Treatment sequencing in mCRPC
what do we know
the Urologist’s perspective

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SEQUENCING - Conclusions

The optimum treatment and sequence of treatments for mCRPC before and after chemotherapy is currently unknown.

Guidance for clinicians and evidence based data is required in this area of clinical medicine.

NCCN Prostate Cancer Guidelines Version 1, 2015 NCCN.
European Society of Medical Oncology, 2015
European Association of Urology Guidelines, 2015
Management of CRPC: what do we know? and what do we need to know?

By and for the Urologists
The Urologist

Knows

• The patient for many years and the natural history of the disease
• The delivery, mechanism of action, indications and side effect of Androgen Deprivation Therapy (ADT)
  • Mono-therapy, TAB, Intermittent and continuous and before and after primary therapy

Needs to know

• Why ADT fails
• When to initiate second line Hormonal therapy
• Understand the indications, delivery, activity, and side effects of the new agents that targets androgen signaling and chemotherapy and why they also fail and what to do about it
• The evidence to continue ADT in mCRPC

Needs NOT

• to be intimidated by the new available agents
• Refer and forget his patient with mCRPC but be engaged in the MDT managing the pt
ADT and Prostate Cancer

• Androgenic Journey:
  – Testosterone - T - is produces in the testes and adrenal and circulates in the blood
  – T is transported to the prostate cell where it is converted by 5AR into DHT
  – DHT binds to the AR resulting in activation
  – Activated AR bind to specific sequences on DNA resulting in stimulation of specific genes which in turn
  – Produce specific proteins in-charge of specific tasks
    • PSA production, cell growth ......
Testosterone (T) synthesised in:
1. Adrenal gland or
2. Intratumorally (CRPC)

Testosterone binds to protective proteins in bloodstream.

Cell Membrane

5α-reductase converts T to DHT (10x more potent)

DHT binds to AR monomer releasing cytoplasmic heat shock proteins.

Activated AR binds to specific sequences on DNA

Increase in proteins which:
1. Perform prostatic functions (e.g. PSA)
2. Affect cell growth
3. Affect cell survival

Degradation in Proteasome or recycling

Cell Nucleus
*Forms of Androgen deprivation*

- **Hormonal therapy**
  - New substances
  - Maximum Androgen blockade
  - Androgen-Synthesis-Inhibitors
  - Steroidal Antiandrogens
  - Non-steroidal Antiandrogens
  - Surgical castration
  - Estrogen
  - LHRH-Agonists
  - LHRH-Antagonists
Side Effects of ADT

- Loss of libido
- Erectile Dysfunction
- Fatigue
- Cardiovascular
- Metabolic Syndrome
- Depression
- Weight Gain Gynecomasty
- Hot flushes
- Osteoporosis Bone fractures

ADT = Androgen deprivation therapy
Hormonal manipulations: therapeutic Option in PSA-Relapse after first ADT

Monotherapy (Antiandrogen/LHRH/Orchidectomy)

MAB

LHRH-Agonist/-Antagonist/Orchidectomy

Changing Antiandrogens

High dose. non-steroidal Antiandrogens

Stopping Antiandrogens ⇒ Antiandrogen-withdrawal-effect

Ketoconazole/Hydrocortisone

Estramustine phosphate

Therapy CRPC

HT = Hormonal therapy
mCRPCa = metastatic castrationresistant prostate cancer
MAB = maximum Androgen blockade
CTx = Chemotherapy

* Exspected accreditation according to US accreditation
Almost all patients with advanced prostate cancer on H.T. will initially respond but eventually fail progressing to CRPC with in a median survival of 18-24 months.

