INTERGRATING NON-HORMONAL THERAPIES INTO PROSTATE CANCER

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Disclosures

- **Consultant**: Astellas, Bayer, BMS, Clovis, Dendreon, Exelixis, Genentech/Roche, Innocrin, Medivation, Merck, Novartis, Pfizer, Sanofi
- **Research Support**: Acerta, Astellas, Bayer, Exelixis, Innocrin, Janssen, Novartis, Pfizer
- **Speaker**: Dendreon, Novartis, Sanofi, Bayer
- **Steering Committees**: Pfizer, NCI
- **DMC**: Acceleron, Janssen, Genentech
Illustrative Case

- 55 yo African American male with prostate cancer:
  - December 2012 – PSA 3.3 cT2b G4+3 5/12 cores, 50% to 75% cores, Metastatic workup: negative
- January 2013 – RALP – GS 4+4 (minor 5) 25% tissue (pT2cN0Mx)
- 2013 -14 PSA rapidly rises to 20 post prostatectomy
- October 2014 CT and bone scan – multiple osseous metastases – started on ADT
- January 2015 PSA nadir of 1.6
- March 2015 PSA 5.5 Treated with sipuleucel-T x 3
- June 2015 PSA 49 Bone scan – multiple new and progressive osseous metastases
Illustrative Case

- June 2015 PSA 49 Started on abiraterone
- September 2015 PSA 26 tolerating well, no discernable side effects
- December 2015 PSA 6.2 (nadir)
- May 2016 PSA 48.4
- July 2016 PSA 114 Bone scan increased osseous mets. CT bone only disease.
- Fatigue and mild left hip and back pain at the end of the day
- What would do next?
What are the therapeutic options for this patient?

- **Immunotherapy**
  - Sipuleucel-T

- **Hormonal strategies**
  - Enzalutamide

- **Chemotherapies**
  - Docetaxel, cabazitaxel, mitoxantrone, cisplatin/etoposide

- **Radiopharmaceuticals**
  - Radium 223
Questions to consider

- Do you consider this patient symptomatic?

- What is the underlying biology driving CRPC progression on abiraterone?

- What would you consider his median survival to be?
Multiple Symptoms Are Associated With Bone Metastases

- Fatigue, generalized weakness
- Interference with sleep
- Dyspnea
- Impaired mobility
- Mild sensory loss, numbness
- Loss of bladder & bowel function
- Loss of appetite
- Anemia, neutropenia and thrombocytopenia
- Interference with daily activities
- Weakness in extremities
- Pain and discomfort
- Neurological impairment

Mechanisms of CRPC Progression

Is NEPC Increasing with Potent AR Inhibition?

abi/enza naive

Histology of 124 Evaluable Biopsies
74% were “pure” with a single histologic subtype (**isolated by LCM). Remainder (26%) were comprised of mixed populations.

- AdenoCA (N = 43) - 35%
- SCNC (N = 16) - 26%
- IAC (N = 33) - 26%
- Mixed (N = 32) - 13%

~70% prior abi/enza

Progression Timeline on PREVAIL

- Initiation of enzalutamide
- 11.2 mo Median PSA progression
- 11.3 mo - Median FACT-P decline (NOT REACHED)
- Median Radiographic progression
- 28.0 mo Median chemotherapy initiation
- 32.4 mo - Median OS

Median Progression To Symptomatic Disease on Prevail (11 months)

CLINICAL PROGRESSION
Presence of symptoms associated with bone metastases

- Fatigue, generalized weakness
- Interference with sleep
- Dyspnea
- Impaired mobility
- Mild sensory loss, numbness
- Loss of bladder & bowel function
- Neurological impairment
- Pain and discomfort
- Weakness in extremities
- Interference with daily activities
- Anemia, neutropenia & thrombocytopenia
- Loss of appetite

0    6         12   18         24  30      36

Progression Timeline on COU-302

Median Progression To Symptomatic Disease on COU-302 (12 months)

- Fatigue, generalized weakness
- Interference with sleep
- Dyspnea
- Impaired mobility
- Mild sensory loss, numbness
- Loss of bladder & bowel function
- Neurological impairment
- Pain and discomfort
- Weakness in extremities
- Interference with daily activities
- Anemia, neutropenia & thrombocytopenia
- Loss of appetite

