Present and Future Perspectives in Treatment of mCRPC Patients

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Disclosures

Astellas,

Takeda, Janssen, Bouchara Recordati, Ipsen, MSD, PFM, GSK, Intuitive Surgical
What do you in your daily practice prescribed to your patients?

1. LHRH Agonist
2. LHRH Antagonist
3. Bicalutamide
4. Enzalutamide
5. Abiraterone acetate
6. Docetaxel
7. Antiangiogenic drugs
4 new active drugs in 4 years for mCRPC!

**Cabazitaxel**, De Bono J, Lancet 2010

**Abiraterone**, Fizazi K, Lancet Oncol 2012

**Enzalutamide**, Scher HI, NEJM 2012

**Radium-223**, Parker J, NEJM 2013

- **Cabazitaxel**: 100% survival at 6 months, 90% at 12 months.
- **Abiraterone**: HR (95% CI): 0.74 (0.54-0.98), p < 0.0001.
- **Enzalutamide**: 18.4 months (95% CI: 17.3–NYR).
- **Placebo**: 13.6 months (95% CI: 11.3–15.8).

- **Radium-223**: Median OS 14.9 mo
- **Placebo**: Median OS 11.3 mo
Improvement of Overall Survival

OS 18.9 mois

- Mitoxantrone
- Docetaxel
- Cabazitaxel

2004

OS 35.3 mois

- Abiraterone (post-chemo)
- Abiraterone (pre-chemo)
- Sipuleucel-T
- Enzalutamide
- Enzalutamide (pre-chemo)
- Radium-223
- Denosumab

2010
2011
2012
2013
2014

Zoledronic acid
Clinical case (back in 2013…)

Valerio G, 62 year old, no symptoms

First PSA assessment : 110 ng/ml
Prostate biopsy: Gleason 5+4 in all cores (cT3)
CT scan: no visceral mets
Bone scan:
Clinical case (back in 2013…)

PSA

- Eligard
- Bone scan: almost complete resolution of all lesions
- 5 ng/ml
- 6 ng/ml
- 12 ng/ml

Testosterone: 25 ng/dL
In patients with castrate levels of testosterone, what is required for the definition of CRPC in your daily practice?

1. Rising PSA (confirmed) on ADT is sufficient

2. Rising PSA (confirmed) on combined androgen blockade (ADT plus AR antagonist) initiated upfront or initiated later

3. PSA has to rise (confirmed) on ADT after stopping AR antagonist therapy and withdrawal period (4–6 weeks)

4. Unqualified to answer

ADT=androgen-deprivation therapy; AR=androgen receptor; CRPC=castration-resistant prostate cancer; PSA=prostate-specific antigen.
In patients with castrate levels of testosterone, what is required for the definition of CRPC in daily practice?

1. Rising PSA (confirmed) on ADT is sufficient

2. Rising PSA (confirmed) on combined androgen blockade (ADT plus AR antagonist) initiated upfront or initiated later

3. PSA has to rise (confirmed) on ADT after stopping AR antagonist therapy and withdrawal period (4–6 weeks)

4. Abstain

5. Unqualified to answer

Option 1: 93.8%
Option 3: 6.3%

% voting results, excluding 'unqualified to answer'

ADT=androgen-deprivation therapy; AR=androgen receptor; CRPC=castration-resistant prostate cancer; PSA=prostate-specific antigen.
## Definition of mCRPC patients

