Radium-223 chloride: extending life in prostate cancer patients by treating bone metastases

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Running title: Radium-223 for prostate cancer treatment

Keywords: radium-223, alpha-emitter, prostate cancer, Xofigo

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Conflict of interest: All authors declare that they do not have a conflict of interest

Word count: 2409 words

Figures and tables: 1 figure, 1 table
Abstract

The treatment scope for patients with metastatic castrate-resistant prostate cancer (mCRPC) is rapidly expanding. On May 15, 2013, the FDA approved radium-223 chloride for the treatment of mCRPC patients whose metastases are limited to the bones. Radium-223 is an alpha-emitting alkaline earth metal ion, which, similar to calcium-ions, accumulates in the bone. In a phase 3 study (ALSYMPCA), mCRPC patients with bone metastases received best standard-of-care with placebo or radium-223 chloride. At a prespecified interim analysis, the primary endpoint of median overall survival was significantly extended by 3.6 months in patients treated with radium-223 compared to placebo (p < 0.001). The radioisotope was well tolerated and gave limited bone marrow suppression. Radium-223 chloride is the first bone targeting antitumor therapy which received FDA approval based on a significant extended median overall survival. Further studies are required to optimize its dosing and to confirm its efficacy and safety in cancer patients.
Introduction

Prostate cancer is the most prevalent and second deadliest cancer in men in the United States and Europe (1). Most morbidity and virtually all mortality from prostate cancer occurs once the tumor has become metastatic and castrate-resistant (mCRPC) (2). Therefore research aimed at the development of novel therapies for prostate cancer has primarily focused on this patient group. Whereas a decade ago no therapy existed with a proven significant benefit on the median overall survival of mCRPC patients, patients now have the options to be treated with multiple life-extending therapies. These therapies consist of agents that selectively target the androgen pathway (abiraterone acetate, enzalutamide) and taxanes (docetaxel, cabazitaxel), which target microtubules (3-8). Furthermore, the immunotherapy sipuleucel-T has been approved for its use in asymptomatic or minimally symptomatic mCRPC patients (9, 10).

Prostate cancer primarily metastasizes to the bone (11). Bone metastases may lead to severe morbidity, such as bone marrow failure, pathological fractures and spinal cord compression, reducing quality of life and potentially resulting in death (12, 13). Hence specific treatment of bone metastases may significantly lower the burden of prostate cancer disease (14, 15). Multiple agents have been approved by the United States Food and Drug Administration (US FDA) for the palliative treatment of bone metastases in mCRPC patients, such as external beam radiotherapy and the beta-emitting radiopharmaceuticals strontium-89 (1.5-2.2 MBq/kg) and samarium-153 (37 MBq/kg) (table 1). Such therapies result in symptomatic relief in over half of patients (16, 17). However, the duration of response is limited; the effect of these treatments on overall
survival has not been studied. Moreover, as surrounding tissue, including the bone marrow, gets damaged too, significant adverse events such as bone marrow failure may occur in treated patients.

On May 15, 2013, the US FDA approved radium-223 chloride (Xofigo, previously named alpharadin) for the treatment of bone metastases in mCRPC patients based on interim results from a phase III 3 randomized clinical trial, the ALSYMPCA study (“Alpharadin in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer”). This marks the first FDA approved radionuclide which has shown to extend overall survival in mCRPC patients in a phase 3 study. In this brief review, we will discuss the (pre-)clinical development of radium-223 chloride, focusing primarily on the most recent results from the ALSYMPCA study. Subsequently we will discuss the US FDA approval and future implications this approval may have in clinical practice.

**Radium-223 chloride**

Radium-223 chloride ($^{223}$RaCl$_2$) is a water soluble radium salt. In ionic form radium accumulates in bones at areas with increased bone turnover due to its chemically similar to calcium-ions; both are alkaline earth metals (18, 19). Radium-223 is an alpha-emitting radioisotope that decays via seven daughter nuclides before it stabilizes as lead-207 (Fig. 1). During the decay of each radium-223 isotope, four alpha-particles and two electrons (beta-particles) are emitted (table 1). Both alpha- and beta-irradiation can induce local therapy by inducing damage in the surrounding tissue. Due to the size and high energy of alpha-particles, these particles highly effectively induce double strand-breaks in DNA.
within 100 µm. The half-life of radium-223 is 11.4 days; the half-lives of its daughter nuclides range from seconds to minutes. These daughter nuclides do not have a chemical similarity to calcium-ions. Therefore, the half-lives of radon-219 (4.0 s), bismuth-211 (2.1 min) and thallium-207 (4.8 min) appear long enough to allow diffusion from the primary accumulation site.

