Optimal Sequence of Treatment for Metastatic Prostate Cancer

Cora N. Sternberg, MD, FACP
Department of Medical Oncology
San Camillo and Forlanini Hospitals
Rome, Italy
Prostate Cancer is a Continuum of Different Disease Stages

**Noncastrate**
Diagnoses: 1,100,000

- Clinically localized disease
- Rising PSA
  - Clinical metastases: Noncastrate
    - ADT
      - Rising PSA or M0: Castrate

**Castration resistant**
Deaths: 307,000

- Clinical metastases: Castrate
  - Pre-chemo
    - Abiraterone
    - Enzalutamide
    - Sipuleucel-T
    - Radium-223
  - Post-chemo
    - Abiraterone
    - Cabazitaxel
    - Enzalutamide
    - Radium-223

Most common cause of cancer in men

With detectable metastases: deaths from cancer exceed those from other causes

http://globocan.iarc.fr (accessed September 2014)
CRPC is clinically and pathologically heterogeneous

Shah RB et al, Cancer Res 2004 Dec 15;64(24):9209-16
Chained rearrangements are common in prostate cancer ("chromoplexy")

P07-4941

P09-1042

Baca et al., Cell (2013)
Genomic Complexity in CRPC: May represent a distinct set of druggable targets

- 50 patients: Rapid Autopsy Program
- Prostate carcinogenesis involves the hijacking/alteration of multiple processes/pathways.

- Next Generation Sequencing
  - DNA repair
  - AR signaling
  - ETS gene rearrangements
  - PTEN loss & PI3K/AKT
  - P53 mutation

- 9 genes significantly mutated + 3 others without described roles in prostate cancer

Grasso AS et al, Nature 2012 July 12 487 (7406) 349-243
Advancing Precision Medicine for Prostate Cancer Through Genomics

# Examples of Genomic Alterations in Prostate Cancer

<table>
<thead>
<tr>
<th>GENE</th>
<th>Alteration type</th>
<th>Frequency</th>
<th>Potential for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>Loss</td>
<td>50%</td>
<td>PI3K inhibitors</td>
</tr>
<tr>
<td>Androgen Receptor</td>
<td>Mutation; Amplification</td>
<td>50%; 50%</td>
<td>AR antagonists, ↓Androgen synthesis</td>
</tr>
<tr>
<td>ETS transcription factors</td>
<td>Rearrangement</td>
<td>50%</td>
<td>PARP inhibitors</td>
</tr>
<tr>
<td>Aurora Kinase</td>
<td>Amplification</td>
<td>5%</td>
<td>Neuroendocrine</td>
</tr>
<tr>
<td>MYC</td>
<td>Amplification</td>
<td>40%</td>
<td>Neuroendocrine</td>
</tr>
<tr>
<td>Rb</td>
<td>Loss</td>
<td>20–60%</td>
<td></td>
</tr>
<tr>
<td>CDK6</td>
<td>Overexpression</td>
<td>50%</td>
<td>CDK4/6 inhibitors</td>
</tr>
<tr>
<td>CCND1 (cyclin D)</td>
<td>Amplification</td>
<td>–</td>
<td>CDK4/6 inhibitors</td>
</tr>
<tr>
<td>CDKN2A (p16)</td>
<td>Amplification</td>
<td>–</td>
<td>CDK4/6 inhibitors</td>
</tr>
</tbody>
</table>

Lim JTE et al., PNAS 2005;102:5156–5161
CRPC Remains Driven by Androgen Receptor Signalling – AR Alterations Selected During Therapy

Up to 80% of CRPCs elevated AR gene copy number, 30% high-level amplification of the gene. AR mutations common 10-30% of the CRPC treated with antiandrogens

Current Treatment Paradigm is Evolving

Androgen deprivation therapy (ADT)

