Prostate Cancer Debate 2013

Evolving treatment options in castration-resistant prostate cancer

Scientific Committee: Per-Anders Abrahamsson, Sweden; Heather Payne, UK; and Peter Iversen, Denmark

Janssen Pharmaceutica NV
Review of chemotherapy data

Maria De Santis
M De Santis – Disclosures

<table>
<thead>
<tr>
<th>Role</th>
<th>Disclosures</th>
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<tbody>
<tr>
<td>Research Support</td>
<td>Pierre Fabre</td>
</tr>
<tr>
<td>Employee</td>
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</tr>
<tr>
<td>Consultant</td>
<td>Novartis, GSK, Pierre-Fabre Oncology, Roche, Amgen, Dendreon, Janssen, Bayer, Sanofi, Pfizer, OncoGenex, Shionogi, Astellas,</td>
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<tr>
<td>Major Stockholder</td>
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<td>Speakers Bureau</td>
<td>Amgen, Janssen, Sanofi, GSK, Bayer</td>
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<td>Honoraria</td>
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<td>Scientific Advisory Board</td>
<td>GSK, Pierre-Fabre Oncology, Amgen, Dendreon, Janssen, Bayer, Sanofi; Astellas, Shionogi</td>
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</table>
The role of chemotherapy in prostate cancer

- Heterogeneous disease
- Improve duration and quality of survival
- Previous trial showed patients could tolerate chemotherapy with mitoxantrone and derived palliative benefit
- In 2004, docetaxel was first chemotherapy showing an improvement in overall survival to be approved in advanced prostate cancer

Changing treatment paradigm in mCRPC

Many more treatments approved, three indicated in the post-docetaxel space

4 de Bono et al. Lancet. 2010; 376(9747): 1147-1154
5 Parker et al. NEJM 2013; 369(2): 213-223

*Approved by FDA
mCRPC: First-line chemotherapy

- Median OS 19.2 mos\(^1\)
- 2.9 mos OS improvement over mitoxantrone\(^1\)
  - 30% cross over
  - definition of PD: PSA\(\uparrow\) at 6 weeks
- 3% neutropenic fever; G3/4 tox uncommon\(^1\)

Docetaxel:
- 23% improvement in QoL (P=0.005)\(^1\)
- Men with reduction in pain lived 
  ~6 months longer\(^2\):
  - HR, 0.59; 95% CI, 0.47-0.73; P<0.001

Docetaxel rechallenge
## Second-line chemotherapy: Docetaxel rechallenge

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No pts</th>
<th>Endpoint</th>
<th>&gt;50% PSA decline (PSAD)</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
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<tbody>
<tr>
<td>Doc₁,₇</td>
<td>25</td>
<td>Retrospective</td>
<td>32</td>
<td>8.0</td>
<td>9.6</td>
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<td>Doc₂,₇</td>
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<td>Retrospective</td>
<td>22.2</td>
<td>NR</td>
<td>15.9</td>
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<td>Doc³,₇</td>
<td>39</td>
<td>Retrospective</td>
<td>38</td>
<td>4.3</td>
<td>15.8</td>
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<td>Doc weekly⁴,₇</td>
<td>35</td>
<td>PSAD</td>
<td>65</td>
<td>6.2</td>
<td>15.3</td>
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<tr>
<td>Doc⁵,₇</td>
<td>45</td>
<td>PSAD</td>
<td>24.5</td>
<td>5.0</td>
<td>13.0</td>
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<tr>
<td>Doc⁶,₇</td>
<td>66</td>
<td>PSAD</td>
<td>47</td>
<td>4</td>
<td>16</td>
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<tr>
<td>Doc⁸</td>
<td>44</td>
<td>Retrospective</td>
<td>10</td>
<td>5.9*</td>
<td>21.8</td>
</tr>
</tbody>
</table>

* PSA PFS

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¹Jankovic et al. Proc Genitourinary Cancers Symposium 2010; Abstract 196
²Ansari et al. Proc Genitourinary Cancers Symposium 2010; Abstract 185
³Loriot et al. Eur J Cancer 2010; 46: 1770-1772
⁴Firek et al. Proc Genitourinary Cancers Symposium 2010; Abstract 93
⁵Di Lorenzo et al. BJU Int 2011; 107(2): 234-239
⁶Germone et al. Proc Genitourinary Cancers Symposium 2010; Abstract 143
⁷Reviewed by Colloca et al. Med Oncol 2011; 29(2):776-85
Cabazitaxel
TROPIC: Study design

- **Stratification factor:**
  - ECOG PS (0,1 vs 2)
  - Measurable/non-measurable

- **Primary endpoint:**
  - Overall survival (OS)

- **Secondary endpoint:**
  - PSA response, PSA progression, PFS, RR, pain progression, safety, PK of cabazitaxel

Enrollment closed: 745/720 pts
Hypothesis: Reduction of 25% in the risk of death or median OS=10.67 months for cabazitaxel vs 8 months 511 events, duration 36 months

de Bono et al. Lancet 2010; 376(9747): 1147-1154
**TROPIC: Overall survival**

30% reduction in risk of death

HR 0.70 (95% CI 0.59–0.83)

