Tubulin-binding drug In prostate cancer

Dr Christophe Massard
Institut Gustave Roussy, Department of Cancer Medicine
christophe.massard@igr.fr

TAT Meeting, Paris, 2011
Clinical progression of Prostate Cancer

- Androgen deprivation (Huggins, 1941)
- Androgen deprivation Docetaxel based chemotherapy (Tannock; Petrylack 2004)

Chemotherapy in Prostate Cancer before 2010...
● Docetaxel based chemotherapy in CRPC

● New tubulin agent in CRPC: Cabazitaxel

● Other drugs and Combination therapy

● Strategy in prostate cancer (early stage)

● Perspectives
Docetaxel based chemotherapy in CRPC: TAX 327 and SWOG 9916

**TAX 327**
- Mitoxantrone 12 mg/m² q 21 days
- Prednisone 5 mg po bid
- Docetaxel 75 mg/m² q 21 days
- Prednisone 5 mg po bid
- Dexamethasone 8 mg 12, 3 and 1 hour prior to D
- Docetaxel 30 mg/m² /wk 5 of 6 wks
- Prednisone 5 mg po bid
- Dexamethasone 8 mg 1 hour prior to D

**N=1006**

**SWOG 9916**
- Mitoxantrone 12 mg/m² q 21 days
- Prednisone 5 mg po bid
- Docetaxel 60 mg/m² IV J2/3 weeks
- Dexamethasone 20 mg x3/d

**N=770**


Docetaxel based chemotherapy in CRPC: Overall Survival

**TAX 327**

Median OS: 18.9 months vs. 16.5 months  
HR: 0.76 (0.62-0.94)

**SWOG 9916**

Median OS: 17.5 months vs. 15.6 months  
HR: 0.80 (0.67-0.97)

Chemotherapy works!

Arising questions

- What to do when docetaxel eventually fails?
- Docetaxel alone or in combination (estramustine)?
- Early (asymptomatic) or late (symptomatic) chemotherapy?
- Docetaxel based chemotherapy in CRPC
- New tubulin agent in CRPC: Cabazitaxel
- Other drugs and Combination therapy
- Strategy in prostate cancer (early stage)
- Perspectives
## Mitoxantrone after first line Docetaxel

<table>
<thead>
<tr>
<th>Author</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michels (n=35)</td>
<td>15%</td>
</tr>
<tr>
<td>Oh (n=35)</td>
<td>6% (PFS: 6 weeks)</td>
</tr>
</tbody>
</table>
Cabazitaxel: A Next-Generation Taxane

- **New semi-synthetic taxane**
  - Selected to overcome the emergence of taxane resistance (poor affinity for drug efflux pomp)
  - Microtubule stabilizer

- **Preclinical data**
  - As potent as docetaxel against sensitive cell lines and tumor models
  - Activity against tumor cells and tumor models that are resistant to taxanes

- **Clinical data**
  - DLT was neutropenia
  - Antitumor activity in taxane resistant CRPC
  - No phase II data in CRPC
Cabazitaxel + prednisone (CBZP) versus mitoxantrone + prednisone (MP) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-based regimen

Final Results of the Phase III TROPIC Trial

Oliver Sartor, MD
Piltz Professor of Cancer Research
Tulane University School of Medicine
New Orleans, USA

Johann de Bono, MD, PhD
Reader in Experimental Cancer Medicine
The Institute of Cancer Research
The Royal Marsden Hospital
Surrey, UK

On behalf of the TROPIC Investigators
TROPIC: Phase III Registration Study
146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

Stratification factors
ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

Primary endpoint: OS
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

- 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)

