CCR Perspectives in Drug Approval

Clinical Cancer Research

Radium Ra 223 Dichloride Injection: U.S. Food and Drug Administration Drug Approval Summary

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Abstract

On May 15, 2013, the U.S. Food and Drug Administration (FDA) approved radium Ra 223 dichloride (Ra-223; Xofigo injection; Bayer HealthCare Pharmaceuticals Inc.) for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. The FDA review was based on clinical trial BC1-06, which randomly allocated patients (2:1) to either Ra-223 plus best standard of care (BSoC) or placebo plus BSoC. The primary endpoint was overall survival (OS) with a key secondary endpoint of time to first symptomatic skeletal event (SSE). A statistically significant improvement in OS was demonstrated [HR, 0.70; 95% confidence interval, 0.55–0.88, $P = 0.0019$]. At the prespecified interim analysis, the median OS durations were 14.0 and 11.2 months in the Ra-223 and placebo arms, respectively. The improvement in OS was supported by a delay in time to first SSE favoring the Ra-223 arm. The most common (>10%) adverse reactions in patients receiving Ra-223 were nausea, diarrhea, vomiting, and peripheral edema. The most common (>10%) hematologic laboratory abnormalities were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Ra-223 is the first α-emitting radiotherapeutic and the first radiopharmaceutical to demonstrate an OS advantage in metastatic prostate cancer. *Clin Cancer Res; 20(1); 9–14. ©2013 AACR.*

Introduction

In the past decade, five systemic therapies have been approved for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) based on an overall survival (OS) benefit. These include hormonal therapies abiraterone acetate and enzalutamide (1–3), cytotoxic chemotherapies docetaxel and cabazitaxel (4–6), and the immunotherapy sipuleucel-T (7). In addition, bone-specific agents such as osteoclast inhibitors and bone-seeking radionucleotides can benefit patients in terms of delaying bone-related morbidity and reducing bone pain. Despite these advances, prostate cancer remains the second leading cause of cancer-related death in U.S. men (8).

Zoledronic acid and denosumab are agents that inhibit osteoclasts and were both approved on the basis of a reduction in the incidence of the composite endpoint, skeletal-related events (SRE). In these trials, an SRE was defined as the occurrence of bone fracture, spinal cord compression, surgery to bone, radiotherapy to bone, or (in the case of zoledronic acid) initiation of cancer therapy to treat bone pain (9, 10). Importantly, trials using the SRE endpoint for these approvals included not-for-cause routine bone imaging to screen for pathologic fractures without regard to symptoms. The inclusion of potentially asymptomatic fractures has been cited as a limitation to the strength of the traditional SRE definition (11).

Another method to deliver bone-specific therapy in prostate cancer is the use of intravenous radioisotopes. Strontium-89 and Samarium-153 are predominantly β-emitting radioisotopes that received U.S. Food and Drug Administration (FDA) approval for the relief of pain in patients with metastatic bone lesions based on reduction in pain scores using various pain measures (12, 13). Trials were not designed to adequately assess OS. Unlike the above radioisotopes, radium Ra 223 dichloride (Ra-223) is a novel first-in-class radiopharmaceutical that emits α particles (2 protons and 2 neutrons) able to transfer a higher linear energy (LET) to areas of increased bone turnover as occurs at or near sites of bone metastases. Although the high LET of Ra-223 provides for increased biologic activity and higher cell kill, the path length of α particles (<100 μm) is significantly shorter than that for β particles, theoretically limiting cellular damage to areas of normal bone marrow (14). The FDA review of Ra-223 is summarized in this report.

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Radiochemistry

The molecular formula of Ra-223 is $^{223}RaCl_2$ and the molecular weight is 293.9. Ra-223 has a physical half-life of 11.43 days and decays into a series of short-lived daughter isotopes (polonium-215, lead-211, bismuth-211, and thallium-207) that are in equilibrium with the parent and decay to stable lead-207. Ra-223 and its daughters emit α particles (95.3% of energy emitted), β particles (3.6% of energy emitted), and γ radiation (1.1% of energy emitted).

Xofigo injection is supplied as a preservative-free, sterile, isotonic, nonpyrogenic, clear aqueous parenteral solution contained in a single-use, clear glass vial for intravenous administration. Each milliliter of solution contains 1,000 kBq (27 microcuries) of Ra-223. This is the amount of radioactivity present on the label reference date because the actual strength decreases throughout the 28-day shelf life.