HOW and WHY this happens?
ADT and Prostate Cancer

Androgen signaling is essential to understand resistance
– normal and cancer cell response to androgen is similar
  BUT
  • Normal cell is terminally differentiated and programmed to die
  • Cancer cell is long – lived – divides

Resistance is secondary to treatment

No treatment  -  No resistance
ADT and Prostate Cancer

Mechanism of resistance:
- AR amplification and mutation to maximize use of low T or switch to use other steroids
- AR co-activator and co-repressor modification
- Aberrant activation and/or post-translational modification
- Altered steroidogenesis, intra-mural androgen production
- AR slice variants

This results in increased AR activation by sensitizing it to non-classical even absent ligands resulting in transcription of downstream target genes and tumor progression despite castrate levels of androgens.
Targets of mCRPC Therapies

- Cell trafficking: Taxanes*
- Ligand depletion: Abiraterone
- AR targeting: Enzalutamide
- Bone targeting: Radium-223
- Immunotherapy: Sipuleucel-T

And more to come ....

*docetaxel, cabazitaxel; AR: androgen receptor
# 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>(\Delta) OS</th>
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<tbody>
<tr>
<td>TAX-327(^1)</td>
<td>DOC/P vs mito/P</td>
<td>1,006</td>
<td>mCRPC</td>
<td>0.76</td>
<td>+2.9</td>
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<tr>
<td>IMPACT(^2)</td>
<td>Sipuleucel-T vs pbo</td>
<td>512</td>
<td>mCRPC (pre-DOC)</td>
<td>0.78</td>
<td>+4.1</td>
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<tr>
<td>COU-AA-302(^3)</td>
<td>ABI/P vs P</td>
<td>1,088</td>
<td>mCRPC (pre-DOC)</td>
<td>0.81</td>
<td>+4.4</td>
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<tr>
<td></td>
<td>COU-AA-301(^4)</td>
<td>1,195</td>
<td>mCRPC (post-DOC)</td>
<td>0.74</td>
<td>+4.6</td>
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<tr>
<td>PREVAIL(^5)</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>AFFIRM(^6)</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>TROPIC(^7)</td>
<td>CAB/P vs mito/P</td>
<td>755</td>
<td>mCRPC (post-DOC)</td>
<td>0.70</td>
<td>+2.4</td>
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<tr>
<td>ALSYMPCA(^8)</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

Docetaxel

Cytostatic effect of Docetaxel due to its binding to microtubules. This leads to stabilization of microtubules and blocks mitosis.

Increasing polymerisation of tubulin to stable, non functional microtubules

Inhibition of depolymerisation

Arresting cells during division phase

20 mm
Summary TAX 327-Study

- 3-weekly Docetaxel (1 h i.v. infusion) 75 mg/m² + Prednisolone 5 mg orally shows significant improvement of overall survival vs. 3-weekly Mitoxantrone (0.5 h i.v. infusion) 12 mg/m² + Prednisolone 5mg orally in patients with mCRPC.

- This benefit is correlated with higher rate of side effects, especially Neutropenia, but also Fatigue (53 % vs. 35 %), Alopecia (65 % vs. 13 %), Diarrhea (32 % vs. 10 %), Stomatitis (20 % vs. 8 %), Dyspnea (15 % vs. 9 %), Peripheral oedema (19 % vs. 1 %).

Tannock IF et al., NEJM 2004; 351: 1502–1512
• Potent microtubules stabiliser, as this result inhibition of cellular functions in mitosis and interphase

• Active in cell lines resistant to Doxorubicin, Vinblastin, Paclitaxel and Docetaxel

• Cabazitaxel potentially passes blood-cerebral-barrier
Cabazitaxel: TROPIC Phase-III-Study

Pats. with mCRPC under progression during/after Docetaxel (n = 755)

randomisation:
ECOG-Performance-Status 0–2 • clinical proofed (RECIST) or biochemical progression (2 consecutively rise of PSA)

Cabazitaxel 25 mg/m² q 3 wk + Prednisone* for 10 cycles (n = 378)

Mitoxantrone 12 mg/m² q 3 wk + Prednisone* for 10 cycles (n = 377)

Primary end point: Overall survival

* Orally Prednisone/Prednisolone: 10 mg/d

De Bono JS et al., Lancet 2010; 376: 1147–1154
TROPIC: Overall survival

Overall survival benefit 2,4 month

MP = Mitoxantron + Prednison
CBZP = Cabazitaxel + Prednison

De Bono JS et al., Lancet 2010; 376: 1147–1154
Enzalutamide (MDV3100)

