Key topics in locally advanced, advanced and metastatic PCa

N. Mottet
Urology department
St Etienne
Chairman EAU-ESTRO-ESUR-SIOG prostate cancer guidelines
Disclosures

Type of affiliation / financial interest

Receipt of grants/research supports:

Name of commercial company
Takeda pharmaceutical / Millenium, Astellas, Pierre Fabre, Sanofi, Pasteur

Receipt of honoraria or consultation fees:

Astellas, Jansen, BMS, Bayer, IPSEN, Ferring, Pierre Fabre, Roche, Sanofi, Steba,

Participation in a company sponsored speaker’s bureau:

None

Stock shareholder:

None

Spouse/partner:

None

Other support (please specify):

None
Locally advanced: local treatment needed

N = 1205,
T3/T4 N0/Nx (70%) OR T2, PSA > 40 µg/l
OR T2, PSA > 20 µg/ml, Gleason: 8-10

Mason J Clin Oncol 2015
## ADT plus RT in locally advanced PCa

<table>
<thead>
<tr>
<th>Design</th>
<th>RTOG 85-31 (N=977)</th>
<th>EORTC 22863 (N=415)</th>
<th>EORTC 22961 (N=970)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT+immediate ADT vs RT+ADT at relapse</strong></td>
<td><strong>RT alone vs RT+3 yr ADT</strong></td>
<td><strong>RT + 6 mo ADT vs RT + 3 yr ADT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>T3 and/or N+</td>
<td>T1-2 grade 3 or T3-4 N0 (N1)</td>
<td>T1-4, N0-2 (or pN1), M0</td>
</tr>
<tr>
<td><strong>PCa death rate</strong></td>
<td>16% vs 22% at 10 yr (P &lt; 0.01)</td>
<td>10% vs 30% at 10 yr (P &lt; 0.0001)</td>
<td>3.2% vs 4.7% at 5 yr (P=0.002)</td>
</tr>
<tr>
<td><strong>OS rate</strong></td>
<td>49% vs 39% at 10 yr (P = 0.002)</td>
<td>58% vs 40% at 10 yr (P = 0.0004)</td>
<td>19% vs 15.2% at 5 yr (not non-inferior)</td>
</tr>
</tbody>
</table>

**GETUG 12: Adding Docetaxel?**

Median follow up: 12 years

T3 or Gleason $\geq 8$ or Psa $> 20$ ng/ml

$N = 413$  ADT (3 years) + local treatment $\pm$ Docetaxel (4 cycles)

**Median RFS**

$11.6$ [9.1; NR] vs $8.1$ [7.3; 9.6] years

HR=$0.71$ [0.55-0.93]  
p=0.0109

$49.4\%$ [42.5%; 56.3%]

$36.3\%$ [29.7%; 43.5%]

NO survival benefit

NO mets free survival benefit

*Fizazi ESMO 2018*
High risk localized

<table>
<thead>
<tr>
<th>Radiotherapeutic treatments</th>
<th>In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (two to three years).</th>
<th>Weak</th>
</tr>
</thead>
</table>

Conventional fractionation

EAU-ESTRO-ESUR-SIOG prostate cancer guidelines 2019 (uroweb.org)
High risk: Canada

*Nabid Eur Urol* 2018

N = 630. T3 - T4 or PSA > 20 ng/ml or Gleason > 7 (60%)

**Primary objective:** OS Superiority trial

EBRT + ADT (18 / 36 months) - EBRT: Prostate 70 Gy - pelvis: 44 Gy. ADT: Combined 1 months then agonist alone.

**Limitations:**

- NOT locally advanced (76% < T3) - median PSA: 16 ng/ml - However: 60% Gleason ≥ 8
- EBRT dose: 70 Gy
- Non compliance: an issue! (50% in the 36 months arm)

**Overall QoL:** same. Less sexual Pb / hot flushes
RP (multimodal) in high risk PCa

N = 1360 high risk patients (surgery ± adjuvant / salvage treatment)

“Simplified” model:
- Low risk: one risk factor
- Int. risk: PSA>20 ng/ml and T3-4
- High risk: all three risk factors

Joniau Eur Urol, 2014
Margings matter in high risk


N = 5290 RARP + ePLND
pN+ current natural history

N = 369 pN+ (1988 - 2010). No adjuvant treatment
87% pT3 - 43% pT3b - 37% R1 - PSA < 0.1 ng/ml

Median 15 nodes / patient (10 - 21)
Specific survival (10 years): 72%
pN+: Combined treatment?