The dosing regimen of Xofigo is 50 kBq (1.35 microcurie) per kg body weight, given at 4-week intervals for six intravenous injections. Each dose should be corrected for the extent of radioactive decay of Ra-223 between the reference date printed on the vial label and the date of dosing. The dose of administered Xofigo is confirmed by measurement of emitted γ radiation using a radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST) traceable Ra-223 standard.

Pharmacology and toxicology

Ra-223, in its divalent cation form, is a calcium ion mimetic agent and forms complexes with hydroxyapatite in areas of increased bone turnover, such as metastases. The high energy transfer from α emission leads to double-strand DNA breaks in nearby cells. The inhibitory activity of Ra-223 was shown *in vitro*, and antitumor activity was demonstrated in animal models.

Toxicities observed in animal studies included decreased white blood cell, platelet, and red blood cell counts and compensatory effects of increased reticulocytes and extramedullary hematopoiesis in the spleen. Effects on bone (bone depletion/fibrosis associated with disorganized growth lines) and teeth (osteocyte depletion and changes in the bone socket of the teeth) were observed in rats, primarily in areas of active growth. Osteosarcomas, often with metastases, were seen 6 months after single or repeat-dose administration of Ra-223 in rats. A mammary carcinoma and a lymphoma were also observed in 1 rat each after repeat dosing.

No genetic toxicology or developmental and reproductive toxicology studies were conducted with Ra-223; however, the mechanism of action as an α particle-emitting radioactive therapeutic agent that becomes incorporated into sites of active bone turnover is sufficient to characterize Ra-223 as genotoxic and having the potential to cause embryo–fetal toxicity if administered to a pregnant female.

Clinical pharmacology

Ra-223 demonstrated a dose-proportional increase in exposure after single doses ranging from 46 to 250 kBq/kg and time-independent pharmacokinetics after multiple doses of 100 kBq/kg. Ra-223 was rapidly cleared from the blood and distributed to bone and intestine. At 4 hours postinjection, approximately 4%, 61%, and 49% of the injected radioactivity was found in blood, bone, and intestine, respectively. Approximately 63% of the administered radioactivity was excreted from the body within 7 days, primarily via the fecal route. Dosimetry data suggested that bone, bone marrow, and the intestinal wall had the highest absorbed radiation doses. Ra-223 was not metabolized, and there was no evidence of hepatobiliary excretion based on imaging data.

No dose adjustment is needed for patients with mild hepatic impairment or patients with mild to moderate renal impairment. Data are insufficient to provide dose recommendations for patients with moderate to severe hepatic impairment or severe renal impairment. No large changes in mean QTc intervals (i.e., >20 ms) were detected up to 6 hours after a single Xofigo dose of 50 kBq/kg.

Study BC1-06

Study design

The BC1-06 trial was a placebo-controlled, double-blind, international phase III clinical trial that enrolled 921 patients with progressive symptomatic CRPC, at least two bone metastases, and no visceral metastatic disease. At the time of the interim analysis, 809 patients were enrolled. Patients were randomly allocated (2:1) to receive six monthly injections of Ra-223 at 50 kBq/kg body weight plus best standard of care (BSoC) or an intravenous saline placebo plus BSoC. BSoC could include external beam radiotherapy (EBRT), corticosteroids, antiandrogens, estrogens, estramustine, or ketoconazole. Randomization was stratified by total alkaline phosphatase (ALP; <220 U/L vs. ≥ 220 U/L), use of bisphosphonates (yes vs. no), and prior use of docetaxel (yes vs. no). Patients were required to be symptomatic as defined by regular use of analgesic medications for cancer-related pain (including nonopiate analgesics) or treatment with EBRT within the last 12 weeks before randomization. Patients could not have been previously treated with hemi-body EBRT or systemic radiopharmaceuticals (e.g., strontium-89 and samarium-154). Patients with visceral metastases or malignant lymphadenopathy exceeding 3 cm in short-axis diameter were excluded.

An independent data monitoring committee was used to monitor safety and evaluate the efficacy and safety results at the time of the protocol-specified interim analysis.

