LHRH Analogue ZOLADEX™ (Goserelin) in the management of Prostate Cancer

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The Nobel Prize in Physiology or Medicine 1966

"for his discoveries concerning hormonal treatment of prostatic cancer"

Charles Brenton Huggins

1/2 of the prize

USA

University of Chicago, Ben May Laboratory for Cancer Research
Chicago, IL, USA

b. 1901
d. 1997
Forms of Androgen deprivation

Hormonal therapy

- Surgical castration
- Estrogen
- LHRH-Agonists
- LHRH-Antagonists

New substances

- Maximum Androgen blockade
- Androgen-Synthesis-Inhibitors
- Steroidal Antiandrogens
- Non-steroidal Antiandrogens

*Zoladex SafeSystem*
Hormonal Control of the Prostate

Testosterone

LHRH

Pituitary

Cortisol

Hypothalamus

LHRH

Prolactin

Adrenal

Adrenal androgens

Testes

Prostate

Oestrogen

LH

ACTH
Primary Androgen deprivation LHRH-Agonists

<table>
<thead>
<tr>
<th>agents</th>
<th>Triptorelin-, Leuprolrelin-, Buserelin-, Goserelin-, Histrelin-Acetate (1/2/3/6- or 12 month-depot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact</td>
<td>Decrease of Testosterones to castration levels by down regulation of receptor</td>
</tr>
<tr>
<td></td>
<td>Negative feedback-Mechanism between testes, Hypophysis und Hypothalamus</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Equivalent to Orchidectomy</td>
</tr>
<tr>
<td></td>
<td>Castration level after 3–4 weeks</td>
</tr>
</tbody>
</table>

Rating: Gold-Standard

*NICE Nationale Institute for Health and Care Excellence, UK - 2014*
GnRH Agonists and Antagonists

GnRH

Leuprolide
Goserecin
Triptorelin
Buserelin
Degarelix
Abarelix
Cetrorelix
Ganirelix

GnRH agonists

GnRH antagonists

Primary Androgen deprivation LHRH-Agonists

Advantage

- Good tolerance
- Long-term data available
- Psychological advantage vs. Orchidectomy
- Intermittent therapy possible
- Individual therapeutic intervals available
  (1,2,3,6 and 12 months depot)

Range of LHRH-Agonists: Gold-Standard
### Forms of Androgen deprivation

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Impact</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Rating</th>
</tr>
</thead>
</table>
| **LHRH-Agonists**        | - Receptor-down-regulation: Negative feedback-mechanism between testes, Hypophysis ⇒ Testosterone ↓  
- Castration level after 3–4 weeks | -well tolerated  
- Long term data available  
- Intermittent therapy possible | - Costs > orchidectomy  
- Flare-Up-Propylaxis | **Gold-Standard** |
| (Triptorelin-, Leuprorelin-, Buserelin-, Goserelin-, Histrelin-Acetate 1-/2-/3-/6- or 12-month long depot) |                                                                     |                                              |                                           |                               |
| **LHRH-Antagonists**     | - Blockade of LHRH-Receptors in Hypophysis directly ⇒ Testosterone ↓  
- Only Blockade of Androgen-Receptor  
⇒ LH-Secretion ↑  
⇒ Testosterone ↑ | - No „Flare-Up“  
- 70–80 % of Testosterone retaining  
⇒ Libido, activity, no fatigue... | - Costs  
- Skin Allergic reactions  
- Only monthly depot | - No long term data ⇒ clinical advantage debated |
| (Degarelix, Abarelix)    |                                                                     |                                              |                                           |                               |
| **Non-steroid. Antiandrogens** | - Blockade of Androgen-Receptor  
⇒ LH-Secretion ↑  
⇒ Testosterone ↓ | - Long term progression-free survival< LHRH  
- Liver dysfunction  
- loss of libido, erektile Dysfunktion | - Gynaecomastia, Nausea, Diarrhea, liver disfunction | - Primarily in combined therapy, limited recommendation for Monotherapy |
| (Flutamide, Bicalutamide) |                                                                     |                                              |                                           |                               |
| **Steroidale Antiandrogens** | - Blockade of Androgen-Receptor  
- Impact on Gestagene: blockade of Gonadotropine ⇒ Testosterone ↓ | - cheap  
- Compliance | - No reversal (No IAD)  
- Surgery  
- Psychic strain | - only for second line therapy (if LHRH or operation failed/contraindicated) |
| (Cyproterone acetate)    |                                                                     |                                              |                                           |                               |
| **Surgical castration**  | - Orchidectomy  
- Castration level after 3–2h ⇒ Testosterone ↓ | - cheap  
- Compliance | - No reversal (No IAD)  
- Surgery  
- Psychic strain | - uncommon |
| **Estrogene**            | - Negative feedback o LH-Secretionin hypophysis  
⇒ Testosterone from Leydig-cells ↓ ⇒ Testosterone ↓ | - Risk of thromobembolic/ cardiac vascular complications↑ | - Mostly obsolete | -                               |
| (Diethylstilbestrol (DES)) |                                                                     |                                              |                                           |                               |
Hormonal Therapy - Current treatment options

