Management of mCRPC
State of the art in 2018

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Disclosure

• Research grant agreement:
  – Sanofi, Janssen, Astellas

• Consulting agreements with:
  – Astellas  AstraZeneca
  – Janssen    Roche
  – MSD       Sanofi
Castrate-resistant prostate cancer (CRPC) Definition

Castrate serum testosterone
<50 ng/mL or 1.7 nmol/L

+ either

Biochemical progression
3 consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL

OR

Radiological progression
The appearance of ≥2 bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)

PSA: prostate-specific antigen
## Phase III clinical trials in mCRPC

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>N</th>
<th>Indication</th>
<th>HR</th>
<th>Δ OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX-327¹</td>
<td>DOC/P vs mito/P</td>
<td>1,006</td>
<td>mCRPC</td>
<td>0.76</td>
<td>+2.9</td>
</tr>
<tr>
<td>IMPACT²</td>
<td>Sipuleucel-T vs pbo</td>
<td>512</td>
<td>mCRPC (pre-DOC)</td>
<td>0.78</td>
<td>+4.1</td>
</tr>
<tr>
<td>COU-AA-302³</td>
<td>ABI/P vs P</td>
<td>1,088</td>
<td>mCRPC (pre-DOC)</td>
<td>0.81</td>
<td>+4.4</td>
</tr>
<tr>
<td></td>
<td>COU-AA-301⁴</td>
<td>ABI/P vs P</td>
<td>mCRPC (post-DOC)</td>
<td>0.74</td>
<td>+4.6</td>
</tr>
<tr>
<td>PREVAIL⁵</td>
<td>ENZ vs pbo</td>
<td>1,717</td>
<td>mCRPC (pre-DOC)</td>
<td>0.71</td>
<td>+2.2 (est)</td>
</tr>
<tr>
<td>AFFIRM⁶</td>
<td>ENZ vs pbo (or P)</td>
<td>1,199</td>
<td>mCRPC (post-DOC)</td>
<td>0.63</td>
<td>+4.8</td>
</tr>
<tr>
<td>TROPIC⁷</td>
<td>CAB/P vs mito/P</td>
<td>755</td>
<td>mCRPC (post-DOC)</td>
<td>0.70</td>
<td>+2.4</td>
</tr>
<tr>
<td>ALSYMPCA⁸</td>
<td>Radium-223 vs pbo</td>
<td>921</td>
<td>mCRPC</td>
<td>0.70</td>
<td>+2.8</td>
</tr>
</tbody>
</table>

ABI: abiraterone; CAB: cabazitaxel; DOC: docetaxel; HR: hazard ratio; OS: overall survival; P: prednisone; pbo: placebo; mito: mitoxantrone

Which drug for which patient?
Docetaxel rechallenge in mCRPC pts

- **In selected patients**¹⁻⁶:
  - Good initial responders (PSA decrease ≥ 50%)¹⁻⁶
  - With Long progression-free interval (≥ 6 months) since last docetaxel administration⁶

- **In case of no cumulative toxicity**⁵,⁶

- **Increased toxicity with subsequent rechallenges**⁶
  - Asthenia and Peripheral neuropathy +++

Frozen gloves/socks can reduce docetaxel-induced nail and skin toxicity

### Skin toxicity (P < 0.0001)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control (n = 45)</th>
<th>Glove (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38%</td>
<td>67%</td>
</tr>
<tr>
<td>1</td>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Lost</td>
<td>9%</td>
<td>9%</td>
</tr>
</tbody>
</table>

### Nail toxicity (P < 0.0001)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Control (n = 45)</th>
<th>Glove (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>49%</td>
<td>89%</td>
</tr>
<tr>
<td>1</td>
<td>29%</td>
<td>11%</td>
</tr>
<tr>
<td>2</td>
<td>22%</td>
<td>0</td>
</tr>
</tbody>
</table>

Scotté F et al, J Clin Oncol 2005;23:4424-9
Scotté F et al, Cancer 2008;112:1625-31
Prostate cancer progression in low testosterone environment: 2 co-existing mechanisms

- Luminal secretory cells (AR+)
- Intermediate cells (AR-)
- Transit amplifying cells (AR-)
- Prostate adult stem cells (AR-)

