New perspectives in the use of LHRH agonists and antagonists
GnRH Agonists: indirect mode of action

- Agonists over-stimulate pituitary gland
- Overrides pulsatile release of natural GnRH
- Leads to surge in LH and FSH
- Surge in LH leads to surge in testosterone
- Constant stimulation leads to down-regulation of GnRH receptors
- Lack of LH production leads to drop in testosterone

Princivalle M et al. J Pharmacol Exp Ther 2007; 320: 1113–1118
Suboptimal testosterone control associated with GnRH Agonists

Initial surge / clinical flare

Failure to reach adequate suppression

Microsurges (Acute-on-chronic)

Breakthroughs (Late escapes)

SEM, standard error of the mean
Incidence of clinical disease flare in luteinizing hormone–releasing hormone agonist trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients, N</th>
<th>Patients with Flare (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawford et al</td>
<td>231</td>
<td>10</td>
</tr>
<tr>
<td>Kuhn et al</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>Waxman et al</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>Leuprolide Study Group</td>
<td>86</td>
<td>8</td>
</tr>
<tr>
<td>Peeling</td>
<td>300</td>
<td>4</td>
</tr>
<tr>
<td>Smith et al</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td>Murphy et al</td>
<td>27</td>
<td>10</td>
</tr>
</tbody>
</table>
Imaging the tumour flare

Perfusion studies of bone metastases in metastatic prostate cancer patients

Lecouvet F et al. 4th Degarelix International Advisory Board, Amsterdam, 14 January 2010
Perfusion and endothelial permeability

<table>
<thead>
<tr>
<th>Untreated</th>
<th>Zoladex (goserelin) 3-month depot</th>
<th>FIRMAGON (degarelix) 1-month depot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Day 0</td>
<td>Day 0</td>
</tr>
<tr>
<td>Day 30</td>
<td>Day 30</td>
<td>Day 30</td>
</tr>
<tr>
<td>Day 90</td>
<td>Day 90</td>
<td>Day 60</td>
</tr>
</tbody>
</table>

Lecouvet F et al. 4th Degarelix International Advisory Board, Amsterdam, 14 January 2010
How low should you go?

### Defining castrate levels of Testosterone (T)

<table>
<thead>
<tr>
<th>Standard</th>
<th>ng/dL</th>
<th>ng/mL</th>
<th>nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old*</td>
<td>T &lt; 50</td>
<td>T &lt; 0.5</td>
<td>T &lt; 1.7</td>
</tr>
<tr>
<td>New**</td>
<td>T &lt; 20</td>
<td>T &lt; 0.2</td>
<td>T &lt; 0.7</td>
</tr>
</tbody>
</table>

*based on inadequate assay methods available at the time
**benchmarked to surgical castrate levels, better assays
Orchiectomy – testosterone levels


- Mean testosterone levels range from 50 ng/dL (1.7 nmol/L) to 20 ng/dL (0.7 nmol/L).

- The graph compares mean testosterone levels of Oefelein, Rohl, Kaisary, Lin, and Vogelzang.
Percentage of patients who fail to reach testosterone $\leq 50$ ng/dL


Adapted from Tombal B & Berges R. Eur Urol Suppl 2005;4:30–6
1 M, 1-month formulation
3 M, 3-month formulation
Percentage of patients who fail to reach testosterone ≤ 20 ng/dL

Adapted from Tombal B & Berges R. Eur Urol Suppl 2005;4:30-6

Diagram showing percentages of patients not reaching testosterone levels after different treatments and durations.
Testosterone breakthroughs

27% of patients have a breakthrough ≥0.7 nmol/L

- 0.7–1.1 nmol/L: 20.0%
- 1.1–1.7 nmol/L: 2.9%
- >1.7 nmol/L: 3.6%
- None: 73.0%

<table>
<thead>
<tr>
<th>nmol/L</th>
<th>ng/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>20</td>
</tr>
<tr>
<td>1.1</td>
<td>32</td>
</tr>
<tr>
<td>1.7</td>
<td>50</td>
</tr>
</tbody>
</table>
Survival free of AIP according to serum testosterone behaviour