Local therapy

Therapies after ADT

Death

Hormone sensitive

mCRPC asymptomatic (failed ADT)

mCRPC mildly symptomatic

mCRPC symptomatic

mCRPC post-docetaxel

ADT

Abiraterone

Enzalutamide

Docetaxel

Radium 223

Abiraterone

Enzalutamide

Docetaxel

Cabazitaxel

Sipuleucel-T

supportive care (eg denosumab/bisphosphonates)

ADT + Docetaxel in high volume disease?
Phase 3
• N=755 patients
• Confirmed progressive mCRPC post-docetaxel

Primary endpoint
• OS

25 mg/m² cabazitaxel IV every 3 weeks + prednisone 10 mg QD (n=378)

12 mg/m² mitoxantrone* IV every 3 weeks + prednisone 10 mg QD (n=377)

TROPIC: Study design
TROPIC Trial Survival (n=755)

HR=0.70 (95% CI: 0.59–0.83); p<0.0001
30% reduction in risk of death

OS (%)

Time to event (months)

Mitoxantrone*: 12.7 months

Cabazitaxel: 15.1 months

Median follow-up 13.7 months

de Bono JS et al. Lancet 2010;376:1147-54
Abiraterone inhibits CYP17: 17α-hydroxylase/17,20-lyase

ACTH=adrenocorticotropic hormone; CYP=cytochrome P450; DHEA=dehydroepiandrosterone.

Enzalutamide an AR signalling inhibitor: targets multiple steps in the (AR) signaling pathway

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding

Abiraterone and Enzalutamide in mCRPC Phase III Studies Post-docetaxel (Primary Endpoint: OS)

**COU-AA-301**

- n=1195 progressive mCRPC
- Failed 1 or 2 chemo regimens

Abiraterone 1000 mg QD + prednisone 5 mg BID (n=797)

Placebo BID + prednisone 5 mg BID (n=398)

**AFFIRM**

- n=1199 progressive mCRPC
- Failed 1 or 2 chemo regimens

Enzalutamide 160 mg QD (n=800)

No prednisone

Placebo QD (n=399)

No prednisone
COU-AA-301 Overall Survival
Median Benefit 4.6 Months

Median follow-up 20.2 months

HR=0.74 (95% CI, 0.638–0.859) p<0.0001
26% reduction in risk of death

Abiraterone + prednisone: 15.8 months
Placebo: 11.2 months

Abiraterone (n) 797 657 473 273 15 0
Placebo (n) 398 306 183 100 6 0

AFFIRM Overall Survival
Median Benefit 4.8 Months

Enzalutamide: 18.4 months
(95% CI: 17.3–NYR)

Placebo: 13.6 months
(95% CI: 11.3–15.8)

HR=0.631 (95% CI: 0.529, 0.752) p<0.0001
37% reduction in risk of death


No. at risk:
Enzalutamide (n) 800 775 701 627 400 211 72 7 0
Placebo (n) 399 376 317 263 167 81 33 3 0
Radium-223: Mechanism of action

- Calcium mimetic
- Short range of alpha emitter reduces bone marrow exposure
- Selective uptake at bone metastases
Radium-223: ALSYMPCA trial

Phase 3
• 921 patients
• Progressive symptomatic mCRPC
• Prior docetaxel or unfit for docetaxel therapy

Randomized 2:1

Six injections radium-223 chloride 50 kBq/kg IV every 4 weeks (n=614)

Primary endpoint
• OS

Six injections placebo every 4 weeks (n=307)
ALSYMPCA: Overall Survival
3.6 month improvement vs placebo

Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001
22% reduction in risk of death
### Post-Doc options that improve survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trial</th>
<th>Visceral disease allowed</th>
<th>HR</th>
<th>Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabzitaxel/prednisone vs Mitoxantrone/prednisone</td>
<td>TROPIC¹</td>
<td>YES</td>
<td>0.70</td>
<td>15.1 vs 12.7</td>
</tr>
<tr>
<td>Abiraterone/prednisone vs Placebo/prednisone</td>
<td>COU-301²</td>
<td>YES</td>
<td>0.74</td>
<td>14.8 vs 10.9</td>
</tr>
<tr>
<td>Enzalutamide vs Placebo</td>
<td>AFFIRM³</td>
<td>Yes</td>
<td>0.63</td>
<td>18.4 vs 13.6</td>
</tr>
<tr>
<td>Radium 223 vs Placebo /BSC</td>
<td>ALSYMCA⁴</td>
<td>No</td>
<td>0.70</td>
<td>14.1 vs 11.3</td>
</tr>
</tbody>
</table>

¹de Bono et al. Lancet. 2010;376(9747):1147-1154  
³Scher et al. NEJM 2012;367(13):1187-1197  
⁴Parker et al. NEJM 2013;369(2):213-223
Abiraterone and Enzalutamide in mCRPC
Phase III Studies Pre-docetaxel
(Primary Endpoint: rPFS and OS)

COU-AA-302

• n=1088 progressive chemonaïve patients with mCRPC
• Asymptomatic or mildly symptomatic

Abiraterone 1000 mg QD + prednisone 5 mg BID

Placebo BID + prednisone 5 mg BID

PREVAIL

• n=1715 progressive chemonaïve patients with mCRPC
• Asymptomatic or mildly symptomatic
• Visceral mets permitted

Enzalutamide 160 mg QD

Placebo QD

No prednisone

No prednisone
COU-AA-302: Interim Analysis Results of rPFS

HR = 0.43 (95% CI, 0.35–0.52) p < 0.0001
57% reduction in risk of progression

Abiraterone + prednisone: NYR

Placebo: 8.3 months

Data cutoff 12/20/2010

rPFS: Radiological progression-free survival

COU-AA-302: Overall survival 3rd Interim Preplanned Analysis — Median Benefit 5.2 Months

HR = 0.79 (95% CI, 0.66–0.95) p = 0.0151
21% reduction in risk of death

Rathkopf DE et al. J Clin Oncol 2013;31(Suppl 6:abstr 5) ASCO GU; Mulders P. Poster 97; EAU 2013
PREVAIL: Enzalutamide 81% Decrease in Risk of Progression

Hazard Ratio: 0.186
(95% CI: 0.15, 0.23)
P < 0.0001

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at Risk</td>
<td>832</td>
<td>801</td>
</tr>
<tr>
<td>0 1</td>
<td>514</td>
<td>305</td>
</tr>
<tr>
<td>3 6</td>
<td>256</td>
<td>79</td>
</tr>
<tr>
<td>6 9</td>
<td>128</td>
<td>20</td>
</tr>
<tr>
<td>9 12</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>12 15</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>15 18</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>18 21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Estimated median rPFS, months (95% CI): Enzalutamide: NYR (13.8, NYR); Placebo: 3.9 (3.7, 5.4) NYR = Not Yet Reached

Enzalutamide Reduced Risk of Death by 29%

Estimated median OS, months (95% CI):  Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

Enzalutamide: 872
Placebo: 845

Hazard Ratio: 0.706 (95% CI: 0.60, 0.84)  
P<0.0001

Patients at Risk
Enzalutamide 872 863 850 824 797 745 566 395 244 128 33 2 0
Placebo 845 835 781 744 701 644 484 328 213 102 27 2 0

Patients still alive at data cut off
Enzalutamide: 72%; Placebo: 63%

Sipuleucel-T: The IMPACT trial

- N=512
- Asymptomatic or minimally symptomatic mCRPC
- Gleason score ≤7
- Prior docetaxel or unfit for docetaxel therapy
- No visceral metastases

Primary endpoint
- OS

**IMPACT: Overall Survival**

*4.1 month improvement vs placebo*

- **Sipuleucel-T** $n = 341$
  - Median survival: 25.8 months

- **Placebo** $n = 171$
  - Median survival: 21.7 months

*P* = 0.03 (Cox model)

HR = 0.78 [95% CI: 0.61, 0.98]