<table>
<thead>
<tr>
<th>2011 definition&lt;sup&gt;1&lt;/sup&gt;</th>
<th>2015 definition&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Castrate serum testosterone &lt;50 ng/dL</td>
<td>• Castrate serum testosterone &lt;50 ng/dL plus either:</td>
</tr>
<tr>
<td>• Three consecutive rises of PSA, 1 week apart (resulting in two 50% increases over the nadir, with a PSA &gt;2 ng/mL)</td>
<td>• Biochemical progression: Three consecutive rises in PSA 1 week apart (resulting in two 50% increases over the nadir, with PSA &gt;2 ng/mL) or,</td>
</tr>
<tr>
<td>• Anti-androgen withdrawal for ≥4 weeks for flutamide and ≥6 weeks for bicalutamide</td>
<td>• Radiological progression: Appearance of ≥2 new bone lesions on a bone scan or enlargement of a soft tissue lesion using RECIST</td>
</tr>
<tr>
<td>• PSA progression, despite consecutive hormonal manipulations</td>
<td></td>
</tr>
<tr>
<td>Anti-androgen withdrawal or hormonal manipulations are necessary before a diagnosis of CRPC</td>
<td></td>
</tr>
</tbody>
</table>

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CRPC=castration-resistant prostate cancer; mCRPC=metastatic castration-resistant prostate cancer; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumours.

THE PAST: 2005

Hormone naive

Metastatic CRPC
Asymptomatic / symptomatic
(failed ADT)

ADT + Docetaxel

Medical Oncologist
THE PRESENT: 2016

Hormone naive

Metastatic CRPC
Asymptomatic / symptomatic (failed ADT)

ADT + Docetaxel
ADT+ Abiraterone
ADT + Enzalutamide
ADT + Sipuleucel-T
ADT + Radium 223
ADT + Cabazitaxel

Urologist + Medical Oncologist + Nuclear medicine

All these compounds have shown to improve survival of men with mCRPC in large Phase 3 Trials and have been approved in this setting.
CRPC: should we stop ADT?

In the absence of prospective data, the **modest potential benefits** of a continuing castration outweigh the **minimal risk of treatment**.

In addition, all subsequent treatments have been studied in men with **ongoing androgen suppression** and therefore it should be continued indefinitely in these patients.
# “First line Metastatic CRPC”: Inclusion criteria

<table>
<thead>
<tr>
<th>Drug (Study)</th>
<th>Treatment arms</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (TAX 327)</td>
<td>Docetaxel (3 weeks + pred vs mito + pred)</td>
<td>CRPC. Visceral M+ Chemotherapy naïve 45% were symptomatic</td>
</tr>
<tr>
<td>Enzalutamide (PREVAIL)</td>
<td>Enza vs placebo</td>
<td>CRPC Chemotherapy naïve 10% Visceral M+ Asymptomatic or mildly symptomatic</td>
</tr>
<tr>
<td>Abiraterone (CU-11-302)</td>
<td>Abi + pred vs placebo + pred</td>
<td>Progressive CRPC Chemotherapy naïve Asymptomatic or mildly symptomatic No known visceral M+</td>
</tr>
<tr>
<td>Sipuleucel – T (IMPACT)</td>
<td>Sipuleucel – T vs control arm</td>
<td>CRPC Chemotherapy naïve. No visceral M+ Asymptomatic or mildly symptomatic</td>
</tr>
<tr>
<td>Radium 223 (ALSYMPCA)</td>
<td>Radium 223 + BSC vs placebo + BSC</td>
<td>Symptomatic CRPC &gt;= 2 bone mets No known visceral M+ Post doxetacel or unfit to docetaxel (&gt;40% of recruited patients)</td>
</tr>
</tbody>
</table>
Docetaxel inhibits depolymerization of the microtubule while polymerization continues to occur.

This results in the disruption of cellular activities including cell-cycle arrest and inhibition of mitosis.

TAX-327: first trial showing a survival benefit of chemotherapy in the context of CRPC (OS: primary endpoint)

The median survival was 18.9 months vs. 16.4 months in the group of patients who received mitoxantrone/prednisone ($p=0.009$), the pain response was 35% vs. 22%

*Tannock et al. NEJM 2004;351:1502-12*
Abiraterone is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17, a critical enzyme in testosterone synthesis.
**Abiraterone Acetate: COU-AA-302**

- At a median follow-up of 49.2 months (IQR 47.0–51.8), Overall, 365 (67%) patients in the abiraterone acetate group and 435 (80%) in the placebo group received subsequent treatment with one or more approved agents.

