Metastatic castration resistant prostate cancer (mCRPC)

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Conflicts of interest

Speakers Bureau:
Janssen, Novartis

Consulting activities (including IDMC):
AAA International, Active Biotech, Astellas, BMS, Bayer, Clovis, Curevac, Dendreon, Ferring, Janssen, MaxiVAX, Nectar, Orion, ProteoMediX, Roche, Sanofi Aventis

Pending patent application for a method for biomarker
WO 2009138392 A1
Development of castration-resistance

Upon initiation of ADT

- Testosterone reduced to very low levels in blood (<1.7nmol/l)
- PSA decline
- Some cancer cells die, others “hibernate”
Castration-resistance

Mechanisms of resistance to ADT
- Adrenal androgens
- Paracrine/Intracrine androgen production
- AR amplification
- AR mutations

• ADT is continued to keep testicular testosterone suppressed
Definition of Castration-Resistance

Progression of disease by PSA or radiographic progression despite ADT with adequately suppressed testosterone (< 50ng/dl or 1.7nmol/l)

• Consecutive rises: Rising PSA has to be confirmed!

• Testosterone level needs to be measured

• Perform Imaging
Prostate Cancer: Castration resistant (CRPC)

**Localised Prostate Cancer**

**Advanced Prostate Cancer: Castration-sensitive/naive**

- M0: By imaging no evidence of metastases
- M1: Metastases detected by imaging

- ADT: Androgen Deprivation Therapy

**Advanced Prostate Cancer: Castration-resistant**

- M0
- ADT

**Local Therapy (RT/OP/Active Surveillance)**

- PSA Rise
- ADT +/-Docetaxel
- ADT +/-Abiraterone

- De Novo M1

- 1st-line
  - mOS 32-35m

- 2nd-line
  - mOS 18-20m

- 3rd-line
  - mOS 10-12m

**mCRPC treatment options with overall survival benefit:**
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223

ADT: Androgen Deprivation Therapy
M0: By imaging no evidence of metastases
M1: Metastases detected by imaging
### Table 1. Practice-Changing Trials of Treatments for Metastatic Prostate Cancer That Improve Survival.

<table>
<thead>
<tr>
<th>Trial and Registration No.</th>
<th>Treatment</th>
<th>Median Overall Survival</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>Year of Initial Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study Treatment</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>months</td>
<td>months</td>
<td></td>
</tr>
<tr>
<td>No previous ADT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAARTED, NCT00309985</td>
<td>Docetaxel plus ADT</td>
<td>57.6</td>
<td>44.0</td>
<td>0.61 (0.47–0.80)</td>
</tr>
<tr>
<td>STAMPEDE, NCT00268476</td>
<td>Docetaxel plus ADT</td>
<td>60.0</td>
<td>45.0</td>
<td>0.76 (0.62–0.92)</td>
</tr>
<tr>
<td>LATITUDE, NCT017115285</td>
<td>Abiraterone and prednisone, plus ADT</td>
<td>Not reached</td>
<td>34.7</td>
<td>0.62 (0.51–0.76)</td>
</tr>
<tr>
<td>STAMPEDE, NCT00268476</td>
<td>Abiraterone and prednisolone, plus ADT</td>
<td>Not reached</td>
<td>48.0</td>
<td>0.61 (0.49–0.75)</td>
</tr>
<tr>
<td>Recurrent disease after ADT without chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAX 327‡</td>
<td>Docetaxel and prednisone</td>
<td>18.9</td>
<td>16.5</td>
<td>0.76 (0.62–0.94)</td>
</tr>
<tr>
<td>SWOG 9916, NCT00004001</td>
<td>Docetaxel and estramustine</td>
<td>17.5</td>
<td>15.6</td>
<td>0.80 (0.67–0.97)</td>
</tr>
<tr>
<td>COU-302, NCT00887198 (minimal or no symptoms)</td>
<td>Abiraterone and prednisone</td>
<td>Prednisone</td>
<td>Not reached</td>
<td>0.75 (0.61–0.93)</td>
</tr>
<tr>
<td>PREVAIL, NCT01212991 (minimal or no symptoms)</td>
<td>Enzalutamide</td>
<td>Placebo</td>
<td>32.4</td>
<td>0.71 (0.60–0.84)</td>
</tr>
<tr>
<td>Recurrent disease after ADT and docetaxel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TROPIC, NCT00417079</td>
<td>Cabazitaxel and prednisone</td>
<td>15.1</td>
<td>12.7</td>
<td>0.70 (0.59–0.83)</td>
</tr>
<tr>
<td>COU-301, NCT00638690</td>
<td>Abiraterone and prednisone</td>
<td>Prednisone</td>
<td>14.8</td>
<td>10.9</td>
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<tr>
<td>AFFIRM, NCT00974311</td>
<td>Enzalutamide</td>
<td>Placebo</td>
<td>18.4</td>
<td>13.6</td>
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<tr>
<td>Recurrent disease after ADT, docetaxel status unspecified</td>
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<tr>
<td>IMPACT, NCT00065442 (minimal symptoms)</td>
<td>Sipuleucel-T</td>
<td>Placebo</td>
<td>25.8</td>
<td>21.7</td>
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<tr>
<td>ALSYMPCA, NCT00699751 (symptomatic)</td>
<td>Standard of care plus radium-223</td>
<td>Standard of care</td>
<td>14.9</td>
<td>11.3</td>
</tr>
</tbody>
</table>

