Incorporating Xofigo® (radium Ra 223 dichloride) into Clinical Practice

Objectives

- Review the metastatic castration-resistant prostate cancer (mCRPC) disease state and the impact of bone metastases
- Describe the Xofigo® (radium Ra 223 dichloride) mechanism of action
- Highlight key data from the phase III ALSYMPCA study
- Describe the Xofigo safety profile
- Discuss the integration of Xofigo into clinical practice

Bone-Predominant Disease Is Common in CRPC

233,000 new cases of prostate cancer expected in 2014

~14% of patients achieving surgical or medical castration will develop CRPC

~90% of men with mCRPC have metastases in the bone

5-year survival is reduced to 4% once CRPC metastasizes to bone

References:
Progression to mCRPC\(^1,2\)

- 4% of patients with prostate cancer present with M1-hormone sensitive disease\(^3\)

Progression of Metastatic Disease to Bone in CRPC

- What do you do in your practice to facilitate earliest detection of bone metastases?
- What do you do in your practice to facilitate earliest detection of symptoms related to bone metastases?

Prostate Tumor Cells May Colonize the Bone

- In vitro data show that colonization of bone tissue may be driven by chemoattraction and preferential attachment\(^1,3\)
- Prostate cancer metastases are associated with osteoblastic activity\(^4,6\)
  - Balance shifts from bone destruction to bone deposition
  - Correlates with higher levels of alkaline phosphatase (ALP) and osteocalcin
Bone Metastases Associated With Shortened Survival

- 56% alive at 5 years (95% CI: 54.9-56.7)
- 3% alive at 5 years (95% CI: 2.2-3.4)

Time After Initial Prostate Cancer Diagnosis (years)

Probability of Survival (%)

Skeletal tumor burden is an independent predictor of death in patients with advanced prostate cancer

XOFIGO® (radium Ra 223 dichloride)

CLINICAL PROFILE, EFFICACY, AND SAFETY

Xofigo® (Radium Ra 223 Dichloride) Indication

- Xofigo is indicated for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease

- Important safety information
  - Contraindications: Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman

Please see additional Important Safety Information throughout this presentation and full Prescribing Information available at this presentation.
**Xofigo® (Radium Ra 223 Dichloride)**

**Mechanism of Action**

- **Mimics Calcium**
  - Xofigo mimics calcium, forming complexes with the bone mineral hydroxyapatite at areas of increased bone turnover such as bone metastases.

- **Short Range**
  - The short range of alpha particles emitted by Xofigo (<10 cell diameters) limits damage to surrounding normal tissue.

- **High Linear Energy**
  - Xofigo emits alpha particles that predominantly cause double-strand DNA breaks in adjacent cells, resulting in an antitumor effect on bone metastases.

Xofigo can be absorbed by organs other than bone, primarily the bone marrow and gastrointestinal system, which can result in side effects in those healthy tissues.

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**Phase III ALSYMPCA Study Design, Patient Eligibility**

- **Patients**
  - N=921
    - CRPC with ≥2 symptomatic bone metastases
    - No known visceral metastases
    - Symprolacropathy ≤1 cm only

- **Stratification**
  - Prior docetaxel: Yes vs no
  - Current biphosphonate use: Yes vs no
  - Total ALP: <220 U/L vs ≥220 U/L

- **Treatment**
  - Xofigo® (radium Ra 223 dichloride) (50 kBq/kg) + Best standard of care (BSoC) (n=614)
  - Placebo (saline) + BSoC (n=307)

- **Overall survival**
  - 6 injections at 4-week intervals
  - 136 centers in 19 countries

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**Phase III ALSYMPCA Best Standard of Care (BSoC)**

- In the ALSYMPCA trial, BSoC was defined as treatment with:
  - Local external-beam radiation therapy (EBRT)
  - Glucocorticoids
  - Antiandrogens
  - Ketoconazole
  - Estrogens (e.g., diethylstilbestrol, estramustine)

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• Symptomatic skeletal event (SSE) was defined as the first use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or non-vertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention


Phase III ALSYMPCA Other Endpoints

Secondary Endpoints
- Median time to first SSE
- Median time to ALP progression
- Median time to ALP normalization
- Median time to PSA progression

Other Exploratory Secondary Endpoints
- Safety
- Quality of life

Other Exploratory Secondary Endpoints

1. Xofigo® (radium Ra223 dichloride), n=614
   Placebo, n=307
   Median age (years) 71 71
   ECOG PS (%)
   ≤1 8 8
   ≥2 7 7
   Opiate pain medications (%) 57 54
   Nonopiate pain medications (%) 42 45
   No pain medications (%) 2 1
   Prior docetaxel (%) Yes 57 57
   No 43 43
   Current bisphosphonate use (%) Yes 41 40
   No 59 60
   Total ALP (%) <220 U/L 55 57
   ≥220 U/L 45 43
   Median PSA 146 173


Phase III ALSYMPCA Definition of Symptomatic and Patient Demographics

• In the ALSYMPCA trial, patients were required to have symptomatic disease, with regular use of analgesic medication or EBRT for cancer-related bone pain

OS Benefit Consistent Across Planned Interim and Exploratory Updated Analyses

• An exploratory updated OS analysis was performed before patient crossover, incorporating an additional 214 events, resulting in findings consistent with the interim analysis.


