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CLINICAL TRIAL

A phase IIa, nonrandomized study of radium-223 dichloride in advanced breast cancer patients with bone-dominant disease

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Abstract Radium-223 dichloride (radium-223) mimics calcium and emits high-energy, short-range alpha-particles resulting in an antitumor effect on bone metastases. This open-label, phase IIa nonrandomized study investigated safety and short-term efficacy of radium-223 in breast cancer patients with bone-dominant disease. Twenty-three advanced breast cancer patients with progressive bone-dominant disease, and no longer candidates for further endocrine therapy, were to receive radium-223 (50 kBq/kg IV) every 4 weeks for 4 cycles. The coprimary end points were change in urinary N-telopeptide of type 1 (uNTX-1) and serum bone alkaline phosphatase (bALP) after 16 weeks of treatment. Exploratory end points included sequential ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (FDG PET/CT) to assess metabolic changes in osteoblastic bone metastases. Safety data were collected for all patients. Radium-223 significantly reduced uNTX-1 and bALP from baseline to end of treatment. Median uNTX-1 change was −10.1 nmol bone collagen equivalents/mmol creatinine (−32.8 %; $P = 0.0124$); median bALP change was −16.7 ng/mL (−42.0 %; $P = 0.0045$). Twenty of twenty-three patients had FDG PET/CT identifying 155 hypermetabolic osteoblastic bone lesions at baseline: 50 lesions showed metabolic decrease (≥25 % reduction of maximum standardized uptake value from baseline) after 2 radium-223 injections [32.3 % metabolic response rate (mRR) at week 9], persisting after the treatment period (41.5 % mRR at week 17). Radium-223 was safe and well tolerated. Radium-223 targets areas of increased bone metabolism and shows biological activity in advanced breast cancer patients with bone-dominant disease.

Keywords Breast cancer · Bone metastases · Alpha-emitter · Radiopharmaceutical · Radium-223 dichloride · Radiation therapy

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Introduction

Up to 80 % of patients with metastatic breast cancer develop bone metastases, which often cause significant morbidity and/or skeletal complications such as bone pain, pathologic fracture, spinal cord or nerve root compression, and hypercalcemia [1, 2]. Current bone-targeted therapies reduce skeletal morbidity but have little effect on survival in the advanced cancer setting, and many of the approved anticancer treatments are associated with substantial side effects [3]. Thus, there remains a need for treatment to further reduce skeletal complications, improve quality of life, and ultimately extend survival in breast cancer patients with bone metastases.

Radium-223 dichloride (radium-223) is an alpha-emitting pharmaceutical that is Food and Drug Administration (FDA) approved for the treatment of patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases [4]. Radium-223 is a calcium mimetic that preferentially targets bone metastases with high-energy alpha-particles of short range (<100 μm), resulting in double-strand DNA breaks and highly localized cytotoxic effects with minimal myelosuppression [5–9]. Potent antitumor effects of radium-223 seen in animal models led to the evaluation of its efficacy and safety in clinical trials in patients with bone-metastatic prostate cancer [6, 8, 10–13]. These studies demonstrated promising responses in palliation of bone pain, positive effects on changes in bone alkaline phosphatase (bALP) and prostate-specific antigen (PSA) levels, and improved survival with limited toxicity. A phase III study of radium-223 in 921 patients with CRPC and symptomatic bone metastases showed that radium-223, compared with placebo, significantly improved median overall survival by 3.6 months [hazard ratio (HR) = 0.70; 95 % confidence interval (CI) 0.58–0.83; $P < 0.001$], significantly delayed the time to first symptomatic skeletal event (HR = 0.66; 95 % CI 0.52–0.83; $P < 0.001$), and had a positive impact on quality of life [14]. A recent preclinical study showed that radium-223, alone or in combination with doxorubicin or zoledronic acid, increased survival and reduced serum bone biomarkers in a mouse model of breast cancer bone metastasis [15].

The mechanism of action and efficacy of radium-223 in preclinical studies and in clinical trials in patients with bone-metastatic prostate cancer suggests that the agent may be effective in other cancers that have a propensity to metastasize to the bone. Breast cancer patients with bone-dominant metastatic disease who are no longer benefiting from hormone therapy are typically treated with systemic chemotherapy. However, a targeted therapy such as radium-223, with an expectation of fewer systemic adverse effects, may be an effective alternative or complementary treatment for these patients.