* ADT denotes androgen-deprivation therapy, and CI confidence interval.
† The date of the initial report may not be the same as the date of the cited publication.
‡ There is no trial registration number for TAX 327.
Approved systemic therapies

- **CRPC**
  - Cabazitaxel + P* vs Mitoxantrone + P*  
    - LANCET 2010  
    - **15.1** vs **12.7**
  - Abiraterone + P* vs Placebo + P  
    - NEJM 2013  
    - **15.8** vs **11.2**
  - Enzalutamide vs Placebo  
    - NEJM 2012  
    - **18.4** vs **13.6**

- **Docetaxel + P* vs Mitoxantrone + P***  
  - NEJM 2004  
  - **19.2** vs **16.3m**

- **Enzalutamide vs Placebo**  
  - NEJM 2014  
  - **32.4** vs **30.2**

- **Radium-223 vs Best standard of care**  
  - NEJM 2013  
  - **14.9** vs **11.3**

- **Prednisone**

- **Median Overall Survival**

- **Zoledronate vs Placebo**  
  - JNCI 2004; **16** vs **10.5m**

- **Denosumab vs Zoledronate**  
  - LANCET 2011; **20.7** vs **17.1m**

- **Time to first skeletal event**
What is the optimal sequence?

Unclear!

• In none of the before mentioned trials the new substance has been tested against a regimen that would be considered «standard» nowadays and not against each other

• None of the trials has included patients with ADT plus docetaxel or plus abiraterone in the castration-sensitive setting
Direct comparison: FIRSTANA

A

Overall Survival (%)

C20 v D75
HR 1.01 (0.85 to 1.20)
Log-rank \(P = .997\)

C25 v D75
HR 0.97 (0.82 to 1.16)
Log-rank \(P = .757\)

B

Progression-Free Survival (%)

C20 v D75
HR 1.06 (0.91 to 1.24)
Log-rank \(P = .422\)

C25 v D75
HR 0.99 (0.85 to 1.15)
Log-rank \(P = .804\)

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<thead>
<tr>
<th>No. at Risk</th>
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<th>6</th>
<th>9</th>
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<td>389</td>
<td>356</td>
<td>319</td>
<td>296</td>
<td>234</td>
<td>192</td>
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</tr>
<tr>
<td>C25</td>
<td>388</td>
<td>345</td>
<td>325</td>
<td>296</td>
<td>239</td>
<td>197</td>
<td>138</td>
<td>70</td>
<td>28</td>
<td>5</td>
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<tr>
<td>D75</td>
<td>391</td>
<td>366</td>
<td>336</td>
<td>307</td>
<td>243</td>
<td>192</td>
<td>133</td>
<td>57</td>
<td>18</td>
<td>3</td>
<td>0</td>
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<th>6</th>
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<th>18</th>
<th>21</th>
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<th>27</th>
<th>30</th>
<th>33</th>
<th>36</th>
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</thead>
<tbody>
<tr>
<td>C20</td>
<td>389</td>
<td>145</td>
<td>83</td>
<td>39</td>
<td>15</td>
<td>6</td>
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<tr>
<td>C25</td>
<td>388</td>
<td>149</td>
<td>94</td>
<td>48</td>
<td>19</td>
<td>5</td>
<td>1</td>
<td>0</td>
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<tr>
<td>D75</td>
<td>391</td>
<td>152</td>
<td>83</td>
<td>37</td>
<td>16</td>
<td>8</td>
<td>3</td>
<td>0</td>
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</tbody>
</table>
First Line Therapy mCRPC

Options of Standard of Care (according to Phase III trials)

**Abiraterone/Prednisone (COU-302):** Asymptomatic, mildly symptomatic; no visceral metastases

**Docetaxel/Prednisone (TAX-327)**

**Enzalutamide (PREVAIL):** Asymptomatic, mildly symptomatic

**Radium-223 (ALSYMPCA):** Symptomatic, no lymph node bulk, no visceral metastases
Sequencing: Factors to help treatment decisions