- Oral androgen receptor inhibitor:
  - Competitive inhibitor of ligand binding – DHT - to AR (8-fold stronger than Bicalutamide)
  - Inhibits translocation of AR complex to nucleus
  - Inhibits binding of receptor to DNA

Science 8 May 2009; 324 (5928): 787–790
DOI: 10.1126/science.1168175
AFFIRM: Enzalutamide after Docetaxel

- 1,199 patients with advanced CRPCa after chemotherapy with Docetaxel included

Inclusion criteria:
- Pathological proofed PCa
- Testosterone on castration level (< 50 ng/dl)
- Previous therapy with Docetaxel
- Progression according to PCWG2 criteria

- 2:1 randomisation stratified according to ECOG-Performance-State (0 or 1 vs. 2): 800 patients had Enzalutamide orally 160 mg once daily, 399 patients had placebo once daily. Prednison or other Glucocorticoids were possible but not required.

- Primary end point: overall survival
- Secondary end points: PSA response, objective response, FACT-P QoL, time to PSA progression, rPFS, time to first skeletal event

Scher HI et al., NEJM 2012; 367: 1187–1197
**AFFIRM: Overall survival**

Median OS [month]:
- Enzalutamide: 18.4
- Placebo: 13.6

Hazard Ratio (95% CI): 0.63 (0.53–0.75)

$OS = \text{Overall survival}$

Scher HI et al., NEJM 2012; 367: 1187–1197
AFFIRM: radiographic progression free survival

Median rPFS [month]:
Enzalutamide: 8.3
Placebo: 2.9

Hazard Ratio (95% KI):
0.40 (0.35-0.47)

rPFS = radiographisches progressionsfreies Überleben

Scher HI et al., NEJM 2012; 367: 1187-1197
**PREVAIL: Enzalutamide before Docetaxel Phase-III-Study**

- 1,717 patients with mCRPCa under ongoing LHRH therapy or after orchidectomy
- Inclusion criteria:
  - Pathological verified diagnosis of Pca
  - Clinical verified metastasis
  - Progression of PSA
  - Testosterone on castration level (< 50 ng/dl)
  - ECOG 0 or 1, asymptomatic oder minimal symptomatic
- 1:1 randomisation: 872 patients got 160mg Enzalutamide orally once daily, 845 Patient got placebo once daily. Prednison or Glucocorticoides were permitted, but not required.
- Primary endpoint: Overall survival and radiological proofed progression free survival
- Secondary endpoints: time to chemotherapy, time to first bone metastasis, PSA progression, objective response and QoL

*Beer TM et al., NEJM 2014; 371: 424–33*
**PREVAIL: Overall survival**

- **Median OS [month]:**
  - Enzalutamide: 32.4
  - Placebo: 30.2

- **Hazard Ratio (95% KI):**
  - 0.71 (0.60–0.84)
  - p < 0.001

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**Overall survival (%)**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>872</td>
<td>863</td>
<td>850</td>
<td>824</td>
<td>797</td>
<td>745</td>
<td>566</td>
<td>395</td>
<td>244</td>
<td>128</td>
<td>33</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>845</td>
<td>835</td>
<td>781</td>
<td>744</td>
<td>701</td>
<td>644</td>
<td>484</td>
<td>328</td>
<td>213</td>
<td>102</td>
<td>27</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
**PREVAIL: Radiographic progression free survival**

- **Median rPFS [month]:**
  - **Enzalutamide:** not achieved in interim analysis
  - **Placebo:** 3.9

- **Hazard Ratio (95% CI) rPFS und OS combined:**
  - 0.19 (0.15-0.23)
  - p < 0.001

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**Enzalutamide**
- 832
- 514
- 256
- 128
- 34
- 5
- 1

**Placebo**
- 801
- 305
- 79
- 20
- 5
- 0
- 0

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rPFS = radiographic progression free survival

Beer TM et al., NEJM 2014; 371: 424–33
Abiraterone acetate

- Androgen synthesis inhibitor:
  Inhibits enzyme CYP17 in testis, adrenal gland and tumor tissue, which catalyzes conversion of pregnenolone and progesterone in precursors of Testosteronee, DHEA or androstenedione.