This open-label, phase IIa nonrandomized study was performed to investigate whether radium-223 has evidence of potentially clinically relevant effects on bone and tumor metabolism in breast cancer patients with bone-dominant disease.

Methods

Patients

Eligible patients had histologically confirmed primary breast cancer with radiologically confirmed bone-dominant disease with or without metastases in soft tissue, lymph nodes, and/or skin, with ≥1 nonirradiated bone metastasis on bone scintigraphy [planar imaging with or without single-photon emission computed tomography (SPECT) with or without computed tomography (CT)] within 12 weeks prior to first study drug administration; had progressed on endocrine therapy (confirmed by imaging and/or other clinically relevant information) and were no longer considered suitable for endocrine therapy; and were on stable bisphosphonate therapy for at least 3 months prior to treatment with no change to that therapy expected during treatment, or were not receiving or planning to receive bisphosphonates during the study period. Additional eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 and adequate hematologic, renal, and liver function.

Patients were excluded if they had unequivocal visceral metastases requiring chemotherapy treatment in the next 6 months, based on investigator's judgment, or had other serious illness. Brain metastases were permitted only if well-controlled and not associated with symptoms. Additional exclusion criteria were treatment with an investigational drug, chemotherapy, immunotherapy, or external beam radiation therapy (EBRT) in the previous 4 weeks. All patients provided written informed consent.

Study design and treatment

In this open-label, phase IIa nonrandomized study, patients were to receive an intravenous injection of radium-223 at a fixed dose of 50 kBq/kg body weight administered as a slow bolus over 1 min every 4 weeks. The treatment period extended from the first administration of study drug (week 1) to 4 weeks after the last administration of study drug (week 17) (Fig. 1). Patients who were receiving bisphosphonates prior to study entry continued on their current type, dose, and schedule of treatment.

The coprimary end points were levels of urinary N-telopeptide of type 1 (uNTX-1), given as a ratio to urinary creatinine, and serum bALP. Main secondary end points

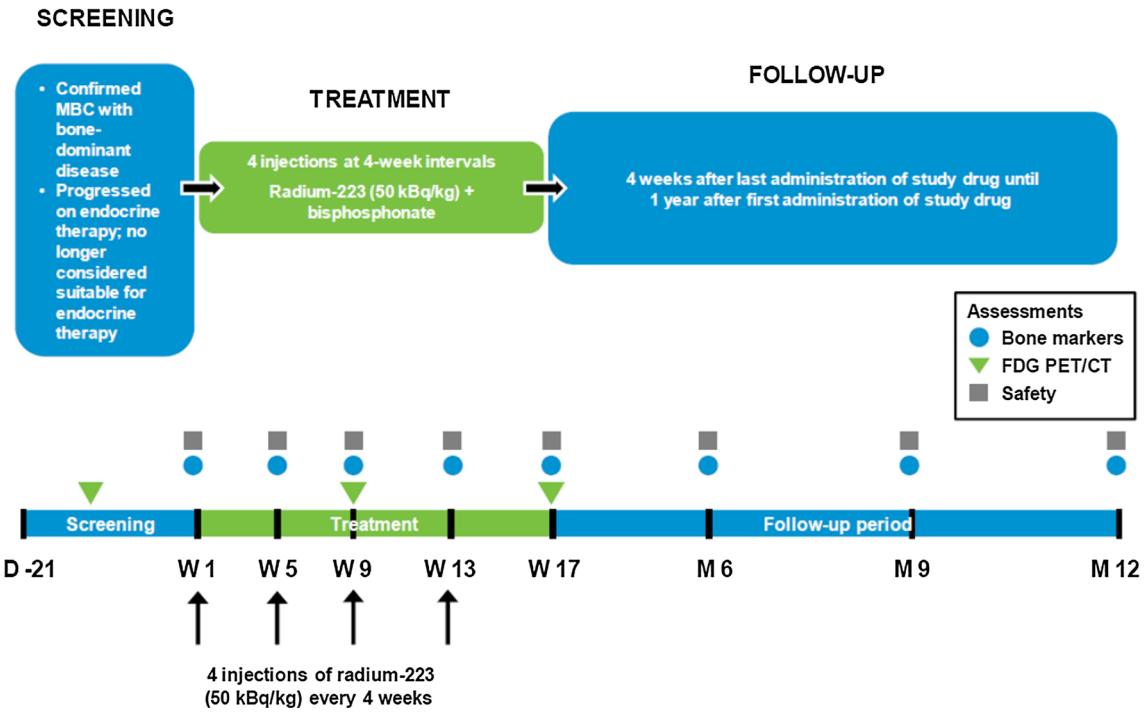

Fig. 1 Study design. *D* day, *FDG PET/CT* ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography, *M* month, *MBC* metastatic breast cancer, *W* week

