METASTATIC PROSTATE CANCER

Uro-oncology
Advanced Urology Course 2015
Case Scenario and Discussion

A 70 year old gentleman with good performance status presents with bone pain and diagnosed with Gleason 4+5 CaP, T3 with PSA 200ng/mL.

What is the current thinking of first line treatment of metastatic prostate cancer?
Introduction

• Despite the steady decline in the incidence of newly diagnosed metastatic prostate cancer and microscopic lymph node metastasis, from 20% in the 1970s to 3.4% in the 1990s, the risk of extraprostatic disease in patients with clinically localized disease remains high, at 30-60%.

• Relative to stage of diagnosis, local and regional stages have a 100% 5-year survival rate.

• However, distant-stage prostate cancer has a 28% 5-year survival rate.\(^1\)
Staging

• Distant metastasis:
  • **M1a** Non-regional LN(s)
  • **M1b** Bone(s)
  • **M1c** Other site(s) with or without bone disease

• Metastatic:
  • Any T, N1
  • Any T, Any N, M1
Indication for bone scan

• Life expectancy >5 y or symptomatic:

  • Bone scan if any of these:
    • T1 and PSA >20
    • T2 and PSA >10
    • Gleason score ≥8
    • T3, T4
    • Symptomatic

Gleason 4+5, T3, PSA 200
Natural history

• Historically, systemic therapy for metastatic and advanced prostate cancer has involved androgen suppression.

• In metastatic disease, this palliative therapy has yielded a median progression-free survival of 18-20 months and an overall survival of 24-36 months.

• However, virtually all patients develop hormone-refractory disease. With inevitable progression, development of metastases mainly in bone, and death within 2–3 years in most men.
Figure 1. Natural History

- **Hormone-Sensitive**
  - Androgen Deprivation
  - Surgery and Radiation

- **Castrate-Resistant**
  - Therapies After LHRH Agonists + Antiandrogens or GnRH antagonist
  - Chemotherapy
  - Postchemotherapy
  - Radiographically Metastatic
  - Symptomatic
Table 1. Prognostic factors for the heterogeneous M1 population for patients with advanced prostate cancer

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial bone metastasis and/or nodes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicular bone or visceral metastasis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance status &lt; 1</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Performance status ≥ 1</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gleason score &lt; 8</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Gleason score ≥ 8</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PSA &lt; 65</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PSA ≥ 65</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>54</td>
<td>30</td>
<td>21</td>
</tr>
</tbody>
</table>

**Gleason 4+5, T3, PSA 200**
mPCa: Treatment

- Systemic treatment of men with metastatic prostate cancer is rapidly evolving - better palliation but also in a survival benefit.

- Androgen deprivation therapy remains first-line treatment for advanced disease and the backbone of sequential strategies.

- For patients with extensive metastatic disease the addition of docetaxel markedly improves survival.

- In case patients develop castration-resistant prostate cancer, several new therapeutic strategies are available.
Hormonal therapy
- Orchidectomy
- LHRH agonist
- LHRH antagonist
- Anti-androgens
- Ketoconazole
- Estrogens
- Prednisolone
- Arbiraterone
- Enzalutamide

Immunotherapy
- Sipuleucel-T

Chemotherapy
- Docetaxel
- Cabazitaxel
- Mitoxantrone

Bone-Targeted Treatments
- Bisphosphonates
- Denozumab
- Radionuclide
  - Radium-223 (Alpharadin)
ADVANCED DISEASE (mPCa): SYSTEMIC THERAPY

- **M0 or low-volume M1^r**
  - Orchiectomy
  - LHRH agonist ± antiandrogen ≥7 days to prevent testosterone flare
  - LHRH agonist + antiandrogen
  - LHRH antagonist
  - Observation^k (for M0 disease only)
  - Continuous ADT and docetaxel 75 mg/m^2 without prednisone for 6 cycles (for castration-sensitive high-volume M1^r only)

- **High-volume M1^r**
  - Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent.
  - High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column.
## EAU Guidelines on PCa

<table>
<thead>
<tr>
<th>M+</th>
<th>Watchful waiting</th>
<th>No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>Not a standard option.</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Not an option for curative intent, therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Hormonal</td>
<td>Standard option. Mandatory in symptomatic patients.</td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>
First line hormonal therapy for mPCa

- ADT is the gold standard for men with metastatic prostate cancer.

