Educational session

Novel and bone targeted agents for CRPC

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Disclosure

• Participation in advisory boards or as a speaker for:
  Amgen, Astellas-Medivation, Astrazeneca, Bayer, BMS, Celgene, Dendreon, Exelixis, Ipsen, Janssen-Cougar, Keocyt, Millennium-Takeda, Novartis, Sanofi-Aventis
Systemic treatment for CRPC in 2012-2013

Local Treatment

PSA relapse (ADT)

Castrate-resistant, M0

Continuous ADT

Metastatic Hormone-Sensitive prostate cancer

Abiraterone

Docetaxel

Zoledronate

Denosumab

Enzalutamide

Radium 223

Cabazitaxel

Metastatic Castrate-Resistant Prostate Cancer
The cornucopia of new drugs for CRPC

- Endocrine agents
  - Abiraterone
  - Enzalutamide
- Immunotherapy
  - Sipuleucel-T
- Chemotherapy
  - Cabazitaxel
- Bone-targeting agents
  - Denosumab
  - Alpharadin
Taxanes for CRPC

**Docetaxel**
- Well-established drug in Oncology

**Main toxicity:**
- Peripheral neurotoxicity
- Nail Toxicity

**Cabazitaxel**
- Crosses the blood-brain barrier *in vivo* (humans?)
- Active in some docetaxel-resistant models

**Main toxicity:**
- Hemato (G-CSF)
- Diarrhea
Cabazitaxel in Second-line CRPC TROPIC Phase III Study

- **mHRPC Progression after TXT**
- **Stratification factor:**
  - ECOG PS (0,1 vs 2)
  - Measurable/non-mesurable
- **Primary Endpoint:**
  - Overall survival
- **Secondary Endpoint:**
  - PSA response, PSA progression, PFS, RR, Pain progression, Safety, PK of cabazitaxel

**Randomisation**
- 360 pts
  - Cabazitaxel 25mg/m2 q3w
  - Prednisone 10mg qd
- 360 pts
  - Mitoxantrone 12mg/m2 q3w
  - Prednisone 10mg qd

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

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<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
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<tbody>
<tr>
<td>Median OS (months)</td>
<td>12.7</td>
<td>15.1</td>
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<tr>
<td>Hazard ratio</td>
<td>0.72</td>
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<td>95% CI</td>
<td>0.61–0.84</td>
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<td>P-value</td>
<td>&lt;.0001</td>
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28% risk of death reduction

Number at Risk

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<th>MTX + PRED</th>
<th>CBZ + PRED</th>
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<td>MTX + PRED</td>
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<td>300</td>
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<td>300</td>
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<tr>
<td></td>
<td>67</td>
<td>11</td>
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<tr>
<td></td>
<td>11</td>
<td>1</td>
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<tr>
<td>CBZ + PRED</td>
<td>378</td>
<td>321</td>
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<td>4</td>
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Median FU: 13.7 mo

De Bono et al., Lancet 2010;376:1147-54
Is prostate cancer a chemosensitive neoplasm?

- **High response rate** (>50%) in first-line
- Benefit in **OS in first-line** (Docetaxel)
- **Second-line** chemotherapy with demonstrated activity (Cabazitaxel)
- Chemotherapy improves PFS/OS when used in the **localized setting** to prevent relapse

First answer in 2014?
Are taxanes and abiraterone cross-resistant?

**Docetaxel after Abiraterone**
- 35 pts
- PSA response rate: 26%
- TTP: 4.6 months
- OS: 12.5 months (10.6-19.4)

**Cabazitaxel after Abiraterone**
- 38 pts with progression after Docetaxel followed by Abiraterone
- PSA response rate: 56%
- Tolerance OK (G-CSF)

→ **Cross-resistance?**  
No (complete) cross-resistance

Mezynski J, Ann Oncol 2012  
Albiges L, ESMO 2012
The “vicious circle” of bone metastases

- Prostate cancer cells

Cytokines and Growth Factors (ET-1, IL-6, IL-8, TNF-α, PTHrP, etc)

Direct effects on tumor?