**ADT**
- Massive apoptosis of luminal AR+ cells

**ADAPTATION**
- Allows growth in low testosterone environment

**CLONAL PROLIFERATION**
- (AR- cells)

Tombal B et al, Eur J Cancer 2011;47:S179-88
Co-existence of AR-positive and AR-negative tumour cells in the same patient

Beltran H. Cancer discovery 2011; 1: 487-95
Primary resistance to AR-targeted agents

Radiological progression-free survival (rPFS)

ABI+P (COU-AA-301)\(^1\)

Primary resistance 1 out of 3 patients

ENZ±P (AFFIRM)\(^2\)

Primary resistance 1 out of 4 patients

- COU-AA-301 and AFFIRM primary endpoint was OS.

Who are the non-responders to ABI?

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)

Phase II trial in 62 patients with mCRPC treated with ABI + P

Transiliac bone marrow biopsies before, at 8 weeks and at end of treatment

P < 0.001

Efstathiou E et al, J Clin Oncol 2011;30:637-43
No PSA decline ≥ 30% at 1 month predicts poor response to AR-targeted agents.

No PSA Decline With ABI Associated With Poor rPFS and Poor OS (COU-AA-302)

ABI, abiraterone; rPFS, radiographic progression

No PSA Decline With ENZA Associated With Poor rPFS, Poor Pain Relief and Worse OS (AFFIRM)

Lack of PSA decline by 80 days following ENZA initiation associated with poor outcomes

ENZA, enzalutamide

Armstrong A et al, Cancer 2017;123:2303-2311
Patients progressing with an AR-targeted agent poorly respond to a another one

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>N pts</th>
<th>Duration of 2\textsuperscript{nd} treatment</th>
<th>↓ PSA ≥ 50%</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENZ → ABI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loriot et al.</td>
<td>2013</td>
<td>38</td>
<td>3 mo</td>
<td>8%</td>
<td>2.7 mo</td>
</tr>
<tr>
<td>Noonan et al.</td>
<td>2013</td>
<td>30</td>
<td>13 wks</td>
<td>3%</td>
<td>3.6 mo</td>
</tr>
<tr>
<td>ABI → ENZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schrader et al.</td>
<td>2013</td>
<td>35</td>
<td>4.9 mo</td>
<td>29%</td>
<td>-</td>
</tr>
<tr>
<td>Badrising et al.</td>
<td>2014</td>
<td>61</td>
<td>3 mo</td>
<td>21%</td>
<td>-</td>
</tr>
<tr>
<td>Bianchini et al.</td>
<td>2014</td>
<td>39</td>
<td>2.9 mo</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>Schmid et al.</td>
<td>2014</td>
<td>35</td>
<td>2.8 mo</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>Brasso et al.</td>
<td>2014</td>
<td>137</td>
<td>3.2 mo</td>
<td>18%</td>
<td>-</td>
</tr>
</tbody>
</table>

Retrospective trials based on a small number of patients

Combination of AR-targeted agents does not overcome primary resistance

- 3 different open-label phase II studies of 60 pts with bone mCRPC treated with ABI/P, ENZ, or combination of both
- Transiliac bone marrow biopsies before tt, at 8 weeks and at end of treatment

- **mPFS**: 5.7 months in the combination group vs 5.6 months in the control group (HR: 0.83; P = 0.22).
- **Secondary end points**: no difference.
- **Tolerability**: Grade 3 hypertension (10% v 2%) and increased ALT (6% v 2%) or AST (2% v 0%) more frequent in the combination than the control group.

Attard G et al, JCO 2018; Sep 1;36(25):2639-2646
### Impaired activity of docetaxel Post ABI?

<table>
<thead>
<tr>
<th></th>
<th>DOC therapy line</th>
<th>Visceral mets</th>
<th>↓ PSA ≥50%</th>
<th>Median PSA-PFS (mths)</th>
<th>OS, median (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VENICE</strong>¹ DOC/Pbo n=612</td>
<td>1</td>
<td>YES</td>
<td>63.5%*</td>
<td>8.1</td>
<td>21.2</td>
</tr>
<tr>
<td><strong>De Bono</strong>² ABI→DOC n=35</td>
<td>2</td>
<td>YES</td>
<td>25.7%*</td>
<td>4.6</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Schweizer</strong>³ ABI→DOC n=95</td>
<td>1</td>
<td>YES</td>
<td>63.0%*</td>
<td>6.7</td>
<td>-</td>
</tr>
<tr>
<td><strong>Azad</strong>⁴ ABI→DOC n=86</td>
<td>2</td>
<td>YES</td>
<td>38.0%*</td>
<td>4.1</td>
<td>-</td>
</tr>
<tr>
<td><strong>De Bono</strong>⁵ (COU-AA-302) ABI→DOC n=261</td>
<td>2</td>
<td>NO</td>
<td>35.0%*</td>
<td>4.0</td>
<td>11.7</td>
</tr>
</tbody>
</table>