included changes in other biochemical markers of bone turnover, including urinary levels of C-telopeptide of type 1 (uCTX-1) given as a ratio to creatinine, serum N-terminal propeptide of type 1 (P1NP), and serum pyridinoline cross-linked carboxyterminal telopeptide (ICTP). Pain as assessed by the Brief Pain Inventory (BPI) was an additional secondary end point.

An exploratory end point was the metabolic effect of radium-223 on osteoblastic bone metastases, assessed by positron emission tomography combined with CT (PET/CT) using ^{18}F-fluorodeoxyglucose (FDG). FDG uptake was quantified by calculating the standardized uptake value corrected for body weight (SUV) on the highest image pixel in the target lesion (SUV_{max}). A core imaging laboratory provided each site with a manual describing the standard procedures for patient preparation, imaging acquisition and protocol schedule, data collection, archiving, and transfer of all study-specific PET/CT scans. The assessment of FDG PET/CT was centralized and performed at the Molecular Imaging Core Laboratory, Department of Nuclear Medicine, Jules Bordet Institute, Brussels, Belgium.

The study was approved by the institutional review board at each participating center; ethics were in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation.

Assessments

Screening assessments included planar bone scintigraphy and, when available, SPECT with or without CT to document progressive bone metastasis within 12 weeks prior to first study drug administration. Chest–abdominal pelvic CT, magnetic resonance imaging (MRI), or FDG PET/CT, when available, were performed to document the presence of unequivocal visceral metastases within 4 weeks prior to first study drug administration.

Efficacy assessments included bone marker measurements at baseline; immediately prior to the second, third, and fourth study drug administrations; 4 weeks after last study drug administration; and at each follow-up visit. Pain severity and pain interference with functions were assessed using the BPI short-form questionnaire, completed by the patient before each study drug administration, at the end of treatment period, and at 6-, 9-, and 12-month follow-up visits.

FDG PET/CT was performed at baseline (within 14 days prior to enrollment), at week 9 (before the third radium-223 administration), and at treatment discontinuation (week 17). A maximum of 12 target bone lesions per patient (2 lesions per skull, thoracic cage, pelvis, and limbs, and 4 lesions in the spine) were identified on baseline PET/CT. Target lesions were defined as (1) osteoblastic on correlative bone scintigraphy, (2) >15 mm in transversal

diameter, and (3) hypermetabolic, with an SUV_{max} more than twice the normal liver uptake. Each lesion was classified as having a metabolic response (≥25 % decrease of SUV_{max} from baseline), stable disease (SD, ≤25 % decrease and <25 % increase of SUV_{max} from baseline), or progressive disease (PD, ≥25 % increase of SUV_{max} from baseline).

Safety end points, assessed at all study visits, included monitoring of adverse events (AEs), concomitant medications and treatments, hematology and clinical chemistries, and physical examination including ECOG PS and vital signs. During follow-up, treatment-related AEs, progression of disease, long-term toxicity, and other cancer-related treatments were assessed.

Statistical analysis

All analyses were performed on the intention-to-treat (ITT) analysis population, consisting of all patients who received at least one administration of radium-223. Statistical programming and analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA). Demographic and baseline characteristics are presented as means [standard deviation (SD)], medians (minimum, maximum), or frequencies (percentage) as appropriate. Changes from baseline of bone marker end points are summarized as median (q1, q3), and statistically analyzed using the Wilcoxon signed-rank test. Pain scores are presented as model-based mean values for change from baseline, 95 % CIs, and corresponding *P* values, based on repeated measures analysis of variance (ANOVA). Given the exploratory character of the study, no formal sample size calculation was performed, and no adjustment for multiplicity has been performed.