- Patient history (symptomatic versus non-symptomatic), co-medication, co-morbidities, clinical exam

- What treatment in castration-sensitive setting (ADT alone or ADT plus), duration of response to this therapy

- Staging
  - Blood counts, renal and liver function, ALP, LDH…
  - PSA value, PSA-DT
  - Imaging: CT Chest and Abdomen, Bone scan, MRI long spine

- Patient preference!
First-line mCRPC Therapy after ADT alone

ADT → Tumor - Volume (PSA) → Docetaxel
Abiraterone
Enzalutamide
Radium-223 Trials

Table 6 – Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options

<table>
<thead>
<tr>
<th>What is your preferred first-line mCRPC treatment option:</th>
<th>Abiraterone or enzalutamide (%)</th>
<th>Cabazitaxel (%)</th>
<th>Docetaxel (%)</th>
<th>Platinum-based chemotherapy (%)</th>
<th>Radium-223 (%)</th>
<th>Sipuleucel-T (%)</th>
<th>No preferred option (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the majority of asymptomatic men who did not receive docetaxel in the castration-naive setting?</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>In the majority of symptomatic men who did not receive docetaxel in the castration-naive setting?</td>
<td>52</td>
<td>0</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Gillessen S et al, Eur Urol 2017
First-line mCRPC Therapy after ADT plus docetaxel

Table 6 – Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>Abiraterone or enzalutamide (%)</th>
<th>Cabazitaxel (%)</th>
<th>Docetaxel (%)</th>
<th>Platinum-based chemotherapy (%)</th>
<th>Radium-223 (%)</th>
<th>Sipuleucel-T (%)</th>
<th>No preferred option (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the majority of asymptomatic men who did receive docetaxel in the castration-naive setting?</td>
<td>90</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
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<tr>
<td>In the majority of symptomatic men who did receive docetaxel in the castration-naive setting?</td>
<td>73</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Gillessen S et al, Eur Urol 2017
First-line mCRPC after ADT + Docetaxel

245 patients from GETUG-15 (Upfront ADT vs ADT + 9x Docetaxel)
Retrospective analysis

<table>
<thead>
<tr>
<th>Docetaxel for CRPC</th>
<th>ADT alone (n=80)</th>
<th>ADT plus Docetaxel (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Decline ≥ 50%</td>
<td>38%</td>
<td>20%</td>
<td>0.14</td>
</tr>
<tr>
<td>Biochem. PFS</td>
<td>6m</td>
<td>4.1m</td>
<td></td>
</tr>
</tbody>
</table>

Lavaud et al, Eur Urol 2018
## First-line mCRPC after ADT + Docetaxel

What to do if rapid progression after ADT plus docetaxel?

**Table 6 - Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options**

<table>
<thead>
<tr>
<th>What is your preferred first-line mCRPC treatment option:</th>
<th>Abiraterone or enzalutamide (%)</th>
<th>Cabazitaxel (%)</th>
<th>Docetaxel (%)</th>
<th>Platinum-based chemotherapy (%)</th>
<th>Radium-223 (%)</th>
<th>Sipuleucel-T (%)</th>
<th>No preferred option (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the majority of asymptomatic men who received chemo-hormonal therapy and who progressed within ≤6 mo after completion of docetaxel in the castration-naive setting?</td>
<td>77</td>
<td>17</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>In the majority of symptomatic men who received chemo-hormonal therapy and who progressed within ≤6 mo after completion of docetaxel in the castration-naive setting?</td>
<td>57</td>
<td>27</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Gillessen S et al, Eur Urol 2017
First-line mCRPC after ADT + Abiraterone/P

- ADT + Abiraterone/P
- Docetaxel
- Cabazitaxel
- Enzalutamide
- Radium-223 Trials

Tumor - Volume (PSA)

?
First-line mCRPC after ADT + Abiraterone/P

No prospective data about activity of the substances after ADT plus Abiraterone/P

- Activity of enzalutamide likely to be low
- In case of oligoprogression on ADT plus Abiraterone → Local Therapy?

<table>
<thead>
<tr>
<th>LATITUDE: FU 30.4m</th>
<th>ADT + Abi</th>
<th>ADT + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>106 (34%)</td>
<td>187 (40%)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>30 (10%)</td>
<td>76 (16%)</td>
</tr>
<tr>
<td>AA-P</td>
<td>10 (3%)</td>
<td>53 (11%)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>11 (4%)</td>
<td>30 (6%)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>11 (4%)</td>
<td>27 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STAMPEDE: FU 40m</th>
<th>ADT</th>
<th>ADT + Abi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>200 (37%)</td>
<td>115 (46%)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>138 (26%)</td>
<td>25 (10%)</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>120 (22%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>24 (5%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>28 (5%)</td>
<td>15 (6%)</td>
</tr>
</tbody>
</table>

