New Drugs for Oligometastatic Prostate Cancer

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Disclosures:

**Speaker:** Astellas, Janssen, Bayer, Sanofi-Aventis

**Advisory Board:** Bayer, Astellas, Janssen

**Clinical Research:** Astellas
Prostate Cancer: Oligometastatic Disease

- One school of thought is to consider isolated lesions on imaging as representing the only sites of disease, where local therapy is sufficient.
- The other viewpoint is that oligometastatic disease is most likely also associated with micrometastatic disease.
- Both three or fewer and five or fewer lesions used in the literature.
- To design a systematic approach to oligometastatic prostate cancer, a universally accepted definition is required.
The Role of Systemic Therapy in Oligometastatic Prostate Cancer

- Castration-Sensitive Disease
- Castration-Resistant Disease
The Role of Systemic Therapy in Oligometastatic Prostate Cancer

- Castration-Sensitive Disease
- Castration-Resistant Disease
# Chemo-hormonal therapy for CSPC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Control arm</th>
<th>Chemotherapy used in experimental arm</th>
<th>Overall Survival (chemo-hormonal vs hormonal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy, 1983</td>
<td>246</td>
<td>Orchiectomy or DES</td>
<td>Cyclophosphamide, estramustine</td>
<td>21 months in both arms</td>
</tr>
<tr>
<td>Murphy, 1986</td>
<td>296</td>
<td>Orchiectomy or DES</td>
<td>Cyclophosphamide, estramustine, 5-FU</td>
<td>33 months in both arms</td>
</tr>
<tr>
<td>Osborne, 1990</td>
<td>137</td>
<td>Orchiectomy or DES</td>
<td>Cyclophosphamide, doxorubicin</td>
<td>22 vs 26 months; ( P=0.55 ) (NS)</td>
</tr>
<tr>
<td>Pummer, 1997</td>
<td>114</td>
<td>Orchiectomy + flutamide</td>
<td>Epirubicin</td>
<td>30 vs 18 months; ( P=0.12 ) (NS)</td>
</tr>
<tr>
<td>Janknegt, 1997</td>
<td>385</td>
<td>Orchiectomy</td>
<td>Estramustine</td>
<td>27 vs 24 months; ( P=\text{NS} )</td>
</tr>
<tr>
<td>Fontana, 1998</td>
<td>55</td>
<td>LHRH agonist</td>
<td>Mitomycin</td>
<td>29 vs 32 months; ( P=\text{NS} )</td>
</tr>
<tr>
<td>Boel, 1999</td>
<td>148</td>
<td>Orchiectomy</td>
<td>Mitomycin</td>
<td>31 months in both arms</td>
</tr>
<tr>
<td>de Reijke, 1999</td>
<td>184</td>
<td>Orchiectomy</td>
<td>Mitomycin</td>
<td>22 vs 26 months; ( P=0.04 )</td>
</tr>
<tr>
<td>Kuriyama, 2001</td>
<td>136</td>
<td>Orchiectomy or DES</td>
<td>UFT (fluoropyrimidine)</td>
<td>( P=\text{NS} )</td>
</tr>
<tr>
<td>Noguchi, 2004</td>
<td>51</td>
<td>LHRH agonist + flutamide</td>
<td>Estramustine</td>
<td>30 months in both arms</td>
</tr>
<tr>
<td>Millikan, 2008</td>
<td>286</td>
<td>Orchiectomy or LHRH agonist</td>
<td>Doxorubicin, vinblastine, estramustine</td>
<td>6.1 vs 5.4 years; ( P=0.41 ) (NS)</td>
</tr>
<tr>
<td>Gravis, 2013</td>
<td>385</td>
<td>Orchiectomy or LHRH agonist</td>
<td>Docetaxel</td>
<td>58.9 vs 54.2 months; ( P=0.955 ) (NS)</td>
</tr>
<tr>
<td>Sweeney, 2014</td>
<td>790</td>
<td>ADT</td>
<td>Docetaxel</td>
<td>57.6 vs 44.0 months; ( P=0.0003 )</td>
</tr>
<tr>
<td>James, 2015</td>
<td>1.087</td>
<td>ADT</td>
<td>Docetaxel</td>
<td>65 vs 43 months; ( P=0.002 )</td>
</tr>
</tbody>
</table>
E3805 – CHAARTED Treatment

Stratification
- Extent of Mets: High vs Low
- Age: ≥70 vs < 70yo
- ECOG PS: 0-1 vs 2
- CAB: > 30 days vs Yes vs No
- SRE Prevention: Yes vs No
- Prior Adjuvant ADT: ≤12 vs > 12 months

Randomize

ARM A: ADT + Docetaxel 75mg/m² every 21 days for maximum 6 cycles

Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

ARM B: ADT (androgen deprivation therapy alone)

Evaluate every 12 weeks

Follow for time to progression and overall survival
Chemotherapy at investigator’s discretion at progression

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed.
- Standard dexamethasone premedication but no daily prednisone.