- Bilateral orchiectomy
- LHRH-A
- LHRH-A + antiandrogen (CAB)
- Bilateral orchiectomy + antiandrogen (MAB)
- Antiandrogen monotherapy
- Second line HT
Adapted from Debruyne et al 1996

ZOLADEX suppresses mean testosterone levels to below 20 ng/dL

Mean testosterone level (nmol/L)

Mean testosterone level (ng/dL)

Castrate level = 2.0 nmol/L (57.7ng/dL)

10.8 mg depot (n=77)

3.6 mg depot (n=83)

Treatment (weeks)
Hormonal Therapy

Issues

- Form
  - Mono-therapy
    - Orchiectomy
    - LHRH Agonist
    - Anti-androgen
  - CAB
- When and where
- Timing
- Duration
- Intermittent therapy
Primary Androgen deprivation
Maximum Androgen blockade

- MAB = Antiandrogen in combination with
  - LHRH-Agonist or LHRH-Antagonist or Orchidectomy

- Data
  - About 30 studies comparing Monotherapy vs. MAB

- Meta-analysis
  - Slight advantage in progression free and PCa-specific survival, if NSA + LHRH-Agonist vs. SA + LHRH-Agonist
  - But: significantly higher risk of side effects!

- EAU 2014
  - No general Recommendations of MAB
Where to use Hormonal Therapy

- Localized disease
- Locally advanced disease
- Adjuvant for Radical P (PSM)
- Salvage following failure of primary treatment; Biochemical or Clinical
- Advanced disease
- CRPC
HT and Localized Prostate Cancer

• Mono-therapy: Elderly

• Adjuvant to radical prostatectomy
  – Decreases PSM but
  – No effect on PSA recurrence

• Adjuvant to EBRT
HT adjuvant to EBRT

Stratification by risk groups

- **LOW RISK**; No need for adjuvant HT
- **Medium Risk**; 6-12 months of HT
- **High Risk**; 18-36 months of HT

HT is usually started around 2-3 months prior to EBRT to allow for shrinkage of tumor and prostate
RTOG 8610: study design

Locally advanced (T2c, T3 + T4) (n=456)

Randomised

Goserelin 3.6mg every 28 days + flutamide 250mg tid for 2 months

Radiotherapy alone (n=232)

Radiotherapy alone (n=224)

RTOG 8610: time to distant metastasis

Radiotherapy n=232
- 47%

Radiotherapy + ADT n=224
- 35%

**p=0.006**

Time from random assignment (years)

Failed (%)

- ADT = androgen deprivation therapy (goserelin 3.6mg every 28 days + flutamide 250mg tid for 2 months)
- Median follow-up 11.9 for RT + ADT and 13.2 years for RT

RTOG 8610: disease-specific mortality

Failed %

Time from random assignment (years)

- Radiotherapy n=232
  - 35.6%
- Radiotherapy + ADT n=224
  - 23.3%

\[ p=0.01 \]

ADT = androgen deprivation therapy (goserelin 3.6mg every 28 days + flutamide 250mg tid for 2 months)

Median follow-up 11.9 for RT + ADT and 13.2 years for RT
RTOG 8610: progression-free survival

36% vs 15% at 5 years; p<0.001

Pilepich MV et al. Int J Radiol Oncol Biol Phys
RTOG 8610: 10-year overall survival

- Radiotherapy n=232
  - MST 7.3
  - 33.8%
- Radiotherapy + ADT n=224
  - MST 8.7
  - 42.6%

\( p=0.12 \) (N.S)
ADT = androgen deprivation therapy  
MST = median survival time
Median follow-up 11.9 for RT + ADT and 13.2 years for RT
Duration of adjuvant hormone therapy?