- All phase-III-studies of Abiraterone were performed under combination with Prednis(ol)one and LHRH therapy.

Attard G et al., Cancer Res 2009; 69: 4937–4941
COU-AA-301: Abiraterone after Docetaxel in mCRPCa:

- 1,195 men with mCRPC
- At least one therapy with Docetaxel (performed or interrupted)
- Ongoing LHRH
- 2:1 randomisation: Abiraterone (1000 mg) + Prednisone/Prednisolone (5 mg b.i.d.) (n = 797)
  
or
  Placebo + Prednison/Prednisolon (5 mg b.i.d.) (n = 398)
- 12 month follow up

De Bono JS et al., NEJM 2011; 364: 1995–2005
Overall survival benefit vs. Placebo  4.6 month

Fizazi K et al., Lancet Oncol 2012; 13: 983–992
COU-AA-302: Abiraterone in mCRPCa before Chemotherapy

- 1.088 men with asymptomatic or mild symptomatic CRPC (BPI-SF-Scores 0–1 or 2–3)
- No chemotherapy
- Ongoing LHRH
- 1:1 randomisation, stratified after ECOG performance status 0 vs. 1: Abiraterone (1000 mg) + Prednisone/Prednisolone (5 mg b.i.d.) (n = 546) or Placebo + Prednisone/Prednisolone (5 mg b.i.d.) (n = 542)
- Median follow up 22.2 months
- Primary endpoints: rPFS, OS

BPI-SF = Brief Pain Inventory – Short Form
rPFS = radiographic progression free survival
OS = overall survival
b.i.d. = twice daily

Ryan CJ et al., NEJM 2013; 368: 138–148
**COU-AA-302: Overall survival**

*Median OS [month]:*
- **Abiraterone**: not achieved
- **Placebo**: 27.2

**Hazard Ratio (95% CI):**
0.75 (0.61–0.93)

**OS = Overall survival**

Ryan CJ et al., NEJM 2013; 368: 138–148
**COU-AA-302: radiographic progression free survival**

Median rPFS [month]:
- Abirateron: 16.5
- Placebo: 8.3

Hazard Ratio (95% CI):
- 0.53 (0.45–0.62)

rPFS = radiographic progression free survival  

*Information Zytiga*® 250 mg Tabletten, January 2013
Radium-223-Dichloride (Alpharadin)

Alpha-transmitter Radium-223-Dichloride (223RaCl2)

- Alpharadin is an analog to Calcium and will be selectively integrated in bone tissue.
- The Alpha emitter is high energy, but has very low permission depth (0.1 mm) in tissue ($t_{1/2} = 11.4$ d).
- In ALSYMPCA-Study median overall survival in 922 men with mCRPCa and bone metastasis for Alpharadin-treated patients was 14 month – compared to 11.3 month under Placebo ($p = 0.00007$; HR: 0.695).¹

¹ Parker et al. Abstract LBA 4512, ASCO 2012
Management of advanced prostate cancer: Current options available

**Metastatic castration-sensitive PCa**
- LHRH agonists
- Anti-androgens
- LHRH antagonists
- Docetaxel*

**Metastatic CRPC (mCRPC) 1st line**
- Docetaxel
- Sipuleucel-T

**mCRPC post-docetaxel**
- Cabazitaxel
- Abiraterone
- Enzalutamide
- Radium-223

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*C: castration-resistant prostate cancer; LHRH: luteinising hormone-releasing hormone
Sweeney C et al. J Clin Oncol 2014;32 (June 20 suppl):abstract LBA2– Docetaxel is not licenced in this population
Management of CRPC: what is known and what is needed?

As the number and class of agents available to treat mCRPC has increased dramatically. There is a need for clear guidance on the optimum treatment and sequence of treatments for mCRPC before and after chemotherapy.

evidence-based strategies are critical to:

– provides suggestions on the continued relevance of conventional approaches to first- and second-line treatment in mCRPC,
– the potential role of novel treatments, and factors that may influence the choice of hormonal agents and/or chemotherapy.
Management of CRPC: what is known and what is needed?