Courtesy from Christopher J. Sweeney, MBBS
CHAARTED: Overall survival by volume of mets

In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival.

82 vs 110 deaths (192 events)

p = 0.012
HR = 0.60 (0.45-0.81)
Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months

19 vs. 26 deaths (45 events)

p = 0.0836
HR = 0.63 (0.34-1.17)
Median OS:
ADT + D: Not reached
ADT alone: Not reached

Courtesy from Michael Morris, MD
GETUG 15 Update

GETUG-AFU 15 TRIAL DESIGN

Arm A

ADT + Docetaxel

D: 75 mg/m² q3 up to 9 cycles

Arm B

ADT alone

ADT:
- LHRH agonist
- or maximum androgen blockade
- or orchiectomy

Met Pca
No prior chemo for mets
<60 days of ADT
If systemic rx for local dz, > 1 yr ago
ECOG PS ≤ 2

Gravis, G. GU ASCO, 2015
The “Extent of Disease” Criteria used in ECOG 3805 was (retrospectively) applied to the GETUG 15 Data

**HIGH Volume**
- ADT-doce: 39 m
- ADT alone: 35.1 m  p = 0.35

**LOW Volume**
- ADT-doce: 83.1 m
- ADT alone: not reached  p = 0.87

Gravis, et al. GU ASCO 2015
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham
on behalf of
Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators
Inclusion criteria

**Newly-diagnosed**
Any of:
- Metastatic
- Node-Positive
- ≥2 of:
  - Stage T3/4
  - PSA ≥40 ng/ml
  - Gleason 8-10

**Relapsing after previous RP or RT with ≥1 of:**
- PSA ≥4 ng/ml and rising with doubling time < 6 m
- PSA ≥20 ng/ml
- Node-positive
- Metastatic

**All patients**
Fit for all protocol treatment
Fit for follow-up
WHO performance status 0-2
Written informed consent

**Full criteria**
www.stampedetrial.org
STAMPEDE: date set for release of results for original comparisons

- **A**: Standard-of-care (SOC) = ADT (+/- RT)
- **B**: SOC + zoledronic acid
- **C**: SOC + docetaxel
- **D**: SOC + celecoxib
- **E**: SOC + zoledronic acid + docetaxel
- **F**: SOC + zoledronic acid + celecoxib
- **G**: SOC + (abi)^
- **H**: SOC + M1/RT (M1)
- **J**: SOC + (enza + abi)^^^

- **Arrows** indicate accrual status:
  - Green: Past accrual
  - Orange: Future accrual
  - Black: FU and main analysis

- Superscripts:
  - ^ Abiraterone
  - ^^ Enzalutamide + abiraterone
Docetaxel: Survival

SOC: 405 deaths
SOC+Doc: 165 deaths

HR (95%CI): 0.76 (0.63, 0.91)
P-value: 0.003

Non-PH p-value: 0.51

Median OS (95% CI)
SOC: 67m (60, 91m)
SOC+Doc: 77m (70, NR)

Restricted mean OS time
SOC: 58.8m
SOC+Doc: 63.4m
Diff (95%CI): 4.6m (1.8, 7.3m)
Docetaxel: Failure-free survival

SOC: 750 FFS events
SOC+Doc: 371 FFS events

HR (95% CI): 0.62 (0.54, 0.70)
P-value: <0.0000000001*

Non-PH p-value: 0.0002

Median FFS (95% CI)
SOC: 21m (18, 24m)
SOC+Doc: 37m (33, 42m)

Restricted mean FFS time
SOC: 35.3m
SOC+Doc: 44.4m
Diff (95% CI): 9.1m (6.3, 11.9m)

*exact p-value 0.0000000000002014
Docetaxel: Survival – M1 Patients

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

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

**Restricted mean OS time**
- SOC: 49.3m
- SOC+Doc: 56.1m

**Diff (95%CI)**: 6.8m (2.8, 11.0m)
Conclusions

- Docetaxel improves survival for hormone-naive prostate cancer
- Zoledronic acid does not improve survival
- Adding both improves survival but offers no obvious benefit over adding just docetaxel
- Multi-arm, multi-stage trials are practicable and efficient