AIP, Androgen independent progression

20 ng/dL = 0.7 nmol/L
50 ng/dL = 1.7 nmol/L
Predictors of cancer specific survival in metastatic patients on continuous ADT

Hazard ratios (Mean, 95% CI)

- Goserelin 10.8 mg every 3 months; Bone-only prostate cancer patients (N=129)

1.333 (1.053-1.687)  P<0.05
1.309 (1.187-1.443)  P<0.01
1.391 (1.141-1.696)  P<0.01
1.037 (0.996-1.078)  P=0.08
Early testosterone breakthroughs impact downstream biochemical control

10 year data

1.1 nmol/L = 32 ng/dL
1.7 nmol/L = 50 ng/dL

Pickles et al. 2010 CARO Annual Scientific Meeting, Vancouver
Pickles et al. 2011 EAU Annual Congress, Vienna
FIRMAGON: direct mode of action

FIRMAGON:

- Well established, direct mechanism of action
- Immediate onset of action with fast testosterone suppression
- No initial stimulation of pituitary GnRH receptors and therefore no testosterone surge

Princivalle M et al. J Pharmacol Exp Ther 2007; 320: 1113–1118
Study design (CS21 – Klotz et al)

- 610 patients
- Monthly dosing
- Antiandrogen flare protection at investigator discretion

Primary endpoint: Degarelix (both arms) was non-inferior to leuprolide in suppressing testosterone to <0.5 ng/mL from Day 28–364
Testosterone suppression (Primary endpoint)

FIRMAGON is non-inferior to leuprolide in suppressing testosterone to <0.5 ng/mL from Day 28–364

Klotz L et al. BJU Int 2008; 102: 1531–1538
Better PSA progression free survival (all patients)

FIRMAGON had a significantly longer time to PSA failure or death compared to leuprolide

*P=0.0495

ITT, intention de traiter
Degarelix rapidly decreased and maintained lower FSH levels compared to leuprolide.
$S$–ALP: baseline disease stage

\[ *P=0.0137 \]

Number of patients (metastatic disease)

<table>
<thead>
<tr>
<th></th>
<th>Degarelix</th>
<th>37</th>
<th>37</th>
<th>36</th>
<th>36</th>
<th>35</th>
<th>34</th>
<th>34</th>
<th>34</th>
<th>31</th>
<th>31</th>
<th>29</th>
<th>28</th>
<th>27</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Leuprolide</td>
<td>47</td>
<td>45</td>
<td>44</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>42</td>
<td>42</td>
<td>41</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>39</td>
</tr>
</tbody>
</table>

Schröder FH et al. BJU Int. 2010 Jul;106(2):182–7
Serum ALP predicts survival

Klotz et al (CS21) adverse events

<table>
<thead>
<tr>
<th></th>
<th>Degarelix 240 mg</th>
<th>Leuprolide 7.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>Injection site AEs</td>
<td>35%</td>
<td>&lt;1%***</td>
</tr>
<tr>
<td>Hot flush</td>
<td>26%</td>
<td>21%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5%</td>
<td>9%*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5%</td>
<td>9%**</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Chills</td>
<td>5%</td>
<td>0%**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, and ***p<0.001 versus degarelix pooled
### Injection site reactions predominantly with starter dose

<table>
<thead>
<tr>
<th></th>
<th>Degarelix 240 mg → 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starter dose</td>
<td>32%</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>4%</td>
</tr>
</tbody>
</table>

<1% discontinuations

Post launch: Leaving needle in situ 30 seconds prior to withdrawal substantially lowers injection site reactions

Klotz L et al. BJU Int 2008; 102: 1531–1538
Treatment switch from leuprolide to degarelix (CS21A extension study)

Day 0
Starter dose

- Degarelix 240 mg (sc)
- Leuprolide 7.5 mg (im)

Months 1 to 12
Maintenance dose

- Degarelix 80 mg (sc)
- Leuprolide 7.5 mg (im)
- Degarelix 160 mg (sc)