- Median overall survival was significantly longer in the abiraterone acetate group than in the placebo group (34.7 months [95% CI 32.7–36.8] vs 30.3 months [28.7–33.3]; hazard ratio 0.81 [95% CI 0.70–0.93]; p=0.0033).

![Graph showing median time to initiate use of prednisone](image)

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone acetate group (n=542)</th>
<th>Placebo group (n=540)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fluid retention/oedema</td>
<td>161 (30%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>87 (16%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>104 (19%)</td>
<td>25 (5%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>81 (15%)</td>
<td>35 (5%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20 (4%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>40 (7%)</td>
<td>28 (5%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>47 (9%)</td>
<td>18 (3%)</td>
</tr>
</tbody>
</table>

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Before crossover.

Enzalutamide

- **Enzalutamide** is a second-generation AR antagonist with significantly more potent binding to the AR than the first-generation antagonists.

- Enzalutamide-bound AR mostly remains **cytoplasmic**, whereas the older drugs actually cause nuclear translocation.

*Hurtwitz et al. Oncology 2013*
Enzalutamide: PREVAIL

- Double-blind, phase 3 randomized trials: 1717 patients (10% visceral mets) assigned to receive either ENZA (160 mg) or placebo once daily

- The rate of progression-free survival at 12 months was 65 vs. 14% for ENZA and placebo (81% RR; HR: 0.19; 95% CI: 0.15-0.23; P<0.001)

- 626 patients (72%) in the ENZA group and 532 patients (63%) in the placebo group were alive at the data-cutoff date (29% RR; HR: 0.71; P<0.001)

Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study

- Longer term analysis with additional 20 months of follow-up for rPFS, 9 months for OS, and 4 months for safety (up to the pre-specified number of deaths)

- Enzalutamide reduced the risk of radiographic progression or death by 68% (p<0.001) and the risk of death by 23% (p=0.0002).

- Median investigator assessed rPFS: 54 mo vs 20 mo
  Median OS was 35.3 mo vs 31.3 mo in the placebo arm.

Most common AE: fatigue, back pain, constipation, arthralgia.

Beer et al, Eur urol, 2016, in press
“YES BUT ...

You showed data against PLACEBO!

I usually prescribe bicalutamide....”
My reply:

“FORGET Bicalutamide....”

And i will prove it right now!
## Historical hormonal manipulations (1/2)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PSA response</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicalutamide&lt;sup&gt;1&lt;/sup&gt;</td>
<td>20%</td>
<td>No impact on OS</td>
</tr>
<tr>
<td>Anti-androgen withdrawal&lt;sup&gt;2&lt;/sup&gt;</td>
<td>21%</td>
<td>No effect on rPFS</td>
</tr>
<tr>
<td>Oestrogen&lt;sup&gt;3&lt;/sup&gt;</td>
<td>20–51%</td>
<td>31% thrombosis 7% heart attack</td>
</tr>
<tr>
<td>Switch LHRH agonist&lt;sup&gt;4&lt;/sup&gt;</td>
<td>24%</td>
<td>No effect on OS and rPFS</td>
</tr>
</tbody>
</table>

OS=overall survival; rPFS=radiographic progression-free survival.

## Historical hormonal manipulations (2/2)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>PSA response (%)</th>
<th>Duration (months)</th>
<th>Impact on OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicalutamide (150 mg/day)&lt;sup&gt;1–4&lt;/sup&gt;</td>
<td>31–52</td>
<td>14–45</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>Flutamide (250 mg, 3/day)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>100</td>
<td>23</td>
<td>4.2</td>
<td>No</td>
</tr>
<tr>
<td>Nilutamide (200–300 mg/day)&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>14–28</td>
<td>29–50</td>
<td>7–11</td>
<td>No</td>
</tr>
<tr>
<td>Ketoconazole (200–400 mg, 3/day) + hydrocortisone ± AA withdraw&lt;sup&gt;8–13&lt;/sup&gt;</td>
<td>20–128</td>
<td>27–63</td>
<td>3.5–20</td>
<td>No</td>
</tr>
<tr>
<td>Distilbene (1–3 mg)&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td>21–44</td>
<td>24–43</td>
<td>≤3.8</td>
<td>No</td>
</tr>
</tbody>
</table>

AA=anti-androgen; OS=overall survival; PSA=prostate-specific antigen.