- 2 years?
  - RTOG 92-02\(^1\) – significant survival benefit; median follow-up 5.8 years

- 3 years?
  - EORTC 22863\(^2\) (HR 0.51; 95% CI 0.36, 0.73; p=0.0002) – significant survival benefit; median follow-up 5.6 years

- Indefinite?
  - RTOG 85-31\(^3\)
    - significant survival benefit; median follow-up 6.7 years

\(^1\)Hanks et al 2003; \(^2\)Bolla et al 2002; \(^3\)Pilepich et al 2003
EORTC 22863 trial design

- Locally advanced (T1-4, Nx, M0) (n=415)

Randomised

- RT + 36 months’ ZOLADEX 3.6 mg (n=207)
  Cyproterone acetate x1mon
  3 years

- RT alone (n=208)

Hormonal therapy at progression

EORTC, European Organisation for Research and Treatment of Cancer

Adjuvant ZOLADEX significantly improves DFS
Adjuvant ZOLADEX significantly improves OS
Adjuvant ZOLADEX significantly reduces Prostate Cancer Mortality
RTOG 92-02 trial: study design

*1554 patients recruited and randomised, but only 1514 fulfilled trial or follow-up criteria

Hanks GE et al 2003
# RTOG 92-02 trial: patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LTAD (n=753) (% pts)</th>
<th>STAD (n=761) (% pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage: T2c/T3/T4</td>
<td>45/50/5</td>
<td>45/52/3</td>
</tr>
<tr>
<td>Node status: NX/N0/N+</td>
<td>86/11/3</td>
<td>87/9/4</td>
</tr>
<tr>
<td>PSA &gt;30 ng/mL</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Differentiation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Poor</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Gleason score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>8–10</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

Hanks GE et al 2003
RTOG 92-02 trial: Disease Specific Survival

Follow-up >11 years

Eric M. Horwitz et al 2008
RTOG 92-02 trial: Distant Metastasis Failure

Follow-up >11 years

Eric M. Horwitz et al 2008
RTOG 92-02 trial: Biochemical Failure

Follow-up >11 years

Eric M. Horwitz et al 2008
RTOG 92-02 trial: Overall Survival

Follow-up >11 years

Eric M. Horwitz et al 2008
RTOG 92-02 trial: Overall Survival, Gleason 8-10

Follow-up >11 years

Eric M. Horwitz et al 2008
RTOG 85-31 trial design

Locally advanced (T1–2, N+; T3) (n=945)

Stratification; High mets risk
Pos nodes, ext cap involve, hi gl

Randomisation

RT + indefinite ZOLADEX 3.6 mg (n=477)

RT alone + ZOLADEX 3.6 mg at relapse (n=468)

RTOG, Radiation Therapy Oncology Group
RT, radiotherapy

Pilepich et al 2005
Adjuvant ZOLADEX significantly improves biochemical DFS

RTOG 85-31: 10-year estimates

Patients (%)

RT + ZOLADEX (n=477) 31%

RT alone (n=468) 9%

p<0.0001 were high risk at baseline (T3 N0/1 or T1-2 N1);
DFS, disease-free survival

Pilepich et al 2005
Adjuvant ZOLADEX significantly reduces risk of local failure and distant metastases and prolongs DFS

RTOG 85-31: 10-year estimates

All patients were high risk at baseline (T3 N0/1 or T1-2 N2)

Pilepich et al 2005
Adjuvant H.T. to radical prostatectomy and positive nodes.
Observation until progression (n=51)

Randomised

RP + lymph node dissection (n=98)

Randomised

Adjuvant hormone ablation (70% ZOLADEX, 28% bilateral orchiectomy, 2% refused treatment) (n=47)

RP, radical prostatectomy

Messing et al 2006
Adjuvant hormone ablation significantly * improves OS in N+ patients