**↓ PSA ≥50%**

- **VENICE**: 63.5%*
- **De Bono**: 25.7%*
- **Schweizer**: 63.0%*
- **Azad**: 38.0%*
- **De Bono**: 35.0%*

**Median PSA-PFS (mths)**

- **VENICE**: 8.1
- **De Bono**: 4.6
- **Schweizer**: 6.7
- **Azad**: 4.1
- **De Bono**: 4.0

**OS, median (mths)**

- **VENICE**: 21.2
- **De Bono**: 12.5
- **Schweizer**: -
- **Azad**: -
- **De Bono**: 11.7

[2-5] = retrospective analyses; *confirmed PSA responses; **TTPP: time to PSA progression (not PSA-PFS) was obtained in only 100 patients

## ABI or ENZA Prior to CABA – No impact?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year Published</th>
<th>N pts</th>
<th>Visceral Mets, %</th>
<th>↓ PSA ≥50%</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prior ABI or ENZA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Bono&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2010</td>
<td>378</td>
<td>25%</td>
<td>39.2%</td>
<td>2.8 mo</td>
</tr>
<tr>
<td><strong>ABI or ENZA → CABA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pezaro&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2012</td>
<td>37</td>
<td>35%</td>
<td>41%</td>
<td>5.5 mo</td>
</tr>
<tr>
<td>Al Nakouzi&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2014</td>
<td>79</td>
<td>14%</td>
<td>35%</td>
<td>4.4 mo</td>
</tr>
<tr>
<td>Sella&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2014</td>
<td>24</td>
<td>29%</td>
<td>31.5%</td>
<td>-</td>
</tr>
<tr>
<td>Wissing&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2014</td>
<td>Prior ABI, 69 No ABI, 63</td>
<td>-</td>
<td>31.9% 49.2%</td>
<td>6.5 mo 8.1 mo</td>
</tr>
</tbody>
</table>

[1] is a prospective randomized study of CABA/P vs Mito/P in mCRPC (post-DOC); [2 and 5] trials are retrospective studies in mCRPC pts (post-DOC).

**ABI:** abiraterone acetate; **ENZA:** enzalutamide; **CABA:** cabazitaxel; **P:** prednisone; **Mito:** mitoxantrone

CARD study
A ‘practice changing’ trial

mCRPC with primary resistance to an AR-targeted agent (progression ≤ 12 months on ABI or ENZA) before or after Docetaxel

n=324

Stratification factors:
- ECOG PS (0/1 vs 2),
- Time to progression (≤6 vs 6–12 mo),
- Timing of AR-targeted agent (before vs after DOC)

Primary endpoint: radiographic PFS
Secondary endpoints: PSA response, ECOG PS, PFS (clinical or radiological), objective tumor response, pain, QoL, time to SSEs, OS, safety, biomarkers

Sponsor: Sanofi

n=162

n=162

1:1

CABAZITAXEL

Swith to another AR-targeted agent (ABI or ENZA depending of first therapy)

NCT02485691. ClinicalTrials.gov.
How to identify patients poorly responding to AR-targeted agents?
Short response to 1\textsuperscript{st} ADT may predict poor response to Enza

- Retrospective cohort of 173 patients, including 57 treated with enzalutamide in AFFIRM phase III trial

### PSA decrease $\geq 50%$

<table>
<thead>
<tr>
<th>TTCRPC</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 mo</td>
<td>8%</td>
</tr>
<tr>
<td>$\geq$ 12 mo</td>
<td>58%</td>
</tr>
</tbody>
</table>

$P<0.001$

### TTCRPC and PFS

- TTCRPC: time to castration resistance; PFS: progression-free survival
- HR: 0.58 (95% CI: 0.42-0.82)
- Median PFS: 5.8 mo vs 2.8 mo
- Log-rank $P=0.002$

Optimal management of mCRPC: highlights from a European Expert Consensus Panel

- **Early imaging** should be performed to detect primary resistance to novel agents targeting the AR pathway.