TERRAIN: Study design

- A randomised, double-blind, Phase 2, efficacy and safety study of enzalutamide versus bicalutamide in castrate men with mCRPC

**Patient population**
- 375 men with mCRPC who have progressed on LHRHa therapy or after bilateral orchiectomy
- Asymptomatic/mildly symptomatic
- Chemotherapy-naïve
- No requirement for steroids

**R 1:1**

**Primary endpoint:**
- PFS
  - Radiographic progression (central review)
  - Skeletal-related event
  - Initiation of new antineoplastic therapy
  - Death

**Secondary endpoints:**
- PSA response
- Time to PSA progression

**Enzalutamide 160 mg QD (n=184)**

**Bicalutamide 50 mg QD (n=191)**

LHRHa=luteinizing hormone-releasing hormone analogue; mCRPC=metastatic castration-resistant prostate cancer; PFS=progression-free survival; PSA=prostate-specific antigen; QD=once daily; R=randomised.

# TERRAIN: Patient baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Enzalutamide (n=184)</th>
<th>Bicalutamide (n=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>71 (50–96)</td>
<td>71 (48–91)</td>
</tr>
<tr>
<td>ECOG PS=0, n (%)</td>
<td>130 (71)</td>
<td>146 (76)</td>
</tr>
<tr>
<td>Pain 0–1 on BPI-SF Q3, n (%)</td>
<td>101 (55)</td>
<td>117 (61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>Enzalutamide (n=184)</th>
<th>Bicalutamide (n=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score ≥8 at initial diagnosis, n (%)</td>
<td>102 (55)</td>
<td>110 (58)</td>
</tr>
<tr>
<td>PSA, median, ng/mL</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Alkaline phosphatase, median, U/L</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Bone disease only, n (%)</td>
<td>83 (45)</td>
<td>92 (48)</td>
</tr>
<tr>
<td>Soft tissue disease only, n (%)</td>
<td>36 (20)</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Bone and soft tissue disease, n (%)</td>
<td>64 (35)</td>
<td>69 (36)</td>
</tr>
</tbody>
</table>

**TERRAIN: Progression-free survival**

HR=0.44 (95% CI: 0.34–0.57); p<0.0001
56% reduction in the risk of progression

Enzalutamide: 15.7 months
(95% CI: 11.5–19.4)

Bicalutamide: 5.8 months (95% CI: 4.8–8.1)

