Novità sul trattamento delle neoplasie urologiche

Carcinoma prostatico

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S.C. di Oncologia - Terni

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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
ANDROGEN-DEPRIVATION THERAPY using bilateral orchiectomy or an LHRH agonist/antagonist is the first-line treatment

- Moderate decrease (17%) in relative risk for prostate cancer-specific mortality
- Symptoms control

META-ANALISI PCTCG (Lancet 2000)

- Data from 27 trials (8275 pts)
- Castration alone (orchiectomy or LHRH agonist) vs CAB (castration + antiandrogens, flutamide, nilutamide or ciproterone acetato)
- Median follow-up: 5 years
- 5-year survival: 23.6% for castration alone vs 25.4% for CAB (p=0.11)
INTERMITTENT OR CONTINUOUS ANDROGEN DEPRIVATION?

- Efficacy (OS, PFS)
- Differences in adverse effects and quality of life
- Costs
- Delay the development of a castration-resistant status
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?
METASTATIC HORMONE-SENSITIVE DISEASE

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

Metastatic Hormone-naïve 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
CHARTED and GETUG 15

Primary endpoint: OS

**Metastatic hormone-naïve prostate cancer**

**RANDOMIZE**

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

**ARM B:**
ADT alone

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

- Trial arm A: SOC = ADT (+/- RT)
- Trial arm B: SOC + zoledronic acid
- Trial arm C: SOC + docetaxel
- Trial arm D: SOC + celecoxib
- Trial arm E: SOC + zoledronic acid + docetaxel
- Trial arm F: SOC + zoledronic acid + celecoxib
- Trial arm G: SOC + (abi)^
- Trial arm H: SOC + M1 | RT {M1}
- Trial arm J: SOC + (enza + abi)^^  

A = ~1200 pts --> ~404 primary outcome measure events
B = ~600 pts, C = ~600 pts, E = ~600 pts

^ Abiraterone
^ Enzalutamide + abiraterone
**Presenting features**

<table>
<thead>
<tr>
<th></th>
<th><strong>CHAARTED</strong></th>
<th><strong>GETUG 15</strong></th>
<th><strong>STAMPEDE</strong></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>
</tbody>
</table>

**Outcomes**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Improved PSA/clinical PFS</td>
<td>20.7m vs 14.7m</td>
<td>22.9m vs 12.9m</td>
<td>FFS: 37m vs 21m</td>
</tr>
<tr>
<td>HR</td>
<td>HR 0.56 (0.44-0.70)</td>
<td>HR 0.72 (0.57-0.91)</td>
<td>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

- SOC: 49.3m
- SOC+Doc: 56.1m
- Diff (95% CI): 6.8m (2.8, 11.0m)

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

Time from randomisation (months)

Overall survival
### 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 D</th>
<th>Stampe D</th>
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<tbody>
<tr>
<td>ADT+ D</td>
<td>ADT</td>
<td>ADT+ D</td>
<td>ADT</td>
<td>ADT+ D</td>
<td>ADT</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
CONSIDERATIONS

- Don’t put too much emphasis on a single trial – repetition of important results is essential before changing practice.
**METASTATIC HORMONE-SENSITIVE DISEASE**

Forest plot of overall survival for the 3 studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAARTED</td>
<td>30.3%</td>
<td>0.61 [0.47, 0.80]</td>
</tr>
<tr>
<td>GETUG-15</td>
<td>30.8%</td>
<td>0.90 [0.70, 1.18]</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>38.9%</td>
<td>0.73 [0.59, 0.89]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>100.0%</td>
<td>0.74 [0.60, 0.90]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.02; \ Chi^2 = 4.26, df = 2 \ P = 0.12$
Test for overall effect: $Z = 2.92 \ P = 0.003$

* weight by inverse variance
METASTATIC HORMONE-SENSITIVE DISEASE

CONSIDERATIONS

- Don’t put too much emphasis on a single trial – repetition of important results is essential before changing practice.
- Don’t extend the results of trials to patients that are not represented by their participants.
- These trials do NOT represent men with slowly progressive disease who develop metastases several years after diagnosis (+/- local treatment).
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
There is no evidence supporting the introduction of ZOLEDRONIC ACID in metastatic hormone-sensitive disease.
METASTATIC CASTRATION-RESISTANT PROSTATE CANCER
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
<table>
<thead>
<tr>
<th>Presenting features</th>
<th>COU-AA-302 (ABI)</th>
<th>PREVAIL (ENZA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1088</td>
<td>1717</td>
</tr>
<tr>
<td>Age</td>
<td>70.5</td>
<td>71</td>
</tr>
<tr>
<td>PSA at entry</td>
<td>40 ng/ml</td>
<td>49 ng/ml</td>
</tr>
<tr>
<td>Time from initial diagnosis or first treatment of prostate cancer to randomization</td>
<td>63 months</td>
<td>63 months</td>
</tr>
<tr>
<td>Distribution of disease at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>49.5%</td>
<td>50.5%</td>
</tr>
<tr>
<td>Visceral disease</td>
<td>0.7%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>
### 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>
</tbody>
</table>
# Asymptomatic or Mildly Symptomatic Metastatic CRPC