22% reduction in risk of death

---

IMPACT overall survival: primary endpoint

Intent-to-treat population

## Front-line options that improve survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trial</th>
<th>Visceral disease allowed</th>
<th>HR</th>
<th>Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel/prednisone vs Mitoxantrone/prednisone</td>
<td>TAX 327(^1)</td>
<td>YES</td>
<td>0.79</td>
<td>18.9 vs 16.5</td>
</tr>
<tr>
<td>Sipuleucel-T vs control</td>
<td>IMPACT(^2)</td>
<td>No</td>
<td>0.78</td>
<td>25.8 vs 21.7</td>
</tr>
<tr>
<td>Abiraterone/prednisone vs Placebo/prednisone</td>
<td>COU-302(^3)</td>
<td>No</td>
<td>0.75</td>
<td>NYR vs 27.2</td>
</tr>
<tr>
<td>Enzalutamide vs Placebo</td>
<td>PREVAIL(^4)</td>
<td>Yes</td>
<td>0.70</td>
<td>32.4 vs 30.4</td>
</tr>
<tr>
<td>Radium 223 vs Placebo/BSC</td>
<td>ALSYMCA(^5)</td>
<td>No</td>
<td>0.70</td>
<td>16.1 vs 11.5</td>
</tr>
</tbody>
</table>

\(^5\)Parker et al. NEJM 2013;369(2):213-223
Which drug for which patient?

- How can therapies for mCRPC best be utilized?
- Is there an optimal sequence of therapies?
- Not all patients respond to AR-targeted agents
- Is there cross resistance among therapies?
- None of these new therapies have been directly compared to each other
- Separation of trials into pre and post docetaxel is artificial
- No prospective sequencing trials
Does Progression on Enzalutamide Decrease the Efficacy of Abiraterone, and Vice Versa?

Abiraterone after enzalutamide\textsuperscript{1}

Enzalutamide after abiraterone\textsuperscript{2}

<table>
<thead>
<tr>
<th>Percent Change From Baseline</th>
<th>Maximum PSA Remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>Abiraterone</td>
</tr>
<tr>
<td>-20</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td>-30</td>
<td></td>
</tr>
<tr>
<td>-40</td>
<td></td>
</tr>
<tr>
<td>-50</td>
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<tr>
<td>-60</td>
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<tr>
<td>-70</td>
<td></td>
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<tr>
<td>-80</td>
<td></td>
</tr>
<tr>
<td>-90</td>
<td></td>
</tr>
<tr>
<td>-100</td>
<td></td>
</tr>
</tbody>
</table>

PSA decline >50% = 3%

PSA decline >50% = 29%

# Does Abiraterone Decrease the Efficacy of Docetaxel?

<table>
<thead>
<tr>
<th></th>
<th>TAX327&lt;sup&gt;1&lt;/sup&gt; DOC q3w N=1006</th>
<th>Mezynski&lt;sup&gt;2&lt;/sup&gt; ABI→ DOC q3w N=35</th>
<th>Schweizer&lt;sup&gt;3&lt;/sup&gt; DOC N=95</th>
<th>Schweizer&lt;sup&gt;3&lt;/sup&gt; ABI→ DOC N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA decrease ≥50%</strong></td>
<td>45%</td>
<td>26%</td>
<td>63%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>7.7</td>
<td>4.6</td>
<td>6.7</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>19</td>
<td>12.5</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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Small Retrospective studies

Does Progression on Abiraterone Decreases the Efficacy of Enzalutamide?

<table>
<thead>
<tr>
<th></th>
<th>AFFIRM(^1)</th>
<th>Schrader(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOC→ENZA N=1199</td>
<td>DOC→ABI→ENZ N=35</td>
</tr>
<tr>
<td>PSA decrease ≥50%</td>
<td>54%</td>
<td>29%</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>18.4</td>
<td>8.4 if PSA ↓ ≥50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.4 if PSA ↓ &lt;50%</td>
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</tbody>
</table>

Small Retrospective study

Does Progression on Enzalutamide Decreases the Efficacy of Abiraterone?