Results

Patients and treatment

Twenty-three patients were enrolled from 4 study centers in Europe and included in the ITT and safety populations. Patient demographics and baseline characteristics are shown in Table 1. All patients had received prior or concomitant treatment for breast cancer with bisphosphonates; many had also received hormone therapy or a luteinizing hormone–releasing hormone agonist (22 patients, 96 %), palliative radiotherapy (17 patients, 74 %) or chemotherapy (15 patients, 65 %). A deviation was recorded for one patient who had not received hormone therapy. Smaller numbers of patients had received other types of treatment. On study entry, almost all (22 patients, 96 %) were treated with a bisphosphonate. Eligible patients were scheduled to receive 4 doses of radium-223 at a fixed dose of 50 kBq/kg body weight at intervals of 4 weeks. No dose delay occurred. Fifteen patients (65 %) received all 4 radium-223 injections, 4 patients (17 %) received 3 injections, and 4

Table 1 Patient demographics and baseline characteristics

Parameter	Radium-223, $n = 23$
Age, mean (SD), years	60 (10)
Histologic type, *n* (%)	
Ductal carcinoma	14 (61)
Lobular carcinoma	7 (30)
Other	2 (9)
Baseline ECOG score, *n* (%)	
0	11 (48)
1	12 (52)
Time since initial diagnosis, mean (SD), years	10 (7)
Time from initial identification of bone metastases, mean (SD), years	4 (3)
Extent of metastatic disease, *n* (%)	
<6 metastases	2 (9)
6–20 metastases	5 (22)
>20 metastases/superscan	16 (69)
Urinary N-telopeptide of type 1 corrected by creatinine (uNTX-1/creatinine, nmol BCE/mmol creatinine), *n* (%)	
<20 nmol BCE/mmol creatinine	7 (30)
20–50 nmol BCE/mmol creatinine	11(48)
>50 nmol BCE/mmol creatinine	5 (22)
Previous treatment for metastatic disease, *n* (%)	
Bisphosphonate	23 (100)
Hormone therapy or LHRH agonist	22 (96)
Adjuvant only	1
1 line	2
2 lines	6
3 lines	6
>3 lines	5
Chemotherapy	15 (65)
Palliative radiotherapy	17 (74)
Orthopedic surgery	4 (17)
Bisphosphonates; ongoing treatment at screening, *n* (%)	22 (96 %)
Exposure to radium-223, *n* (%)	15 (65)
4 injections	4 (17)
3 injections	4 (17)
2 injections	
Patients with baseline osteoblastic target lesions on FDG PET/CT, *n* (%)	20 (87)[a]

BCE Bone collagen equivalents, *ECOG* Eastern Cooperative Oncology Group, *FDG PET/CT* ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography, *LHRH* luteinizing hormone–releasing hormone, *SD* standard deviation

[a] Three patients did not have FDG PET/CT

patients (17 %) received 2 injections. Reasons for not receiving all 4 radium-223 injections included disease progression (6 patients), death (1 patient died of heart failure unrelated to radium-223), and distance to travel (1 patient). FDG PET/CT was performed in 20 of 23 (87 %) patients. All patients were included in safety and efficacy analyses.

Efficacy

Radium-223 consistently reduced uNTX-1 and serum bALP levels during the 16-week treatment period (Fig. 2). The overall pattern for uNTX-1 level was a general reduction over the treatment period, with some increase thereafter, and the mean or median returning essentially to baseline by the 12-month time point. The median change in uNTX-1 from baseline was −4.1 [interquartile range (IQR): −17.0 to 1.7] nmol bone collagen equivalents (BCE)/mmol creatinine (−19.9 %; $P = 0.0218$) at week 9 ($n = 23$) and −10.1 (IQR: −27.9 to −0.8) nmol BCE/mmol creatinine (−32.8 %; $P = 0.0124$) at end of treatment (week 17, $n = 16$). Prespecified subgroup analyses indicated that, in general, those with the highest baseline values had a greater median percentage decrease (<20 nmol BCE/mmol creatinine, −5 %; 20–50 nmol BCE/mmol creatinine, −28 %; >50 nmol BCE/mmol creatinine, −58 %). At the end of study treatment (week 17), 5 patients (22 %) had a ≥50 % and 4 patients (17 %) had a ≥30 to <50 % decrease in uNTX-1 from baseline.