CLINICAL PROGRESSION
Presence of symptoms associated with bone metastases

The Case for Sipuleucel-T

- FDA-approved therapy
- Overall survival advantage seen in two independent studies
- Low, transient toxicity
- Broad coverage by payers
- Benefit does not stop with treatment completion
1. Cell that STARTS immune response = APC (Dendritic Cell)
2. Cell that does the work = CD8 T Cell (Killer T Cell)
3. CD8 T Cells
   1. Traffic widely
   2. Serial killers

Sipuleucel-T: Generate Fresh (Functional) APC Outside the Body and Re-Infuse

Overall Survival

$P=0.032$ (Cox model)

HR$=0.775$ (95% CI: 0.614-0.979)

Median survival benefit$=4.1$ mo

Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sipuleucel-T (n=601) (%)</th>
<th>Control† (n=303) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>53.1</td>
<td>10.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41.1</td>
<td>34.7</td>
</tr>
<tr>
<td>Fever</td>
<td>31.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Back pain</td>
<td>29.6</td>
<td>28.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>21.5</td>
<td>14.9</td>
</tr>
<tr>
<td>Joint ache</td>
<td>19.6</td>
<td>20.5</td>
</tr>
<tr>
<td>Headache</td>
<td>18.1</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Sipuleucel-T: Evidence for an Induced Immune Response

Antibody Production

T Cells Proliferate

T Cells Make IFN-γ

To Fusion Protein

To PAP

Sheikh NA et al, Cancer Immunology and Immunotherapy, 2013; 62:137-47
Trend Toward Greater Survival Benefit with Lower Baseline PSA

<table>
<thead>
<tr>
<th></th>
<th>Baseline PSA (ng/mL)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 22.1 (n=128)</td>
<td>&gt;22.1–50.1 (n=128)</td>
<td>&gt;50.1–134.1 (n=128)</td>
<td>&gt;134.1 (n=128)</td>
<td></td>
</tr>
<tr>
<td>Median OS (mos)</td>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>13.0</td>
<td>7.0</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>Sipuleucel-T</td>
<td>0.51</td>
<td>(0.31, 0.85)</td>
<td>0.74</td>
<td>(0.47, 1.17)</td>
</tr>
</tbody>
</table>

Prolonged OS for AA vs matched CA patients treated with sipuleucel-T

Barriers to Implementing in Clinic

- Provider experience and belief in the clinical data
- Coordination of care / operational implementation
- Frequency of visits and treatments
- IV access issues
- Lack of individual patient efficacy
- Identifying the right timing in patients
- Costs
What is the evidence for Chemotherapy in mCRPC?

- 2 regimens demonstrate survival advantage in sequence:
  - Docetaxel/prednisone
  - Cabazitaxel/prednisone
- Rare variant histologies can respond to platinum-based regimens
- Chemotherapy demonstrates palliative benefit for cancer-related bone pain
TAX 327: Phase III Multicenter, Randomized Study in Metastatic CRPC

Stratification:

Pain level
PPI ≥ 2  or AS ≥ 10
vs.
PPI < 2  or AS < 10

KPS
≤70  vs.  ≥ 80

Docetaxel 75 mg/m² Q3 wks + Prednisone 5 mg bid

Docetaxel 30 mg/m² wkly
5 of 6 wks +
Prednisone 5 mg bid

Mitoxantrone 12 mg/m²
Q3 wks +
Prednisone 5 mg bid

Premedication: weekly docetaxel arm-dexamethasone 8 mg 1 hr prior to infusion; q3week
docetaxel arm: dexamethasone 8 mg 12, 3, and 1 hour prior to infusion

N=1006
Update 2007: TAX327

5-year follow-up: 3-month survival advantage maintained
16.3 → 19.2 months

Log rank p=0.0108
HR 0.79 (0.67-0.93)

Berthold, DR et al. J Clin Oncol. 2008;26:242-245
Overall the survival advantage appears small. Is 6 months or more of docetaxel chemotherapy really worth it?
PSA decline from baseline predictive of OS

TAX 327 Confirms ≥30% PSA Decline Predictive of OS

PSA Normalization

Median survival:
- PSA normalized: 33.3 mo
- PSA not normalized: 15.8 mo

12% of subjects (n=115)

HR 0.30 (95% CI: 0.23–0.39); p<0.0001

Rationale for Cabazitaxel following Docetaxel Chemotherapy

- 67% of patients in TAX-327 responded to Docetaxel chemotherapy with a > 30% reduction in PSA, associated with a 10.8 month median greater OS\(^1\).
  - Retreatment with a Taxane may further benefit
- Roughly 30% of patients demonstrated no response to docetaxel chemotherapy
  - Cabazitaxel is not a substrate for drug efflux membrane pumps\(^2\)
- Over time treatment with docetaxel may select resistance
  - Cabazitaxel demonstrated preclinical activity in docetaxel-resistant prostate cancer cell lines\(^3\)

