Xofigo (Radium Ra 223 Dichloride): The First Alpha Particle–Emitting Radioactive Agent for the Treatment of Castration-Resistant Prostate Cancer with Symptomatic Bone Metastases

By Lisa A. Raedler, PhD, RPh

Currently, 4 bone-targeted therapies are available for men with prostate cancer, including zoledronic acid (Zometa), denosumab (Prolia), samarium-153 ethylene diamine tetramethylene phosphate (EDTMP; Quadramet), and strontium-89 (Metastron). None of these 4 agents has been proved to prolong overall survival (OS) in large phase 3 randomized trials.

The 2 radiopharmaceuticals, strontium-89 and samarium-153 EDTMP, are beta-particle emitters. Both were approved by the US Food and Drug Administration (FDA) on the basis of randomized phase 3 clinical trials that demonstrated an improvement in pain in patients with metastatic prostate cancer.7

By contrast, sipuleucel-T (Provenge), abiraterone (Zytiga), and enzalutamide (Xtandi) have demonstrated advantages in OS in patients with metastatic prostate cancer, but these agents do not target disease that has spread to bone and are not indicated specifically for patients with prostate cancer plus bone metastases.4,5

The availability of radium-223 offers a novel therapeutic alternative for patients with CRPC and bone metastasis, particularly for those who wish to avoid the side effects of chemotherapy. According to Nicholas J. Vogelzang, MD, a genitourinary oncologist at Comprehensive Cancer Centers of Nevada, Las Vegas, “In general, about half of [patients with advanced prostate cancer] say they will not take chemotherapy. For them, [radium-223] is a wonderful option because it suppresses the cancer, controls the pain, and extends their life.”13

According to the drug manufacturer, 6 cycles of treatment with radium-223 cost $69,000.16

Mechanism of Action and Pharmacodynamics

The active component in Xofigo is the alpha particle–emitting isotope radium-223, which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. The high energy transfer of alpha emitters increases the breaking frequency of double-strand DNA in adjacent cells, leading to an antitumor effect on bone metastases. The alpha particle range from radium-223 dichloride localizes the impact of the drug and limits damage to the surrounding normal tissue.17 In a phase 2 randomized trial that compared radium-223 and placebo, a significant difference was seen in favor of radium-223 in all 5 biomarkers for bone turnover.17

Dosing and Administration

The recommended dose and schedule for radium-223 is 50 kBq/kg intravenously every 4 weeks for 6 cycles plus standard of care (N = 541) or to matching placebo plus standard of care (N = 268). Best standard of care included local external beam radiation therapy [EBRT], corticosteroids, antiandrogens, estramustine, or ketoconazole.17

Therapy was continued until unacceptable toxicity or until initiation of cytotoxic chemotherapy, other systemic radioisotope, hemibody EBRT, or other investigational drugs.

The primary efficacy end point was OS. A key secondary efficacy end point was time to first symptomatic skeletal event, which was defined as EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments performed during the study. All patients were to continue androgen-deprivation therapy.17

ALYMPCA: A Pivotal Phase 3 Clinical Trial

Radium-223 was approved by the FDA based on the results of a single, phase 3 clinical trial—the Alpharadin in Patients with Symptomatic Hormone Refractory Prostate Cancer with Skeletal Metastases (ALSYMPCA) trial—a randomized, multicenter, double-blind study of more than 800 patients with CRPC and symptomatic bone metastases. Patients were stratified by baseline alkaline phosphatase, bisphosphonate use, and previous docetaxel exposure.17

Trial Design

In the ALSYMPCA trial, patients were randomly assigned in a 2:1 ratio to receive radium-223 50 kBq/kg intravenously every 4 weeks for 6 cycles plus best standard of care (N = 541) or to matching placebo plus best standard of care (N = 268). Best standard of care included local external beam radiation therapy [EBRT], corticosteroids, antiandrogens, estramustine, estrusumine, or ketoconazole.17

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Patient Population

Patient demographics and baseline disease characteristics were balanced between the 2 arms. The patients’ median age was 71 years (range, 44-94 years), with a racial distribution of 94% white, 4% Asian, 2% black, and <1% other. The Eastern Cooperative Oncology Group performance status was 0 to 1 in 86% of patients.17

Overall, 85% of the patients had ≥6 bone scan lesions; of those, 40% had >20 lesions or a superscan. For cancer-related pain, 54% of the patients received opiate pain medications, 44%
received nonopioid pain medications, and 2% received no pain medication. Overall, bisphosphonates were used by 41% of patients. More than half (58%) of the patients had previously received docetaxel.17