Log-rank p < 0.0001

**Comparison of Median OS**

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>377</td>
<td>378</td>
</tr>
<tr>
<td>Probability of overall survival (%)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Months</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Probability of overall survival (%)</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Months</td>
<td>24</td>
<td>30</td>
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**Median OS**

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
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<tr>
<td>Median OS, Mos</td>
<td>12.7</td>
<td>15.1</td>
</tr>
<tr>
<td>HR</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.59-0.83</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.0001</td>
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**Improvement in overall survival with cabazitaxel is 2.4 months**

**Combined median follow-up: 12.8 months**

*de Bono et al. Lancet 2010; 376(9747): 1147-1154*
### TROPIC: Hematological adverse events

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone (n=371)(^1)</th>
<th>Cabazitaxel (n=371)(^1)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>88%</td>
<td>58%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>-</td>
<td>1%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>92%</td>
<td>42%</td>
</tr>
<tr>
<td>Anemia</td>
<td>81%</td>
<td>5%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43%</td>
<td>2%</td>
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</tbody>
</table>

- First instance of grade ≥3 neutropenia generally occurred during the first two treatment cycles\(^2\)
- Consider prophylactic Granulocyte colony-stimulating factor

1de Bono et al. Lancet 2010; 376(9747): 1147-1154
2Ozguroglu et al. J Clin Oncol 2011; 29(7S): abstract A38 (Poster Presentation)
Cross resistance
Potential mechanism of cross-resistance: Tubulin-targeting agents and AR-targeting agents

- Preclinical study of AR translocation
- Inhibition of AR nuclear transport
  - Docetaxel 21%
  - Cabazitaxel 34%
  - Abiraterone 58%
  - Enzalutamide 100%
  - Mitoxantrone (control) 0%
- Role of microtubules in AR nuclear transport

Response to docetaxel after abiraterone acetate: cross-resistance?

<table>
<thead>
<tr>
<th></th>
<th>TAX-327(^1)</th>
<th>COU-AA-001(^2)</th>
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<tbody>
<tr>
<td>(\geq 50%) PSA decline</td>
<td>45%</td>
<td>26%</td>
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<tr>
<td>Median OS from commencing docetaxel</td>
<td>18.9 months</td>
<td>12.5 months</td>
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</table>

Activity of cabazitaxel post-abiraterone and post-docetaxel

- Retrospective analysis
- 89 patients treated with third-line cabazitaxel
  - After docetaxel (median 8 cycles; range: 4-12)
  - After AA (median duration of treatment 4.8 months, range: 1-55 months)
- Median 6 cycles of cabazitaxel (range 1-15)
- 44 patients (49%; 95% CI 39-60%) had a 50% or greater PSA decline
- 35 patients with RECIST evaluable disease, 7 (20%; 95% CI 8-37%) had a partial response

Predictors of response to chemotherapy or abiraterone/enzalutamide

- No single prognostic marker

Candidates for chemotherapy?

- Patients with <16 months sensitivity to ADT may respond better to chemotherapy than to AA
  - 108 patients from 5 clinical studies\(^1\)
    - Duration of sensitivity to ADT (≥16 months and <16 months)
      - Predicted PSA response (58% vs 18%, p=0.01)
      - Median PFS
        - 5 months (95%CI: 3.46-6.53)
        - 3 months (95%CI: 2.10-3.89, p<0.043)

- COU-AA-302: 38% patients treated with abiraterone acetate did not have a ≥50% decline in PSA (n=546)\(^2\)

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Candidates for chemotherapy?

- Response to taxanes independent from
  - Response to ADT (docetaxel, cabazitaxel)$^{1,2}$
  - Gleason score$^3$
    - Gleason $\geq 7$ three-weekly docetaxel vs mitoxantrone
      - median OS: 18.9 vs 14.5 mo; $p=0.009$
  - Visceral metastases (not included in COU-AA-302 study)

$^2$Oudard et al. 933P (ESMO 2012); post-hoc analysis
Small cell and neuroendocrine differentiation in prostate cancer

- Population not well defined, and may coexist with prostate adenocarcinoma

- Characteristics include:
  - Low or no PSA production
  - Metastases (hepatic, brain, lymph)
  - Resistance to ADT
  - Lytic bone disease

- Presence of high-grade prostate cancer, visceral disease and low/no PSA should prompt a biopsy

- Phase I/II studies of platinum-based chemotherapy but few select small cell neuroendocrine populations
  - Response rate with single agent 6-43%
  - Response rate with estramustine, carboplatin and taxane 60-100%

Anaplastic carcinoma characteristics

CRPC with ≥1 of:

- Histology of small cell
- Only visceral metastases
- Lytic bone disease
- Low PSA at diagnosis + high volume disease
- Neuroendocrine markers + LDH, hypercalcemia, CEA
- Short interval to CRPC after hormone therapy, +/- neuroendocrine markers

First-line: docetaxel + carboplatin
Second-line: etoposide + cisplatin
N=120
Median OS: 16 months

Prognostic factors: LDH, bulky disease, carcino-embryonic antigen (CEA)

Summary

- Chemotherapy remains an effective treatment
  - <1 year duration of response to hormone therapy
  - Low/no PSA, visceral metastases, bulky disease, CEA, elevated LDH
  - Symptomatic patients

- Further data are needed to better understand:
  - The optimal sequence and combination of agents
  - Biomarkers to select patient subgroups that might best respond to the different agents
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