ECOG 7887 (EST 3886): 11.9 years’ median follow-up

Adjuvant hormone ablation increases survival by 2.6 years vs RP alone

HR 0.54*; p=0.04
70% of patients received ZOLADEX, 28% received orchiectomy and 2% refused treatment

Messing et al 2006
Adjuvant hormone ablation and radiation significantly * improves OS in N+ patients

- Abdollah et al J Clin Oncol , 2014
  
  – ADT and radiation therapy offers better CSS and OS for select groups with number of positive nodes 1-2 or 3-4.
Metastatic disease
Goserelin 3.6 mg vs orchidectomy: time to treatment failure

\[ p = 0.99 \]

ZOLADEX 3.6 mg and orchiectomy result in similar OS in metastatic disease


ZOLADEX is effective in the palliation of metastatic disease

- ZOLADEX is as effective as orchietomy in terms of relief of disease symptoms

- Of patients who were symptomatic, similar proportions of patients experienced a favourable subjective response
  - 66% for ZOLADEX
  - 73% for orchietomy

Kaisary et al 1991
Immediately vs. delayed Androgen deprivation?

- Symptomatic metastatic Pca
  - Immediate LHRH-Monotherapy

- Asymptomatic metastatic Pca
  - Immediate LHRH-Monotherapy
    - Improvement of progression free survival*
    - Effect on tumor specific or overall survival incertain

* Wilt et al., Cochrane Database Syst Rev 2002; (1): CD00350
**Immediately vs. delayed Androgen deprivation?**

- Prospective randomised study
  - n = 985
  - Follow-up = 7.8 Jahre

- T0–T4 M0 (all newly diagnosed pts.)
  - Early hormonal therapy (n = 493)
  - Or symptomatic tumor progression / severe complications (n = 492)

- Who benefits from early hormonal therapy?
  - If Initial PSA > 50 ng/ml
  - PSA-DT < 12 Monate

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Early entry</th>
<th>Delayed entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 %</td>
<td>42 %</td>
<td>81 %</td>
</tr>
<tr>
<td>HR = 1.25</td>
<td></td>
<td>p = 0.4361</td>
</tr>
</tbody>
</table>

Tumor-specific survival

<table>
<thead>
<tr>
<th></th>
<th>Early entry</th>
<th>Delayed entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>81 %</td>
<td>80 %</td>
<td></td>
</tr>
</tbody>
</table>

**Advantage of early hormonal therapy only in overall survival, not for tumor-specific survival**

PSA-DT = PSA doubling time

Bicalutamide (Casodex) 150mg in prostate cancer

- A randomised, double-blind, parallel-group trial comparing bicalutamide 150mg once daily with placebo in addition to standard care in patients with hormone-naïve, non-metastatic PCa.

- Throughout the 14.6-year follow-up period the addition of early bicalutamide to standard of care resulted in a significant OS benefit in patients with locally advanced PCa. In contrast, patients with localised PCa and low PSA derived no survival benefit from early bicalutamide. The optimal timing for initiating bicalutamide in non-metastatic PCa patients is dependent on disease stage and baseline PSA.

Thomsen, FB etal, scand prostate cancer group, Eur J Cancer, July 2015
Intermittent Androgen Deprivation (IAD)
Definition:
Shift between therapy and therapy free periods

- **Aim/possible advantages:**
  - Less side effects, improvement in quality of life
  - Delay in time until castration resistance occurs
  - Economic

- **Proved advantages e.g.:**
  - Bone density¹
  - Quality of life¹

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¹ Tunn U. BJU International 2007; 99, Supplement 1: 19–22
Many **Phase-II-Studies** regarding feasibility of IAD (> 1.600 pats)

⇒ easy to operate, no negative impact on time to progression, improved quality of life during therapy free intervals

Some prospective, randomised **Phase-III-Studies** comparing IAD versus CAD are published, but showing varying results regarding efficiency and quality of life
## Intermittent Androgen Deprivation (IAD)

