Il carcinoma prostatico metastatico: Quale prima linea? Quale terapia nelle linee successive?

Claudia Caserta
S.C. di Oncologia
Terni
DIFFERENT THERAPEUTIC APPROACHES

✓ Metastatic Hormone-sensitive Disease
✓ Asymptomatic or mildly symptomatic Metastatic CRPC
✓ Symptomatic Chemotherapy-naïve Metastatic CRPC
✓ Post-Docetaxel Metastatic CRPC
METASTATIC HORMONE-SENSITIVE DISEASE
THE NATURAL HISTORY OF METASTATIC PROSTATE CANCER

Time (median: 4–5 years)

ADT

Docetaxel, Cabazitaxel, Enzalutamide, Abiraterone, Radium-223

M1 HSPC

M1 HSPC under control

CRPC

Death
Hypothesis of CHAARTED, GETUG 15, STAMPEDE trials:
- Early docetaxel will postpone progression to CRPC and death

M1 HSPC → M1 HSPC under control → CRPC → Death

Time to progression → Time to death
WHAT ARE WE TALKING ABOUT?
Localized prostate cancer → PSA failure

44% of deaths

Metastatic Hormone-naïve Prostate cancer

De novo metastatic prostate cancer

56% of deaths
Localized prostate cancer → PSA failure

De novo metastatic prostate cancer

Scenario 1:
27% in CHAARTED
28% in GETUG 15
29% in STAMPEDE

Scenario 2:
73% in CHAARTED
72% in GETUG 15
71% in STAMPEDE
Metastatic hormone-naïve prostate cancer

CHAARTED and GETUG 15

**RANDOMIZE**

**ARM A:**
ADT +
DOCETAXEL 75 mg/m2/21d x 6/9 cycles

**ARM B:**
ADT alone

Primary endpoint: OS

**METASTATIC HORMONE-SENSITIVE DISEASE**
STAMPEDE: All docetaxel and zoledronic acid comparisons

A = ~1200 pts --> ~404 primary outcome measure events
B = ~600 pts, C = ~600 pts, E = ~600 pts
<table>
<thead>
<tr>
<th>Presenting features</th>
<th>CHAARTED</th>
<th>GETUG 15</th>
<th>STAMPEDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>790</td>
<td>385</td>
<td>2962 (61% M1)</td>
</tr>
<tr>
<td>Geography</td>
<td>N.America</td>
<td>France/Belgium</td>
<td>UK/Switzerland</td>
</tr>
<tr>
<td>Follow-up</td>
<td>29 months</td>
<td>50 months</td>
<td>NR</td>
</tr>
<tr>
<td>Age</td>
<td>64 years</td>
<td>64 years</td>
<td>65 years</td>
</tr>
<tr>
<td>High volume of metastases</td>
<td>65%</td>
<td>47.5%</td>
<td>Unknown</td>
</tr>
<tr>
<td>PSA at entry</td>
<td>53 ng/ml</td>
<td>26 ng/ml</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved PSA/clinical PFS</td>
<td>20.7m vs 14.7m HR 0.56 (0.44-0.70)</td>
<td>22.9m vs 12.9m HR 0.72 (0.57-0.91)</td>
<td>FFS: 37m vs 21m HR=0.62 (0.54-0.70)</td>
</tr>
</tbody>
</table>
GETUG 15

Hazard ratio for death with ADT + docetaxel, 1.01

ADT + docetaxel (median overall survival, 59 mo)

ADT alone (median overall survival, 54 mo)

CHAARTED

Hazard ratio for death with ADT + docetaxel, 0.61 (95% CI, 0.47–0.80) P<0.001

ADT + docetaxel (median overall survival, 57.6 mo)

ADT alone (median overall survival, 44.0 mo)
GETUG 15: No differences in OS in high or low volume disease
Metastatic Hormone-Sensitive Disease

STAMPEDE

Docetaxel: Survival – M1 Patients

SOC: 343 deaths
SOC+Doc: 134 deaths

HR (95% CI): 0.73 (0.59, 0.89)
P-value: 0.002

Non-PH p-value: 0.23

Median OS (95% CI)
SOC: 43m (24, 88m)
SOC+Doc: 65m (27, NR)

Restricted mean OS time
SOC: 49.3m
SOC+Doc: 56.1m
Diff (95% CI): 6.8m (2.8, 11.0m)
### METASTATIC HORMONE-SENSITIVE DISEASE