2. Plus BSoC.

Xofigo® (Radium Ra 223 Dichloride) Is First Agent to Extend OS by Treating Bone Metastases in CRPC

**Median OS Extended by 3.6 Months vs Placebo in the Exploratory Updated Analysis**

<table>
<thead>
<tr>
<th>Xofigo + BSoC (n=614)</th>
<th>Placebo + BSoC (n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR=0.695 (95% CI: 0.581-0.832)</td>
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</tr>
</tbody>
</table>

**Overall Survival Benefit Supported by Delay in Time to First SSE**

- EBRT to relieve skeletal symptoms
- New symptomatic broken bone caused by disease
- Occurrence of spinal cord compression
- Tumor-related orthopedic surgical intervention

The majority of events consisted of EBRT to bone metastases to relieve skeletal symptoms

**Xofigo® (Radium Ra 223 Dichloride) Improves Key Biomarkers of Disease Progression**

<table>
<thead>
<tr>
<th>Exploratory Updated Analysis of Select Secondary Endpoints</th>
<th>Xofigo (n=614)</th>
<th>Placebo (n=307)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to total ALP progression (months)</td>
<td>7.4</td>
<td>3.8</td>
<td>0.17 (0.13-0.22)</td>
</tr>
<tr>
<td>Total ALP response (≥30% reduction)*</td>
<td>47%</td>
<td>3%</td>
<td>—</td>
</tr>
<tr>
<td>Total ALP normalization**</td>
<td>34%</td>
<td>1%</td>
<td>—</td>
</tr>
<tr>
<td>Median time to PSA progression (months)</td>
<td>3.6</td>
<td>3.4</td>
<td>0.64 (0.54-0.77)</td>
</tr>
</tbody>
</table>

*Number of patients with a total ALP response was not determined in the placebo arm. 1. Parker C, et al. J Clin Oncol. 2013;31:2036-2043.
Hematologic Laboratory Abnormalities Occurring in ≥10% of Patients

- The most common hematologic laboratory abnormalities (all grades) in the Xofigo arm (10%) versus the placebo arm, respectively, were anemia (53% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%) and neutropenia (18% vs 5%).

<table>
<thead>
<tr>
<th>Grades 3-4 (%)</th>
<th>Xofigo (radium Ra 223 dichloride) (n=600)</th>
<th>Placebo (p=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Hematologic Events Stratified by Docetaxel Exposure

<table>
<thead>
<tr>
<th>Grade 3-4 thrombocytopenia (laboratory abnormality)</th>
<th>Patients Without Prior Docetaxel Exposure</th>
<th>Patients With Prior Docetaxel Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Grade 3-4 neutropenia</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Important Safety Information

- **Bone Marrow Suppression:**
  - In the randomized trial, 2% of patients in the Xofigo (radium Ra 223 dichloride) arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo.
  - Two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo, bone marrow failure was ongoing at the time of death.
  - Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression.
  - Deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo (radium 223 dichloride)-treated patients compared to 0.3% of patients treated with placebo.
Important Safety Information (cont’d)

- Bone Marrow Suppression (continued):
  - Incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (≤1%) was similar for patients treated with Xofigo (radium Ra 223 dichloride) and placebo.
  - Myelosuppression—notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia, has been reported in patients treated with Xofigo.
  - Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

Please see additional Important Safety Information throughout this presentation and full Prescribing Information available at this presentation.


Important Safety Information (cont’d)

- Hematological Evaluation:
  - Monitor blood counts at baseline and prior to every dose of Xofigo® (radium Ra 223 dichloride).
  - Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL.
  - Prior to subsequent administrations, the ANC should be ≥1 × 10^9/L and the platelet count ≥50 × 10^9/L.
  - Discontinue Xofigo if hematologic values do not recover within 6-8 weeks after last administration despite receiving supportive care.

Please see additional Important Safety Information throughout this presentation and full Prescribing Information available at this presentation.


Important Safety Information (cont’d)

- Concomitant Use With Chemotherapy:
  - Safety and efficacy of concomitant chemotherapy with Xofigo (radium Ra 223 dichloride) have not been established.
  - Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression.
  - If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

Please see additional Important Safety Information throughout this presentation and full Prescribing Information available at this presentation.