<table>
<thead>
<tr>
<th></th>
<th>COU-AA-301 (^{1-2}) DOC→ABI N=1195</th>
<th>Loriot (^{3}) DOC→ENZ→ABI N=38</th>
<th>Noonan (^{4}) DOC→ENZ→ABI N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA decrease ≥50%</td>
<td>38%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.6</td>
<td>2.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>15.8</td>
<td>7.2</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Small Retrospective studies

Does Prior AR Targeted Agent Decrease the Efficacy of Cabazitaxel?

<table>
<thead>
<tr>
<th>Abiraterone or enzalutamide</th>
<th>TROPIC$^{1-2}$</th>
<th>Pezaro$^3$</th>
<th>Angelergues$^4$</th>
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<tbody>
<tr>
<td></td>
<td>none</td>
<td>Before CBx N = 89</td>
<td>Before CBx N = 42</td>
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<tr>
<td>PSA decrease ≥50%</td>
<td>39.2%</td>
<td>49%</td>
<td>42.9%</td>
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<tr>
<td>Partial Response RECIST</td>
<td>14.4%</td>
<td>20%</td>
<td></td>
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<tr>
<td>Median PFS, months</td>
<td>29.4</td>
<td></td>
<td>5.1</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>29.4</td>
<td></td>
<td>38.2</td>
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</table>

Small Retrospective studies

## Retrospective Trials on Sequential Therapy

<table>
<thead>
<tr>
<th>SEQUENCE</th>
<th>Authors</th>
<th>N° pts</th>
<th>PSA response</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>ABI → ENZA</td>
<td>Bianchini</td>
<td>39</td>
<td>12.8</td>
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<td>Schrader</td>
<td>35</td>
<td>28.6</td>
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<td>7.1</td>
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<td>Schmid</td>
<td>35</td>
<td>10</td>
<td>2.8</td>
<td>3.1</td>
<td>7.5</td>
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<td></td>
<td>Badrising</td>
<td>61</td>
<td>21</td>
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<td>Vera-Badillo FE</td>
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<td>27</td>
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<td>4.9</td>
<td>NA</td>
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<td></td>
<td>Sandhu</td>
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<td>17.3</td>
<td>NA</td>
<td>2.3</td>
<td>NA</td>
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<td>Scholz</td>
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<td>NA</td>
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<td>Stevenson</td>
<td>75</td>
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<td>NA</td>
<td>3.96</td>
<td>NA</td>
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<td>ENZA → ABI</td>
<td>Noonan</td>
<td>30</td>
<td>3</td>
<td>11</td>
<td>3.85</td>
<td>12.5</td>
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<td>Loriot</td>
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<td>8</td>
<td>8</td>
<td>2.7</td>
<td>7.2</td>
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<td>ABI → CABA</td>
<td>Albigies</td>
<td>39</td>
<td>56</td>
<td>15</td>
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<td>NA</td>
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<td>Sella</td>
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<td>31.5</td>
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<td>Sonpavde</td>
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<td>NA</td>
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<td>CABA → ABI</td>
<td>Sonpavde</td>
<td>77</td>
<td>NA</td>
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<td>10.4</td>
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<td>ABI/ENZA → CABA</td>
<td>Pezaro</td>
<td>41</td>
<td>39</td>
<td>14</td>
<td>4.6</td>
<td>15.8</td>
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</tbody>
</table>

Courtesy of O. Caffo with modifications
Microtubules Facilitate AR Nuclear Translocation

Androgens Inhibit Tubulin Expression in Prostate Cancer Cells

Zhu et al. Cancer Res 2010;70:7992
Thadani-Mulero M. Cancer Res 2012;72:4611
Inhibition of AR Nuclear Translocation

- Docetaxel (-21%)
- Cabazitaxel (-31%)
- Abiraterone
- Enzalutamide
- Vehicle
- Mitoxantrone