The most important gaps in our knowledge on the use of newer agents before chemotherapy relate to predicting response to abiraterone and enzalutamide.

Clear and early indicators or biomarkers for lack of efficacy of these newer agents are needed to ensure these more expensive drugs are used wisely and that patients could be switched to chemotherapy appropriately and without delay.
Enzalutamide / Abiraterone Facts

Primary resistance to Enza was observed in 25% of patients in the AFFIRM trial with in 3 months of therapy and Primary resistance to Abi was observed in 30% of patients

WHY and WHAT can be done?
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

**Short response to first ADT (1 year) may predict poor response to AR-targeted therapies**

**Facts**

**AR targeted agents\(^1\)**
- Retrospective analysis in 108 patients with metastatic PCa
- Poor response to subsequent hormone therapies (including abiraterone, enzalutamide) if time to CRPC with first ADT < 16 months

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>&lt; 16 mths</th>
<th>≥ 16 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ PSA ≥50%</td>
<td>18%</td>
<td>58%</td>
</tr>
<tr>
<td>Median TTP</td>
<td>3 mths</td>
<td>5 mths</td>
</tr>
</tbody>
</table>

**Docetaxel\(^2\)**
- 188 patients with mCRPC in 2 prospective databases
- High Gleason score and visceral mets more common if early CRPC (≤1 year)
- Good response to docetaxel irrespective of time to CRPC:

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>≤ 1yr</th>
<th>&gt; 1yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ PSA ≥50%</td>
<td>67%</td>
<td>81%</td>
</tr>
<tr>
<td>Median TTP</td>
<td>6.1 mths</td>
<td>7.1 mths</td>
</tr>
</tbody>
</table>

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1 Loriot Y *et al.* ASCO GU 2012 (abstract 213) ; 2 Huillard ASCO 2013 (abstract 5075)

*TTP: time to progression; mths: months*
May initial Gleason score guide treatment choice in chemonaïve patients?

**Facts**

**Docetaxel**

- Post-hoc analysis of TAX327 randomized trial (n=1006 mCRPC)
- Marked survival benefit with docetaxel q3w in patients with high Gleason score:

<table>
<thead>
<tr>
<th>OS (median)</th>
<th>Whole cohort</th>
<th>Gleason 7-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + P</td>
<td>19.2 mo</td>
<td>18.9 mo</td>
</tr>
<tr>
<td>Mitoxantrone + P</td>
<td>16.3 mo</td>
<td>14.5 mo</td>
</tr>
<tr>
<td>OS benefit vs mitoxantrone</td>
<td>2.9 mo</td>
<td><strong>4.4 mo</strong></td>
</tr>
</tbody>
</table>

**Abiraterone**

- Post-hoc analysis of COU-AA-302 randomized trial (n=1088)

**Gleason <8**

Significant OS benefit with ABI vs P

HR [95% CI] 0.72 [0.54-0.97]  
*p=0.0295*

**Gleason 8-10**

NO survival benefit with ABI vs P

HR [95% CI] 0.84 [0.64-1.09]  
*p=0.1789*

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2. Fizazi K, J Clin Oncol 2014; 32 (suppl 4): abstract 20; *Mo: months; P: prednisone*
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

**Facts**

### Abiraterone

- **PSA response rate**
  - AR-V7 positive: 0% (95% CI: 0-46%)
  - AR-V7 negative: 68.0% (95% CI: 46-85%)
  - *P*=0.004

### Enzalutamide

- **PSA response rate**
  - AR-V7 positive: 0% (95% CI: 0-26%)
  - AR-V7 negative: 52.6% (95% CI: 29-76%)
  - *P*=0.004

### Taxane*

- **PSA response rate**
  - AR-V7 positive: 41% (95% CI: 18-67%)
  - AR-V7 negative: 65% (95% CI: 41-85%)
  - *P*=0.19

*Docetaxel, n=30
Cabazitaxel, n=7

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Enza/Abi Resistance

Mechanism:

– Point mutations to the AR in the regions coding for the ligand-binding domain

– AR variants; truncated versions of the wild type AR generated by genome rearrangement and splicing are often ligand-independent and constitutively active. CRPC and bone mets have higher AR variants

– Both Enza and Abi resistance have been tied to AR-V7
Overcoming resistance

Avoiding AR activation; **Indomethacin**, inhibitor of key enzyme **AKR1C3**

Autophagy inhibitors; **metformin**.