Growth Factors (TGF-β, IGFs, FGFs, PDGFs, BMPs)

RANKL

Bone Resorption

Osteoclast

Osteoblast lineage

Bone

Ca^{2+}

Targeting RANK-L: Proof of concept

RANK-L overexpressed by osteoblasts in bone metastases

Positive randomized Phase II: Denosumab decreases uNTx (biomarker for osteolysis)

Fizazi et al., Clin Cancer Res 2003;9:2587–2597
Fizazi et al., J Clin Oncol 2009; 27: 1564-71
Phase III trial of Denosumab in bone metastases from castrate-resistant prostate cancer (103)

Key Inclusion
- Castration-resistant prostate cancer and bone metastases

Key Exclusion
- Current or prior intravenous bisphosphonate administration

Denosumab 120 mg SC and Placebo IV* every 4 weeks

Zoledronic acid 4 mg IV* and Placebo SC every 4 weeks

n= 1901 patients

+ Supplemental Calcium and Vitamin D
Denosumab: Time to First SRE

HR 0.82 (95% CI: 0.71, 0.95)

\[ P = 0.0002 \text{ (Non-inferiority)} \]
\[ P = 0.008 \text{ (Superiority)} \]

Proportion of Subjects Without SRE

Study Month

<table>
<thead>
<tr>
<th>Subjects at risk:</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>
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<tr>
<td>Zoledronic Acid</td>
<td>951</td>
<td>733</td>
<td>544</td>
<td>407</td>
<td>299</td>
<td>207</td>
<td>140</td>
<td>93</td>
<td>64</td>
<td>47</td>
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<tr>
<td>Denosumab</td>
<td>950</td>
<td>758</td>
<td>582</td>
<td>472</td>
<td>361</td>
<td>259</td>
<td>168</td>
<td>115</td>
<td>70</td>
<td>39</td>
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</table>

Preventing the onset of the worst enemy:
Spinal cord compression

Denosumab (120 mg Q4W) is not approved in the EU for use in patients with advanced cancer to delay SREs. Denosumab is investigational in that setting.

Bone-targeted agents: Are they worth using?

- Significantly reduce morbidity
- Prevention vs treatment of bone morbidity
- Overall good tolerance

- No demonstrated role on survival
- 1-2% risk of ONJ
Bone-targeted agents: Price?

• Much cheaper than new cancer drugs
• Avoid SRE-related costs
• Dmab: avoids IV-related costs
• Europe: Premium Dmab/Zol: ~ +15%

• Cost-effectiveness depends on your country model
• US: Premium Dmab/Zol: ~ +80%...
Radiopharmaceuticals: \( \alpha \) versus \( \beta \)-emitters

**\( \beta \)-emitters:**
- Strontium-89
- Samarium-153

**\( \beta \)-particles:**
- 1 electron
- Relative mass: 1

**\( \alpha \)-emitter:**
- Radium-223

**\( \alpha \)-particles:**
- 2 neutrons + 2 protons
- Relative mass: 7000
Cell killing and marrow penetration: Two advantages of α-emitters

Large molecule + High Linear Energy Transfer → More DNA double-strand breaks in (cancer) cells

Low marrow penetration (≤100 μm) → Limited hematological toxicity
TREATMENT
6 injections at 4-week intervals

Radium-223 (50 kBq/kg) + Best standard of care
Placebo (saline) + Best standard of care

N = 922

PATIENTS
• Confirmed symptomatic CRPC
• ≥ 2 bone metastases
• No known visceral metastases
• Post-docetaxel or unfit for docetaxel

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

Clinicaltrials.gov identifier: NCT00699751.

• Total ALP: < 220 U/L vs ≥ 220 U/L
  • Bisphosphonate use: Yes vs No
  • Prior docetaxel: Yes vs No

RANDOMIZED
2:1

Planned follow-up is 3 years
Radium-223 Phase III trial (ALSYMPCA): Overall Survival

- **Radium-223**, n = 614
  - Median OS: 14.9 months
  - HR = 0.695
  - 95% CI, 0.581, 0.832
  - *P* = 0.00007

- **Placebo**, n = 307
  - Median OS: 11.3 months

Parker C, ASCO 2012
Is Alkaline Phosphatase predictive of an Alpharadin effect on OS?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
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<tr>
<td>Overall Survival</td>
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<td>921</td>
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<td>0.695</td>
<td>0.581–0.832</td>
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<td>Total ALP #</td>
<td>&lt; 220 U/L</td>
<td>517</td>
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<td>0.825</td>
<td>0.635–1.072</td>
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<td>&gt;= 220 U/L</td>
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<td>0.619</td>
<td>0.486–0.788</td>
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<td>Current Use of Bisphosphonates #</td>
<td>Yes</td>
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<td></td>
<td>No</td>
<td>547</td>
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<tr>
<td>Prior Use of Docetaxel #</td>
<td>Yes</td>
<td>526</td>
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<td>No</td>
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<td>Baseline ECOG Status</td>
<td>0 or 1</td>
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<td>2 or Higher</td>
<td>118</td>
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</table>

Parker C, ASCO 2012
The cornucopia of new drugs for CRPC in the future

- **Endocrine agents**
  - **ODM 201** (ESMO 12)
  - **ARN 509** (ASCO 12)
  - **Orteronel**

- **Immunotherapy**
  - **Ipilimumab** (2013?)
  - **Prostvac**
  - **Tasquinimod**

- **Bone-targeting agents**
  - **Cabozantinib** (ASCO 12)
  - **Dasatinib** (2013?)