- **Docetaxel should be:**
  - Considered for routine practice in suitable men with newly-diagnosed metastatic disease
  - Considered for selected men with high-risk non-metastatic disease in view of substantial prolongation of failure-free survival
The Role of Systemic Therapy in Oligometastastic Prostate Cancer

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- Castration-Resistant Disease
SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER

Visceral metastases

No

• Abiraterone with prednisone (category 1)
• Docetaxel with prednisone (category 1)
• Enzalutamide (category 1)
• Radium-223 for symptomatic bone metastases (category 1)
• Clinical trial
• Secondary hormone therapy
  ‣ Antiandrogen
  ‣ Antiandrogen withdrawal
  ‣ Ketoconazole ± hydrocortisone
  ‣ Corticosteroid
  ‣ DES or other estrogen

Yes

• Docetaxel with prednisone (category 1)
• Enzalutamide (category 1)
• Abiraterone with prednisone
• Alternative chemotherapy (mitoxantrone with prednisone)
• Clinical trial
• Secondary hormone therapy
  ‣ Antiandrogen
  ‣ Antiandrogen withdrawal
  ‣ Ketoconazole ± hydrocortisone
  ‣ Corticosteroid
  ‣ DES or other estrogen

Visceral metastases

Progression after:
• Abiraterone
• Enzalutamide
• Docetaxel

See Subsequent Therapy for M1 CRPC: No Visceral Metastases (PROS-12) or
See Subsequent Therapy for M1 CRPC: Visceral Metastases (PROS-13)

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IMPACT: Sipuleucel-T Immunotherapy Improved OS in mCRPC

- Median survival benefit for Sip-T: 4.1 mos

HR: 0.78 (95% CI: 0.62-0.98; P = .03)

**IMPACT: Survival Benefit From Sipuleucel-T Associated With Lower Baseline PSA**

<table>
<thead>
<tr>
<th>Baseline PSA, ng/mL</th>
<th>≤ 22.1 (n = 128)</th>
<th>&gt; 22.1-50.1 (n = 128)</th>
<th>&gt; 50.1-134.1 (n = 128)</th>
<th>&gt; 134.1 (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Difference</td>
<td>13.0</td>
<td>7.1</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.51 (0.31-0.85)</td>
<td>0.74 (0.47-1.17)</td>
<td>0.81 (0.52-1.24)</td>
<td>0.84 (0.55-1.29)</td>
</tr>
</tbody>
</table>

- Earlier use of sipuleucel-T prior to abiraterone/enzalutamide is preferred, given lack of short-term benefits on PSA, disease control, and possible improved survival impact earlier in the disease course

Sipuleucel-T

- FDA approved April 2010
- Toxicities are mild, infusion related: fever, chills
- Consideration of spinal imaging (MRI) in men with high-volume spinal metastases given risk of disease progression in the short term
- Ideally used early with lower volume disease or before numerous other therapies
- No impact on PSA or radiographic response, PFS
- NCCN category 1 recommendation if asymptomatic to minimally symptomatic (no opiates for cancer pain), no liver metastases, life expectancy > 6 mo, ECOG 0-1

NCCN Guidelines® for Prostate Cancer, v.3.2016.
PREVAIL: Enzalutamide in Chemo-Naive CRPC

N = 1717; randomized 1:1 ENZ vs PBO
All subgroups benefited
rPFS: 3.9 mos (PBO) → NYR (ENZ) (15-19 mos)
PSA PFS: 2.8 mos (PBO) → 11.2 mos (ENZ)
OS updated 2015: 35.3 vs 31.3 mos (HR: 0.77; P = .002)
PSA 50/90% or greater decline in 78/47% (ENZ)
RECIST responses in 59% (ENZ)
Time to chemo: 28 mos (ENZ) vs 10.8 mos (PBO)
QoL responses in 40 vs 23%; TTQoL decline 11.3 mos (ENZ) vs. 5.6 mos (PBO)