- PSA value of 4 ng/ml or less after 7 month of ADT in newly diagnosed mPCa is associated with improved patients survival.

  - Optimal ADT
  - Early Versus Delayed Treatment
  - Complete androgen blockade
  - Prevention of flare up
  - Hormonal manipulation
Hormonal Therapy: SBO

• In 1941, Charles Huggins and Clarence Hodges demonstrated that castration halted the progression of prostate cancer implying that testosterone was the driver of prostate cancer cell proliferation and survival.

• Since then, androgen deprivation therapy (ADT) (castration) has become the cornerstone of the systemic treatment of advanced prostate cancer.
Orchidectomy

**ADVANTAGES**

- Simple and safe
- Insures patient compliance
- Suppresses plasma testosterone to 50 ng/dl within 12 hours

**LIMITATIONS**

- Hot flushes > 50% of patients
- Psychological impact of surgical castration
Hormonal Therapy

LHRH Agonist

- Continuously high levels of LHRH lead to ‘exhaustion’ of the pituitary gland: LH is no longer released and testosterone declines to castration levels.

- Leuprolide (Lucrin)
- Goserelin (Zoladex)
- Triptorelin

LHRH Antagonist

- Leads to a rapid decline in luteinizing-hormone and follicle-stimulating hormone and as a result in an immediate decrease of testosterone levels.

- Degarelix
Anti-androgens

Non-steroidal anti-androgen
- Flutamide
- Bicalutamide (Casodex)
- Nilutamide

Steroidal anti-androgen
- Cyproterone (Androcur)
Optimal ADT

- LHRH agonist or antagonist and bilateral orchietomy are equally effective.

- There is no level 1 evidence to choose between an LHRH analogue or antagonist, except in patients with an impending spinal cord compression.

  - In these patients, the choice for first-line treatment is between bilateral orchidectomy and an LHRH antagonist.
Early vs. Delayed Treatment

• Hormone therapy should be offered to all patients with symptomatic metastatic disease to improve symptom control and reduce risk of severe complications (bone fracture, cord compression, urine retention etc.).

• Early initiation of hormone therapy in asymptomatic metastatic patients can prevent the development of symptoms and severe complications.


Combined Androgen Blockade

- Combined androgen blockade (CAB) recognizes the 10% contribution of adrenal androgens to the total body testosterone.

- There are conflicting results from the many studies comparing CAB with monotherapy.

- Labrie and colleagues described the concept of CAB, in which luteinizing hormone-releasing hormone (LHRH) accomplished medical castration and antiandrogens achieved peripheral blockade. Initially, the investigators reported improved response and survival rates.
CAB

- The largest RCT in 1,286 M1b patients found no difference between surgical castration + flutamide compared to surgical castration without flutamide.

- Systematic reviews have shown that CAB using non-steroidal anti-androgen appears to provide a small survival advantage (< 5%) versus monotherapy (surgical castration or LHRH agonists) beyond 5 years.

- The current American Society of Clinical Oncology (ASCO) guidelines recommend castration alone with either an orchiectomy or GnRH agonist.
Non-steroidal anti-androgen monotherapy

- **Flutamide** - In the only published (underpowered) RCT, there was no significant difference in OS for flutamide monotherapy compared to castration in M1b patients with a PSA < 100 ng/mL. *At a higher PSA level, flutamide was inferior to castration.*

- **Bicalutamide** - has been compared to castration in two large prospective RCTs with similar designs, including a total of 1435 patients with locally advanced or M1 PCa - *OS was significantly better with castration*, although the difference in median survival was only 6 weeks.