Months 13 to 60
Extension study

- Degarelix 240 mg (sc)
- Degarelix 80 mg (sc)
- Degarelix 160 mg (sc)

Klotz et al
CS21

Extension study
CS21A

Crawford et al. J Urol 2010; 183 (Suppl): e262 (AUA abstract)
PSA progression–free survival beyond 1 year (time to PSA failure or death – all patients)

Crawford et al. J Urol 2010; 183 (Suppl): e262 (AUA abstract)
Time to PSA failure (PSA increase ≥ 50% from nadir and ≥5 ng/mL on two consecutive occasions at least 2 weeks apart)
If testosterone is suppressed to similar levels between days 28–364, what’s driving this?

Time to Testosterone suppression?

Microsurges?

Time to PSA suppression?

FSH?

Other?

Degarelix 240/80 mg 0.11 0.14 P=0.464
Leuprolide 7.5 mg 0.20 0.08 P=0.003

Crawford et al. J Urol 2010; 183 (Suppl): e262 (AUA abstract)
Time to PSA failure (PSA increase ≥ 50% from nadir and ≥5 ng/mL on two consecutive occasions at least 2 weeks apart)
Time to testosterone suppression

Klotz L et al. BJU Int 2008; 102: 1531–1538
Time to PSA suppression

Values are medians (+/− interquartile range)

Klotz L et al. BJU Int 2008;102:1531–8

11% of leuprolide patients received bicalutamide as flare protection

*P<0.001
Better PSA suppression despite antiandrogens

PSA over 28 days (metastatic patients)

Klotz L et al. BJU Int 2008; 102: 1531–1538
Mean testosterone levels significantly increased following leuprolide injection on Day 252.

Data are means (95% CI).
Klotz L et al. BJU Int 2008;102:1531–8

*P<0.0001
#P<0.0015
Improved FSH control in patients switched to Degarelix after 1 year (CS21/21A)

Crawford ED et al. J Urol, In press
FSH and FSH–receptors in prostatic cancer

FSH and FSH–receptors have been found in

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

+ low prevalence; ++++ high prevalence

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

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

FSH receptors identified on prostate tumour blood vessels

Tumour blood vessels become resistant to therapy

FSH receptor signalling may be associated with tumour cell proliferation

Lowering FSH levels decreases proliferation of PCa cells

CS30: Significant reduction in IPSS with degarelix vs goserelin + bicalutamide before RTx in PCa

- After 12 weeks: Degarelix −1.71 vs goserelin + bicalutamide 0.11
  - Difference: −1.42 (−2.81, 0.03); p=0.044

IPSS reduction before RT is important as RT can cause LUTS.

Degarelix
- Rapid suppression of Testosterone, FSH and PSA irrespective of baseline disease
- Maintained suppression over 3.3 years

Degarelix vs. Leuprolide
- Better Testosterone, FSH and PSA control
- Longer PSA progression-free survival