<table>
<thead>
<tr>
<th>Author</th>
<th>Median follow up (month)</th>
<th>Stage</th>
<th>No. of patients</th>
<th>Therapy</th>
<th>PSA-criteria for IAD (PSA ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calais da Silva et al.</td>
<td>51</td>
<td>Locally advanced or metastatic</td>
<td>314</td>
<td>IAD</td>
<td>LHRH + Cyproterone &lt; 4 or &lt; 80% baseline</td>
</tr>
<tr>
<td>Crook et al.</td>
<td>83</td>
<td>Rising PSA after Radiotherapy</td>
<td>690</td>
<td>CAD</td>
<td>LHRHa + 4 weeks Antiandrogen &lt; 4</td>
</tr>
<tr>
<td>De Leval et al.</td>
<td>29</td>
<td>Locally advanced or metastatic</td>
<td>35</td>
<td>InducGon</td>
<td>Goserealin + Flutamide &lt; 4</td>
</tr>
<tr>
<td>Hering et al.</td>
<td>48</td>
<td>Metastatic</td>
<td>25</td>
<td>Therapy</td>
<td>Cyproterone</td>
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<tr>
<td>Hussain et al.</td>
<td>118</td>
<td>Metastatic</td>
<td>770</td>
<td>Induction</td>
<td>LHRH + Antiandrogen &lt; 4</td>
</tr>
<tr>
<td>Irani et al.</td>
<td>43</td>
<td>All stages</td>
<td>67</td>
<td>Therapy</td>
<td>Goserealin + Flutamide</td>
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<tr>
<td>Langenhuijsen et al.</td>
<td>31</td>
<td>Nodal or metastatic</td>
<td>97</td>
<td>Therapy</td>
<td>Buserelin + Nilutamid &lt; 4</td>
</tr>
<tr>
<td>Miller et al.</td>
<td>NA</td>
<td>Nodal or metastatic</td>
<td>NA – 335 Patienten randomised</td>
<td>Therapy</td>
<td>Goserealin + Bicalutamid &lt; 4 oder &lt; 90% des Baselinewertes</td>
</tr>
<tr>
<td>Mottet et al.</td>
<td>44</td>
<td>Metastatic</td>
<td>86</td>
<td>Therapy</td>
<td>Leuprorelin + Flutamid &lt; 4</td>
</tr>
<tr>
<td>Salonen et al.</td>
<td>65</td>
<td>Metastaticoder or PSA &gt; 60 or T3/4 and PSA &gt; 20 or newly rising PSA</td>
<td>274</td>
<td>Therapy</td>
<td>Goserealin +12,5 d Cyproterone &lt; 10 oder 50% des Baselinewertes</td>
</tr>
<tr>
<td>Tunn et al.</td>
<td>NA</td>
<td></td>
<td>109</td>
<td>Therapy</td>
<td>Leuprorelin &lt; 0,5</td>
</tr>
<tr>
<td>Verhagen et al.</td>
<td>NA</td>
<td>NA – 366 Patienten randomised</td>
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<td>Therapy</td>
<td>Cyproterone</td>
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<tr>
<td>Yamanaka et al.</td>
<td>22 (average)</td>
<td></td>
<td>82</td>
<td>Therapy</td>
<td>LHRH</td>
</tr>
</tbody>
</table>

**IAD** = Intermittent Androgen deprivation

**CAD** = Continuous Androgen deprivation

**PSA** = Prostate Specific Antigen

**LHRH** = Luteinizing Hormone-Releasing Hormone

**Cyproterone**

**Goserelin**

**Flutamide**

**Bicalutamid**

**Leuprorelin**

**Buserelin**

**Nilutamid**

**Cyproterone**

**LHRH**

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*Brungs D et al. Prostate Cancer 2014; 17: 105-111*
**Intermittent Androgen Deprivation (IAD)**

Data (IV):

- **IAD in metastatic Prostate cancer:**
  - Hussain et al.\(^1\): IAD median overall survival vs. CAD: 5.1 vs. 5.8 years;
  - Non-Inferiority of IAD statistically not proven
  - Mottet et al.\(^2\): no significant difference in median overall survival between IAD / CAD

- **IAD in PSA-Relapse after Radiotherapy:**
  - Crook et al.\(^3\): IAD is concerning overall survival statistically significant not inferior to CAD: 8.8 vs. 9.1 Jahre (HR\(_{IAD/CAD}\) = 1.03; 95 %-CI: 0.86–1.23; \(p_{\text{noninfer.}} = 0.01\))

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M. Hussain: „In hormonal sensitive, metastatic Pca Non-Inferiority Of IAD vs. CAD is unproven.“\(^1\)

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IAD = Intermittent Androgen deprivation
CAD = continuous Androgen deprivation
ADT = Androgen deprivation therapy

1. Hussain M et al., J Clin Oncol 2012; 30 (Suppl; abstr: 1
Guideline – EAU 2014

• “IAD should be widely offered to patients with PCa in various clinical settings after a standardized induction period....”