- High-dose bicalutamide may be *an alternative to castration for highly selected, well-informed patients with M1 PCa with a low PSA level.*
Hormonal manipulation

• After an average of 18 to 24 months of primary hormonal treatment the cancer is not longer suppressed by ADT.

• Second-line ADT with anti-androgens produces a PSA response in 14-50% of patients with a median duration of 4-11 months.

• Once progression occurs, a decrease of PSA can be initiated by simply stopping anti-androgenic treatment. This is called the *anti-androgen withdrawal response* and is observed in approximately 10-15% of patients.
Secondary hormonal therapy for advanced PCa

Decrease in Circulating Androgens
  Nonselective Adrenal Inhibition
    Ketoconazole
    Aminoglutethimide
    Liarozole
    Megestrol acetate
    Medroxyprogesterone acetate
Selective Adrenal Inhibition
  Abiraterone acetate

GnRH Antagonist
  Abarelix
Luteinizing hormone suppression
  DES
  Megestrol acetate
  Medroxyprogesterone acetate
Orchectomy
Direct Cytotoxic Effects
  Ketoconazole
  Estrogens
  DES
  Progestins
    CPA
    Megestrol acetate
    Medroxyprogesterone acetate
Androgen Receptor Blockade
  Flutamide
  Bicalutamide
  Nilutamide
  CPA
Other Mechanisms
  Calcitriol
  Liarozole
  PC-SPES (no longer available)
<table>
<thead>
<tr>
<th>References</th>
<th>Treatment (dose)</th>
<th>No. Pts</th>
<th>% Greater Than 50% PSA Response</th>
<th>Median Response Duration (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second line antiandrogens:</strong></td>
<td></td>
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<tr>
<td>Kucuk et al(^{18})</td>
<td>High dose bicalutamide (150 mg/day)</td>
<td>52</td>
<td>20</td>
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<tr>
<td>Joyce et al(^{16})</td>
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<td>31</td>
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<tr>
<td>Scher et al(^{16})</td>
<td>High dose bicalutamide (200 mg/day)</td>
<td>51</td>
<td>14</td>
<td>4.0</td>
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<tr>
<td>Kassouf et al(^{19})</td>
<td>Nilutamide (200 or 300 mg/day)</td>
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<tr>
<td>Desai et al(^{19})</td>
<td>Nilutamide (150 or 300 mg/day)</td>
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<td>50</td>
<td>11.0</td>
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<td>Debruyne et al(^{36})</td>
<td>Cyproterone acetate (100 mg 2 times/day)</td>
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<td>4</td>
<td>3.6</td>
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<td><strong>Adrenal androgen inhibitors:</strong></td>
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<tr>
<td>Small et al(^{22})</td>
<td>Ketoconazole (400 mg 3 times/day) + hydrocortisone + AAWD</td>
<td>128</td>
<td>27</td>
<td>8.6</td>
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<td>Harris et al(^{40})</td>
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<td>46</td>
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<td>Millikan et al(^{41})</td>
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<td>55</td>
<td>8.5</td>
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<tr>
<td>Small et al(^{23})</td>
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<td>63</td>
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<tr>
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<td>Aminoglutethimide (450 mg 2 times/day) + hydrocortisone + AAWD</td>
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<td>48*</td>
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<td>Tannock et al(^{44})</td>
<td>Prednisone (7.5–10 mg/day)</td>
<td>81</td>
<td>22</td>
<td>4.0</td>
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<tr>
<td>Small et al(^{27})</td>
<td>Hydrocortisone (40 mg/day)</td>
<td>230</td>
<td>16</td>
<td>2.3</td>
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<td>Kantoff et al(^{45})</td>
<td>Hydrocortisone (30 mg 1/daily/10 mg/nightly)</td>
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<td>2.3</td>
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<tr>
<td>Morioka et al(^{16})</td>
<td>Dexamethasone (1.5 mg/day)</td>
<td>27</td>
<td>59</td>
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<td>Saika et al(^{47})</td>
<td>Dexamethasone (1.5 mg/day)</td>
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<td>Storlie et al(^{28})</td>
<td>Dexamethasone (0.75 mg bid)</td>
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<td>Debruyne et al(^{36})</td>
<td>Liarozole (300 mg 2 times/day)</td>
<td>160</td>
<td>20</td>
<td>4.6</td>
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<td><strong>Estrogenic compounds:</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Oh et al(^{19})</td>
<td>DES (3 mg)</td>
<td>42</td>
<td>24</td>
<td>3.8</td>
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<tr>
<td>Smith et al(^{17})</td>
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<td>21</td>
<td>43</td>
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<tr>
<td>Oh et al(^{19})</td>
<td>PC-SPES (3 caps)</td>
<td>43</td>
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<td>Oh et al(^{18})</td>
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<td>23</td>
<td>52</td>
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<td>Small et al(^{19})</td>
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<td>54</td>
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<td>Pfeifer et al(^{50})</td>
<td>PC-SPES (9 caps)</td>
<td>16</td>
<td>81</td>
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</table>