<table>
<thead>
<tr>
<th></th>
<th>CHAAR TED</th>
<th>CHAAR TED</th>
<th>GETUG 15</th>
<th>GETUG 15</th>
<th>STAMPE DE</th>
<th>STAMPE DE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT+ D</td>
<td>ADT</td>
<td>ADT+ D</td>
<td>ADT</td>
<td>ADT</td>
<td>ADT+ D</td>
<td>ADT</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>12.4%</td>
<td>33%</td>
<td>45%</td>
<td>80%</td>
<td>14%</td>
<td>41%</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>11%</td>
<td>7%</td>
<td>2%</td>
<td>1%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Abi/Enza</td>
<td>23%</td>
<td>20%</td>
<td>15%</td>
<td>15%</td>
<td>35%</td>
<td>30%</td>
</tr>
</tbody>
</table>

- "Salvage" docetaxel much more frequent in GETUG 15
- GETUG 15 is underpowered in high volume disease
METASTATIC HORMONE-SENSITIVE DISEASE

RECOMMENDATION #1
Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT.
QUESTIONS CONCERNING TREATMENT CHOICE IN METASTATIC CRPC

- Selecting the right treatment for a specific patient
- Optimal sequencing of available agents
- *Combination therapy prospects*
ASYMPTOMATIC OR MILDLY SYMPTOMATIC
METASTATIC CRPC
ASYMPTOMATIC OR MILDLY SYMPTOMATIC
METASTATIC CRPC

Standard Treatment

ABIRATERONE
ENZALUTAMIDE
SIPULEUCEL-T
DOCETAXEL
Asymptomatic or mildly symptomatic metastatic, chemo-naïve CRPC
ECOG 0-1

ARM A: Abiraterone plus prednisone/Enzalutamide

ARM B: Placebo plus Prednisone/Placebo

Coprimary endpoints: OS and radiographic PFS
### Presenting features

<table>
<thead>
<tr>
<th></th>
<th>COU-AA-302 (ABI)</th>
<th>PREVAIL (ENZA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>1088</td>
<td>1717</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>70.5</td>
<td>71</td>
</tr>
<tr>
<td><strong>PSA at entry</strong></td>
<td>40 ng/ml</td>
<td>49 ng/ml</td>
</tr>
<tr>
<td><strong>Time from initial diagnosis or first treatment of prostate cancer to randomization</strong></td>
<td>63 months</td>
<td>63 months</td>
</tr>
</tbody>
</table>

### Distribution of disease at screening

- **Bone only**: 50% (COU-AA-302) vs. 40% (PREVAIL)
- **Lymph node**: 49.5% (COU-AA-302) vs. 50.5% (PREVAIL)
- **Visceral disease**: 0.7% (COU-AA-302) vs. 11.5% (PREVAIL)
### Asymptomatic or Mildly Symptomatic Metastatic CRPC

<table>
<thead>
<tr>
<th>Trial</th>
<th>N. pts</th>
<th>OS (months)</th>
<th>rPFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone/Prednisone vs Placebo/Prednisone</td>
<td>1088</td>
<td>34.7 vs 30.3 HR 0.81 (p=0.0033)</td>
<td>16.5 vs 8.3 HR 0.53 (p&lt;0.001)</td>
</tr>
<tr>
<td>Enzalutamide vs placebo</td>
<td>1717</td>
<td>35.3 vs 31.3 HR 0.71 (p&lt;0.0001)</td>
<td>NR vs 3.9 HR 0.19 (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>COU-AA-302</td>
<td>COU-AA-302</td>
<td>PREVAIL</td>
</tr>
<tr>
<td>----------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>ABI</td>
<td>PLACEBO</td>
<td>ENZA</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>38%</td>
<td>53%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>8%</td>
<td>10%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>5%</td>
<td>10%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>NR</td>
<td>NR</td>
<td>1.0%</td>
</tr>
</tbody>
</table>
Abiraterone and Enzalutamide significantly delayed time to chemotherapy
SYMPTOMATIC CHEMOTHERAPY-NAÏVE METASTATIC CRPC
Standard Treatment

DOCETAXEL 75 mg/mq q21  + Prednisone 5 mg bid
RADIUM-223 50kBq/kg q28 for symptomatic bone metastases, without visceral metastases
Overall more than 1,600 met HRPC pts treated