*Oral prednisone/prednisolone: 10 mg daily.
## Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone (n=377)</th>
<th>Cabazitaxel (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (years)</td>
<td>67 (61–72)</td>
<td>68 (62–73)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>70 (19%)</td>
<td>69 (18%)</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>314 (83%)</td>
<td>317 (84%)</td>
</tr>
<tr>
<td>Asian</td>
<td>32 (8%)</td>
<td>26 (7%)</td>
</tr>
<tr>
<td>Black</td>
<td>20 (5%)</td>
<td>20 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (3%)</td>
<td>15 (4%)</td>
</tr>
<tr>
<td><strong>ECOG performance status 0 or 1</strong></td>
<td>344 (91%)</td>
<td>350 (93%)</td>
</tr>
<tr>
<td><strong>Extent of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>356 (94%)</td>
<td>364 (96%)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>328 (87%)</td>
<td>303 (80%)</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>94 (25%)</td>
<td>94 (25%)</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>20 (5%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Median serum PSA concentration (µg/L)</strong></td>
<td>127.5 (44.0–419.0)</td>
<td>143.9 (51.1–416.0)</td>
</tr>
<tr>
<td>Serum PSA concentration ≥20 µg/L</td>
<td>325 (86%)</td>
<td>329 (87%)</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>204 (54%)</td>
<td>201 (53%)</td>
</tr>
<tr>
<td>Pain at baseline†</td>
<td>168 (45%)</td>
<td>174 (46%)</td>
</tr>
</tbody>
</table>

### Previous therapy

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal‡</strong></td>
<td>375 (99%)</td>
<td>375 (99%)</td>
</tr>
<tr>
<td>Number of chemotherapy regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>268 (71%)</td>
<td>260 (69%)</td>
</tr>
<tr>
<td>2</td>
<td>79 (21%)</td>
<td>94 (25%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>30 (8%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>222 (59%)</td>
<td>232 (61%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>205 (54%)</td>
<td>198 (52%)</td>
</tr>
<tr>
<td>Biological agent</td>
<td>36 (10%)</td>
<td>26 (7%)</td>
</tr>
</tbody>
</table>

### Number of previous docetaxel regimens

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>327 (87%)</td>
<td>316 (84%)</td>
</tr>
<tr>
<td>2</td>
<td>43 (11%)</td>
<td>53 (14%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>7 (2%)</td>
<td>9 (2%)</td>
</tr>
</tbody>
</table>

### Total previous docetaxel dose (mg/m²)

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>529±2</td>
<td>576±6</td>
</tr>
<tr>
<td>(380–9–787±2)</td>
<td>(408–4–761±2)</td>
<td></td>
</tr>
</tbody>
</table>

### Disease progression relative to docetaxel administration

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment</td>
<td>104 (28%)</td>
<td>115 (30%)</td>
</tr>
<tr>
<td>≤3 months from last dose</td>
<td>181 (48%)</td>
<td>158 (42%)</td>
</tr>
<tr>
<td>≥3 months from last dose</td>
<td>90 (24%)</td>
<td>102 (27%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

### Median time from last docetaxel dose to disease progression (months)

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone</th>
<th>Cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.7 (0.0–2.9)</td>
<td>0.8 (0.0–3.1)</td>
</tr>
</tbody>
</table>
Most Frequent Grade $\geq$ 3 Treatment-Emergent AEs*  
Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone (n=371)</th>
<th>Cabazitaxel (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade $\geq$ 3</td>
</tr>
<tr>
<td><strong>Haematological†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>325 (88%)</td>
<td>215 (58%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>$\ldots$</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>343 (92%)</td>
<td>157 (42%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>302 (81%)</td>
<td>18 (5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>160 (43%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td><strong>Non-haematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>39 (11%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>102 (27%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>46 (12%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>45 (12%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>85 (23%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Haematuria</td>
<td>14 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>27 (7%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>17 (5%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>57 (15%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23 (6%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>31 (8%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Urinary-tract infection</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>18 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>19 (5%)</td>
<td>9 (2%)</td>
</tr>
</tbody>
</table>
## Deaths in patients who received at least one dose of study treatment

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone (n=371)</th>
<th>Cabazitaxel (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths during the study</td>
<td>275 (74%)</td>
<td>227 (61%)</td>
</tr>
<tr>
<td>Deaths ≤30 days after last dose of study drug</td>
<td>9 (2%)</td>
<td>18 (5%)</td>
</tr>
<tr>
<td>Causes of death ≤30 days after last dose of study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>6 (2%)*</td>
<td>0</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia and clinical consequences/sepsis</td>
<td>1 (&lt;1%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Dyspnoea†</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration/electrolyte imbalance</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Cerebral haemorrhage</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Deaths &gt;30 days after last dose of study drug</td>
<td>266 (72%)</td>
<td>209 (56%)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). *Includes three patients whose death was reported as an adverse event coded as disease progression. †Dyspnoea was reported as the adverse event leading to death, but the investigator regarded the death as related to disease progression.