Targeting AR variant expression; thus by reintroducing drug sensitivity : anti-helminthic drug “**Niclosamide**” has been shown as an AR-V7 inhibitor

Targeting the N-terminal of the truncated variant; **Niphatenones**, inhibit transactivation of AR and variants

Co-targeting resistance by combination of Abi and Enza

Efstathiou, E, ASCO 2014
Chemotherapy

Side effects,

- Neutropenia,
- Fatigue
- Alopecia
- Diarrhea Stomatitis
- Dyspnea
- Peripheral oedema
Individualized approach

An individualized approach to management of mCRPC is needed, based upon:

– aims and expectations of individual patients and
– the clinician’s expectations of efficacy with minimal toxicity armed with evidence based facts.

These expectations include the need to improve survival, palliate symptoms, control PSA levels and prevent the complications of bone metastases

Knowledge empower decisions
It will be nice ....IF

A randomised, controlled trial comparing abiraterone or enzalutamide with docetaxel chemotherapy in patients with mCRPC and assessing the impact of different treatment sequences on OS would be the theoretical ideal to answer some of these questions, but such a trial may not be feasible due to MANY FACTORS.

The Urologist is a practical person, endorses a workable strategy based on clear evidence integrated with knowledge of his patient and expectations.
Workable strategy

Symptomatic or mildly symptomatic mCRPC

Abiraterone or Enza (with continued ADT) may be considered before chemotherapy in patients with a history of long response to ADT, moderate Gleason and good PS.
Workable strategy

Symptomatic mCRPC

In patients with symptomatic mCRPC, there is currently no data to support the use of abiraterone or Enza before chemotherapy.
Workable strategy

Salvage Treatment after Second-Line Hormonal Treatment Failure (Enza or Abi)

Though Chemotherapy seems the logical next step, there are very limited data on the sequencing of newer treatments. As a result, it is not possible to provide evidence-based guidance on the choice of treatment (chemotherapy or novel hormonal agent).
Workable strategy

Post Docetaxel

Despite the available data on whether a patient would be a candidate for cabazitaxel, abiraterone, or enzalutamide after docetaxel treatment; potential patient selection criteria can be considered:

– Cabazitaxel may be selected as the next-choice agent in those with visceral metastases and short PSA doubling time (<6 months), as those criteria have been suggested to be predictors of poor response to abiraterone/enzalutamide.
The Urologist

Knows
- The patient for many years and the natural history of the disease
- The delivery, mechanism of action, indications and side effect of Androgen Deprivation Therapy (ADT)
  - Mono-therapy, TAB, Intermittent and continuous and before and after primary therapy

Needs to know
- Why ADT fails
- When to initiate second line Hormonal therapy
- Understand the indications, delivery, activity, and side effects of the new agents that targets androgen signaling and chemotherapy and why they also fail and what to do about it
- The evidence to continue ADT in mCRPC

Needs NOT
- to be intimidated by the new available agents
- Refer and forget his patient with mCRPC but be engaged in the MDT managing the patient
Potential therapeutic options after PSA progression following hormonal therapy in mCRPC - 2016

- Asymptomatic Monitoring Conventional anti-androgens
- With evidence of progressive disease Radium-223

mCRPC

PS 2+

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
- Visceral mets

Second line therapies (dependent on previous treatments)

- Docetaxel
- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium-223

Docetaxel Radium-223

Docetaxel
SEQUENCING - Conclusions

Treatment of mCRPC at the moment is both an art and a science, a work in progress empowered by knowledge of the evidence.

The optimum treatment and sequence of treatments for mCRPC before and after chemotherapy is currently unknown.

MDT will enhance our knowledge and provide the best treatment strategies for our patients.

Parker et al., Annals of Oncology Advance Access published July 22, 2015