Study endpoints

The primary efficacy endpoint was overall survival (OS), defined as the time from randomization to death from any cause. Prespecified key secondary efficacy endpoints included (i) time to ALP progression, (ii) total ALP response, (iii) time to occurrence of first symptomatic skeletal event (SSE), (iv) total ALP normalization, and (v) time to prostate-specific antigen (PSA) progression. An SSE was defined as the occurrence of EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord

Table 1. Disease characteristics

	Ra-223 ($N = 541$)	Placebo ($N = 268$)
Disease characteristics at initial prostate cancer diagnosis		
Gleason score		
≤6	90 (19%)	27 (12%)
7	159 (34%)	76 (32%)
8–10	223 (47%)	132 (56%)
Lymph nodes at diagnosis (N1)	45 (12%)	25 (13%)
Metastases at diagnosis (M1)	139 (37%)	97 (49%)
Disease characteristics at study baseline		
Median PSA (μg/L)	159	195
Baseline bone scan findings		
<6 bone metastases	88 (16%)	33 (12%)
6–20 bone metastases	235 (44%)	129 (48%)
>20 but not superscan	169 (31%)	80 (30%)
Superscan	48 (9%)	26 (10%)

NOTE: Percentages are based on the number of patients with nonmissing data. The amount of missing data was balanced between the arms.

compression, or a tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments. Patient-reported pain data were not captured in a rigorous fashion.

Statistical plan

The two-sided overall significance level for OS was 0.05. The planned sample size was 900 patients with 640 expected death events. A single interim analysis of OS was to be performed when 50% of the total events had occurred (320 deaths). To maintain an overall significance level of 0.05, a Lan-DeMets α-spending approach based on the O'Brien-Fleming α spending function was implemented. The overall type I error rate for five key secondary endpoints was controlled using a gatekeeping procedure at a two-sided 0.05 significance level.

The intent-to-treat (ITT) population of all randomized patients, regardless of the actual treatment received, was used for all efficacy analyses. Time-to-event endpoints (OS and time to first SSE) were compared between treatment groups using a stratified log-rank test, and the treatment effect (HR) was estimated using a stratified Cox proportional hazards model. In the analysis of time to first SSE, patients who died before experiencing an SSE were censored at their last disease assessment.

Patient baseline characteristics

For the primary analysis, 809 patients were randomized from study centers located in 19 countries. Only 1.2% of these patients were from the United States, with the United Kingdom (28%), Norway (16%), and Sweden (10%) accruing the most patients. Baseline patient characteristics were well balanced between the treatment arms. Patients were predominantly Caucasian (94%) with a median age of 71. Eastern Cooperative Oncology Group (ECOG) performance status was ≤1 in 86% of patients. Of note, 41% of patients reported current use of bisphosphonates and 58% reported prior docetaxel chemotherapy. The median PSA at baseline was 195 and 159 μg/L for the placebo and Ra-223 arms, respectively. There were more patients on the placebo arm with metastatic disease at diagnosis and a higher Gleason grade (Table 1).

Efficacy Results

At the interim analysis of OS ($N = 809$), there was a statistically significant improvement favoring the Ra-223 arm with an HR of 0.70 [95% confidence interval (CI), 0.55–0.88; $P = 0.0019$]. The Kaplan–Meier estimate of median OS was 14.0 and 11.2 months in the Ra-223 and placebo arms, respectively. An exploratory updated analysis of OS performed on the final number of randomized subjects ($N = 921$) supported the favorable OS finding (Table 2 and Fig. 1). The use of BSoC treatments while on study was balanced between the arms with the exception of antiandrogens (38% vs. 26% of placebo and Ra-223 patients, respectively). There were no substantial imbalances in subsequent anticancer therapies that would have favored the Ra-223 arm. Improvements in survival were seen across all prespecified subgroups with the exception of the small subgroup ($N = 50$) of non-Caucasian ethnicity (HR, 1.72; 95% CI, 0.35–8.5). Both the docetaxel-naïve (HR, 0.61; 95% CI, 0.42–0.88) and docetaxel-pretreated subgroups (HR, 0.76; 95% CI, 0.57–1.0) seemed to benefit from Ra-223 treatment. Multiple sensitivity analyses conducted by the FDA supported the OS results, including univariate and multivariate analyses adjusting for imbalances in disease characteristics, including Gleason grade,

Table 2. OS results (ITT population)

	Ra-223		Placebo
Interim (primary) analysis			
Subjects randomized	541		268
Death	191 (35.3%)		123 (45.9%)
Censored	350 (64.7%)		145 (54.1%)
Median OS in months (95% CI)	14.0 (12.1–15.8)		11.2 (9.0–13.2)
P value[a]		0.00185[c]	
HR (95% CI)[b]		0.70 (0.55–0.88)	
Updated analysis			
Subjects randomized	614		307
Death	333 (54.2%)		195 (63.5%)
Censored	281 (45.8%)		112 (36.5%)
Median OS in months (95% CI)	14.9 (13.9–16.1)		11.3 (10.4–12.8)
HR (95% CI)[b]		0.70 (0.58–0.83)	

[a]*P* value obtained by a stratified log-rank test.
[b]Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. HR < 1 favors Ra-223 dichloride.
[c]O'Brien-Fleming threshold was 0.0027.