But still some issues are uncleared...

- No common criteria for timeline in On-/ Off-treatment-periods
- No real option in metastatic Pca
- No data concerning Monotherapy vs. MAB
- No data for IAD mit LHRH-Antagonists
Side Effects of ADT

- Loss of libido
- Erectile Dysfunction
- Weight Gain
- Gynecomastia
- Depression
- Hot flushes
- Metabolic Syndrome
- Bone fractures
- Osteoporosis
- Fatigue
- Cardiovascular
Management of Side Effects from ADT

- **Gynecomastia (66-73%)**
  - Pre-therapeutic prophylaxis: Mamma radiation (1 x 10 or 3 x 5 Gy)
  - Therapy: 10 mg Tamoxifen/d

- **Hot flushes**
  - Estrogens
  - Gestagens
  - Antidepressants
  - Acupuncture

McLeod et al., BJU Int 2006; 97: 247-254
Hovsen et al., BJU Int 2001; 87: 47-56
Wirth et al., J Urol 2002; 168: 429-435
Management of Side Effects from ADT

- **Osteoporosis / Fractures**
  - Due to BMD relatively higher incidence of fractures
  - Increasing risk with time of therapy
  - Additional risk factors: Smoking, low Calcium, lack of Vitamin D, physical inactivity
  - Actions:
    - Changing life style
    - Sports
    - Reducing risk factors
    - Nutrition
    - Vitamin D
    - Calcium
    - Bisphosphonates
Management of Side Effects from ADT

• **Changes in lipid metabolisms**
  - Total cholesterol: ↑ (negative effect)
  - Triglycerides: ↑ (negative effect)
  - LDL-Cholesterol: ↑ (negative effect)
  - HDL-Cholesterol: ↑ (positive effect)

• **Obesity/Sarcopenia**
  - Testosterone: negative correlation to adipose tissue
  - Low testosterone levels increases body fat (9–11 %) and reduces muscle mass (2,9–3,6 %).
Insulin resistance (= causing Diabetes Mellitus Type 2)

- ADT increases fasting-Insulin-concentration (= marker for Insulin resistance)
- Risk for Diabetes mellitus Type 2 under ADT: +1.44
- Actions:
  - Weight loss
  - Increasing physical activity
  - HbA$_{1c}$-control
  - Insulin-glucose tolerance test once a year
# Cardiovascular Risk and ADT

## SEER-Medicare-Data due to time of therapy

<table>
<thead>
<tr>
<th>Time of LHRH</th>
<th>Diabetes mellitus adjusted HR, 95 % CI</th>
<th>Heart attack adjusted HR, 95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 month</td>
<td>p &lt; 0.001</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>5–12 month</td>
<td>p &lt; 0.001</td>
<td>p = 0.21</td>
</tr>
<tr>
<td>13–24 month</td>
<td>p &lt; 0.001</td>
<td>p = 0.42</td>
</tr>
<tr>
<td>≥ 25 month</td>
<td>p &lt; 0.001</td>
<td>p = 0.24</td>
</tr>
</tbody>
</table>

### Time of ADT does not influence cardiovascular risk!

Increasing risk for Diabetes mellitus, no significant increase of myocardial infarction due to ADT!