* Greater than 80% decrease in serum PSA.
Intermittent vs. Continuous ADT

- Castration resistance occurs in most patients with metastatic hormone-sensitive prostate cancer who are receiving androgen-deprivation therapy.

- After an average period of 24 months, the tumor relapses, characterized by a castrate-independent state of growth.

- Replacing androgens before progression of the disease is hypothesized to prolong androgen dependence.
Table 2. Patient population and treatment cycles in seven phase III trials on IAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SEUG9401 (20)</th>
<th>FINN VII (21)</th>
<th>SWOG9346 (22)</th>
<th>NCT3657 (23)</th>
<th>TULP (24)</th>
<th>TAP22 (25)</th>
<th>De Leval (26)</th>
<th>PSA (ng/mL) at inclusion</th>
<th>Therapy</th>
<th>Induction period (mo)</th>
<th>PSA (ng/mL) level to stop on-phase</th>
<th>PSA (ng/mL) level to restart on-phase</th>
<th>Time off therapy</th>
<th>Follow-up (mo) median</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>766</td>
<td>554</td>
<td>1535</td>
<td>1386</td>
<td>193</td>
<td>173</td>
<td>68</td>
<td>4-100</td>
<td>CAD</td>
<td>3</td>
<td>&lt; 4</td>
<td>&gt; 10 for symptomatic and &gt; 20 for asymptomatic</td>
<td>50% at least 52 weeks; 29% for 36 mo</td>
<td>50</td>
</tr>
<tr>
<td>Tumour stage</td>
<td>Locally advanced/metastatic</td>
<td>Locally advanced/metastatic</td>
<td>Metastatic</td>
<td>After RT</td>
<td>Metastatic</td>
<td>Metastatic</td>
<td>Locally advanced/metastatic/biochemical recurrence</td>
<td>Any value</td>
<td>6</td>
<td>7</td>
<td>&lt; 10</td>
<td>&lt; 4</td>
<td>10.9-33.5 weeks</td>
<td>108</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>Any value</td>
<td>&gt; 5</td>
<td>&gt; 3</td>
<td>Any value</td>
<td>&gt; 20</td>
<td>Any value</td>
<td>Any value</td>
<td>&lt; 100</td>
<td>CAD</td>
<td>8</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>40% of time</td>
<td>84</td>
</tr>
<tr>
<td>Therapy</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>CAD</td>
<td>6</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>20-59.6 mo</td>
<td>31</td>
</tr>
<tr>
<td>Induction period (mo)</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>50-65</td>
<td>CAD</td>
<td>6</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>0.7-4.9 mo</td>
<td>44</td>
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<tr>
<td>PSA (ng/mL) level to stop on-phase</td>
<td>&lt; 4</td>
<td>&lt; 10</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>48-5</td>
<td>CAD</td>
<td>6</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>1.0-48.9 mo</td>
<td>31</td>
</tr>
<tr>
<td>PSA (ng/mL) level to restart on-phase</td>
<td>&gt; 10</td>
<td>&gt; 20</td>
<td>&gt; 10</td>
<td>&gt; 10 no metastatic</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>3.3-8.3 mo</td>
<td>CAD</td>
<td>6</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>70%</td>
<td>31</td>
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<tr>
<td>Time off therapy</td>
<td>50% at least 52 weeks; 29% for 36 mo</td>
<td>10.9-33.5 weeks</td>
<td>&gt; 40% of time</td>
<td>20-59.6 mo</td>
<td>0.7-4.9 mo</td>
<td>1.0-48.9 mo</td>
<td>3.3-8.3 mo</td>
<td>50-65</td>
<td>CAD</td>
<td>6</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>40% of time</td>
<td>84</td>
</tr>
<tr>
<td>Follow-up (mo) median</td>
<td>50</td>
<td>65</td>
<td>108</td>
<td>84</td>
<td>31</td>
<td>44</td>
<td>31</td>
<td>50-65</td>
<td>CAD</td>
<td>6</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>40% of time</td>
<td>84</td>
</tr>
</tbody>
</table>