M1 disease at initial diagnosis, and baseline PSA. Exploratory FDA analyses suggested that higher total body weight (i.e., higher total dose) was associated with improved OS.

The Kaplan–Meier estimates of median time to first SSE were 13.5 and 8.4 months in the Ra-223 and placebo arms, respectively (HR, 0.61; 95% CI, 0.46–0.81; $P < 0.0005$). The majority (79%) of SSEs were EBRT to painful skeletal metastases. There were 208 patients (26%) who died before a documented SSE, leading to a high degree of informative censoring. A sensitivity analysis was performed including

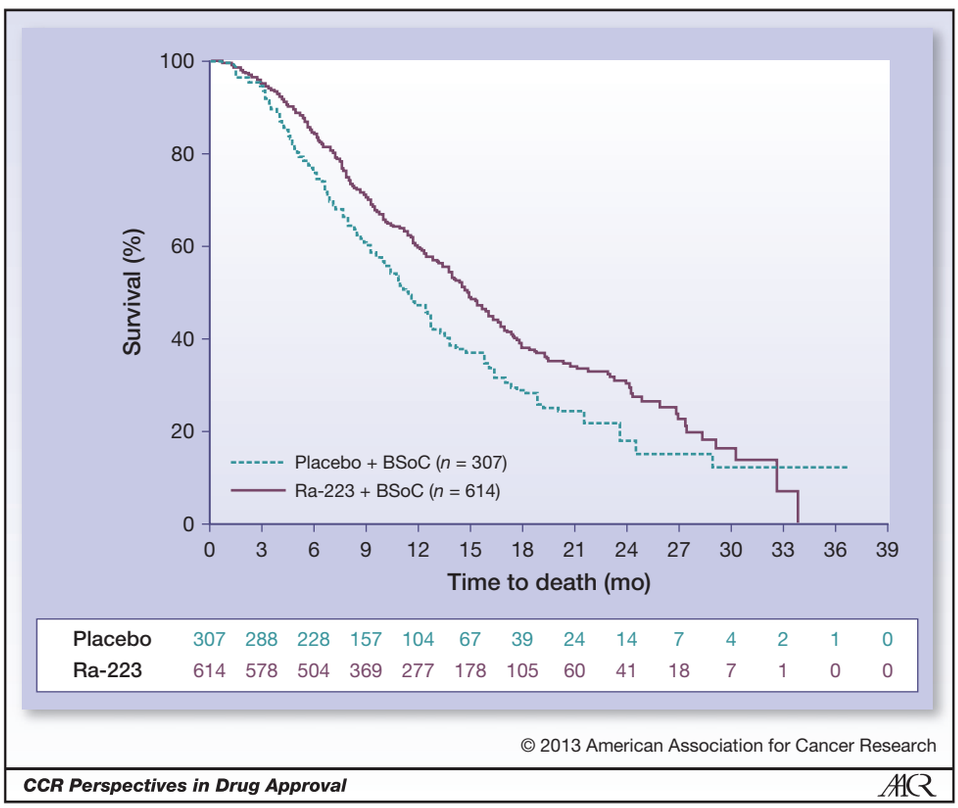

Figure 1. Kaplan–Meier OS curves (updated analysis), ITT population.

Table 3. Common adverse reactions and hematologic laboratory abnormalities

	Ra-223 $N = 600$		Placebo $N = 301$	
	Grade 1–4 (%)	Grade 3–4 (%)	Grade 1–4 (%)	Grade 3–4 (%)
Adverse drug reactions (Safety population)[a]				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
Peripheral edema	13	2	10	1
Hematologic laboratory abnormalities (Safety population)[b]				
Anemia (Hgb)	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia (WBC)	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia (ANC)	18	2	5	<1

[a]Adverse reactions occurring in ≥10% of patients and occurring at a higher incidence in the Ra-223 arm.
[b]Laboratory abnormalities occurring in ≥10% of patients and occurring at a higher incidence in the Ra-223 arm. Laboratory evaluation was conducted at baseline and before each 4-week cycle.

death as an event (SSE-free survival), verifying a benefit in favor of Ra-223 with an HR of 0.66 (95% CI, 0.54–0.80). The estimated median SSE-free survival (SSE-FS) was 8.2 months for Ra-223 compared with 6.1 months in the placebo arm. There were no substantial imbalances in the use of bisphosphonates between the arms.