---

*Keating NL et al., J Clin Oncol 2006; 24: 4448–4456*
Cardiovascular morbidity and mortality

- **ADT increases risk of cardiovascular morbidity** and CHD.¹,² (EAU-guidelines)
- No changes of risk due to time of therapy.²
- Pts. with cardiovascular diseases or elderly pts have higher risk.³
- Risk of cardiovascular mortality is not affected.⁵,⁶
- No cardio-check before starting ADT necessary: Risk-Benefit-Ratio by Urologist.⁴
- Care: unspecific
  - Weight loss
  - Sports
  - Nutrition
  - Reducing risk factors

¹ Saigal CS et al., Cancer 2007; 110:1493–1500
² Keating NL et al., J Clin Oncol 2006; 24:4448–4456
³ D'Amico AV et al., J Clin Oncol 2007; 25:939–945
⁴ Levine GN et al., J Clin Oncol 2010; 28:2359–2366
⁵ Breau R et al., AUA 2011; #463
⁶ Nguyen PL et al., JAMA 2011; 306: 2359–2366

ADT = Androgendependent-Therapie
ADT and CRPC

• There is an ongoing discussion on the value and need of ADT in mCRPC. Should ADT be continued when Abiraterone, Enzalutamide or Chemotherapy is started?

  – Side effects
  – Cost
  – The value of combing ADT or not with other therapies has not been investigated

Morote J etal, J Urol 178, 2007
ADT and CRPC

Guidelines in

• AUA
• NCCN; National Comprehensive Cancer Network
• EAU

All recommend the continuation of ADT in mCRPC and even nmCRPC

Heidenreich A etal, Eur Urol 65, 2014
Cookson MS etal, AUA Guidelines 2014
NCCN, Prostate Cancer 2014
ADT and CRPC

- CRPC is still hormonal sensitive and addicted to signals from Androgen receptor (AR). Therefore maintenance of ADT combined with Abiraterone, Enzalutamide and chemotherapy is an essential part in therapy of CRPC.

- Nearly all studies of therapeutic substances after ADT were performed under maintenance of ADT. There are no prospective data to stop ADT.

- All admission studies concerning Abiraterone and Enzalutamide were performed under maintenance of ADT due to LHRH or orchidectomy.

Merseburger AS et al, World j Urol sept 2014
Mostaghel EA et al, Cancer Res 67, 2007
EAU Guide lines 2014
ADT and Abiraterone

- Experimental evidence suggests that T suppression achieved by Abiraterone is not sustained in non-castrate men and is overcome by 2-3 fold increase in LH levels hence maintaining ADT is needed.

- **SPARE** trial (German) is evaluating the impact of Abiraterone monotherapy vs ADT and Abiraterone (results in 2016)
ADT and Enzalutamide

• Enza has 8X more affinity to AR than Bicalutamide
• AR signaling persist during castration
• At the present time there is no trial evaluating Enza monotherapy vs ADT and Enza
• Study evaluated Enza in hormone-naïve men in 67 men
  – Less gynecomastia than Bicalutamibe
  – PSA response as ADT
  – T level increased
ADT and Chemotherapy

• The rationale is that ADT is needed to continue suppression of the hormone sensitive clones / elements of the tumor.
  – Need for well-designed prospective trial
    • 2 clinical trials are investigating the issue

– No data that combining ADT and Chemotherapy causes harm or benefit
ADT and CRPC

Conclusions

• Even resistant tumors to first-line ADT therapy are still dependent on androgens to expand and progress.
• Until further strong data is available, ADT should be continued with all forms of secondary or tertiary hormonal as well as chemotherapy in CRPC.
Prescribing Information

ZOLADEX® 3.6 mg Implant and ZOLADEX® LA 10.8 mg Implant (goserelin)

Consult Summary of Product Characteristics before prescribing

Use  Zoladex 3.6mg and 10.8mg: Treatment of prostate cancer in the following settings: Treatment of metastatic prostate cancer, treatment of locally advanced prostate cancer, as an alternative to surgical castration; adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer, neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer; adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

Zoladex 3.6mg: Advanced breast cancer in pre- and peri-menopausal women suitable for hormonal manipulation. An alternative to chemotherapy in the standard of care for pre-menopausal women with oestrogen receptor (ER) positive early breast cancer. Management of endometriosis. Prethinking of uterine endometrium prior to endometrial ablation or resection. In conjunction with iron therapy in the haematological improvement of anaemic patients with uterine fibroids prior to surgery. Pelvicir downregulation in preparation for superovulation in assisted reproduction.