3 months recommended as the appropriate minimum time point based on the imaging modalities currently available.

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Of 265 chemonaive mCRPC patients with radiological progression and evaluable PSA levels on ENZA, 65 (24.4%) had a non rising PSA

Monitoring mCRPC patients by PSA alone is not enough
Patients with Radiological Progression & No PSA Progression Have a Worse Prognosis (PREVAIL)

Monitoring mCRPC patients by PSA alone is not enough

Bryce AH et al, Prostate Cancer Prostatic Dis 2017; 20: 221-227
Timing of Progression Events with First-Line AR-Targeted Agents (COU-AA-302 or PREVAIL)

- **Bony mCRPC ABI or ENZA Initiation**
  - 11 mths\(^{1-3}\)
  - \(\text{PSA} \uparrow\)
  - 5-9 mths\(^{1-4}\)
  - Radiological Progression
  - 8-9 mths\(^{1-3}\)
  - Clinical Progression

**Insidious PSA Low Progression (25\%)\(^5\)**

Most patients unfit to receive chemo at that stage

COU-AA-302 – Post-Hoc Analysis
Pain Associated with Worse Prognosis with ABI

Switch to another life-extending therapy before symptom progression
→ Regular radiological monitoring

ABI, abiraterone; BPPI-SF, Brief Pain Inventory- Short Form; P, prednisone

Mild pain associated with worse OS in mCRPC treated with 1Line Chemotherapy

Retrospective analysis of 145 mCRPC pts treated with first-line chemotherapy at HEGP from 2000 to 2002

Oudard S et al. BJU Int 2009; 103: 1641-46
CATS international database

- Retrospective review of 669 consecutive mCRPC patients treated in daily practice with 3 LETs in 7 countries (France, Austria, Greece, Italy, Israel, Spain, UK) from 2012 to 2016

- Type of progression at initiation of LETs [PSA only, radiological (± PSA), clinical (± PSA ± Radiological)*)] evaluable in 661 patients

ART: next generation AR-targeted agent (abiraterone acetate or enzalutamide) ; LET: Life-extending Therapy
*Clinical progression defined by worsening of cancer related pain or symptoms as per physician judgment

Delanoy N et al, Eur Urol Oncol 2018 (epub ahead of print); Oudard S et al, ASCO 2018 (abstract e17007)
### Progression type at initiation of each LET

| Type of progression       | First LET  
N = 661 pts | Second LET  
N = 630 pts | Third LET  
N = 617 pts |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA rise only</strong></td>
<td>151 (22.8%)</td>
<td>142 (22.5%)</td>
<td>91 (14.7%)</td>
</tr>
<tr>
<td><strong>Radiological progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No PSA rise</td>
<td>225 (34%)</td>
<td>140 (22.2%)</td>
<td>107 (17.3%)</td>
</tr>
<tr>
<td></td>
<td>35/225 (15.6%)</td>
<td>26/140 (18.6%)</td>
<td>22/107 (20.6%)</td>
</tr>
<tr>
<td><strong>Clinical progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No PSA rise</td>
<td>285 (43.1%)</td>
<td>348 (55.2%)</td>
<td>419 (67.9%)</td>
</tr>
<tr>
<td></td>
<td>24/285 (8.4%)</td>
<td>79/348 (22.7%)</td>
<td>85/419 (20.3%)</td>
</tr>
</tbody>
</table>

Clinical progression at LET initiation increases with the number of lines.

LET: life-extending therapies

Oudard et al, ASCO 2018 (abstract e17007)
OS by progression type at initiation of 1\textsuperscript{st} LET in the CATS study

- Median 44.9 mths [95% CI, 38.0; 49.4]
- Median 37.85 mths [95% CI, 35.1; 44.2]
- Median 30.7 mths [95% CI, 27.5; 32.9]

Log rank p<0.001

Clinical progression associated with worse OS

LET: life extending therapy

Oudard et al, ASCO 2018 (abstract e17007)
AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