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**Table 5: Deaths in patients who received at least one dose of study treatment**
Overall Survival and Progression Free Survival (TROPIC trial)

Median OS: 15.1 months (CBZ) vs. 12.7 months (M)
HR: 0.70 (0.59-0.83)

Median PFS: 2.8 months (CBZ) vs. 1.4 months (M)
HR: 0.74 (0.64-0.86)

De Bono et al, Lancet 2010
Overall Survival in subgroups of patients (TROPIC trial)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patient number</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomised patients</td>
<td>755</td>
<td>0.70 (0.59-0.83)</td>
</tr>
<tr>
<td>ECOG status: 0, 1</td>
<td>694</td>
<td>0.68 (0.57-0.82)</td>
</tr>
<tr>
<td>ECOG status: 2</td>
<td>61</td>
<td>0.81 (0.48-1.38)</td>
</tr>
<tr>
<td>Measurable disease: no</td>
<td>350</td>
<td>0.72 (0.55-0.93)</td>
</tr>
<tr>
<td>Measurable disease: yes</td>
<td>405</td>
<td>0.68 (0.54-0.85)</td>
</tr>
<tr>
<td>Number of previous chemotherapies: 1</td>
<td>528</td>
<td>0.67 (0.55-0.83)</td>
</tr>
<tr>
<td>Number of previous chemotherapies: ≥2</td>
<td>227</td>
<td>0.75 (0.55-1.02)</td>
</tr>
<tr>
<td>Age: &lt;65 years</td>
<td>295</td>
<td>0.81 (0.61-1.08)</td>
</tr>
<tr>
<td>Age: ≥65 years</td>
<td>460</td>
<td>0.62 (0.50-0.78)</td>
</tr>
<tr>
<td>Pain at baseline: no</td>
<td>374</td>
<td>0.55 (0.42-0.72)</td>
</tr>
<tr>
<td>Pain at baseline: yes</td>
<td>342</td>
<td>0.77 (0.61-0.98)</td>
</tr>
<tr>
<td>Rising PSA at baseline: no</td>
<td>159</td>
<td>0.88 (0.61-1.26)</td>
</tr>
<tr>
<td>Rising PSA at baseline: yes</td>
<td>583</td>
<td>0.65 (0.53-0.80)</td>
</tr>
<tr>
<td>Total docetaxel dose: ≤225 mg/m²</td>
<td>59</td>
<td>0.96 (0.49-1.86)</td>
</tr>
<tr>
<td>Total docetaxel dose: ≥225-450 mg/m²</td>
<td>206</td>
<td>0.60 (0.43-0.84)</td>
</tr>
<tr>
<td>Total docetaxel dose: ≥450-675 mg/m²</td>
<td>217</td>
<td>0.83 (0.60-1.16)</td>
</tr>
<tr>
<td>Total docetaxel dose: ≥675-900 mg/m²</td>
<td>131</td>
<td>0.73 (0.48-1.10)</td>
</tr>
<tr>
<td>Total docetaxel dose: ≥900 mg/m²</td>
<td>134</td>
<td>0.51 (0.33-0.79)</td>
</tr>
<tr>
<td>Progression during docetaxel treatment</td>
<td>219</td>
<td>0.65 (0.47-0.90)</td>
</tr>
<tr>
<td>Progression &lt;3 months after docetaxel</td>
<td>339</td>
<td>0.70 (0.55-0.91)</td>
</tr>
<tr>
<td>Progression ≥3 months after docetaxel</td>
<td>192</td>
<td>0.75 (0.51-1.11)</td>
</tr>
</tbody>
</table>
Chemotherapy works in second line!