During the study period, 83% of the patients in the radium-223 arm and 82% of the patients in the placebo arm were also using gonadotropin-releasing hormone agonists; 21% and 34% of patients, respectively, were using concomitant androstenedione. The use of systemic corticosteroids (41%) and bisphosphonates (40%) was equal between the 2 arms.17

**Efficacy**

The prespecified interim analysis of ALSYMPCA revealed a significant improvement in OS in patients receiving radium-223 plus best standard of care compared with patients receiving placebo plus best standard of care (Figure), with a median OS of 14.0 months with radium-223 versus 11.2 months with placebo, for a 3.6-month difference (Table 1).17 The median duration of treatment was 20 weeks (6 cycles) with radium-223 and 18 weeks (5 cycles) with placebo.17

An updated OS analysis performed before the patient crossover with an additional 214 events yielded findings that confirmed the OS advantage of radium-223 versus placebo, resulting in a median OS of 14.9 months with radium-223 versus 11.3 months with placebo, for a 3.6-month difference (Table 1).17 The survival results were supported by a delay in the time to first symptomatic skeletal event favoring the radium-223 arm. The majority of events consisted of treatment with EBRT to bone metastases.17

**Safety Profile**

The most common (>10%) adverse reactions in patients receiving radium-223 were nausea, diarrhea, vomiting, and peripheral edema (Table 2).18 Grade 3 or 4 adverse events were reported in 57% of patients receiving radium-223 and in 63% of patients receiving placebo.17

The most common (>10%) hematologic laboratory abnormalities in patients receiving radium-223 were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Grade 3 or 4 lymphocytopenia was reported in 20% of patients receiving radium-223 and in 7% of patients receiving placebo (Table 3).17

Dehydration occurred in 3% of patients receiving radium-223 and in 1% of patients receiving placebo. Treatment discontinuations resulting from adverse events occurred in 17% of patients who received radium-223 and in 21% of patients who received placebo.17

**Warnings and Precautions**

*Fluid status.* Radium-223 can result in adverse reactions such as diarrhea, nausea, and vomiting, which may result in dehydration. Patients’ oral intake and fluid status should be carefully monitored, and patients who display signs or symptoms of dehydration or hypovolemia should be promptly treated.17

*Secondary malignant neoplasms.* Radium-223 contributes to a patient’s overall long-term cumulative radiation exposure, which may be associated with increased risk of cancer and hereditary defects. Because of its mechanism of action and neoplastic changes, including osteosarcomas in rats after receiving radium-223, radium-223 may increase the risk of osteosarcoma or other secondary malignant neoplasms.

However, the overall incidence of new malignancies in the randomized ALSYMPCA trial was lower in the radium-223 arm compared with the placebo arm (<1% vs 2%, respectively). The expected latency period for the development of secondary malignancies exceeds the duration of follow-up for patients in the trial.17

*Subsequent treatment with cytotoxic chemotherapy.* In the ALSYMPCA trial, 16% of patients included in the

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**Table 1** Overall Survival of Radium-223 versus Placebo: Interim and Updated Analyses from the Phase 3 Trial

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 plus best standard of care</th>
<th>Placebo plus best standard of care</th>
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<tbody>
<tr>
<td><strong>Interim analysis</strong></td>
<td></td>
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</tr>
<tr>
<td>Randomized patients, N</td>
<td>541</td>
<td>268</td>
</tr>
<tr>
<td>Deaths, N (%)</td>
<td>191 (35.3)</td>
<td>123 (45.9)</td>
</tr>
<tr>
<td>Censored, N (%)</td>
<td>350 (64.7)</td>
<td>145 (54.1)</td>
</tr>
<tr>
<td>Median survival, mo*</td>
<td>14.0</td>
<td>11.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12.1-15.8)</td>
<td>(9.0-13.2)</td>
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<tr>
<td><strong>Updated analysis</strong></td>
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<td></td>
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<tr>
<td>Randomized patients, N</td>
<td>614</td>
<td>307</td>
</tr>
<tr>
<td>Deaths, N (%)</td>
<td>333 (54.2)</td>
<td>195 (63.5)</td>
</tr>
<tr>
<td>Censored, N (%)</td>
<td>281 (45.8)</td>
<td>112 (36.5)</td>
</tr>
<tr>
<td>Median survival, mo*</td>
<td>14.9</td>
<td>11.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(13.9-16.1)</td>
<td>(10.4-12.8)</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td>0.695 (0.352-0.875)</td>
<td>0.695 (0.581-0.832)</td>
</tr>
</tbody>
</table>

*Survival time is calculated as months from date of randomization to date of death from any cause. Patients who are not deceased at time of analysis are censored on the last date a patient was known to be alive or was lost to follow-up.