Changes in serum bALP showed a pattern similar to that for uNTX-1. The median change in bALP from baseline was −3.4 (IQR: −16.0 to −1.2) ng/mL (−32.8 %; $P = 0.0001$) at week 9 ($n = 22$) and −13.9 (IQR: −20.5 to −4.2) ng/mL (−42.0 %; $P = 0.0027$) at week 17 ($n = 16$). The greatest decrease in bALP was observed at the end of treatment, week 17, when 8 patients (35 %) had a ≥50 %, and 4 patients (17 %) had a ≥30 to <50 % reduction from baseline.

In general, changes in the other bone markers, uCTX-1 and serum P1NP, showed a pattern similar to that for changes in uNTX-1 and serum bALP. Serum ICTP showed no consistent pattern of change during the study (Table 2).

Of 23 patients, 20 had FDG PET/CT that identified 155 hypermetabolic osteoblastic bone target lesions at baseline. Of 155 bone target lesions, 50 showed ≥25 % reduction of

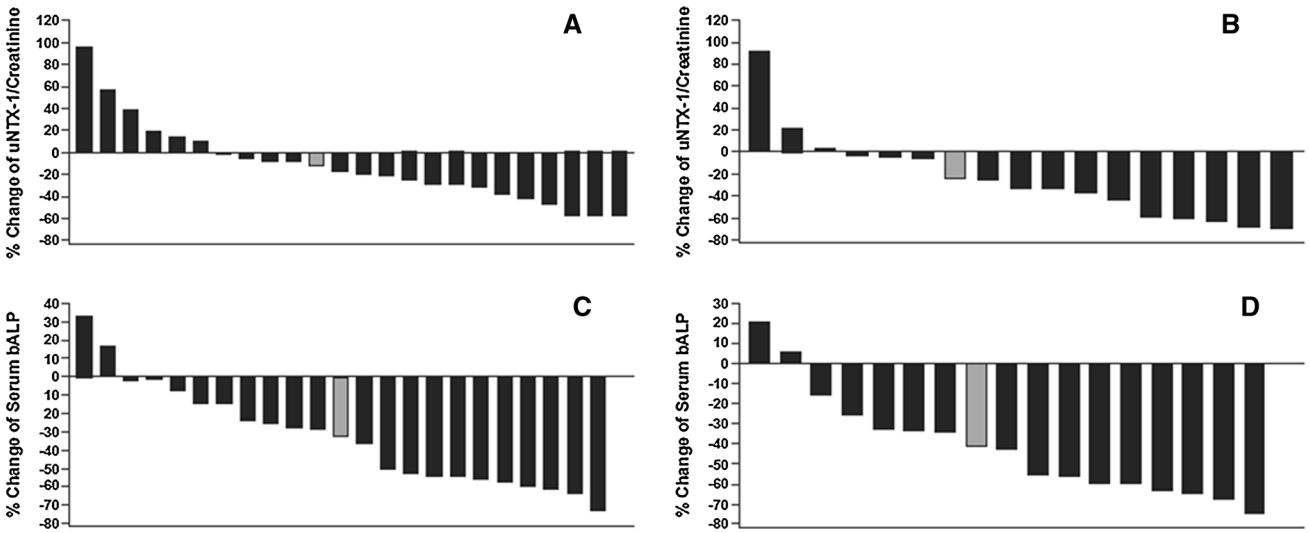

Fig. 2 Waterfall plots of percentage change from baseline for uNTX-1 corrected by creatinine (nmol BCE/nmol creatinine) at weeks 9 (**a**) and 17 (**b**); and for serum bone alkaline phosphatase (bALP) (ng/mL) at weeks 9 (**c**) and 17 (**d**). *Gray bars* represent mean values

Table 2 uCTX-1, serum P1NP, and serum ICTP median change from baseline

Parameter	Radium-223 ($n = 23$)			
	Visit	n	Median change from baseline	P value
uCTX-1 corrected by creatinine, nmol BCE/mmol creatinine	Week 9	23	−20.0 (IQR: −80.0 to 6.0)	0.0606
	Week 17	16	−29.0 (IQR: −70.5 to −4.0)	0.0124
P1NP	Week 9	22	−7.82 (IQR: −26.9 to −0.90)	0.0105
	Week 17	16	−38.80 (IQR: −57.4 to −7.29)	0.0124
ICTP	Week 9	21	−0.99 (IQR: −2.49 to 1.57)	0.5127
	Week 17	16	−1.42 (IQR: −3.99 to 1.42)	0.3173