Docetaxel improves OS and TTP in advanced hormone-refractory prostate cancer patients

**TAX 327: Study Design**

**Stratification:**
- Pain level: PPI ≥ 2 or AS ≥ 10 vs PPI < 2 or AS < 10
- KPS ≤ 70 vs ≥ 80

**Randomize**
- Docetaxel 75 mg/m² q 3 wk + Prednisone 5 mg bid
- Docetaxel 30 mg/m² wkly 5 of 6 wks + Prednisone 5 mg bid
- Mitoxantrone 12 mg/m² q 3 wk + Prednisone 5 mg bid

Treatment duration in all 3 arms = 30 wks

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**SWOG 9916: Study Design**

**D/E**
- Docetaxel 60 mg/m² IV D2 every 21 days
- Estramustine 280 mg po TID, D1-5
- Premedication: Dexamethasone 20 mg PO TID starting evening of D1

**M/P**
- Mitoxantrone 12 mg/m² IV every 21 days
- Prednisone 5 mg po BID continuously

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*Per protocol amendment January 15, 2001: Coumadin 2 mg PO daily + ASA 325 mg PO daily was added.
Docetaxel and mitoxantrone doses could be increased to 70 mg/m² and 14 mg/m², respectively, if no grade 3 or 4 toxicities were seen in cycle 1.

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Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer
POST-DOCETAXEL METASTATIC CRPC
Standard Treatment

**ABIRATERONE**
**ENZALUTAMIDE**
**CABAZITAXEL**
**RADIUM-223**
## POST-DOCETAXEL METASTATIC CRPC

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>N. pts</th>
<th>OS (months)</th>
<th>Radiographic PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone vs placebo</td>
<td>1195</td>
<td>15.8 vs 11.2 (p&lt;0.0001)</td>
<td>5.6 vs 3.6 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Enzalutamide vs placebo</td>
<td>1199</td>
<td>18.4 vs 13.6 (p&lt;0.001)</td>
<td>8.3 vs 2.9 (p&lt;0.001)</td>
</tr>
<tr>
<td>Cabazitaxel vs Mitoxantrone</td>
<td>755</td>
<td>15.1 vs 12.7 (p&lt;0.0001)</td>
<td>2.8 vs 1.4 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Radium-223 vs placebo</td>
<td>921</td>
<td>14.9 vs 11.3 (p=0.001)</td>
<td>Time to the first symptomatic skeletal event 15.6 vs 9.8 (p&lt;0.001)</td>
</tr>
</tbody>
</table>
METASTATIC PROSTATE CANCER: CONCLUSIONS

- Placebo-controlled trials may no longer be ethical or feasible in men with mCRPC
- Is it still realistic to demand that new agents increase OS among patients with metastatic castration-resistant prostate cancer?
- None of these new therapies have been directly compared to each other
- No prospective sequencing trials
- Is there cross resistance among therapies?
METASTATIC PROSTATE CANCER: CONCLUSIONS

- Selection of the patients who will be responsive could significantly improve the outcomes
- Clinical, radiologic, biologic and genomic predictive biomarkers should be identified and validated

ORIGINAL ARTICLE

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.
**PROPOSED TREATMENT PARADIGM OF mCRPC**

**SCENARIO 1:**
M1 at diagnosis or short response to ADT mCRPC

- ADT
- DOCETAXEL
- CABAZITAXEL
- ABI/ENZA

**SCENARIO 2:**
Asymptomatic or mildly symptomatic mCRPC

- ADT
- ABI
- DOCETAXEL
- ENZA
- CABAZITAXEL

**SCENARIO 3:**
Symptomatic mCRPC

- ADT
- DOCETAXEL
- ABI/ENZA
- CABAZITAXEL
PROPOSED TREATMENT PARADIGM OF mCRPC

SCENARIO 1:
Symptomatic mCRPC

ADT  RADIUM-223  DOCETAXEL  ABI/ENZA

SCENARIO 2:
Mildly symptomatic mCRPC

ADT  ABI  RADIUM-223  DOCETAXEL

SCENARIO 3:
Post-docetaxel mCRPC

ADT  ABI  DOCETAXEL  RADIUM-223
METASTATIC PROSTATE CANCER