N = 1107  pN+ Median follow up: 7.1 years  Abdolah J Clin Oncol 2014

External validation (3158 pts from SEER database)

If RX: > 75% pelvis [50.4 Gy] + prostate [70.2 Gy]
ADT: mainly prolonged
# Treatment based on risk groups

<table>
<thead>
<tr>
<th>Locally-advanced disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical prostatectomy</strong></td>
<td>Offer RP to highly selected patients with (cT3b-T4 N0 or any T N1) <strong>only as part of multi-modal therapy</strong>.</td>
</tr>
<tr>
<td><strong>Extended pelvic lymph node dissection</strong></td>
<td>Perform an ePLND in high-risk PCa.</td>
</tr>
<tr>
<td></td>
<td>Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.</td>
</tr>
<tr>
<td><strong>Radiotherapeutic treatments</strong></td>
<td>In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT.</td>
</tr>
<tr>
<td></td>
<td>Offer long-term ADT for two to three years.</td>
</tr>
<tr>
<td><strong>Therapeutic options outside surgery and radiotherapy</strong></td>
<td>Do not offer whole gland treatment or focal treatment to high-risk patients.</td>
</tr>
<tr>
<td></td>
<td>Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment and who are either symptomatic or asymptomatic, but with a PSA-doubling time (DT) &lt; twelve months or a PSA &gt; 50 ng/mL, or a poorly differentiated tumour.</td>
</tr>
</tbody>
</table>

Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics:

1. Offer adjuvant ADT for node-positive (pN+).
2. Offer adjuvant ADT with additional radiotherapy.
3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.
**Definition of M1 disease**

<table>
<thead>
<tr>
<th>High-risk localised PCa/locally advanced PCa</th>
<th>LE</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use prostate mpMRI for local staging.</td>
<td>2b</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.</td>
<td>2a</td>
<td>Strong</td>
</tr>
</tbody>
</table>

*EAU-EANM-ESTRO-ESUR-SIOG guidelines 2019*

**NO data ever reported with M1 definition NOT based on BS + CT**
**Intermittent in M1**

*Hussain J Clin Oncol 2015*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Prespecified NIM</th>
<th>Median OS in CAD Arm (years)</th>
<th>Absolute Difference Between Arms Corresponding to NIM (months)</th>
<th>Median OS in CAD Arm (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S9346</td>
<td>1.20</td>
<td>3</td>
<td>6</td>
<td>5.8</td>
</tr>
<tr>
<td>PR.7</td>
<td>1.25</td>
<td>7</td>
<td>16.8</td>
<td>9.1</td>
</tr>
<tr>
<td>SEUG 9901</td>
<td>1.21</td>
<td>4.25</td>
<td>8.9</td>
<td>5.8†</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, continuous androgen deprivation; NIM, noninferiority margin; OS, overall survival; SEUG, South European Urological Group.

*Calculated as: median CAD – (median CAD/NIM), where respective observed or prespecified median CAD measure is used. Maximum difference between arms that would still be considered noninferior based on NIM.

†Extrapolated from Fig 1 (Kaplan-Meier curve of OS for CAD) from primary publication.¹³

In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major prostate-specific antigen (PSA) response after the induction period. **Strong**

**We have clearly lowered the indication for intermittent in M1**

_EAU-ESTRO-ESUR-SIOG guidelines 2018_
Upfront Docetaxel in M1

**Absolute 9% OS benefit** - Most men: newly diagnosed PCa

Sathianathen Cochrane rev 2018
Upfront Abiraterone in M1

Overall survival
Results based on 2,201 men / 774 deaths

Absolute 14% OS benefit at 3 years Most men: newly diagnosed PCa

Rydzewska Eur J Cancer 2017
Abi / Doc: OS difference?

566 patients randomised contemporaneously to either research arm.

This analysis is exploratory and underpowered.