Phase III TROPIC Study

**PRIMARY ENDPOINT:** OS

**SECONDARY ENDPOINTS:** Progression-free survival (PFS), investigator-assessed response rate, and safety

**INCLUSION CRITERIA:** Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression.

**STRATIFICATION FACTORS**
- ECOG PS (0, 1 vs 2)
- Measurable vs nonmeasurable disease

**STATISTICAL PLAN:** N=720 patients (n=360 in each arm), 10 cycles maximum treatment duration, 511 events to detect 25% reduction in hazard ratio, 90% power, 2-sided 5% alpha level.

*Oral prednisone/prednisolone: 10 mg daily.

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

  - **Cabazitaxel 25 mg/m² q 3 wk + prednisone^a for 10 cycles** (n=378)
  - **mitoxantrone 12 mg/m² q 3 wk + prednisone^a for 10 cycles** (n=377)

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# TROPIC: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>cabazitaxel + prednisone (n=378)</th>
<th>mitoxantrone + prednisone (n=377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 (%)</td>
<td>64.9</td>
<td>57.0</td>
</tr>
<tr>
<td>ECOG PS (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1</td>
<td>92.6</td>
<td>91.2</td>
</tr>
<tr>
<td>2</td>
<td>7.4</td>
<td>8.8</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [range]</td>
<td>143.9 [2–7842]</td>
<td>127.5 [2–11220]</td>
</tr>
<tr>
<td>Measurability of disease (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable</td>
<td>53.2</td>
<td>54.1</td>
</tr>
<tr>
<td>Nonmeasurable</td>
<td>46.8</td>
<td>45.9</td>
</tr>
<tr>
<td>Disease site (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>80.2</td>
<td>87.0</td>
</tr>
<tr>
<td>Lymph node</td>
<td>45.0</td>
<td>44.8</td>
</tr>
<tr>
<td>Visceral</td>
<td>24.9</td>
<td>24.9</td>
</tr>
</tbody>
</table>

Cabazitaxel Significantly Improved OS vs Mitoxantrone

- Median OS with cabazitaxel was 15.1 months compared to 12.7 months with mitoxantrone
- 30% reduced risk of death (HR=0.70) with cabazitaxel compared to mitoxantrone

## Adverse Events with Cabazitaxel vs Mitoxantrone

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Cabazitaxel 25 mg/m² q 3 wk + prednisone 10 mg qd (n=371)</th>
<th>mitoxantrone 12 mg/m² q 3 wk + prednisone 10 mg qd (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1–4 n (%)</td>
<td>Grade 3–4 n (%)</td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>347 (94)</td>
<td>303 (82)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>27 (7)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Anemia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>361 (98)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Leukopenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>355 (96)</td>
<td>253 (69)</td>
</tr>
<tr>
<td>Thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>176 (48)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Arrhythmia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (5)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>173 (47)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>127 (34)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>83 (22)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>76 (20)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;c&lt;/sup&gt;</td>
<td>64 (17)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dyspepsia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>36 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>136 (37)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>76 (20)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>45 (12)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

<sup>b</sup> de Bono JS, et al. *Lancet*. 2010;376:1147-1154
**PROSELICA: Study Design**

mCRPC patients progressing during and after treatment with a docetaxel-based regimen  
N = 1,200  

172 centers worldwide

- **CBZ 20 + PRED**  
  Cabazitaxel 20 mg/m² Q3W  
  + prednisone 10 mg/d for 10 courses  
  n = 598

- **CBZ 25 + PRED**  
  Cabazitaxel 25 mg/m² Q3W  
  + prednisone 10 mg/d for 10 courses  
  n = 602

Presented by: Johann de Bono

Presented by Johann De Bono at 2016 ASCO Annual Meeting
**PROSELICA: Overall Survival**