PREVAIL: Pattern of Disease Spread And Activity of Enzalutamide in mCRPC

PREVAIL: Enzalutamide Safety

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Enzalutamide (N=871)</th>
<th>Placebo (N=844)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td><strong>Most common adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>310 (36)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>235 (27)</td>
<td>22 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>193 (22)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>177 (20)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>158 (18)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>157 (18)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>142 (16)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>117 (13)</td>
<td>59 (7)</td>
</tr>
<tr>
<td><strong>Asthenia</strong></td>
<td>113 (13)</td>
<td>11 (1)</td>
</tr>
<tr>
<td><strong>Fall</strong></td>
<td>101 (12)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>100 (11)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>92 (11)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Headache</td>
<td>91 (10)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td><strong>Specific adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiac adverse event</td>
<td>88 (10)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16 (2)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>7 (1)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>32 (4)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Ischemic or hemorrhagic cerebrovascular event</td>
<td>12 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Elevation in alanine aminotransferase level</td>
<td>8 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (&lt;1)†</td>
<td>1 (&lt;1)†</td>
</tr>
</tbody>
</table>

Abiraterone Acetate in Chemo-Naive mCRPC

- Superiority over prednisone previously demonstrated post-docetaxel and in chemo-naive men with mCRPC
- Dose: 1000 mg daily + prednisone 5 mg bid
- Improved OS accompanied by improvements in QoL, pain, PFS, response rates, and fewer adverse events than placebo
- Prevention of pain, PS deterioration, need for chemotherapy improved pre-docetaxel
- Abiraterone acetate with prednisone is now FDA approved for men with mCRPC prior to docetaxel
- Has not been evaluated in men with chemo-naive mCRPC and visceral mets

OS 30.3 mos (PBO) → 34.7 mos (ABI); HR 0.81; $P = .0033$

### Abiraterone Acetate: Safety Profile

<table>
<thead>
<tr>
<th>Event</th>
<th>Abiraterone acetate group (n=542)</th>
<th>Placebo group (n=540)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fluid retention/oedema</td>
<td>161 (30%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>87 (16%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>104 (19%)</td>
<td>25 (5%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>81 (15%)</td>
<td>35 (6%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20 (4%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>40 (7%)</td>
<td>28 (5%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>47 (9%)</td>
<td>18 (3%)</td>
</tr>
</tbody>
</table>

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Before crossover.

## Differences in drug characteristics

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Prednisone required</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Drug interactions (CYP)</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Lowers seizure threshold</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Potential liver toxicity</td>
<td>yes</td>
<td>less</td>
</tr>
<tr>
<td>Risk for hypertension</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Risk for CV events, atrial fib</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Dose</td>
<td>250 mg x 4</td>
<td>40 mg tablets x 4</td>
</tr>
<tr>
<td>Empty stomach</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
Timing and Selection of Secondary AR-Directed Therapies

• Choice of abiraterone vs enzalutamide cannot be dictated based on differences in efficacy
  – Similar OS, PFS from cross-trial comparisons
  – Enzalutamide has been evaluated in men with visceral metastases in the chemo-naive setting
  – Both are category 1 recommendations in NCCN guidelines

• Therefore choice is based on differential toxicity
  – Abiraterone acetate for seizure-prone men and those more frail, elderly (> 75 years old) men at high risk for falls
  – Enzalutamide for men with significant CV risk factors, contraindications to prednisone, brittle diabetes, and metabolic syndrome
  – Significant cross-resistance, so initial choice is likely most important one
**ALSYMPCA: Phase III Study Design**

**PATIENTS**

- N = 921
  - Confirmed symptomatic CRPC
  - ≥ 2 bone metastases
  - No known visceral metastases
  - Post-docetaxel or unfit for docetaxel*

**STRATIFICATION**

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

**TREATMENT PHASE**

- Radium-223 dichloride (55‡ kBq/kg) + best standard of care†
- Placebo (saline) + best standard of care†

- 6 injections at 4-week intervals
- 136 centers in 19 countries
- Planned follow-up is 3 years

**PRIMARY ENDPOINT: OVERALL SURVIVAL**

*Unfit for docetaxel includes pts who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.
†Best standard of care defined as a routine standard of care at each center, eg, local external-beam radiotherapy, corticosteroids, antiandrogens, estrogens (e.g., diethylstilbestrol or estramustine), or ketoconazole.
‡NIST update 2016.