**Key:**
- HR<1 favours SOC+AAP
- HR>1 favours SOC+DocP

**Interact** = test for interaction (heterogeneity of treatment effect)

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
<th>P-val</th>
<th>Interact&lt;sup&gt;n&lt;/sup&gt; test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.16 (0.82 to 1.65)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>1.51 (0.58 to 3.93)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>1.13 (0.77 to 1.66)</td>
<td>0.53</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Sydes. Ann Oncol 2018*
## Disease classification

2 Volume stratification, partly overlapping

<table>
<thead>
<tr>
<th>VOLUME</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>≥ 4 bone mets, at least 1 extra axial OR Visceral met</td>
</tr>
<tr>
<td></td>
<td>2 out 3 risk factors:</td>
</tr>
<tr>
<td></td>
<td>- Gleason ≥ 8</td>
</tr>
<tr>
<td></td>
<td>- 3 bone met</td>
</tr>
<tr>
<td></td>
<td>- Measurable visceral met</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>NOT high volume</td>
</tr>
<tr>
<td></td>
<td>The others</td>
</tr>
</tbody>
</table>

Visceral met: lung, liver. NOT RetroP lymph node
CHAARTED updated: volume

High-volume

- ADT plus docetaxel: 48.0 months
- ADT alone: 33.1 months

No. at risk:
- ADT plus docetaxel: 214
- ADT alone: 207

Survival (proportion)

HR, 0.63 (95% CI, 0.49 to 0.81); P < .001

Low-volume

- ADT plus docetaxel: 58.3 months
- ADT alone: 59.8 months

No. at risk:
- ADT plus docetaxel: 75
- ADT alone: 79

Survival (proportion)

HR, 0.86 (95% CI, 0.52 to 1.42); P = .55

Kyriakopoulos J Clin Oncol 2018
### STAMPEDE: ADT + Abi volume / risk

#### LATITUDE criteria (All M1 patients)

<table>
<thead>
<tr>
<th></th>
<th>ADT Alone</th>
<th>ADT + AAP</th>
<th>Adjusted HR (95% CI)</th>
<th>Interaction between metastatic subgroups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>195/452</td>
<td>135/449</td>
<td>0.61 (0.49–0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>53/220</td>
<td>41/208</td>
<td>0.66 (0.44–0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>142/232</td>
<td>94/241</td>
<td>0.54 (0.41–0.70)</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

#### CHAARTED criteria (All M1 patients)

<table>
<thead>
<tr>
<th></th>
<th>ADT Alone</th>
<th>ADT + AAP</th>
<th>Adjusted HR (95% CI)</th>
<th>Interaction between metastatic subgroups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>195/452</td>
<td>135/449</td>
<td>0.61 (0.49–0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>53/196</td>
<td>39/206</td>
<td>0.64 (0.42–0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>142/256</td>
<td>96/243</td>
<td>0.60 (0.46–0.78)</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

---

*Hoyle Eur Urol 2019*
STAMPEDE: ADT + Docetaxel volume / risk

Clarke Ann Oncol 2019
From Stampede.
Based on Charteed classification
Median follow up: 78.2 months

STAMPEDE: ADT + Docetaxel volume / risk

HR: 0.81 (0.69 - 0.95)

HR: 0.91 (0.64 - 1.02)

HR: 0.76 (0.54 - 1.07)
Disease “volume”

REMEMBER

Trials NOT designed to answer the “volume” question
Trials to be considered as a whole: M1 (most patients newly diagnosed)

STAMPEDE (post hoc): treatment impact constant

Therefore relevance of the volume definition ? ? ? ? ?
ADT ± other new ARTA

**TITAN: Apalutamide**
*Chi. N Engl J Med 2019*

![Overall Survival Graph]

- **Hazard ratio for death:** 0.67 (95% CI, 0.51–0.89)
- **P-value:** 0.005

*No. at Risk*:
- Apalutamide: 525, 513, 473, 387, 142, 16, 0
- Placebo: 527, 509, 473, 387, 142, 16

**Arches: Enzalutamide**
*Armstrong J Clin Oncol 2019*

![Overall Survival Graph]

- **Hazard ratio, 0.67 (95% CI, 0.52–0.86)**
- **P-value:** 0.002 by log-rank test

*No. at Risk*:
- Enzalutamide: 563, 358, 541, 527, 480, 340, 189, 106, 45
- Standard care: 562, 351, 531, 501, 452, 311, 174, 86, 32