*CAD = complete androgen deprivation; n = number of patients; PSA = prostate specific antigen.*
Intermittent vs. Continuous ADT in mPCa

Maha Hussain et.al N Engl J Med 2013; 368:1314-1325

- A phase 3 trial compared continuous ADT to intermittent ADT, but the study was statistically inconclusive for non-inferiority.

- Quality-of-life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months off ADT compared to the continuous ADT arm.

- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.
Figure 2. Median Survival from Randomization in the Two Treatment Groups.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at Risk</th>
<th>Median Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous therapy</td>
<td>765</td>
<td>5.8</td>
</tr>
<tr>
<td>Intermittent therapy</td>
<td>770</td>
<td>5.1</td>
</tr>
</tbody>
</table>

No. of Deaths

- Continuous therapy: 445
- Intermittent therapy: 483
Table 3. Oncological results in the 7 phase III trials on IAD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SEUG9401 (20)</th>
<th>FINN VII (21)</th>
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<th>TULP (24)</th>
<th>TAP22 (25)</th>
<th>De Leval (26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End points considered</td>
<td>Time to progression/survival</td>
<td>Time to progression/survival</td>
<td>Time to progression/survival</td>
<td>Time to progression/survival</td>
<td>Time to progression</td>
<td>Time to progression/continuous survival</td>
<td>Time to progression</td>
</tr>
<tr>
<td>Time to progression</td>
<td>HR 0.81 in favour continuous arm.</td>
<td>IAD 34.5 mo Continuous 30.2 mo HR 1.08; p = 0.43</td>
<td>IAD 16.6 mo Continuous 11.5 mo p = 0.17</td>
<td>-</td>
<td>IAD 18.0 mo Continuous 24.1 mo</td>
<td>IAD 20.7 mo Continuous 15.1 mo p = 0.74</td>
<td>IAD 28 mo Continuous 21 mo</td>
</tr>
<tr>
<td>PCa-specific survival</td>
<td>IAD 23.6% dead. Continuous 20.8% dead. HR 0.88</td>
<td>IAD 43% dead; 45.2 mo Continuous 47% dead; 44.3 mo HR 1.17; p = 0.29</td>
<td>IAD 64% dead. Continuous 56% dead</td>
<td>IAD 17.4% dead. Continuous 13.5% dead. HR 1.23; p = 0.13</td>
<td>-</td>
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</tr>
<tr>
<td>Overall survival</td>
<td>IAD 54.1% dead. Continuous 54.2% dead. HR 0.99; p = 0.84</td>
<td>IAD 45.2 mo Continuous 45.7 mo HR 1.15; p = 0.17</td>
<td>IAD 5.1 years. Continuous 5.8 yr. HR 1.09</td>
<td>IAD 38.8% dead; 8.8 yr. Continuous 36.8% dead; 9.1 yr. HR 1.02</td>
<td>-</td>
<td>IAD 56.9% dead; 42.2 mo Continuous 54.2% dead; 52.0 mo p = 0.75</td>
<td>-</td>
</tr>
</tbody>
</table>