Constitutively active splice variant

AR-FL: Full-Length Androgen Receptor; NTD: N-Terminal Domain; DBD: DNA-Binding Domain; LBD: Ligand-Binding Domain; U: Unique N- or C-terminal sequence
AR-V7 in CTCs seems a promising predictor of treatment response


Data support an association between AR-V7 and resistance to abiraterone and to enzalutamide

PSA response rate:

**Abiraterone**

- AR-V7 positive: 0% (95% CI: 0-46%)
- AR-V7 negative: 68.0% (95% CI: 46-85%)
- \( P = 0.004 \)

**Enzalutamide**

- AR-V7 positive: 0% (95% CI: 0-46%)
- AR-V7 negative: 52.6% (95% CI: 29-76%)
- \( P = 0.004 \)

**Taxane**

- AR-V7 negative: 65% (95% CI: 41-85%)
- \( P = 0.19 \)

CTC: circulating tumour cell


*Docetaxel, N=30
Cabazitaxel, N=7
Is there an optimal sequence of life-extending therapies?
Systematic review of 13 published retrospective studies in mCRPC (n=1016)

12-month OS rate by sequence in post-Docetaxel

Survival %

0 10 20 30 40 50 60 70 80 90 100

0 1 2 3 4 5 6 7 8 9 10 11 12

Months

Poor outcome when ART are prescribed in sequence

ART: Androgen receptor targeted agents; CABA: cabazitaxel

FLAC International database (HEGP)

- Records of 387 consecutive mCRPC patients treated with cabazitaxel after docetaxel in 5 countries (France, Greece, Spain, Turkey)

- Retrospective data collection:
  - Disease history (duration and response to 1st ADT), treatment sequences received, clinical characteristics at initiation of the next life-extending therapy post-docetaxel (i.e., cabazitaxel or ART)
  - Efficacy of cabazitaxel (PSA response, radiological and/or clinical PFS)
  - Overall survival

FLAC study - OS from diagnosis of mCRPC

FLAC - OS from First life-extending therapy received in mCRPC

Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database

CATS International Database

- Retrospective analysis of 669 consecutive patients treated with DOC, CABA and one ART in 34 centers in 8 countries (France, Austria, Greece, Italy, Israel, Denmark, Spain, UK)

669 mCRPC pts treated with DOC, CABA and ART

DOC → CABA → ART (N=158)

DOC → ART → CABA (N=456)

ART → DOC → CABA (N=55)

Doc: docetaxel; CABA: Cabazitaxel; ART: Androgen Receptor–Targeted agent

Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database

Doc: docetaxel; CABA: Cabazitaxel; ART: Androgen Receptor–Targeted agent

PSA response on DOCETAXEL was lower in post ART than upfront (p=0.02)

Doc: docetaxel; CABA: Cabazitaxel; ART: Androgen Receptor–Targeted agent; LET: first life-extending
PSA response on DOC was lower in post ART than upfront (p = 0.02)

PSA response on CABA was higher in 2nd than 3rd line (p = 0.001)
Overall Survival by treatment sequence in the CATS study

- mOS was longer in DOC starting sequence compared to ART (p= 0.007).
- CABA seemed to retain its activity regardless of treatment sequence.

Delanoy N et al, Eur Urol Oncol 2018 (epub ahead of print)
Cabazitaxel every two weeks: is it not a new drug?

- 2 teams have evaluated adapted schedules of administration of Cabazitaxel 16 mg/ m²/ 2 weeks with Prednisone:
  - A French monocenter study (EGP)¹: 27 pts with G-CSF
  - A Finnish multicenter (Prosty II)²: 40 pts wo G-CSF

- **Safety profile:**
  - Good tolerability with less diarrhea
  - Lower hematotoxicity than in the TROPIC trial.

- **Efficacy¹:**
  - PSA response ≥ 50%: 42.3%
  - Time to PSA progression: 3.4 mths

<table>
<thead>
<tr>
<th>Grade ¾ toxicity</th>
<th>Prosty</th>
<th>French trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>3 (7.5%)</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (15%)</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>NR</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>NR</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (2.5%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>NR</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>sepsis</td>
<td>1 (2.5%)</td>
<td>1 (4.2%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (2.5%)</td>
<td>/</td>
</tr>
</tbody>
</table>

¹Clément-Zhao A et al, BJU Int. 2018 Feb;121(2):203-208
²Kellokumpu-Lehtinen PL et al, abstract 276, ASCO GU 2015
CABASTY phase III randomized trial in mCRPC