**Enzamet**
*Davis. N Engl J Med 2019*
ADT + something else: STAMPEDE

Preplanned / powered sub group analysis:
Extend of disease: Chaarted definition

M1 newly diagnosed
RCT: ADT / ADT + EBRT (prostate)
Low volume: N = 819

Median follow up: 37 months

Low volume: not high volume
High volume > 4 bone mets, 1 extra axial OR M1c

*Parker Lancet. 2018.*
<table>
<thead>
<tr>
<th>Symptomatic patients</th>
<th>Offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic patients</td>
<td>Offer immediate systemic treatment to improve survival, defer progression to an asymptomatic stage and prevent serious disease progression-related complications to M1 patients asymptomatic from their tumour.</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Discuss deferred castration with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment side effects, provided the patient is closely monitored.</td>
<td>Weak</td>
</tr>
</tbody>
</table>

EAU-EANM-ESTRO-ESUR-SIOG guidelines 2019
<table>
<thead>
<tr>
<th>M1 - 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Offer castration combined with chemotherapy (docetaxel)</strong> to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.</td>
</tr>
<tr>
<td><strong>Strong</strong></td>
</tr>
<tr>
<td><strong>Offer castration combined with abiraterone acetate plus prednisone</strong> to all patients whose first presentation is M1 disease and who are fit enough for the regimen.</td>
</tr>
<tr>
<td><strong>Strong</strong></td>
</tr>
<tr>
<td><strong>Offer castration combined with prostate radiotherapy</strong> to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.</td>
</tr>
<tr>
<td><strong>Weak</strong></td>
</tr>
<tr>
<td><strong>Do not offer castration combined with any local treatment (radiotherapy/surgery)</strong> to patients with high volume M1 disease outside of clinical trials (except for symptom control).</td>
</tr>
<tr>
<td><strong>Strong</strong></td>
</tr>
<tr>
<td><strong>Offer castration alone</strong> with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone or RT.</td>
</tr>
<tr>
<td><strong>Strong</strong></td>
</tr>
</tbody>
</table>

In 2020: equally true with Enzalutamide / Apalutamide
**Castrate-resistant prostate cancer (CRPC) Definition**

3 main criteria: *Castrate serum testosterone* < 50 ng/dL 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

**Radiological progression**
Appearance of ≥2 lesions (bone scan) or soft tissue lesion enlargement RECIST

Symptomatic progression alone to be questioned and not sufficient to define mCRPC

*EAU guidelines on prostate cancer, 2017*
nmCRPC: what do we know?

**MO CRPC:** time to metastases linked to PSA DT

From a RCT with 1432 men

*Smith J Clin Oncol 2013*

Linking mets free survival and SS / OS

NEVER REPORTED in CRPC
Available trials

MO: based on bone scan and C scan (N1 possible < 2 cm in the pelvis)
PSA > 2 ng/ml. PSA DT < 10 months

Stratification: PSA-DT (6 months) / bone protection / N0/1

Randomization 2:1:

Objective: mets free survival (metastases [imaging] or death)
ADT ± ARTAs in MO CRPC

Three positive trials

SPARTAN\textsuperscript{1}  \hspace{1cm} PROSPER\textsuperscript{2}  \hspace{1cm} ARAMIS\textsuperscript{3*}

NO comparison between trials

\textsuperscript{1} Smith \textit{N Engl J Med} 2018; \textsuperscript{2} Hussain. \textit{N Engl J Med} 2018; \textsuperscript{3} Fizazi \textit{N Engl J Med} 2019
What about survival?

ADT ± apalutamide (240 mg/day)$^1$

ADT ± enzalutamide (160 mg/day)$^2$

ADT ± darolutamide (600 mg twice daily)$^3$

ADT ± Apalutamide in MO CRPC

SPARTAN

A Time to Symptomatic Progression

Patients without Symptomatic Progression (%)

Hazard ratio for progression, 0.45 (95% CI, 0.32–0.63)
P<0.001

Symptomatic progression (defined as the time from randomization to a skeletal-related event, pain progression, or worsening of disease-related symptoms leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy), overall survival, and time to the
# Phase III clinical trials in mCRPC