- **CBZ 20 + PRED**
- **CBZ 25 + PRED**

**Median OS, months (95% CI)**
- **CBZ 20 + PRED:** 13.4 (12.19–14.88)
- **CBZ 25 + PRED:** 14.5 (13.47–15.28)

**HR (20 vs 25):** 1.024

One-sided 98.9% upper-bound CI: 1.184

Within the non-inferiority margin (1.214)
### PROSELICA: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>CBZ 20 + PRED N = 580</th>
<th>CBZ 25 + PRED N = 595</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade TEAE</td>
<td>529 (91.2)</td>
<td>559 (93.9)</td>
</tr>
<tr>
<td>Grade 3–4 TEAE</td>
<td>230 (39.7)</td>
<td>324 (54.5)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>177 (30.5)</td>
<td>257 (43.2)</td>
</tr>
<tr>
<td>TEAE leading to permanent treatment discontinuation</td>
<td>95 (16.4)</td>
<td>116 (19.5)</td>
</tr>
</tbody>
</table>

**Most frequent Grade 3–4 TEAEs reported in ≥ 5% pts, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>CBZ 20 + PRED N = 580</th>
<th>CBZ 25 + PRED N = 595</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>12 (2.1)</td>
<td>55 (9.2)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>11 (1.9)</td>
<td>25 (4.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (1.4)</td>
<td>24 (4.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (2.6)</td>
<td>22 (3.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10 (1.7)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>10 (1.7)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (1.9)</td>
<td>12 (2.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (1.2)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (0.7)</td>
<td>7 (1.2)</td>
</tr>
</tbody>
</table>
Chemotherapy Challenges

- Sequential use of secondary hormonal agents prior to chemotherapy
- Identifying symptomatic patients before they are too symptomatic
- Convincing patients that chemotherapy is clinically beneficial
- Managing toxicity risks in older patients
What is the evidence for radiopharmaceuticals for mCRPC

• 2 agents FDA-approved for palliative benefit
  – Strontium-89; Samarium-153
• 1 agent FDA-approved for survival advantage
  – Radium-223
• Generally well tolerated but with dose limiting cytopenias
• Radium-223 first alpha –emitting particle
  – Limited penetrance
  – Fewer cytopenias
  – Dosed sequentially
Radium-223 Targets Bone Metastases

- Alpha-particles induce double-strand DNA breaks in adjacent tumour cells\(^1\)
  
  - Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue

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

**PATIENTS**
- 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**
- 6 injections at 4-week intervals
- Radium-223 (50 kBq/kg) + Best standard of care
- Placebo (saline) + Best standard of care

**RANDOMISED**
N = 922

Planned follow-up is 3 years

ALSYMPCA: Overall Survival

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)

No. at Risk

| Radium-223 | 614 | 578 | 504 | 369 | 274 | 178 | 105 | 60 | 41 | 18 | 7 | 1 | 0 | 0 |
| Placebo   | 307 | 288 | 228 | 157 | 103 | 67  | 39  | 24 | 14 | 7  | 4 | 2 | 1 | 0 |

ALSYMPCA: Time to SSE

B  Time to First Symptomatic Skeletal Event

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>614</td>
<td>307</td>
</tr>
<tr>
<td>3</td>
<td>496</td>
<td>211</td>
</tr>
<tr>
<td>6</td>
<td>342</td>
<td>117</td>
</tr>
<tr>
<td>9</td>
<td>199</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>129</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>63</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>21</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>24</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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)
Table 3. Adverse Events That Occurred in at Least 5% of Patients in Either Study Group in the Safety Population.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Radium-223 (N=600)</th>
<th>Placebo (N=301)</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>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>65 (11)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>9 (2)</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>35 (6)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>154 (26)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Deterioration in general physical health</td>
<td>27 (4)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>76 (11)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>38 (6)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18 (3)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>47 (8)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>69 (12)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>102 (17)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35 (6)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>120 (20)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>9 (2)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Pathologic fracture</td>
<td>22 (4)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Progression of malignant neoplasm</td>
<td>77 (13)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>43 (7)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>25 (4)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>30 (5)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>25 (4)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>49 (8)</td>
<td>10 (2)</td>
</tr>
</tbody>
</table>
What we learned since this trial?

- Radium can be safely given with other agents/strategies:
  - Docetaxel
  - Abiraterone
  - Enzalutamide
  - External beam therapy
  - Sipuleucel – T

- Efficacy in these combinations awaits randomized trial results
Key Takeaways

- Diverse treatment portfolio for patients with mCRPC
  - Aggressive use of non-hormonal therapies should be used in conjunction with or following hormonal strategies
- Variations in histology, driver biology, clinical phenotype and prognostic factors help divide this disease already
- Treatments have been shown to work in sequence
- Working hypothesis: Many of these mechanisms may be synergistic if used in combination