Results from secondary endpoints associated with PSA and ALP met statistical significance in favor of Ra-223. The magnitude of delay in time to PSA progression was less robust than the ALP findings. The data from these serum biomarkers were felt to be less clinically relevant and were not included in the final product label.

Safety Results

The safety population consisted of 600 patients receiving at least one dose of 50 kBq/kg of Ra-223 plus BSoC and 301 patients receiving placebo plus BSoC. The median durations of treatment were 20 weeks (6 cycles) and 18 weeks (5 cycles) for Ra-223 and placebo, respectively. Key safety results are presented in Table 3. The most common adverse reactions (≥10%) in patients receiving Ra-223 were nausea, diarrhea, vomiting, and peripheral edema. Grade 3 and 4 adverse events were reported among 57% of Ra-223–treated patients and 63% of placebo-treated patients. Laboratory measurements were collected monthly, but were not obtained at the time of expected nadir (2–3 weeks after dosing) observed in a phase I study (15). The most common hematologic laboratory abnormalities in Ra-223–treated patients (≥10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

As an adverse reaction, grade 3–4 thrombocytopenia was reported in 6% of patients on the Ra-223 arm and in 2% of patients on placebo. Two percent of the patients on the Ra-223 arm experienced bone marrow failure or ongoing pancytopenia compared with no patients treated with placebo. Both dehydration and renal failure/impairment occurred in 3% and 1% of patients receiving Ra-223 and placebo, respectively. Erythema, pain, and edema at the injection site were reported in 1% of patients on Ra-223.

On the basis of its mechanism of action and the occurrence of neoplasms in rats, Ra-223 may increase the risk of osteosarcoma or other secondary malignancies. However, the overall incidence of new malignancies in BC1-06 was lower on the Ra-223 arm than on placebo (<1% vs. 2%, respectively). Importantly, the expected latency period for the development of secondary malignancies exceeds the duration of follow-up for patients on this trial. The safety and efficacy of concomitant chemotherapy with Ra-223 have not been established. Adequate safety monitoring and laboratory testing were not performed to assess how patients treated with Ra-223 will tolerate subsequent cytotoxic chemotherapy.

Discussion

Full approval was granted for Ra-223 on the basis of the demonstration of a clinically and statistically significant improvement in OS in the setting of an acceptable safety profile. Because of its mechanism of action and the exclusion of patients with visceral metastatic disease from the clinical trial, the approved indication for Ra-223 is limited to the treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease. Given CBCs were not assessed at the expected nadir period (2–3 weeks), the degree of bone marrow toxicity may be underreported. In addition, the risks of long-term bone marrow suppression and secondary malignancies prompted several postmarketing requirements for additional data. The FDA clinical pharmacology reviewer conducted an exploratory

analysis of OS by weight quartiles adjusted by total ALP, current use of bisphosphonates, prior use of docetaxel, and baseline ECOG grade, which revealed reduced efficacy in the lowest weight quartile. Because the incidence of grade $\geq$3 adverse events was similar across body weights ranging from 40 to 139 kg and no maximum tolerated dose was determined after single doses up to 250 kBq/kg in the phase I dose-escalation trial, a postmarketing commitment was requested to further optimize the dosing of Ra-223.

The BC1-06 trial did not obtain routine radiographs or bone scans and, therefore, pathologic fractures were likely to be identified by a radiographic evaluation triggered by symptoms. This more symptom-driven method for detection of pathologic fractures led the FDA review team to term the endpoint "symptomatic skeletal event (SSE)" to differentiate this definition from prior SRE results. Although symptomatic fractures are considered more clinically meaningful, the lower number of fractures contributing to the SSE endpoint in BC1-06 resulted in an endpoint driven more by EBRT events. The decision to use EBRT or obtain further imaging is based on investigator discretion, which is subject to bias. If one wishes to use time to SSE or SSE-FS as an endpoint in future trials, particularly those in which routine imaging may be required to evaluate radiographic progression, data will be necessary to support that fractures and EBRT use are indeed related to bone pain. Support may be in the form of correlating these events with well-developed and carefully collected patient-reported pain assessments and analgesic use.

In summary, the FDA review confirmed a clinically and statistically significant improvement in OS. A delay in the time to first SSE for Ra-223 when compared with placebo was also seen. Future trials in CRPC using SSE as an endpoint should mitigate the potential for bias and take into account informative censoring due to deaths.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: P.G. Kluetz, W. Pierce
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W. Pierce
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