- What to do when docetaxel eventually fails?
  - Cabazitaxel or Abiraterone or …clinical trials

- Docetaxel alone or in combination (estramustine)?

- Early (asymptomatic) or late (symptomatic) chemotherapy?
Docetaxel based chemotherapy in CRPC

New tubulin agent in CRPC: Cabazitaxel

Other drugs and Combination therapy

Strategy in prostate cancer (early stage)

Perspectives
Epothilones and prostate cancer

New class of cytotoxic tubulin agents (Sorangium cellulosum)

Large antineoplastic activity

In particular in taxane-resistant models (breast, prostate cancer)

<table>
<thead>
<tr>
<th></th>
<th>Pts (n)</th>
<th>Decline PSA</th>
<th>RR</th>
<th>mOS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixabepilone+/- EMP</td>
<td>92</td>
<td>48-69%</td>
<td>32-48%</td>
<td>NA</td>
</tr>
<tr>
<td>Patupilone</td>
<td>45</td>
<td>13% (3/6 previous taxane)</td>
<td>0%</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Galsky et al, 2005
Hussain et al, 2009
New drugs in CaP (w/ wt Docetaxel)

- Targeting bone
  - ZD 4054, Atrasentan
  - Samarium
  - Denosumab
  - Bevacizumab
  - VEGF-Trap
  - ZD 64 74
  - Centocor
    - Abiraterone, MDV3100, TAK700…

- Targeting angiogenesis
  - Bevacizumab
  - VEGF-Trap
  - ZD 64 74

- Targeting IL6

- Targeting IGF-R

- Vitamin D analog
  - DN-101 (calcitriol)

- Chemotherapy
  - Estramustine, Satraplatin

- Vaccines
  - APC 8015 (Provenge)
  - GVAX
Estramustine: Nornitrogen mustard-estradiol conjugate

- Tubulin Subunits
- Polymerization
- Depolymerization
- Docetaxel
- Estramustine
- Microtubule
- MAP

Metaphase microtubules forming spindles

Mitosis interrupted

Mitotic spindles broken down
Overall survival: chemotherapy + estramustine versus chemotherapy alone

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Events / No. Entered</th>
<th>OE</th>
<th>Variance</th>
<th>Hazard ratio (Estramustine / Control)</th>
<th>Risk Redn (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Taxanes and epothilones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSKCC</td>
<td>24/47</td>
<td>-2.0</td>
<td>12.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USO N</td>
<td>70/81</td>
<td>-11.5</td>
<td>36.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aventis</td>
<td>31/48</td>
<td>-1.9</td>
<td>15.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (a)</td>
<td>125/176</td>
<td>-15.4</td>
<td>63.8</td>
<td>21% ± 11</td>
<td></td>
</tr>
<tr>
<td>(b) Vinblastine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDA</td>
<td>28/29</td>
<td>1.6</td>
<td>13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoosier</td>
<td>94/94</td>
<td>-11.5</td>
<td>46.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (b)</td>
<td>122/123</td>
<td>-9.9</td>
<td>59.7</td>
<td>15% ± 12</td>
<td></td>
</tr>
<tr>
<td>Total (a ... b)</td>
<td>247/299</td>
<td>-25.3</td>
<td>123.5</td>
<td>19% ± 8</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 2.07 \) \( p = 0.72 \)
Test for interaction: \( \chi^2 = 0.17 \) \( p = 0.68 \)

Estramustine effect with \( p = 0.02 \)
Chemotherapy + Estramustine

vs Chemotherapy alone

HR = 19%, p = 0.02

Patients at risk

<table>
<thead>
<tr>
<th>Control</th>
<th>Estramustine</th>
</tr>
</thead>
<tbody>
<tr>
<td>304</td>
<td>299</td>
</tr>
<tr>
<td>235</td>
<td>255</td>
</tr>
<tr>
<td>153</td>
<td>180</td>
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<tr>
<td>101</td>
<td>107</td>
</tr>
<tr>
<td>46</td>
<td>62</td>
</tr>
</tbody>
</table>