*HR = hazard ratio; IAD = intermittent androgen deprivation.*
Considerations for choosing intermittent or continuous ADT
All patients with metastatic disease should be treated initially with ADT. After 7 months of ADT, patients can be assigned a risk category based on the PSA value at that time point\textsuperscript{223}: low risk is defined by a PSA less than 0.2 ng/mL (median survival of 75 months); intermediate risk is defined by PSA between 0.2 and 4.0 ng/mL (median survival 44 months), and high risk is defined by PSA higher than 4.0 ng/mL (median survival 13 months). Those patients who have few or no symptoms related to ADT after 7 months of therapy will not benefit from intermittent ADT in terms of quality of life, and therefore continuous therapy makes sense as it is easier to administer.\textsuperscript{221}
Adverse effects of ADT

• Hot flashes
• Loss of libido and erectile dysfunction, shrinkage of penis and testicles
• Loss of muscle mass and strength
• Fatigue
• Depression
• Hair loss
• Osteoporosis

• Greater incidence of clinical fractures
• Obesity
• Insulin resistance
• Alterations in lipids
• Greater risk for diabetes and cardiovascular disease
Chemotherapy for mPCA

- Continuous ADT and docetaxel (75 mg/m$^2$) without prednisolone for 6 cycles for high-volume metastatic disease.

- Based on results from a phase III trial (ECOG 3805, or CHAARTED) and is anticipated to become the new standard for patients with high-burden metastases.

- Docetaxel should not be offered to men without metastatic PCa or to men with low volume mPCa, as this subgroup has not been shown to have improved survival outcomes in the ECOG study or a similar European trial (GETUG-AFU 15).
Androgen suppression plus docetaxel

• Early results from a randomized, controlled study of 790 men with hormone-sensitive metastatic prostate cancer indicated that patients treated with the chemotherapy drug docetaxel at the beginning of standard hormone therapy with androgen deprivation therapy (ADT) have improved survival compared with those treated with hormone therapy alone.

• Patients were treated with either ADT alone or ADT combined with docetaxel, every 3 weeks for 18 weeks. Patients who received docetaxel had a significant improvement in overall 3-year survival, as compared with those treated with ADT alone (69.0% vs. 52.5%). In patients with a high extent of metastatic disease, 3-year survival rates were 63.4% for ADT plus docetaxel treatment versus 43.9% for ADT alone.
Surgery for LN metastasis

- To date, there is no consensus on the role of local therapy in the setting of lymph node metastasis.

- Studies have demonstrated that radical prostatectomy, despite pathologically confirmed lymph node metastasis, may improve both cancer-specific survival (CSS) and overall survival compared with ADT alone.

- Currently, data do not support the widespread adoption of prostatectomy in the face of metastatic disease.
Surgery in mPCa

- Transurethral resection is sometimes needed in men who develop obstruction secondary to local tumor growth.

- An indication for immediate bilateral orchiectomy is spinal cord compression, because it avoids the potential flare response that can occur during the first 3 weeks of treatment with an LHRH agonist.
Radiation for distant metastasis

- In patients with metastatic prostate cancer, radiation is also applied for palliative purposes. Effective means for bone metastasis.