Enzalutamide, n 184 159 131 107 86 71 52 33 21 13 8 5

Bicalutamide, n 191 133 85 61 44 30 13 7 4 2 2 1

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.
# TERRAIN: PFS improvement across subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Enz/Bic, n</th>
<th>HR for PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>184/191</td>
<td>0.44 (0.34–0.57)</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>45/47</td>
<td>0.33 (0.19–0.57)</td>
</tr>
<tr>
<td>Age 65–75</td>
<td>85/80</td>
<td>0.44 (0.30–0.66)</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>54/64</td>
<td>0.55 (0.35–0.87)</td>
</tr>
<tr>
<td>Geographic region – North America</td>
<td>75/79</td>
<td>0.45 (0.30–0.67)</td>
</tr>
<tr>
<td>Geographic region – Europe</td>
<td>109/112</td>
<td>0.44 (0.31–0.61)</td>
</tr>
<tr>
<td>ECOG PS at BL=0</td>
<td>130/146</td>
<td>0.43 (0.32–0.59)</td>
</tr>
<tr>
<td>Total Gleason score at diagnosis ≥8</td>
<td>102/110</td>
<td>0.46 (0.32–0.65)</td>
</tr>
<tr>
<td>Disease location at BL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>83/92</td>
<td>0.53 (0.36–0.78)</td>
</tr>
<tr>
<td>Soft tissue only</td>
<td>36/29</td>
<td>0.32 (0.16–0.63)</td>
</tr>
<tr>
<td>Bone and soft tissue</td>
<td>64/69</td>
<td>0.38 (0.25–0.59)</td>
</tr>
<tr>
<td>PSA BL value above median*</td>
<td>91/96</td>
<td>0.45 (0.32–0.65)</td>
</tr>
<tr>
<td>LHRH/orchiectomy after metastasis</td>
<td>101/114</td>
<td>0.47 (0.34–0.67)</td>
</tr>
</tbody>
</table>

*Overall median baseline PSA was 21 μg/L.
Bic=bicalutamide; BL=baseline; CI=confidence interval; ECOG PS=European Cooperative Oncology Group performance status; Enz=enzalutamide; HR=hazard ratio; LHRH=luteinising hormone-releasing hormone; PFS=progression-free survival; PSA=prostate-specific antigen.
TERRAIN: Safety

- The median time on study treatment was 11.7 months for the enzalutamide arm and 5.8 months for the bicalutamide arm.

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Grade 1–2</th>
<th></th>
<th>Grade 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzalutamide (n=183)</td>
<td>Bicalutamide (n=189)</td>
<td>Enzalutamide (n=183)</td>
<td>Bicalutamide (n=189)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>16</td>
<td>16</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hot flush</td>
<td>15</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9</td>
<td>15</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

No Grade 4–5 AEs were reported for any of the events listed. AE=adverse event.
**TERRAIN**

HR = 0.44 (95% CI: 0.34–0.57); p < 0.0001
56% reduction in the risk of progression

Enzalutamide: 15.7 months
(95% CI: 11.5–19.4)

Bicalutamide: 5.8 months (95% CI: 4.8–8.1)

**PREVAIL**

<table>
<thead>
<tr>
<th></th>
<th>Median rPFS (95% CI), mo</th>
<th>HR (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>20.0 (15.9–22.1)</td>
<td>0.32 (0.28–0.39), p &lt; 0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.4 (4.0–5.6)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with PFS event (%)
HR = 0.44 (95% CI: 0.34–0.57); p < 0.0001
56% reduction in the risk of progression

Enzalutamide: 15.7 months (95% CI: 11.5–19.4)

Bicalutamide: 5.8 months (95% CI: 4.8–8.1)
Take Home Message

**TERRAIN**

<table>
<thead>
<tr>
<th>Patients without PFS event (%)</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 0.44 (95% CI: 0.34–0.57); p &lt; 0.0001 56% reduction in the risk of progression</td>
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<tr>
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**PREVAIL**

<table>
<thead>
<tr>
<th>Median rPFS (95% CI); mo</th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0 (15.9–22.1)</td>
<td>5.4 (4.0–5.6)</td>
<td></td>
</tr>
</tbody>
</table>

**PREScribe DIRECTLY ENZALUTAMIDE**
Autologous vaccine consisting of antigen-presenting cells that are exposed to the fusion protein prostatic acid phosphatase and GCSF, and then re-infused in the patient.

*Kantoff et al. NEJM 2010;363;5:411*
Sipuleucel-T: IMPACT

- Median survival with sipuleucel-T was 25.8 months compared with 21.7 months with placebo.

- Only patients with good performance status, asymptomatic or mildly symptomatic osseous metastases, and absence of visceral metastases were included in the trial.

Kantoff et al. NEJM 2010;363;5:411
Radium-223: ALSYMPCA

- Radium-223 mimics calcium, forming complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases.