Fizazi et al., Lancet Oncol 2007
Bone metastases from prostate cancer
New drugs in CaP (w/ wt Docetaxel)

**Targeting bone**
- ZD 4054, Atrasentan
- Samarium, Strontium…
- Denosumab
- Bevacizumab
- VEGF-Trap
- ZD 64 74

**Targeting angiogenesis**
- Endothelin-1
- Rx-pharms
- Rank-L axis
- Bevacizumab
- VEGF-Trap
- ZD 64 74

**Targeting IL6**

**Targeting IGF-R**
- Centocor
- Abiraterone, MDV3100, TAK700…
- DN-101 (calcitriol)
- Anti-IGF-R
- Estramustine, Satraplatin
- APC 8015 (Provenge)

**Chemotherapy**

**Vaccines**

**Vitamin D analog**

**Targeting AR**
CRPC and bone metastases

**Induction regimen:** n=43
- docetaxel 70 mg/m^2^ day 2
- estramustine 10 mg/Kg/day, day 1-5 (1 cycle every 3 weeks)

**Response (n=31) or stabilization (n=11)**

**Progression**
- n=1

**Consolidation regimen:** n=42
- docetaxel 20 mg/m^2/w x 6 w
- samarium 1 injection week 1 (37 MBq/Kg)

**1-year survival rate:** 76% (62%-87%)
**2-year survival rate:** 63% (47%-77%)

**Median:** 29 months (20 – 34)
Secretory clusterin is a stress activated cytoprotective chaperone.
A Phase I Study of OGX-011, a 2’-Methoxyethyl Phosphorothioate Antisense to Clusterin, in Combination with Docetaxel in Patients with Advanced Cancer

Kim N. Chi, Lillian L. Siu, Hal Hirte, Sebastien J. Hotte, Jennifer Knox, Christian Kollmansberger, Martin Gleave, Emma Guns, Jean Powers, Wendy Walsh, Dongsheng Tu, and Elizabeth Eisenhauer

- 40 pts enrolled with Combination with docetaxel
  - 640 mg of OGX-011
  - No major side effects

- Randomized phase II in CRPC 5 (Chi et al, 2010)
  - 82 pts enrolled with CRPC
  - No major side effect
  - mOS: 23.8 months vs 16.9 months (with OGX-011 versus without)

- Large phase III ongoing
Chemotherapy works in first and second line!

- What to do when docetaxel eventually fails?
  - Cabazitaxel or Abiraterone or …clinical trials

- Docetaxel alone or in combination (estramustine)?
  - Other drugs in development
  - Combination treatment in development

- Early (asymptomatic) or late (symptomatic) chemotherapy?
- Docetaxel based chemotherapy in CRPC
- New tubulin agent in CRPC: Cabazitaxel
- Other drugs and Combination therapy
- Strategy in prostate cancer (early stage)
- Perspectives
Early vs. Late chemotherapy in Prostate cancer: A French perspective

Early cancer

- GETUG 12 trial
  - N=413
  - High risk localized PCa

Advanced cancer

- R-PSA CP03 trial
- GETUG 15 trial
- Rising PSA
- Metastatic hormone-sensitive

Con’s: Impaired QoL related to chemotherapy in asymptomatic pts

No randomised trial

Pro’s: Better clinical conditions, lower cancer burden
High risk prostate cancer
GETUG 12 trial

Stratification
- Gleason ≥ 8
- PSA>20
- T3
- pN+ / pN-

Primary endpoint: Progression-free survival
n = 413/400 pts

ADT (3 years) + RXT
Docetaxel + Estramustine
(4 cycles)

ADT (3 years) + RXT

PI: K. Fizazi
Early vs. Late chemotherapy in Prostate cancer: A French perspective

Early cancer
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Pro's: Better clinical conditions, lower cancer burden
Con’s: Impaired QoL related to chemotherapy in asymptomatic pts

No randomised trial
Docetaxel rechallenge in CRPC...