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>N</th>
<th>Indication</th>
<th>Inclusion criteria</th>
<th>HR [95% CI]</th>
<th>Δ OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX-327</td>
<td>DOC/P vs mito/P</td>
<td>1,006</td>
<td>mCRPC</td>
<td>Visceral mets 22% Symptomatic or not</td>
<td>0.76 [0.62-0.94]</td>
<td>+2.9</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Sipuleucel-T vs pbo</td>
<td>512</td>
<td>mCRPC (pre-DOC)</td>
<td>No visceral mets No/mild symptoms</td>
<td>0.78 [0.61-0.98]</td>
<td>+4.1</td>
</tr>
<tr>
<td>TROPIC</td>
<td>CABA/P vs mito/P</td>
<td>755</td>
<td>mCRPC (post-DOC)</td>
<td>Visceral mets 25% Symptomatic or not</td>
<td>0.70 [0.59-0.83]</td>
<td>+2.4</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>ABI/P vs P</td>
<td>1,088</td>
<td>mCRPC (pre-DOC)</td>
<td>No visceral mets No/mild symptoms</td>
<td>0.81 [0.70-0.93]</td>
<td>+4.4</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>ABI/P vs P</td>
<td>1,195</td>
<td>mCRPC (post-DOC)</td>
<td>Visceral mets 11% Symptomatic or not</td>
<td>0.74 [0.64-0.86]</td>
<td>+4.6</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>ENZA vs pbo</td>
<td>1,717</td>
<td>mCRPC (pre-DOC)</td>
<td>Visceral mets 11% No/mild symptoms</td>
<td>0.77 [0.67-0.88]</td>
<td>+4.0</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>ENZA vs pbo</td>
<td>1,199</td>
<td>mCRPC (post-DOC)</td>
<td>Visceral mets 23% Symptomatic or not</td>
<td>0.63 [0.53-0.75]</td>
<td>+4.8</td>
</tr>
<tr>
<td>ALSYMPCA</td>
<td>Radium-223 vs pbo</td>
<td>921</td>
<td>mCRPC (43% pre-DOC)</td>
<td>No visceral mets Symptomatic or not</td>
<td>0.70 [0.55-0.88]</td>
<td>+2.8</td>
</tr>
<tr>
<td>FIRSTANA</td>
<td>DOC/P vs CABA 25/P vs CABA 20/P</td>
<td>1,168</td>
<td>mCRPC (pre-DOC)</td>
<td>Visceral mets 23% Symptomatic or not</td>
<td>1.01 [0.85-1.19]</td>
<td>+0.7</td>
</tr>
<tr>
<td>PROSELICA</td>
<td>CABA 25/P vs CABA20/P</td>
<td>1,200</td>
<td>mCRPC (post-DOC)</td>
<td>Visceral mets 31% Symptomatic or not</td>
<td>1.02 [non inferior]</td>
<td>+1.1</td>
</tr>
</tbody>
</table>

### Key points

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure that testosterone levels are confirmed to be $&lt; 50 \text{ ng/mL}$, before diagnosing castration-resistant PCa (CRPC).</td>
<td>Strong</td>
</tr>
<tr>
<td>Do not treat patients for non-metastatic CRPC outside of a clinical trial.</td>
<td>Strong</td>
</tr>
<tr>
<td>Counsel, manage and treat patients with metastatic CRPC in a multidisciplinary team.</td>
<td>Strong</td>
</tr>
<tr>
<td>Treat patients with mCRPC with life-prolonging agents</td>
<td>Strong</td>
</tr>
<tr>
<td>Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive metastatic PCa (HSPC) (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).</td>
<td>Strong</td>
</tr>
</tbody>
</table>

**Ongoing castration mandatory**

No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist.
Practical points

Hormonal approach is the first line in the majority of patients with mCRPC in practice *Gillessen Ann Oncol. 2015*

Bicalutamide: NO place left.

However: does NOT fit all

Up to 20% primary refractory to Abi / Enza
Tools for early identification of primary resistance

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes (%)</th>
<th>Only in combination with other unfavourable factors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-endocrine differentiation on a tumour biopsy and/or low or absent androgen receptor (AR) expression</td>
<td>71</td>
<td>27</td>
</tr>
<tr>
<td>Exclusive visceral metastases</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>Rapid progression without correlation with PSA kinetics</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>Low PSA levels relative to tumour burden</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>Predominantly lytic bone metastases</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>Short response to androgen deprivation therapy (≤12 months) for metastatic prostate cancer</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td>Bulky tumour masses</td>
<td>21</td>
<td>65</td>
</tr>
</tbody>
</table>
Upfront Docetaxel in M1: later impact

Upfront DOC + ADT in M1 disease (GETUG 15)

PSA response
Abiraterone or Enzalutamide

PSA response
Doc. rechallenge

Lavaud Eur Urol 2018
Follow-up in practice

Clinical / symptomatic efficacy: the priority

Patients with no objective benefit should have treatment modified. This panel stressed that such treatments should not be stopped for PSA progression alone. Instead at least two of three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment.