- **HSP-targeting drugs**
  - **OGX 011, OGX 427**
Targeting CTLA4: Ipilimumab for CRPC

**Docetaxel-naive patients: the «95» trial**

- 2 \( \text{Ipilimumab 10 mg/kg} \)
- 1 \( \text{Placebo} \)

\( n = 600 \)

OS (HR: 0.7)

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**Docetaxel-pretreated patients: the «43» trial**

- \( \text{Ipilimumab + XRT to bone} \)

\( n = 800 \)

OS (HR: 0.76)

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Diagram showing the mechanism of action of Ipilimumab on T cells.
Prostvac: Poxviral-based PSA targeted immunotherapy

Tasquinimod

Tasquinimod:
- Anti-angiogenesis (VEGF-dependent and independent)
- Immuno-modulation (Target: S100A9 protein)

n= 101 asymptomatic CRPC patients
Randomized phase II

Phase III trial asymptomatic CRPC

Phase II trial maintenance post-doce

Pili R, J Clin Oncol 2011, 29
Targeting sRc: Dasatinib

Phase III « Ready » trial

Docetaxel + Dasatinib

Docetaxel + Placebo

Phase II Docetaxel-dasatinib
n= 46

PSA response: 49%   RECIST: 42%
HGF and VEGF may be key factors mediating cross-talk between tumor cells, osteoblasts, and osteoclasts
Cabozantinib in CRPC

Activity reported on Pain, CTC conversion, bone markers

Cabozantinib Phase 3 Trials in CRPC

Key Eligibility Criteria
- CRPC with bone metastases
- Prior treatment with docetaxel + abiraterone and/or enzalutamide
- No limit on the number of prior therapies

COMET-1
Primary Endpoint: Overall Survival

CRPC (N = 960)
Randomization
- Cabozantinib (60 mg qd)
- Prednisone

COMET-2
Primary Endpoint: Confirmed Pain Response

CRPC with bone pain (N = 246)
Randomization
- Cabozantinib (60 mg qd)
- Mitoxantrone + Prednisone
Targeting clusterin: OGX-011

Randomized phase II trial

Phase III trial 1st line chemotherapy (Synergy)

- Docetaxel + OGX-011
- Docetaxel

n= 800
OS (HR: 0.72)

Phase III trial 2nd line chemotherapy (Affinity)

- Cabazitaxel + OGX-011
- Cabazitaxel

n= 630
OS (HR: 0.75)

Chi K, J Clin Oncol 2010, 4247-54
Targeting Hsp27: OGX-427

- Heat Shock Protein 27 (Hsp27)
  - Stress activated, small heat shock protein
  - Phospho-activated to form chaperoning oligomer which regulates multiple cell signaling and survival pathways
    - Inhibits apoptosis
    - Involved in proteasome mediated degradation
    - Facilitates normal protein folding and function
      - **Steroid receptors: AR, ER**
      - Growth factor: IGF-1, VEGF-1, FGF
      - Cytokine: IL-6, TGF-beta

OGX-427 in CRPC: PSA Waterfall Plots

OGX-427 + Prednisone

Prednisone

+ activity reported on Recist, CTC conversion, cross-over

Chi K et al., ASCO 2012
Conclusion: a rich cornucopia of new drugs for CRPC

**Endocrine**
- ADT
- Abiraterone
- MDV3100
- Orteronel?
- ODM 201?
- ARN 509?
- TOK 001?

**Chemotherapy**
- Docetaxel
- Cabazitaxel

**Bone-targeted Treatment**
- Zoledronic acid
- Denosumab
- Alpharadin
- Dasatinib?

**Bone-targeted agents**
- Cabozantinib?
- Tasquinimod?
- OGX-011?
- OGX-427?

**Immunotherapy**
- Sipuleucel-T
- Ipilimumab?
- Prostvac?