**Early preclinical and clinical studies**

In a preclinical study, nude rats with MT-1 human breast cancer xenografts were treated with pamidronate, a bisphosphonate used against skeletal complications of cancer, with or without radium-223 (18). While all rats treated with pamidronate only had to be sacrificed within 21 days, 40% of rats treated with pamidronate and radium-223 at 10 or 30 kBq survived beyond 50 days. Compared to beta-emitting particles such as strontium-89, rodents treated with radium-223 showed no signs of bone marrow suppression or other toxicities (20).

In a phase 1 study, radium-223 chloride was administered to 15 prostate and 10 breast cancer patients with bone metastases (21). Patients received a single intravenous injection of radium-223 with activities up to 250 kBq/kg. Over 50% of patients reported pain relief, while toxicity was low. Grade 3 leukopenia occurred in three patients, the maximum-tolerated dose (MTD) was not established. Radium-223 accumulated in the skeleton, particularly in sites with metastases. In the blood, radioactivity levels diminished quickly: to 6% after 1 hour and to <1% 24 hours after injection. Recently, similar findings were presented from another phase I study (22). In this study, ten
mCRPC patients received radium-223 up to 200 kBq/kg, of which six patients received a second dose of 50 kBq/kg. The MTD was again not established, and radium-223 was rapidly cleared from the blood, primarily into the small bowel.

A subsequent phase 2 study compared treatment of 50 kBq/kg radium-223 with placebo treatment in 64 CRPC patients with painful bone metastases (23, 24). Median time to skeletal-related event (SRE) was 14 weeks in the radium-223-treated group versus 11 weeks in patients treated with placebo (p = 0.257) (23). Low toxicity of radium-223 was confirmed in this phase 2 study. None of the 33 radium-223-treated patients discontinued treatment due to adverse events. Grade 3 and 4 adverse events occurred in 3 (9.1%) and 0 (0%) radium-223-treated patients and in 1 (3.3%) and 1 (3.3%) placebo-treated patients, respectively. Severe non-hematological adverse events occurred in 3 (9.1%) radium-223-treated patients and in 5 (16.7%) placebo-treated patients. In a follow-up report 24 months after the first injection of study medication, no long-term treatment-related toxicity was reported (24). Median overall survival was 65 weeks in the radium-223-treated group, and 46 weeks in the placebo-treated group (p = 0.056).

**ALSYMPCA**

The ALSYMPCA phase 3 study was initiated in 2008, in which the efficacy and safety of radium-223 chloride was compared to placebo (a saline injection) in patients with symptomatic CRPC with bone metastases (25). Patients needed to have at least two bone metastases, diagnosed by bone scintigraphy. Patients were eligible if they had previously received docetaxel, if they were unfit for docetaxel, if they declined therapy...
with docetaxel or if docetaxel was not available. Patients were excluded if they had visceral metastases. Patients received an intravenous injection (50 kBq/kg) once every 4 weeks for a maximum of 6 cycles.

In total, 921 patients were included at 135 study locations worldwide, primarily in North America, Australia and Europe (26). Six hundred fourteen patients received radium-223, of whom 352 had received docetaxel prior to radium-223 treatment (57.3%). In the placebo-group a similar percentage had received prior docetaxel (56.6% (174 patients)). Other baseline characteristics, such as age, disease stage and baseline opioid use, were similar between the two treatment groups as well (25).

The primary endpoint of the ALSYMPCA study was overall survival. In general, median overall survival in patients treated with radium-223 was extended by 3.6 months compared to placebo-treated patients (p < 0.001) (25). For patients who had received docetaxel prior to participation in the ALSYMPCA trial, median overall survival was 14.4 months in radium-223-treated patients versus 11.3 months in placebo-treated patients (hazard ratio (HR) = 0.71 (95% confidence interval (CI) 0.56-0.89)); for patients who had not received prior docetaxel, median overall survival was 16.1 and 11.5 months, respectively (HR =0.74 (95% CI 0.56-0.99))(25).

The key secondary endpoint in the ALSYMPCA trial was time to symptomatic skeletal event (SSE), defined as the time to first use of external-beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fractures, spinal cord compression, or tumor-related orthopedic surgery. Imaging to assess for skeletal events was only performed when clinically indicated, to avoid registration of asymptomatic
fractures. Time to SSE was 15.6 months in radium-223-treated patients versus 9.8 months in the placebo-treated group (p < 0.001; HR = 0.66 (95% CI 0.52-0.83)) (25).

Time to initial opioid use and time to external beam radiotherapy were both increased in patients treated with radium-223 (HR = 0.670 and HR = 0.621, respectively) (27).

Sixteen and 24 weeks after initiation of radium-223 treatment, patients had significantly less pain compared to baseline (p < 0.001 and p = 0.001, respectively).