Fizazi K et al, NEJM 2017 63% 50%

James N et al, NEJM 2017 39% 63%
Second Line after Docetaxel

Options of Standard of Care (according to Phase III trials)

Abiraterone/Prednisone (COU-301)

Cabazitaxel/Prednisone (TROPIC and PROSELICA)

Enzalutamide (AFFIRM)

Radium-223 (ALSYMPCA): Symptomatic, no lymph node bulk, no visceral metastases
Second Line after Enzalutamide or Abiraterone/P

More frequent situation, but no large prospective, randomised Phase III trials published yet!
Abiraterone/P after Enzalutamide

PLATO Trial (n= 509)

Enzalutamide

PSA Progression after initial response

Enzalutamide + Abiraterone/P

Abiraterone/P + Placebo

PSA Response
0.8%
2.5%

• Prospective data in selected Patients (PSA responders to Enzalutamide)

• Confirms retrospective data that showed only minimal activity of Abiraterone/P after Enzalutamide

Attard G et al ASCO 2017; Attard G et al J Clin Oncol 2018
Enzalutamide after Abiraterone/P

Multicentre, single-arm, open-label study
214 men with mCRPC and PD after ≥24 wk Abiraterone
- 145 chemotherapy-naïve
- 69 post chemotherapy

Median duration of therapy with Enza 5.7m
Median rPFS 8.1m
mOS not reached
PSA Decline ≥50%: 27% (48 of 181)
- pre-chemo: 28%
- post-chemo: 26%

De Bono et al, Eur Urol 2017
Docetaxel after Abiraterone in COU-302

N=100
PSA response rate: 40%

De Bono et al, Eur Urol 2016
Combination Therapies in mCRPC

All combinations with **docetaxel** failed in Phase III trials:

- Oblimersen
- DN-101
- Bevacizumab
- VEGF-Trap
- Lenalidomide
- Atrasentan
- Zibotentan
- GVAX
- Dasatinib
- Custirsen
Combination Therapies in mCRPC

Radium-223 plus Abiraterone/P versus Abiraterone/P alone: Failed (more fractures, more deaths)

Abiraterone added to Enzalutamide not effective:

Attard G et al J Clin Oncol 2018
In daily practice:

- Staging: Always before start of a new therapy
- Monitoring: Risk-adapted
## When to switch treatment: Defining Progression

Generally 2 out of 3 criteria should be fulfilled:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cave!</th>
</tr>
</thead>
</table>
| **1. PSA Progression** | • Easily done, but….  
                         • Can rise in the first 9-12 weeks of a new treatment, PSA rise on Radium-223 very common  
                         • Not reliable in very advanced disease  
                         • PSA can be low in relation to tumour volume (aggressive variants!)  |
| **2. Radiographic progression** | • 90% of patients with advanced prostate cancer have bone metastases  
                          • Flare on bone scintigraphy very common  
                          • Increasing sclerosis on CT scans often miss-interpreted as progression  
                          • Epidural tumour difficult to appreciate on CT  
                          • Malignant superscan not uncommon in advanced disease |
| **3. Clinical Progression** | • Bone pain in elderly patients with advanced prostate cancer can also have other causes (e.g. degenerative disease, osteoporosis…) |

*Scher et al, J Clin Oncol 2016; Gillessen et al, Ann Oncol 2015*
Progression of disease in the presence of falling PSA

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>AR IHC</th>
<th>PSA IHC</th>
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</thead>
<tbody>
<tr>
<td>Liver metastasis</td>
<td>![H&amp;E Image]</td>
<td>![AR IHC Image]</td>
<td>![PSA IHC Image]</td>
</tr>
</tbody>
</table>

Log PSA decline on docetaxel-based chemotherapy (red arrows: CT scan timepoints)

CT 23/07/2012

CT 09/10/2012

Pezaro et al, Eur Urol 2014
Several survival prolonging treatment options

“Optimal” sequence of therapies unclear

Situation more complex with the advent of combination therapies for mCSPC

Most experts are using Abi/P or Enza as first-line for men with mCRPC

Abiraterone after Enzalutamide low activity, Enzalutamide after Abiraterone modest activity in selected patients
Take home messages for mCRPC II

- Do not rely on PSA alone for treatment decisions in men with mCRPC
- Do not change treatment because of early “increase” in bone lesions alone
- In case of neurological symptoms: MRI long spine!
- Combination therapies not successful until now
- No validated predictive markers yet
- New options on the horizon: PARP inhibition, 177-Lu-PSMA therapy...
Save the date
Advanced Prostate Cancer Consensus Conference (APCCC 2019)
Basel 29-31 August 2019
Thank you very much for your attention!