Response to therapy according to prior duration of ADT

Hormonal therapy
- Retrospective analysis in 108 patients with metastatic PCa

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>&lt;16 months</th>
<th>≥16 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ PSA ≥50%</td>
<td>18%</td>
<td>58%</td>
<td>0.01</td>
</tr>
<tr>
<td>Median TTP, months</td>
<td>3.0</td>
<td>5.0</td>
<td>&lt;0.043</td>
</tr>
</tbody>
</table>

Docetaxel
- 188 patients with mCRPC in two prospective databases

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>≤1 year</th>
<th>&gt;1 year</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ PSA ≥50%</td>
<td>67%</td>
<td>81%</td>
<td>0.10</td>
</tr>
<tr>
<td>Median TTP, months</td>
<td>6.1</td>
<td>7.8</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Including abiraterone, ketoconazole, hydrocortisone, DES and bicalutamide).
Benefit with enzalutamide irrespective of duration of prior response to ADT

- *Post-hoc* analysis post-chemotherapy AFFIRM trial

<table>
<thead>
<tr>
<th>Duration of response to ADT</th>
<th>≤12 months</th>
<th>12–26.9 months</th>
<th>&gt;26.9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to radiographic progression, median (months)</td>
<td>ENZ</td>
<td>Placebo</td>
<td>ENZ</td>
</tr>
<tr>
<td>5.7</td>
<td>2.8</td>
<td>8.3</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.44 (0.33–0.60)</td>
<td>0.42 (0.31–0.58)</td>
<td>0.33 (0.23–0.46)</td>
</tr>
<tr>
<td>OS, median (months)</td>
<td>15.4</td>
<td>9.1</td>
<td>NYR</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.34–0.70)</td>
<td>0.69 (0.47–1.01)</td>
<td>0.54 (0.35–0.82)</td>
</tr>
</tbody>
</table>

de Bono JS, *et al.* ECC 2013; Poster presentation P369.
OS and rPFS with abiraterone according to baseline Gleason score

- *Post-hoc* analysis Phase 3 COU-AA-301 and COU-AA-302 trials

<table>
<thead>
<tr>
<th></th>
<th>Gleason score &lt;8</th>
<th></th>
<th>Gleason score ≥8</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (months)</td>
<td>HR (95% CI)</td>
<td>Median (months)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>AA + P</td>
<td></td>
<td></td>
<td>AA + P</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>mCRPC post-docetaxel</td>
<td></td>
<td></td>
<td>mCRPC chemotherapy-naïve</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>342</td>
<td>161</td>
<td>356</td>
<td>189</td>
</tr>
<tr>
<td>OS</td>
<td>16.3</td>
<td>13.4</td>
<td>15.5</td>
<td>10.3</td>
</tr>
<tr>
<td>rPFS</td>
<td>6.4</td>
<td>5.5</td>
<td>5.6</td>
<td>2.9</td>
</tr>
</tbody>
</table>

OS and rPFS with enzalutamide according to baseline Gleason score

**Post-hoc analysis Phase 3 AFFIRM and PREVAIL trials**

<table>
<thead>
<tr>
<th></th>
<th>Gleason score &lt;8</th>
<th></th>
<th>Gleason score ≥8</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (months)</td>
<td>HR (95% CI)</td>
<td>Median (months)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>ENZ</td>
<td></td>
<td></td>
<td>ENZ</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>mCRPC post-docetaxel¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>360</td>
<td>0.67 (0.51–0.88)</td>
<td>366</td>
<td>0.60 (0.47–0.76)</td>
</tr>
<tr>
<td>OS</td>
<td>18.4</td>
<td></td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>rPFS</td>
<td>–</td>
<td></td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>mCRPC chemotherapy-naïve²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>414</td>
<td>0.66 (0.51–0.85)</td>
<td>424</td>
<td>0.77 (0.60–0.97)</td>
</tr>
<tr>
<td>OS</td>
<td>NYR</td>
<td>30.0</td>
<td>31.5</td>
<td>30.2</td>
</tr>
<tr>
<td>rPFS</td>
<td>14.1</td>
<td>0.16 (0.11–0.22)</td>
<td>NYR</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Primary resistance to AR-targeted agents