<table>
<thead>
<tr>
<th></th>
<th>COU-AA-302</th>
<th>COU-AA-302</th>
<th>PREVAIL</th>
<th>PREVAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td>ABI</td>
<td>PLACEBO</td>
<td>ENZA</td>
<td>PLACEBO</td>
</tr>
<tr>
<td></td>
<td>38%</td>
<td>53%</td>
<td>32.8%</td>
<td>56.7%</td>
</tr>
<tr>
<td><strong>Cabazitaxel</strong></td>
<td>8%</td>
<td>10%</td>
<td>5.8%</td>
<td>13.0%</td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>5%</td>
<td>10%</td>
<td>20.5%</td>
<td>45.6%</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>NR</td>
<td>NR</td>
<td>1.0%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>
Abiraterone and Enzalutamide significantly delayed time to chemotherapy

Abiraterone and Enzalutamide significantly reduced the risk of a first skeletal-related event
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
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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Overall more than 1.600 met HRPC pts treated.
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

**A Overall Survival**

![Graph showing overall survival](image)

- **Hazard ratio, 0.70 (95% CI, 0.58–0.83)**
- **P<0.001**

- **Radium-223 (median overall survival, 14.9 mo)**
- **Placebo (median overall survival, 11.3 mo)**

**B Time to First Symptomatic Skeletal Event**

![Graph showing time to first symptomatic skeletal event](image)

- **Hazard ratio, 0.66 (95% CI, 0.52–0.83)**
- **P<0.001**

- **Radium-223 (median time to first symptomatic skeletal event, 15.6 mo)**
- **Placebo (median time to first symptomatic skeletal event, 9.8 mo)**
POST-DOCETAXEL METASTATIC CRPC
Standard Treatment

- ABIRATERONE
- ENZALUTAMIDE
- CABAZITAXEL
- RADIUM-223
<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>
Questions Concerning Treatment Choice in Metastatic CRPC

- 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?
QUESTIONS CONCERNING TREATMENT CHOICE IN
METASTATIC CRPC

- Selecting the right treatment for a specific patient
A total of 31 enzalutamide-treated pts and 31 abiraterone-treated pts were enrolled, of whom 39% and 19%, respectively, had detectable AR-V7 in circulating tumor cells.
Genomic predictive and prognostic factors from plasma cell-free DNA (cfDNA) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) commencing enzalutamide (ENZ)

Chi K, et al. ECC 2015

- Plasma samples were collected from 61 mCRPC pts commencing ENZ. DNA was extracted from plasma and subjected to array Comparative Genomic Hybridization for chromosome copy number analysis and AR gene sequencing for mutation analysis.

- CN changes in 61 baseline samples included AR gain/amp (31%), MYC gain/amp (30%), RB1 loss (21%), MET gain/amp (13%).

- Presence of AR gain/amp, MYC gain/amp, RB1 loss, MET gain/amp was associated with significantly lower PSA50RR and shorter PFS.
Selecting the right treatment for a specific patient

Optimal sequencing of available agents
**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
QUESTIONS CONCERNING TREATMENT CHOICE IN METASTATIC CRPC

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Summary of trial</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Docetaxel vs Docetaxel+Bevacizumab</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>VEGF-trap</td>
<td>Docetaxel vs Docetaxel+Aflibercept</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Antiangiogenic</td>
<td>Docetaxel vs Docetaxel+Lenalidomide</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Atrasentan</td>
<td>Endothelin receptor</td>
<td>Docetaxel vs Docetaxel+Atrasentan</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Zibotentan</td>
<td>Endothelin receptor</td>
<td>Docetaxel vs Docetaxel+Zibotentan</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Src kinase</td>
<td>Docetaxel vs Docetaxel+Dasatinib</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Cuttrirsen</td>
<td>Clusterin</td>
<td>Docetaxel vs Docetaxel+Cuttrirsen</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Vitamin D receptor</td>
<td>Docetaxel vs Docetaxel+Calcitriol</td>
<td>NEGATIVE</td>
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<tr>
<td>GVAX</td>
<td>Whole-cell vaccine</td>
<td>Docetaxel vs Docetaxel+GVAX</td>
<td>NEGATIVE</td>
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</table>
METASTATIC PROSTATE CANCER