</tr>
<tr>
<td></td>
<td>PR: 39% vs. 4%</td>
<td>PR: 25% vs. 12%</td>
</tr>
</tbody>
</table>
Question-In pre-docetaxel setting

• PREVAIL/Cougar 302 are positive
  • Give enzalutamide first?
    • No steroids, No food effect
    • Fluid retention (NYHA), IDDM
  • Give abiraterone first?
    • More experience with drug
    • Seizure (neuro)history
    • Does baseline T level matter?
    • Sequencing more favorable?
  • Give as combination?
Cross Resistance Between Abiraterone and Enzalutamide
Sequencing-Non-mCRPC

- No therapy has been shown to improve survival in this setting
- Observation is reasonable for those with slow PSAV
- Consider secondary hormonal therapies
- Phase III trials (ARSI)-Enzalutamide & ARN-509
Practice-Changing Results for Metastatic Prostate Cancer

Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)

“Upfront” chemotherapy (docetaxel) plus ADT vs ADT alone in men with metastatic prostate cancer

Dr. Christopher Sweeney

Sweeney et al. J Clin Oncol. 32:5s, 2014 (suppl; abstr LBA2)
Clinical States In Prostate Cancer

- Organ Confined
- Locally Advanced Disease
- Rising PSA Hormone Naive
- Rising PSA Castrate
- Metastatic Disease (De novo)
- Metastases Castrate-Resistant Asymptomatic
- Metastases Castrate Resistant Symptomatic
- Metastases Castrate Resistant Post Docetaxel Post Abiraterone
- Metastases Castrate Resistant Post Cabazitaxel

- Docetaxel/ADT
- Sipuleucel-T
- Cabazitaxel
- Radium 223
- Enzalutamide
- Abiraterone
- Denosumab
- Zolendronic Acid

Key Questions

- Are there therapies that are better given early?
- Are certain therapies designed to work better later in CRPC? Or not?
- Is the efficacy of prior therapies diminished by subsequent treatment?
- Is the efficacy of the administration of later agents diminished by their precedents?
- Can therapeutic resistance be modulated by specific concurrent targeted therapy?
- Are there patient characteristics or biomarkers that help match patients and specific therapies?
- Since Docetaxel is being given earlier (non CRPC) should these be also.
CHAARTED (E3805): ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

- 790 patients
- Stratification
  - PS
  - 4 or > bone mets
  - Amount previous ADT rx

Randomize

- Androgen Deprivation
- Androgen Deprivation + 6 cycles of Docetaxel (every 3 weeks for 18 weeks)

Primary endpoint: Overall survival
Secondary endpoint: TT mCRPC

ClinicalTrials.gov Identifier: NCT00309985
CHAARTED
Overall Survival (OS)

- Median OS was **improved by 13 months** in patients treated with **ADT plus docetaxel**
  - 57.6 months for men on ADT plus docetaxel
  - 44.0 months for men on ADT alone

- Median time to CRPC and time to clinical progression was greater for ADT + docetaxel

Sweeney et al. *J Clin Oncol.* 32:5s, 2014 (suppl; abstr LBA2)
CHAARTED
OS by Extent of Disease

- The median OS was **improved by 17 months in men with high-volume disease**
  - 49.2 months for men on ADT + docetaxel
  - 32.2 months for men on ADT alone

- The median OS for low-volume disease has not yet been reached.

Sweeney et al. *J Clin Oncol*. 32:5s, 2014 (suppl; abstr LBA2)
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

Stable plaque

Vulnerable plaque

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

2328 Patients

- 1491 Degarelix
  - 463 (31%) CVD history

- 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</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>
## Results: Overall incidence of CV events*

<table>
<thead>
<tr>
<th></th>
<th>Degarelix, n (%)</th>
<th>GnRH agonist, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1491</td>
<td>n=837</td>
</tr>
<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

Tom Keane is planning to show this table and the next three KM curves but keep to reinforce data and make the point that most of the OS difference is likely due to CV events.
Lower risk of CV event or death with degarelix (all patients)

HR=0.60 (95% CI 0.41-0.87)  
p=0.008

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

HR=0.44 (95% CI 0.26–0.74)
p=0.002

Tombal B, et al. EAU 2013;Poster 677
Overall survival

HR=0.47 (95% CI 0.25–0.90)
p=0.022

CVD, cardiovascular disease