*P value* is stratified by total alkaline phosphatase, current use of bisphosphonates, and previous use of docetaxel.

1Hazard ratio adjusted for total alkaline phosphatase, current use of bisphosphonates, and previous use of docetaxel; hazard ratio <1 favors radium-223 dichloride.

CI indicates confidence interval.

Source: Xofigo (radium Ra 223 dichloride) injection [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc; May 2013.

**Table 2** Adverse Reactions ≥2% Higher with Xofigo than with Placebo in the Phase 3 Trial

<table>
<thead>
<tr>
<th>System/organ class preferred term</th>
<th>Xofigo (N = 600)</th>
<th>Placebo (N = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4, %</td>
<td>Grades 3-4, %</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure and impairment</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Xofigo (radium Ra 223 dichloride) injection [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc; May 2013.
radium-223 cohort and 18% of patients in the placebo cohort received cytotoxic chemotherapy after completion of the study treatments. Adequate safety monitoring and laboratory testing were not performed to assess how patients who were treated with radium-223 will tolerate subsequent cytotoxic chemotherapy.17

**Contraception.** Because of the potential effects on spermatogenesis that is associated with radiation treatment, men who are sexually active and their female partners of reproductive potential should be advised to use highly effective contraceptives during and for 6 months after completing treatment with radium-223.17 This new therapy is not to be used in women.

**Bone marrow failure.** In the ALSYMPCA trial, 2% of patients in the radium-223 arm had bone marrow failure or ongoing pancytopenia compared with none of the patients receiving placebo. In addition, 2 deaths resulted from bone marrow failure. For 7 of the 13 patients who were treated with radium-223, bone marrow failure was ongoing at the time of death. Among the 13 patients who had bone marrow failure, 54% required blood transfusions. In that study, 4% of patients in the radium-223 arm and 2% of patients in the placebo arm discontinued therapy as a result of bone marrow suppression.17

**Myelosuppression.** Deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of patients receiving radium-223 compared with 0.3% of patients receiving placebo. The incidence (2%) of infection-related deaths, serious infections (10%), and febrile neutropenia (<1%) was similar for patients receiving radium-223 and for patients receiving placebo.17

Myelosuppression (ie, thrombocytopenia, neutropenia, pancytopenia, and leukopenia) has been reported in patients treated with radium-223. Complete blood counts were obtained every 4 weeks before each dose. Nadir complete blood counts and bone marrow recovery times were not well characterized in ALSYMPCA.17 In a single-dose phase 1 study of radium-223, neutrophil and platelet count nadirs occurred 2 to 3 weeks after the administration of radium-223 at doses of 1 to 5 times that of the recommended dose. Most patients recovered 6 to 8 weeks after administration.17

**Monitoring.** Hematologic evaluation of patients must be performed at baseline and before every dose of radium-223. Absolute neutrophil counts, platelet counts, and hemoglobin levels must meet minimum requirements as specified in the product’s labeling information. If these values do not recover within 6 to 8 weeks after the last administration of radium-223, despite supportive care, treatment should be discontinued.17

Patients with evidence of compromised bone marrow reserve should be monitored closely and should be provided with supportive-care measures when clinically indicated. Radium-223 should be discontinued in patients who experience life-threatening complications despite supportive care for bone marrow failure.17

The safety and efficacy of concomitant chemotherapy with radium-223 have not been established. Outside of a clinical trial, the concomitant use of radium-223 with chemotherapy is not recommended because of the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemobidity external radiotherapy are administered during the treatment period, radium-223 should be discontinued.17

**Conclusion**

For patients with advanced prostate cancer and bone metastases, single-agent radium-223 offers clinically and statistically significant efficacy benefits, with a favorable tolerability profile and a convenient dosing schedule. Experts suggest that this bone-targeting radiopharmaceutical is a viable treatment option for men with CRPC who have received, or who are ineligible for, or who prefer to delay or to avoid cytotoxic chemotherapy.

Combination studies with radium-223 and hormonal agents, immunomodulatory agents, and docetaxel are pending or are under way to further elucidate the role of radium-223 as a part of the armamentarium for patients with prostate cancer.17

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**Table 3 Hematologic Reactions ≠10% Higher with Xofigo than with Placebo in the Phase 3 Trial**

<table>
<thead>
<tr>
<th>Hematologic laboratory abnormalities</th>
<th>Xofigo (N = 600)</th>
<th>Placebo (N = 301)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4, %</td>
<td>Grades 3-4, %</td>
</tr>
<tr>
<td>Anemia</td>
<td>93</td>
<td>6</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>72</td>
<td>20</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: Xofigo (radium Ra 223 dichloride) injection [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc; May 2013.

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**References**