- The short-range of alpha particles emitted by Radium-223 limits the damage to the surrounding normal tissue.

- Radium-223 emits alpha particles that cause double-strand DNA breaks in the adjacent cells, resulting in antitumor activity.

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Parker et al. NEJM 2013;369:213-23
Radium-223: ALSYMPCA

✓ 921 patients assigned to **radium-223** or placebo

✓ Radium-223 significantly improved **overall survival** compared to placebo (14.9 vs. 11.3 mo, respectively)

✓ Radium-223 was also associated with low **myelosuppression rates** and fewer **adverse events** compared to placebo

*Parker et al. NEJM 2013;369:213-23*
Clinical case (back in 2008...)

NO SYMPTOMS

Bone scan:
- 3 new lesions in the lumbar vertebrae
- CT Scan: no visceral mets

Testosterone: 25 ng/dL

WHICH DRUG IS INDICATED?

1. TAXOTERE
2. ABIRATERONE
3. ENZALUTAMIDE
4. RADIUM 223
5. SIPULEUCEL T

PSA

LHRH Agonist
Metastatic CRPC: which drug to be given first?

**Docetaxel if:**
1. Asymptomatic and symptomatic fit for chemo
2. Bone and or visceral mets
3. Rapidly progressing disease and short ADT response

**Enzalutamide if:**
1. Asymptomatic and midly symptomatic
2. Bone and visceral mets

**Abiraterone if:**
1. Asymptomatic and midly symptomatic
2. Bone mets only

**Radium-223**
1. Symptomatic
2. Bone mets only (>= 2)

**Sipuleucel-T**
1. Asymptomatic and midly symptomatic
2. Bone mets only
FIRST LINE THERAPIES IN MEN WITH mCRPC

- mCRPC
  - Good performance status 0 or 1
    - Mildly symptomatic or asymptomatic men with no evidence of visceral metastasis
      - Abiraterone
      - Sipuleucel T
      - Enzalutamide
      - ? Docetaxel
    - Men with symptomatic disease and/or visceral metastases
      - No visceral mets
        - Docetaxel
        - Radium-223
      - Visceral mets
        - Docetaxel
  - PS 2+
    - Asymptomatic Monitoring
    - Conventional anti-androgens
    - With evidence of progressive disease
      - Radium-223
Clinical case (back in 2013…)

- **PSA**
  - **LHRH Agonist**
  - Change treatment in case of at least two of three criteria:
    - PSA progression
    - Radiographic progression
    - Clinical deterioration

- **Testosterone:** 25 ng/dL

- **Bone scan:** Stable
- **CT Scan:** Retroperitoneal thoracic lymphadenopaties with a short diameter axis >2.5 mm

- **PSA values:**
  - **12 ng/ml** Docetaxel
  - **14 ng/ml**
Metastatic CRPC: first and second line therapies

First-line therapy
- Docetaxel
- Enzalutamide
- Abiraterone
- Sipuleucel-T
- Radium-223

Second-line therapy (dependent on previous treatment)
- Docetaxel
- Enzalutamide
- Abiraterone
- Radium-223
- Cabazitaxel

ADT^ MAB^
Abiraterone Acetate: COU-AA-301

- 1195 patients with progressive mCRPC who failed docetaxel-based chemotherapy

- Overall survival was significantly improved from 10.9 mo in the placebo arm to 14.8 mo in the AA/P arm (p<0.001)

- All secondary end points were met and all end points demonstrated a significantly improved benefit for the AA/P group

*de Bono et al. NEJM 2011;364;21:1995-2005*
Enzalutamide: AFFIRM

✓ 1199 patients with CRPC after chemotherapy assigned to ENZ or placebo

✓ Median overall survival: 18.4 mo vs. 13.6 mo (p<0.0001) in the ENZ vs. placebo groups, with a 37% reduction in relative risk for death

✓ All secondary end points were met with a statistically significant benefit in the ENZ arm

Scher et al. NEJM 2012;367:1187-97
Cabazitaxel plus Prednisone: TROPIC

- Cabazitaxel (CBZ) is a tubulin-binding taxane drug as potent as docetaxel in cell lines.