Further analysis revealed that an increase in the levels of total alkaline phosphatase was associated with an increased risk for death in the patient population studied in the ALSYMPCA trial (p < 0.0001) (28). In patients treated with radium-223, a 30% reduction in total alkaline phosphatase levels compared to the baseline was seen in 47% of patients versus 3% of placebo-treated patients (25).

In general, radium-223 was well tolerated by patients, with grade 3 or 4 adverse events occurring more frequently in the placebo-treated group (62%) than in patients treated with radium-223 (56%). The only reported non-hematologic grade ≥3 adverse events that occurred more frequently in the radium-223 treated patient group, were anorexia (2% versus 1%) and a decreased appetite (2 patients versus 0 patients). Comparing grade ≥3 hematologic adverse events in the radium-223-treated group to the placebo-group, anemia occurred in 13% and 13%, neutropenia in 3% and 1%, and thrombocytopenia in 6% and 2%, respectively (25). Analysis of these hematologic adverse events revealed that a baseline total alkaline phosphatase of ≥220 U/L strongly predicted anemia (29). Apart from the use of radium-223 instead of placebo, other baseline predictors for neutropenia and thrombocytopenia were prior docetaxel use.
and more than six bone metastases. On the other hand, prior external beam radiotherapy to the bone was associated with a decrease in anemia and neutropenia.

FDA approval

Interim results from the ALSYMPCA phase 3 clinical trial resulted in approval of radium-223 by the US FDA for the treatment of mCRPC patients who have symptomatic bone metastases and no visceral metastases. It was recommended to be administered at 50 kBq/kg every 4 weeks with a maximum of 6 doses, which is equal to the treatment regimen in the ALSYMPCA trial. This approval makes radium-223 the first agent available for mCRPC patients that significantly increases overall survival by exclusively treating bone metastases.

Despite its decision to approve radium-223, the FDA required four additional studies, besides final analysis of ALSYMPCA study results (30). Non-compliance to this decision, or negative results could result in the FDA revoking the approval.

As mentioned previously, no MTD for radium-223 has been established (21, 22). Phase 1 studies suggested concentrations higher than 50 kBq/kg could be administered to patients with relatively few changes in the toxicity profile of the agent. Two recent phase 2 studies confirm that treatment up to 100 kBq/kg have similar toxicities compared to radium-223 at 50 kBq/kg, while the efficacy of radium-223 is increased (31, 32). Therefore the FDA required a randomized phase 2 study to further assess the efficacy and safety of radium-223 in CRPC patients with bone metastases at concentrations higher than 50 kBq/kg. If these results suggest a beneficial risk-benefit
profile for higher doses, an additional phase 3 study is required to confirm the optimal
activity level.

The FDA required the company to perform three studies to further assess the safety of
radium-223: an observational study in 1200 CRPC patients with bone metastases,
evaluating the long-term safety of radium-223 administered at the recommended dose.
A randomized clinical trial in CRPC patients with bone metastases and no visceral
metastases to further assess the safety of radium-223 was required, particularly for
enhanced assessment of the effect of radium-223 on healthy bone marrow and
secondary malignancies, such as acute myeloid lymphoma (AML) and myelodysplastic
syndrome (MDS) (33). Finally, to assess the short- and long-term safety of an radium-
223 rechallenge, the company was required to perform a study re-treating CRPC
patients with bone metastases with radium-223.

Discussion

With the US FDA approval of radium-223 chloride for CRPC patients with symptomatic
bone metastases regardless of prior chemotherapy, the treatment scope for mCRPC
patients has further expanded. By excluding patients with visceral metastases, the most
rational step for oncologists would be to use radium-223 primarily as a first-line therapy
in mCRPC patients. This said, a subpopulation may also be eligible for radium-223
treatment as second-line therapy or later.

Considering the results of radium-223 treatment in the robustly designed and well
conducted ALSYMPCA trial, it is expected that the approval and consequently clinical
use of radium-223 will expand beyond the US in the near future. Additionally, radium-223 may improve the quality of life and survival for patients with other tumor types that suffer from bone metastases. However, such expansions require additional clinical investigations. Finally, with radium-223 being the first metastasis-targeting agent approved by the US FDA based on an improved median overall survival, it confirms that selectively treating metastases may be an effective strategy in patients with advanced solid tumors for whom palliative treatment is the only option, strengthening the development of such agents.