Presentation  An implant, in a prefilled syringe containing goserelin acetate (equivalent to 3.6mg or 10.8mg goserelin).

Dosage and administration  One depot injected subcutaneously into the anterior abdominal wall every 28 days (Zoladex 3.6mg) or every 12 weeks (Zoladex 10.8mg).

Zoladex 3.6mg: Endometriosis: for a period of up to six months only. Endometrial thinning: four or eight weeks treatment. Uterine fibroids: for up to three months (with supplementary iron) before surgery. Assisted reproduction: one depot is administered to downregulate the pituitary gland (see SmPC).

Contraindications  Zoladex should not be given to patients with a known hypersensitivity to the active substance, to other LHRH analogues, or to any of the excipients of this product. Zoladex should not be used in pregnancy.

Precautions  Zoladex is not indicated for use in children. Zoladex 10.8mg is not indicated for use in females.

Males: Caution in patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. May cause a reduction in bone mineral density and a reduction in glucose tolerance, which may manifest as diabetes or loss of glycaemic control in pre-existing diabetes mellitus. Consider monitoring blood glucose. Females: Zoladex should not be used in pregnancy, which should be excluded prior to treatment. Zoladex is not recommended during breast feeding. May cause a reduction in bone mineral density. In patients receiving Zoladex for endometriosis, the addition of hormone replacement therapy has been shown to reduce bone mineral density loss and vasomotor symptoms. Caution in women with known metabolic bone disease. May cause increase in uterine cervical resistance. No clinical data on treating benign gynaecological conditions in excess of six months. Zoladex should only be administered as part of a regimen for assisted reproduction under the supervision of a specialist and should be used with caution in patients with polycystic ovarian syndrome.

There have been reports of ovarian hyperstimulation syndrome (OHSS) associated with Zoladex in combination with gonadotrophin. Monitor stimulation cycle to identify patients at risk of OHSS because its severity and incidence may be dependent on the dose regimen of gonadotrophin. General: An increase in benign pituitary tumours has been observed in male rats following long-term repeated dosing. This finding is similar to that previously noted in this species following surgical castration (relevance to man not established). In mice, long-term repeated dosing with multiples of the human dose produced pancreatic islet cell hyperplasia and a benign proliferative condition of the pyloric region, also reported as a spontaneous lesion in the species (clinical relevance unknown).

Undesirable events  Males: Hot flushes, sweating, decrease in libido and infrequent breast swelling and tenderness. Initially, temporary increase in bone pain. Isolated cases of spinal cord compression. A reduction in glucose tolerance has been observed which may manifest as diabetes or loss of glycaemic control in pre-existing diabetes mellitus. Females: Hot flushes, sweating, loss of libido, headaches, mood changes including depression, vaginal dryness and change in breast size. Vaginal bleeding during early treatment. Rarely women may enter menopause during treatment and not resume menses after therapy. In women with fibroids, degeneration of fibroids may occur. In women with breast cancer, initially, temporary increase in signs and symptoms and rarely hypercalcemia on initiation of treatment. In assisted reproduction, there have been reports of OHSS associated with Zoladex in combination with gonadotrophin. Monitor stimulation cycle to identify patients at risk of OHSS. Follicular and luteal ovarian cysts have been reported following LHRH therapy. General: Arthralgia, non-specific paraesthesia, skin rashes (generally mild). Occasional local reactions including mild bruising at injection site have been reported following administration of Zoladex 3.6mg. May cause a reduction in bone mineral density. Occasionally hypotension or hypertension rarely requiring intervention or withdrawal of treatment. Rare hypersensitivity including manifestations of anaphylaxis. Very rare cases of pituitary apoplexy have been reported following initial administration of Zoladex 3.6mg. Isolated cases of uterine obstruction have been recorded following administration of Zoladex 3.6mg.

Legal category  POM.


Basic NHS cost  Zoladex 3.6mg Implant: £84.14 per depot; Zoladex LA 10.8mg Implant: £267.48 per depot.

Further information  is available from the Marketing Authorisation holder, AstraZeneca UK Limited, 600 Capability Green, Luton, LU1 3LU. UK ZOLADEX is a trade mark of the AstraZeneca group of companies, AZ 02/2008

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to AstraZeneca on 0800 783 0033.