Radiological progression-free survival

Abiraterone\(^1\) (COU-AA-301)

- Primary resistance 1 out of 3 patients

Enzalutamide\(^2\) (AFFIRM)

- Primary resistance 1 out of 4 patients

Who are the non responders to abiraterone?

Primary resistance in 1 out of 4 patients

Who are the NON responders?
(defined as patients treated for ≤4 months)

Bone marrow biopsy:
- Intense AR nuclear expression
- CYP17 expression

- YES 82% responders (12/13)
- NO 18% responders (2/12)

P<0.001

AR-V7 as a predictor of treatment outcome to enzalutamide and abiraterone in mCRPC

AR-V7 characteristics
- Most abundant splice variant
- Constitutively active
- 20-fold increased expression in mCRPC
- Produces functional protein product unaffected by nonsense-mediated mRNA decay

PSA responses according to AR-V7 status

- Patients previously receiving chemotherapy, abiraterone or enzalutamide were included

rPFS according to AR-V7 status

- Prospective biomarker study of 62 patients receiving enzalutamide or abiraterone

**Enzalutamide**

- HR = 8.5 (95% CI: 2.8–25.5) \( p < 0.001 \)

**Abiraterone**

- HR = 16.5 (95% CI: 3.3–82.9) \( p < 0.001 \)

AR-V7 associated with primary and acquired resistance to enzalutamide and abiraterone

- Prospective biomarker study of 62 patients receiving enzalutamide or abiraterone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AR-V7(-) to AR-V7(-) (n=36)</th>
<th>AR-V7(-) to AR-V7(+) (n=6)</th>
<th>AR-V7(+) to AR-V7(+) (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA response, % (95% CI)</td>
<td>68 (52–81)</td>
<td>17 (4–58)</td>
<td>0 (0–19)</td>
</tr>
<tr>
<td>PSA PFS, months (95% CI)</td>
<td>6.1 (5.9–NYR)</td>
<td>3.0 (2.3–NYR)</td>
<td>1.4 (0.9–2.6)</td>
</tr>
<tr>
<td>PFS, months (95% CI)</td>
<td>6.5 (6.1–NYR)</td>
<td>3.2 (3.1–NYR)</td>
<td>2.1 (1.9–3.1)</td>
</tr>
</tbody>
</table>

Antonarakis E, et al. ASCO 2014; oral presentation abstract 2910.
Co-Targeting Androgen Receptor and Androgen Biosynthesis

Maximal PSA Decline

≥PSA 50 decline in 78% of patients (47 out of 60)
≥PSA 90 decline in 50% of patients (30 out of 60)
PSA ≤ 0.1 ng/ml in 13% of patients (8 out of 60)

Exploratory: association of lack of PSA decline with primary resistance (p=0.008)

Efstathiou E et al. presented at ASCO 2014, abstract 5000
ALLIANCE Study Design
Phase III Pre-chemo

Phase 3 trial of enzalutamide versus enzalutamide, abiraterone + prednisone in mCRPC pre-chemotherapy

- 1224 patients with progressive mCRPC
- No prior taxane for M+ disease

Total of 616 deaths, log-rank statistic 90% power (one sided type I error rate of 0.025) to detect HR of 0.77 in favor of arm B

Primary endpoint:
- OS
PLATO: Continued enzalutamide treatment in prostate cancer patients

Period 1: Open-label enzalutamide
- Enzalutamide 160 mg QD
- PSA response evaluation (Week 13)
- Continue enzalutamide until confirmed PSA progression**
- Safety Follow-up
- No PSA response