Patients switched to Degarelix
- Improved PSA progression-free survival
- Improved FSH suppression
### Where could a GnRH blocker make a difference?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
| T1a–T2c     | - **Symptomatic** patients requiring palliation unfit for curative treatment. Antiandrogens not recommended  
- For **high-risk** patients **NHT** and concomitant ADT + RT increases overall survival |
| T3–T4       | - Overall survival improved with concomitant and adjuvant (3 year) ADT + RT  
- **Symptomatic** patients, extensive T3–T4, high PSA (＞25–50 ng/mL), PSA doubling time ＜1 year  
- Patient-driven, unfit patients |
| N+, M0      | Standard adjuvant therapy in ＞1 +ive node |
| M+          | Standard therapy, mandatory in **symptomatic** patients |
Thank you!
### CS30: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Degarelix (n=180)</th>
<th>Goserelin + bicalutamide (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean±SD, years)</strong></td>
<td>70.6±6.4</td>
<td>70.8±6.0</td>
</tr>
<tr>
<td><strong>BMI (mean±SD, kg/m²)</strong></td>
<td>27.8±4.0</td>
<td>26.8±3.7</td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>41 (23%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>7</td>
<td>97 (54%)</td>
<td>42 (66%)</td>
</tr>
<tr>
<td>8–10</td>
<td>42 (23%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2a</td>
<td>73 (41%)</td>
<td>30 (47%)</td>
</tr>
<tr>
<td>T2b/c</td>
<td>43 (24%)</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>T3/4</td>
<td>64 (36%)</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Tx</td>
<td></td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Testosterone (median [range], ng/mL)</strong></td>
<td>3.92 (0.6–11)</td>
<td>4.42 (0.2–8.1)</td>
</tr>
<tr>
<td><strong>PSA (median [range], ng/mL)</strong></td>
<td>10 (2.5–339)</td>
<td>9.8 (2.9–80)</td>
</tr>
<tr>
<td><strong>IPSS (median [range], points)</strong></td>
<td>8 (0–32)</td>
<td>7 (0–25)</td>
</tr>
<tr>
<td><strong>TPV (median [range], mL)</strong></td>
<td>43 (30–121)</td>
<td>48 (31–110)</td>
</tr>
</tbody>
</table>
CS30: LUTS Relief in Symptomatic Patients

Moderate LUTS (IPSS 8–19)

Degarelix (n=72)

G+B (n=23)

Mean change in IPSS total score at Week 12

P=0.085

IPSS ≥13

Degarelix (n=53)

G+B (n=17)

Mean change in IPSS total score at Week 12

P=0.06
First study of degarelix as IAD (CS29)

Open-label, uncontrolled, 2-cycle trial in patients with PCa (all stages)

Primary endpoint:
- Time to PSA >4 ng/mL in off-phase

Secondary endpoints included:
- Time to testosterone >0.5 ng/mL in off-phase
- Safety/tolerability

Interim data available for 213 pts
CS29: Inclusion criteria

- Histologically confirmed (Gleason graded) adenocarcinoma of the prostate and in need of ADT

- Locally advanced or metastatic prostate cancer
  - PSA level must be $>4$ ng/mL and $\leq 50$ ng/mL

- Patients with localised prostate cancer or patients with previous therapy with curative intention and a rising PSA
  - PSA doubling time must be $<24$ months
  - PSA must be $\leq 50$ ng/mL

- Male, aged 18 years or older with a life expectancy of $\geq 24$ months

- ECOG (Eastern Cooperative Oncology Group) score of $\leq 2$
PSA recovery during the OFF period

Time to PSA >4 ng/mL = 364 days

aPSA >4 ng/mL
PSA and testosterone recovery during the OFF period

228 days between testosterone and PSA recovery

\(^a\)PSA > 4 ng/mL and testosterone > 0.5 ng/mL
PSA and testosterone recovery during the OFF period

- PSA > 4 ng/mL
- T > 2.2 ng/mL

#At risk (PSA)
183
184

#At risk (T)
183
184

Off-treatment period (days)
0 56 112 168 224 280 336 392 448 504

Probability of achieving prespecified level (%)
Effect of baseline PSA on PSA recovery during the OFF period

Probability of achieving prespecified level (%)

- <2 ng/mL
- 2–10 ng/mL
- 10–20 ng/mL
- >20 ng/mL

Off-treatment period (days)

p < 0.0001

>20 ng/mL: 35 79 35 79 35 77 69 69 61 57 42 31 28 22 21 21 19
10–20 ng/mL: 46 46 43 39 31 17 13 10 8 6 3 2 1 19
2–10 ng/mL: 30 30 25 18 10 8 3 2 1
<2 ng/mL: 32 32 32 32 32 32 32 32 32 32 32 32 32 32 32 32 32

aPSA >4 ng/mL
CS29 summary

• Degarelix is suitable for IAD – it suppresses testosterone and PSA significantly faster than leuprolide\(^1\)

• PSA and testosterone recovery demonstrated

• Sexual function tends to improve in off-period

• Questions remain:
  ‣ Induction phase – how long?
  ‣ Survival benefit over LHRH agonists?