### Safety Profile Established in ALSYMPCA Study

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xofigo&lt;sup&gt;a&lt;/sup&gt; (radium Ra 223 dichloride)&lt;sup&gt;a&lt;/sup&gt; (n=600)</td>
<td>Placebo&lt;sup&gt;a&lt;/sup&gt; (n=301)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Renal failure and</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Please see additional Important Safety Information throughout this presentation and full Prescribing Information available at this presentation.*

### Overall Grade 3-4 AEs and Discontinuations Due to AEs

- The most common hematologic laboratory abnormalities leading to discontinuation of Xofigo were anemia (2%) and thrombocytopenia (2%).

### Important Safety Information

- **Administration and Radiation Protection<sup>1</sup>**
  - Xofigo should be received, used and administered only by authorized persons in designated clinical settings.
  - The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

*Please see additional Important Safety Information throughout this presentation and full Prescribing Information available at this presentation.*

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<sup>1</sup> Refer to the prescribing information for a complete discussion of the radiation risks associated with Xofigo.
Important Safety Information

- **Fluid status**
  - Dehydration occurred in 3% of patients on Xofigo (radium Ra 223 dichloride) and 2% of patients on placebo
  - Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting, which may result in dehydration
  - Monitor patients’ oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia

- **Injection site reactions (reported in 1% Xofigo patients)**
  - Erythema
  - Pain
  - Edema

Important Safety Information (cont’d)

- **Secondary malignant neoplasms**
  - Xofigo (radium Ra 223 dichloride) contributes to a patient’s overall long-term cumulative radiation exposure
  - Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects
  - Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms due to its MOA and neoplastic changes
  - However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs 2%, respectively), but the expected latency period for development of secondary malignancies exceeded the duration of follow up for patients on the trial

Important Safety Information (cont’d)

- **Subsequent treatment with cytotoxic chemotherapy**
  - In the randomized clinical trial, 16% patients in the Xofigo (radium Ra 223 dichloride) group and 18% patients in the placebo group received cytotoxic chemotherapy after completion of study treatments
  - Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy
Currently Approved Therapies for Advanced Prostate Cancer
National Comprehensive Cancer Network® (NCCN®) category 1 evidence

<table>
<thead>
<tr>
<th>Hormone Sensitive</th>
<th>CRPC</th>
<th>Asymptomatic mCRPC</th>
<th>Symptomatic mCRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abiraterone</td>
<td>Abiraterone</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Abiraterone</td>
<td>Abiraterone</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

EBRT=external beam radiation therapy
This table is based on available treatment options in the various stages of mCRPC treatment paradigm: Disease is not proportional to risk. Tumor biology is the primary determinant of treatment decision, with risk of visceral metastatic disease serving an unmet medical need. The table is not intended to be an all-inclusive listing. The NCCN Guidelines for Prostate Cancer Search: May 2013. NCCN.org

When Is It the Right Time to Administer Xofigo® (Radium Ra 223 Dichloride)?

- Xofigo is indicated for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease.

At the earliest onset of symptoms from bone metastases...

| Bone metastases | Symptoms | Administer Xofigo
|-----------------|----------|------------------|
| Patients in the phase III ALSYMPCA trial had 2 or more bone metastases | Regular OTC analgesics (42% patients in ALSYMPCA were on non-opioid pain medications, 57% were on opioid pain medications) Use of ERRT to treat bone pain | Added to BisC (bisphosphonates, corticosteroids, antiandrogens, ketoconazole, estrogenic (e.g., exemestane)) 6 injections at 4-week intervals (the median number of injections was 6 in the Xofigo arm and 5 in the placebo arm)

Xofigo is not recommended in combination with chemotherapy

<table>
<thead>
<tr>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 30% reduction in risk of death vs placebo (HR=0.695)</td>
</tr>
<tr>
<td>- Exploratory updated analysis: 3.6-month increase in median OS vs placebo (HR=0.695; 95% CI: 0.581-0.832)</td>
</tr>
<tr>
<td>- Prespecified interim analysis: 2.8-month increase in median OS vs placebo, P=0.00185 (HR=0.695; 95% CI: 0.552-0.875)</td>
</tr>
</tbody>
</table>

*An exploratory updated OS analysis was performed before patient crossover, incorporating an additional 214 events, resulting in findings consistent with the interim analysis. The NCCN Guidelines for Prostate Cancer Search: May 2013.
Summary (2 of 2)

- OS benefit supported by delay in time to first SSE, favoring Xofigo®
  - The majority of events consisted of EBRT to bone metastases
- Xofigo® (radium Ra 223 dichloride) is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman
- The most common adverse reactions (≥10%) in the Xofigo® arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%)

*An exploratory updated OS analysis was performed before patient crossover, incorporating an additional 214 events, resulting in findings consistent with the interim analysis.

+Plus BSC