A major limitation of the ALSYMPCA phase 3 study is that the group of patients selected for this study may not correspond to the patient population in clinical practice that will receive radium-223 treatment. Patients with visceral metastases were excluded for participation in the trial. Considering that beta-emitting radionuclides, such as samarium-153, have shown to induce pain-relief in patients with advanced prostate cancer, further research is required to address whether radium-223 provides clinical benefit for patients with visceral metastases (16, 17). By approving radium-223, physicians may decide to administer this agent to this group of patients too, while its efficacy has not been proven. Furthermore, patients were excluded from the ALSYMPCA study when docetaxel was available, patients were fit for (and willing to receive) docetaxel-treatment and had not received docetaxel before. Nevertheless, the FDA does not exclude this group of patients for radium-223 treatment in its approval letter. Until the required post-marketing studies have been conducted which will indicate whether
mCRPC patients eligible for docetaxel-treatment will also benefit from radium-223, its clinical benefit in this patient group remains uncertain. Currently, no long-term follow-up is known of patients in the ALSYMPCA trial, limiting the toxicity profile of the drug. While the high number of therapeutic emissions in the decay process of radium-223 may yield a strong therapeutic effect, the daughter-nuclides, which do not have affinity to the bone, may diffuse throughout the body and cause damage in healthy tissue. Although no bone marrow suppression was seen in the short term, it will be important to follow patients over time to ensure that there are no long-term harmful effects from radium-223 treatment. Most of FDA’s post-marketing requirements therefore focus on drug safety, particularly on the long-term effects of radium-223 treatment and safety of radium-223 rechallenge at a later stage.
Reference List


(30) United States Food and Drug Administration [Internet]. Silver Spring, MD; c2013 [updated 2013 May 14; cited 2013 Aug 1].Summary review of Xofigo, application number: 203971Orig1s000. Available from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203971Orig1s000SumR.pdf.


Legend

**Figure 1.** Radioactive decay of radium-223. Radium-223 decays via seven daughter nuclides to lead-207, resulting in the emission of both alpha-particles (vertical step in diagram) and beta-particles (horizontal step in diagram). $T_\frac{1}{2}$, half-life.
Table

**Table 1.** Characteristics of radiopharmaceutical agents regularly used in clinic for the treatment of prostate cancer related bone metastases.

<table>
<thead>
<tr>
<th>Therapeutic isotope</th>
<th>Rhenium-186</th>
<th>Samarium-153</th>
<th>Strontium-89</th>
<th>Radium-223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (days)</td>
<td>3.8</td>
<td>1.9</td>
<td>50.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Administered agent</td>
<td>$^{186}$Re-HEDP</td>
<td>$^{153}$Sm-EDTMP</td>
<td>$^{89}$SrCl$_2$</td>
<td>$^{223}$RaCl$_2$</td>
</tr>
<tr>
<td>Binding inducing factor</td>
<td>Bisphosphonate ligand</td>
<td>Lexidronam ligand</td>
<td>Ca$^2+$ similarity of Sr$^2+$</td>
<td>Ca$^2+$ similarity of Ra$^2+$</td>
</tr>
<tr>
<td>Therapeutic irradiation</td>
<td>1 $\beta$-particle</td>
<td>1 $\beta$-particle</td>
<td>1 $\beta$-particle</td>
<td>4 $\alpha$-particles, 2 $\beta$-particles</td>
</tr>
<tr>
<td>Stable decay product</td>
<td>$^{186}$Os</td>
<td>$^{153}$Eu</td>
<td>$^{89}$Y</td>
<td>$^{207}$Pb</td>
</tr>
<tr>
<td>Standard dose</td>
<td>1295 MBq</td>
<td>37 MBq/kg</td>
<td>1.5-2.2 MBq/kg</td>
<td>50 kBq/kg</td>
</tr>
<tr>
<td>FDA approval based on</td>
<td>not approved</td>
<td>relief of bone pain</td>
<td>relief of bone pain</td>
<td>improved median overall survival</td>
</tr>
<tr>
<td>Targeted prostate cancer population</td>
<td>patients with painful skeletal metastases</td>
<td>patients with confirmed osteoblastic metastatic bone lesions</td>
<td>patients with painful skeletal metastases</td>
<td>CRPC patients with symptomatic bone metastases and no known visceral metastatic disease</td>
</tr>
</tbody>
</table>
219-Radon (gas)  
$T_{1/2} = 3.96$ s  
$100\% \alpha$-emitter

215-Polonium  
$T_{1/2} = 1.78$ ms  
$>99.99\% \alpha$-emitter  
$<0.001\% \beta$-emitter

211-Lead  
$T_{1/2} = 0.516$ s  
$100\% \beta$-emitter

207-Thallium  
$T_{1/2} = 4.77$ min  
$100\% \beta$-emitter  
(Stable-isotope)

211-Bismuth  
$T_{1/2} = 2.14$ min  
$99.73\% \alpha$-emitter  
$0.27\% \beta$-emitter

211-Polonium  
$T_{1/2} = 0.52$ s  
$100\% \alpha$-emitter

207-Lead  
(Stable-isotope)
Clinical Cancer Research

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Clin Cancer Res  Published OnlineFirst September 19, 2013.

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