  - Isolated symptomatic bone metastasis can be managed by ERBT. Single 8 Gy x 1 or 20 G

- Patient with mCRPC, symptomatic bone mets and no visceral metastatic disease.

  - Radium-223 dichloride is an alpha–particle-emitting radioactive therapeutic agent that was approved by the FDA in May 2013.
  - ALSYMPCA trial – improve OS and prolonged time to SRE
## Recommendations for hormonal therapy

<table>
<thead>
<tr>
<th>Castration</th>
<th>Benefits</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 symptomatic</td>
<td>To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>M1 asymptomatic</td>
<td>Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.</td>
<td>1b</td>
<td>A</td>
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<tr>
<td></td>
<td>An active clinical surveillance protocol is an acceptable option in clearly informed patients if survival is the main objective.</td>
<td>3</td>
<td>B</td>
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... recommendations con’t

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<thead>
<tr>
<th>Anti-androgens</th>
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<tbody>
<tr>
<td>Short-term administration</td>
<td>To reduce the risk of the ‘flare-up’ phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist (91,92).</td>
<td>2a</td>
<td>A</td>
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<tr>
<td></td>
<td>It may be sufficient to give an anti-androgen for some weeks of concomitant use, starting treatment on the same day as an LHRH analogue is started, or for up to 7 days before the first LHRH analogue injection.</td>
<td>4</td>
<td>B</td>
</tr>
<tr>
<td>Long-term administration as monotherapy</td>
<td>This is an option in highly selected and motivated patients with a low PSA.</td>
<td>3</td>
<td>B</td>
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<thead>
<tr>
<th>Intermittent treatment</th>
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<tbody>
<tr>
<td>Threshold to start and stop ADT</td>
<td>The threshold is empirically chosen. However, it should reproduce what has been used in clinical trials. In trials, treatment is usually stopped when the PSA level is &lt; 4 ng/mL (M1) and &lt; 0.5-4 ng/mL (relapsing). Treatment is usually re-started when the PSA is &gt; 4-10 (relapsing) and &gt; 10-20 ng/mL (M1).</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Drug</td>
<td>Combined treatment with LHRH agonists and NSAA. Antagonists might be an option.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Population:</td>
<td>Metastatic patients: asymptomatic, very motivated, with a major PSA response after the induction period.</td>
<td>1b</td>
<td>B</td>
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<tr>
<td></td>
<td>Relapsing after radiotherapy: patients with a clear response after the induction period.</td>
<td>1b</td>
<td>A</td>
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</table>
# Contraindications for various therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Contraindications</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral orchiectomy</td>
<td>Psychological reluctance to undergo surgical castration.</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>Known cardiovascular disease.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>LHRH agonists monotherapy</td>
<td>Patients with metastatic disease at high risk for clinical ‘flare-up’ phenomenon.</td>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>ADT, anti-androgen</td>
<td>Localized PCa as primary monotherapy (except in some high-risk localized situations in patients unwilling or unable to receive any form of local treatment).</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

*ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone.*
Conclusion

• ADT is the gold standard for men with metastatic prostate cancer.
  
  o ADT may reduce mortality compared with no treatment in men with metastatic prostate cancer, but no one regimen has been shown to be more effective compared with the others.

  o Immediate ADT may slightly improve 10 year survival compared with deferred therapy in men with advanced, asymptomatic prostate cancer, and may reduce the risk of major complications.

  o Systematic reviews have shown that CAB using non-steroidal anti-androgen appears to provide a small survival advantage (< 5%) versus monotherapy (surgical castration or LHRH agonists) beyond 5 years.

  o IAD might be an option in metastatic situations, even if the benefits are fewer compared to those with less advanced Pca.
• Chemotherapy is anticipated to become the new standard for patients with high-burden metastases.

• To date, there is no consensus on the role of local therapy in the setting of lymph node metastasis.

• Currently, data do not support the widespread adoption of prostatectomy in the face of metastatic disease.
THANK YOU