- Progressive mCRPC patients
- Age ≥70 years
- Prior DOC
- ECOG PS status: 0-2

N=170 pts

Countries: France, Germany, Finland, Sweden

Prophylactic G-CSF in all patients

Primary endpoint: incidence of grade ≥3 neutropenia and/or neutropenic infection

Secondary endpoints: dose intensity, PSA response, PFS, OS, quality of life, geriatric evaluation

https://clinicaltrials.gov/ct2/show/NCT02961257
Prior abi or enza or enza naïve

with abi or enza

Concurrent abi or enza as 2nd line

**mOS**: 17 months

**TEAE**: 93/184 (51%) pts during treatment and 11 (6%) during FU

**Post hoc analyses**: pts with 3 prior anticancer medications, baseline ECOG PS 2, and lower baseline hemoglobin received less cycle of radium 223 and unlikely to benefit from radium-223.

**Tolerability**: Radium-223 well tolerated regardless of concurrent or prior abiraterone or enzalutamide.

Phase III randomized studies on radium 223 in mCRPC pts with abiraterone + Prednisone or enzalutamide

**Phase III ERA223 trial**
- Phase III, multicenter study, placebo-controlled
- Primary endpoint: symptomatic skeletal event-free survival (SSE-FS)

**Stratification factors**
- Use of bone health agents
- Total alkaline phosphatase
- Geographic region

**Planned evaluations**
- OS
- Time to first skeletal-related event (SRE)
- Time to cytotoxic chemotherapy
- RrPFS
- QoL

**Statistical analysis**
- 389 events to detect a 39% increase in SSE-FS
- 90% power
- 8.2 month difference (29.2 vs 21 months)
- 2-sided type 1 error 0.05

**Recruiting**
- R2:1

**EORTC PEACE III study**
- A Phase 3, randomised, multicentre study
- Primary endpoint: rPFS

**Planned evaluations**
- rPFS
- OS
- TT first SRE
- Subsequent therapy
- Pain
- QoL

**Statistical analysis**
- 233 events (Month 51)
- 90% power
- 9 month difference (17 vs. 26 months)
- 1-sided type 1 error 0.025

**Recruiting**
- R2:1

---

Bayer, the manufacturer of radium-223, reported that the unblinding follows the recommendation of an IDMC, which observed more fractures and deaths in patients receiving both radium-223 and abiraterone acetate compared with patients receiving abiraterone alone (1 December 2017, press release).
PTEN Loss as a Predictive Biomarker for the Akt Inhibitor Ipatasertib + Abiraterone Acetate in mCRPC pts

• Co-Primary Endpoint: rPFS With 400 mg Ipatasertib or Placebo + Abiraterone by ICR IHC

<table>
<thead>
<tr>
<th></th>
<th>ICR IHC PTEN Loss</th>
<th>ICR IHC PTEN Non-Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipat 400 mg + Abi</td>
<td>Median 4.6 mo</td>
<td>Median 5.6 mo</td>
</tr>
<tr>
<td>Pbo + Abi</td>
<td>Median 11.5 mo</td>
<td>Median 7.5 mo</td>
</tr>
</tbody>
</table>

HR\(^a\), 0.39 (0.22-0.70) HR\(^a\), 0.84 (0.51-1.37)

► rPFS was prolonged in the ipatasertib 400 mg + abiraterone arm vs the placebo + abiraterone arm in the primary analysis

Dx, diagnostic.\(^a\) Unstratified HR; 90% CI; P value from log-rank test.

De Bono J et al, ESMO 2016, abstract 718O
Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial


intention-to-treat population

Olaparib + AAP: clinical efficacy benefit in mCRPC compared to AAP alone
Conclusions

• Prostate cancer is a heterogeneous disease
• Short response to ADT in 1st-line seem prognostic and predictive of lower response to AR-targeted agents
• AR-V7 splice variant evaluation in CTCs is promising but requires validation
• Cross resistance between new hormonal treatments (abi-enza; enza-abi)
• Survival benefit is related to the number of life-extending therapies received
• Do not miss the window of opportunity for chemotherapy
• Personalized medecine (PARP and pTEN inhibitors) seem promosing
• Treatment choice should be based on MDT
• Patients should be put into clinical trials