Period 2: Randomized treatment
- 1:1
- Enzalutamide 160 mg QD + Abiraterone acetate 1000 mg QD + Prednisone 5 mg BID
- Placebo + Abiraterone acetate 1000 mg QD + Prednisone 5 mg BID
- Continue therapy until radiographic or unequivocal clinical progression or death
- Safety follow-up

• Phase 4, randomized, double-blind, placebo-controlled study
• Patients with metastatic CRPC (n=500)
  • No prior chemotherapy or prior treatment with abiraterone acetate
  • Primary endpoint: progression-free survival (PFS)

ClinicalTrials.gov:/NCT01995513
Ongoing combination studies: Abiraterone or enzalutamide with radium-223

**Phase 3¹**
- 560 patients with mCRPC to the bone
- Ongoing ADT
- Asymptomatic/mildly symptomatic

**Endpoints**
- rPFS
- OS
- PCSS
- Time to first SRE

**Radium-223 (50 kBq/kg)**
- 6 monthly
- + enzalutamide (160 mg QD)

**Enzalutamide (160 mg QD)**

**Phase 3²**
- 800 patients with chemotherapy-naïve mCRPC to the bone
- Testosterone ≤50 ng/dL
- Asymptomatic/mildly symptomatic
- ECOG PS 0–1

**Endpoints**
- SSE-FS
- OS
- Time to opiate use for cancer pain, pain progression and cytotoxic therapy

**Radium-223 (50 kBq/kg)**
- + abiraterone (1000 mg QD)
- + prednisone (5 mg BID)

**Placebo**
- + abiraterone (1000 mg QD)
- + prednisone (5 mg BID)

---

1. NCT02194842. Available at http://clinicaltrials.gov..
Early Chemo + ADT

- **Pro**
  - Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
  - Some patients at the time of progression are too frail for chemo

- **Con**
  - ADT will take cells out of cycle and be less responsive to cytotoxics
  - Some patients respond for a long time and never need chemo
**E3805-CHAARTED Treatment**

**STRATIFICATION**
- Extent of Mets: High vs Low
- Age: ≥70 vs < 70yo
- ECOG PS: 0-1 vs 2
- CAB: > 30 days vs No
- SRE Prevention: Yes vs No
- Prior Adjuvant ADT: ≤12 vs > 12 months

**RANDOMIZE**

**ARM A:**
- ADT + docetaxel 75mg/m2 every 21 days for maximum 6 cycles

**Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks**

**Follow for time to progression and overall survival**
- Chemotherapy at investigator’s discretion at progression

**ARM B:**
- ADT (androgen deprivation therapy alone)

**Evaluate every 12 weeks**

**• ADT allowed up to 120 days prior to randomization**
**• Intermittent ADT dosing was not allowed**
**• Standard dexamethasone premedication but no daily prednisone**
Primary endpoint: Overall survival

HR = 0.61 (0.47-0.80) \ p = 0.0003

Median OS:
- ADT + D: 57.6 months
- ADT alone: 44.0 months

Presented by: Christopher J. Sweeney, MBBS
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
Current treatment paradigm is evolving

Androgen deprivation therapy (ADT)

Therapies after ADT

Hormone sensitive

mCRPC asymptomatic (failed ADT)

mCRPC mildly symptomatic

mCRPC symptomatic

mCRPC post-docetaxel

Local therapy

Death

ADT

Abiraterone

Enzalutamide

Abiraterone

Enzalutamide

Radium 223

Docetaxel

Cabazitaxel

Sipuleucel-T

supportive care (eg denosumab/bisphosphonates)

ADT + Docetaxel in high risk?
Therapeutic strategies for metastatic CRPC

- Prostate cancer is a heterogeneous disease
- Unequivocal evidence of continued involvement of the AR signaling axis
- Multiple new treatments available with proven OS benefit
- Evidence of cross resistance among agents targeting AR
- Best sequence and combination is undefined – prospective trials
- Clinical or molecular predictive factors are urgently needed
Thank you