- Additionally, the drug has antitumour activity in models resistant to paclitaxel and docetaxel.

- TOPIC trial: 755 patients with mCRPC who progressed after docetaxel-based chemotherapy randomized to CBZ/P or mitoxantrone/prednisone.

*de Bono et al. Lancet 2010;376:1147-54*
Cabazitaxel plus Prednisone: TROPIC

✓ Median overall survival of 15.1 mo in the CBZ/P vs. 12.7 mo in the mitoxantrone/prednisone group

de Bono et al. Lancet 2010;376:1147-54
In patients with mCRPC and progression following docetaxel chemotherapy offer further life prolonging treatment options, which include cabazitaxel, abiraterone, enzalutamide and radium-223.

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Base second-line treatment decisions of mCRPC on pre-treatment performance status, comorbidities and extent of disease.

|  | B |
## HOW TO FOLLOW OUR PATIENTS?

<table>
<thead>
<tr>
<th>BASELINE EXAMINATIONS</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and clinical examination as well as baseline bloods (PSA, FBC, renal function, LFTs, ALP), bone scan and CT of chest abdomen and pelvis</td>
<td>1. Regular review and repeat blood profile every 2-3 months</td>
</tr>
<tr>
<td></td>
<td>2. Bone scintigraphy and CT scans at least every 6 months even in the absence of a clinical indication</td>
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The Future

NEXT EXIT
Success stories of Personalized Medicine

**Breast cancer:**
Trastuzumab in HER2+ tumors

**Colo-rectal cancer:**
Cetuximab in K-ras wt tumors

**Non-small cell lung cancer:**
Crizotinib in Alk+ tumors
(Shaw AT, ESMO 2012, Abstr 2862)
AR splice variants (V7)

Splice variant -> AR constitutively active (no need for androgens)
Response to Enzalutamide and Abiraterone by AR-V7 status

AR-V7 in circulating tumor cells

Antonarakis E, NEJM 2014
Response to Taxane by AR-V7 status

Taux de réponse du PSA:
- AR-V7 positif : 41 % (IC à 95 % : 18-67 %)
- AR-V7 négatif : 65 % (IC à 95 % : 41-85 %)

\[ p = 0.19 \]

*Docétaxel, n = 30
*Cabazitaxel, n = 7
Olaparib, an inhibitor of PARP

Poly (ADP-ribose) polymerase-1 (PARP-1)

Enzymes involved in ADP ribose polymerases

Act in DNA repair

Deregulation in cancer

Especially in BRAC2 patients

Weickhardt
Australia
SIU 2015
Olaparib: response and rPFS are predicted by BRCA2 and ATM
AR splice variants: Toward N-term targeting drugs?

Splice variant -> AR constitutively active (no need for androgens)
Results: Updated OS

- n=799
- Primary endpoint= OS

<table>
<thead>
<tr>
<th></th>
<th>Ipi (n=399)</th>
<th>Pbo (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>11.2 (9.6–12.6)</td>
<td>10.0 (8.4–11.2)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
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<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.72–0.98)</td>
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<tr>
<td>Stratified log-rank*</td>
<td>P=0.03</td>
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<tr>
<td>1-yr OS rate</td>
<td>47%</td>
<td>41%</td>
</tr>
<tr>
<td>2-yr OS rate</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>3-yr OS rate**</td>
<td>12%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Fizazi k et al., ESMO 2014
Personalized mCRPC treatments

• AR V7 +
  – Docetaxel
  – N-Term part of AR: Olaparib

• DNA Repair signature
  – PARP inhibitor?
Conclusion

• Major improvement of Overall Survival

• New therapies in CRPC since few years

• A lot of promising molecules

• Need of personalized medicine in order to limit treatment costs
Service d’Urologie

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