Switch only if unequivocal progression (NOT PSA progression)

At least 2 criteria out of
- PSA progression
- clear Bone scan progression
- clear CT progression
- Clinical deterioration

EAU-ESTRO-ESUR-SIOG guidelines 2018

Do not duplicate or distribute without permission from the author and ESO
Second line of treatment

<table>
<thead>
<tr>
<th>Base second-line treatment decisions of mCRPC on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease.</th>
<th>Strong</th>
</tr>
</thead>
</table>

**Abi after Enza OR Enza after Abi**

**Primary resistance**
- Not recommended (70% voted for a Taxane)

**Acquired resistance**
- Not recommended (taxane: 57% if asymptomatic / 90% if symptomatic)
  or in a minority of selected cases 53%)

EAU-EANM-ESTRO-ESUR-SIOG guidelines 2019

Gillessen Eur Urol 2017
Cross-resistance between ART

PLATO: N = 251 chemo-naïve mCRPC with PSA response to ENZA > 3 months @ PSA progression randomized: ENZA + ABI + P vs pbo + ABI + P
PFS (primary endpoint): 5.7 vs 5.6 months, HR: 0.83, P = 0.22

Attard J Clin Oncol 2018
CARD study

Study design

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 - Nov 2018
- Median follow-up: 9.2 mo
- Patients with mCRPC who progressed ≤ 12 months on prior alternative ARTAs (before or after) N = 255
- ARMS with PSA progression above were eligible, whichever the treatment duration
- Randomization
- Cabazitaxel (25 mg/m² q3w) + P + or CF
  - N = 129
- Abiraterone (1000 mg OD) + P OH
  - Enzalutamide (100 mg OD)
  - N = 126
- Endpoints
  - Primary: rPFS
  - Key secondary: OS, PFS, PSA response, tumor response
  - Other secondary: Pain response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

Radiographic PFS (primary endpoint) Overall survival (key secondary endpoint)

De Wit R N Engl J Med 2019
Heterogeneity: DNA repair defects

Phase II, olaparib (PARP inhibitor)
N=50 patients with mCRPC following chemotherapy (taxane)

rPFS

p<0.001 by log-rank test

Biomarker: DNA repair defects
Biopsy: 33% patients (n=16)

Deletions/mutations in BRCA2, ATM, BRCA1, PALB2, CHEK2, FANCA, HDAC2

OS

p=0.05 by log-rank test

PARP inhibitor?

**Primary objective**

Toxicity: treatment stop: 30%/10%
Serious AE: 34/18%. Serious CV AE: 10/1%

Real place for PARP inhibitors?

Clarke Lancet Oncol 2018
PROfound trial: rPFS and interim OS

Hussain # LBA12 PR. ESMO 2019,

**Primary endpoint**

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN BRCA1, BRCA2, OR ATM (COHORT A)

- 6-mo rate: 59.7%
- 12-mo rate: 28.1%
- Median rPFS (months): 7.39
- Hazard ratio (95% CI): 0.34 (0.25, 0.47)
- P=0.0001

**Interim** OVERALL SURVIVAL

Cohort A
- Median OS (months): 18.3
- Hazard ratio (95% CI): 0.64 (0.43, 0.97)
- P=0.0177

Cohort A+B
- Median OS (months): 17.54
- Hazard ratio (95% CI): 0.67 (0.48, 0.93)
- P=0.006 (pooled)

**Key eligibility criteria**
- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HR/R

**Stratification factors**
- Previous taxane
- Measurable disease

**Primary Endpoint**
- Radiographic progression-free survival (rPFS) in Cohort A
- RECIST 1.1 & PCWG3 by BICR

**Secondary Endpoints**
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR)
- Time to radiographic progression (TTP)

*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test*

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPFIA1, RAD51B, RAD51C, RAD51D and/or RAD54L in their tumor tissue.
## Bone problems

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.</td>
<td>Strong</td>
</tr>
<tr>
<td>Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.</td>
<td>Strong</td>
</tr>
<tr>
<td>In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.</td>
<td>Strong</td>
</tr>
</tbody>
</table>