- Common practise in medical oncology
  - Platinum based chemotherapy: ovarian, SCLC, NSCLC...
  - Oxaliplatine in colon cancer

- Only small retrospective trials in CRPC
  - No randomized trial
  - No clear definition of « taxane sensitive » disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Pts (N)</th>
<th>PSA response</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loriot et al, 2010</td>
<td>39</td>
<td>38-64%</td>
<td>4.3 months</td>
</tr>
<tr>
<td>Ross et al, 2008</td>
<td>34</td>
<td>18%</td>
<td>3 months</td>
</tr>
</tbody>
</table>

- Phase III trial docetaxel versus docetaxel+OGX011
When to start chemotherapy?

- What to do when docetaxel eventually fails?
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Targeting IGF-R
- Satraplatin

Alkylating agent
- APC 8015 (Provenge)

Vaccines
- GVAX

How to accelerate drug development?

Courtesy K Fizazi
We need to design clinical trials that can test and answer critical biological questions about disease drivers utilizing targeted drugs and biomarkers (DeBono, ASCO 2008)

- Molecular biology
  → Personalized Medicine

- CTC evaluation is one of the most promising biomarker in cancer
  → Previous studies in breast, colon and prostate cancer have shown that CTC correlate with survival

Moreno et al, Urology 2001; Moreno et al, Urology 2006; Cristofanilli et al, NEJM 2004; Meropol et al, ASCO 2007
Isolation/Detection of CTC in peripheral blood

In vivo
- Intravital flow cytometry in mice
- Venous puncture

In vitro
- Size
- Density
- Marker proteins
- Enrichissement
- RNA
- cDNA
- DNA
- Protein secretion
- ICC
- FISH
- WGA
- qPCR
- FAST
- Low-density array

Pantel et al. Nat Cancer Rev. 2008
VERIDEX: CellSearch™ System

1. Selection positive EPCAM
2. Staining: CK 8/18/19, CD45, DAPI
3. Others: HER2/Neu, MUC1, EGF-R
Potential Applications for detection of Micrometastatic Tumor Cells (CTCs)

Prediction of prognosis and real-time monitoring of the efficacy of systemic therapies

- Marker of recurrence (prognosis and stratification)

- Marker of response to therapy (surrogate marker)

- More readily available source of tumor to measure target modulation (biological therapies)

- Source of material to study biology of metastasis
Circulating tumor cells (CTCs) and epithelial cancers
Prognostic and predictive information in advanced solid tumors
Breast cancer, colon cancer, prostate cancer...

CTC at baseline and 2-5 week after start of therapy predict survival in men undergoing treatment for CRPC

DeBono et al, CCR 2008
CTC as a « Surrogate » marker of tumor? Molecular characterization

The CellTracks® technology also supports the molecular evaluation of isolated CTC by:

- Immunofluorescence (IF) for protein expression
- Fluorescent in-situ hybridization (FISH) for DNA amplification
- Androgen receptor sequencing
- Detection of TMPRSS2/ETS gene translocations

What is Prostate Cancer? An Old view

The same treatment for everybody?
For different disease?

Schiller et. al., NEJM 02
Pathology-based therapy

cytotoxic

Molecular classification and Target-oriented therapy

- PTEN loss
- AR amplification mutation
- BRACness
- MYC amplification
- IGF-1R activation
- Bcl2 expression
- P53
- Pim Kinase
Pathology-based therapy

cytotoxic

Molecular classification and Target-oriented therapy

PTEN loss
AR amplification
BRACness
MYC amplification
IGF-1R activation
Bcl2 expression
P53
Pim Kinase

Courtesy to Dr Besse
Synthetic lethal concept

Ashworth A, JCO 2008; Fong et al, NEJM 2009
Conclusion

- Docetaxel based chemotherapy is the standard of care in metastatic CRPC patients

- Cabazitaxel is a potential new therapeutic option for the treatment of patients with mCRPC after failure of docetaxel-based therapy

- Other agents are in development, alone or in combination with docetaxel/cabazitaxel based chemotherapy

- We need to incorporate molecular biology in our clinical daily practice in the next decade…
Thank you

• IGR GU Oncology group

...and Discussion
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Pr Soria
Pr Fizazi
Dr Besse, Dr Andre
....
SITEP collaborators

Thank you for your attention