**ALSYMPCA Updated Analysis: OS**

- **Radium-223 dichloride (n = 614)**
- **Placebo (n = 307)**

<table>
<thead>
<tr>
<th></th>
<th>Median OS (mos)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radium-223</strong></td>
<td>14.9</td>
<td>0.70</td>
<td>0.58-0.83</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>11.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Median Δ: 3.6 mos
- 30% reduction in risk of death

## ALSYMPCA: Predictors of Radium-223 Benefit?

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Radium-223</th>
<th>Placebo</th>
<th>Radium-223</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>614</td>
<td>307</td>
<td>14.9</td>
<td>11.3</td>
<td>0.70 (0.58–0.83)</td>
</tr>
<tr>
<td>Total ALP level at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;220 U/liter</td>
<td>348</td>
<td>169</td>
<td>17.0</td>
<td>15.8</td>
<td>0.82 (0.64–1.07)</td>
</tr>
<tr>
<td>≥220 U/liter</td>
<td>266</td>
<td>138</td>
<td>11.4</td>
<td>8.1</td>
<td>0.62 (0.49–0.79)</td>
</tr>
<tr>
<td>Current bisphosphonate use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>250</td>
<td>124</td>
<td>15.3</td>
<td>11.5</td>
<td>0.70 (0.52–0.93)</td>
</tr>
<tr>
<td>No</td>
<td>364</td>
<td>183</td>
<td>14.5</td>
<td>11.0</td>
<td>0.74 (0.59–0.92)</td>
</tr>
<tr>
<td>Previous docetaxel use</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>352</td>
<td>174</td>
<td>14.4</td>
<td>11.3</td>
<td>0.71 (0.56–0.89)</td>
</tr>
<tr>
<td>No</td>
<td>262</td>
<td>133</td>
<td>16.1</td>
<td>11.5</td>
<td>0.74 (0.56–0.99)</td>
</tr>
<tr>
<td>Baseline ECOG performance-status score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>536</td>
<td>265</td>
<td>15.4</td>
<td>11.9</td>
<td>0.68 (0.56–0.82)</td>
</tr>
<tr>
<td>≥2</td>
<td>77</td>
<td>41</td>
<td>10.0</td>
<td>8.4</td>
<td>0.82 (0.50–1.35)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 metastases</td>
<td>100</td>
<td>38</td>
<td>27.0</td>
<td>NE</td>
<td>0.95 (0.46–1.95)</td>
</tr>
<tr>
<td>6–20 metastases</td>
<td>262</td>
<td>147</td>
<td>13.7</td>
<td>11.6</td>
<td>0.71 (0.54–0.92)</td>
</tr>
<tr>
<td>&gt;20 metastases</td>
<td>195</td>
<td>91</td>
<td>12.5</td>
<td>9.1</td>
<td>0.64 (0.47–0.88)</td>
</tr>
<tr>
<td>Superscan</td>
<td>54</td>
<td>30</td>
<td>11.3</td>
<td>7.1</td>
<td>0.71 (0.40–1.27)</td>
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<td>Opioid use</td>
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<tr>
<td>Yes</td>
<td>345</td>
<td>168</td>
<td>13.9</td>
<td>10.4</td>
<td>0.68 (0.54–0.86)</td>
</tr>
<tr>
<td>No</td>
<td>269</td>
<td>139</td>
<td>16.4</td>
<td>12.8</td>
<td>0.70 (0.52–0.93)</td>
</tr>
</tbody>
</table>

## ALSYMPCA Updated Analysis: Select Adverse Events

<table>
<thead>
<tr>
<th>Patients with AEs n, (%)</th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 n = 600</td>
<td>Placebo n = 301</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>92 (31)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>17 (6)</td>
</tr>
<tr>
<td><strong>Non-Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>187 (62)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>104 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18)</td>
<td>41 (14)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>64 (21)</td>
</tr>
</tbody>
</table>

Safety of taxane chemotherapy following radium-223 not well characterized

Radium-223: Summary

**Administration:**
- Once every 4 wks for 6 infusions
- 60-second IV infusion
- Given by radiation oncologist or nuclear medicine radiologist
- Enteric excretion
- No pre-medication, no post-medication
- CBC check before each treatment

**Clinical Benefit:**
- Primary endpoint of improvement in symptomatic SRE
- 3.6-mo benefit in OS
- Should be considered in symptomatic men with bone-predominant mCRPC
- Consider spinal imaging for epidural disease in men with high burden of disease and rapid progression; palliative EBRT should be used if high risk for spinal cord compression
Conclusions

• A number of unanswered questions remain relevant to the discussion of oligometastatic prostate cancer
• It clearly has a longer natural history and a more indolent biology, most of the time
• there is growing evidence that more aggressive therapy early in the course of disease leads to improved outcome
  • Docetaxel improve survival for metastatic hormone-naive prostate cancer
  • Enzalutamide, abiraterone, and radium-223 are all options, with OS benefit, prior to chemotherapy
Obrigado pela Atenção!

Thank you!

igormorbeck@yahoo.com.br