ICTP serum pyridinoline cross-linked carboxyterminal telopeptide, *IQR* interquartile range, *P1NP* serum N-terminal propeptide of type 1, *uCTX-1* urinary C-telopeptide of type 1

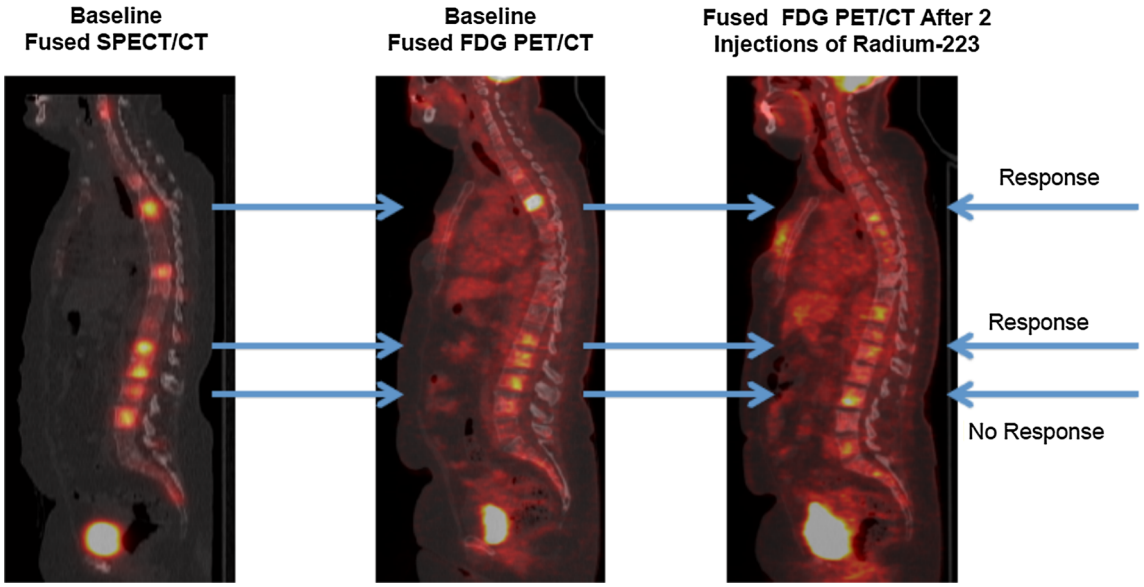

Fig. 3 *Left* Baseline co-registered technetium-99m methylene diphosphonate bone single-photon emission computed tomography scintigraphy and computed tomography (^{99m}Tc-MDP SPECT/CT) of a single patient showing multiple osteoblastic metastases in the vertebral column. *Middle* Baseline, co-registered FDG PET/CT image showing focal increase in metabolic activity of the osteoblastic metastases. *Right* FDG PET/CT image of the same patient after two injections of radium-2233

SUV_{max} from baseline after 2 treatments of radium-223 [32.3 % metabolic response rate (mRR) at week 9] that persisted after 4 treatments (41.5 % mRR at week 17). Most of the analyzed lesions showed SD; many decreased in intensity, but with less than 25 % reduction of SUV_{max} from baseline. Figure 3 shows images from a single patient obtained at baseline and after 2 injections of radium-223. After treatment, there was a decrease in the FDG uptake intensity in multiple bone metastases in the thoracic and lumbar spine, with the exception of 1 lesion in L3, suggesting a degree of within-patient response heterogeneity.

Pain

The median observed change in BPI pain severity index mean across all time points showed a consistent reduction (−0.25 to −1.25, −9.5 to −45.6 %). The model-based mean change from baseline in the BPI pain severity index at week 17 was −0.63 (95 % CI −1.44 to 0.19; $P = 0.24$), and the BPI functional interference index mean change from baseline at week 17 was −1.01 (95 % CI −1.83 to −0.20; $P = 0.0310$).

Safety

Of 151 AEs, 81 were considered to be possibly or probably treatment-related and were reported in 20 patients (87 %); most were mild and reversible [Common Terminology Criteria for Adverse Events (CTCAE) ≥grade 3 in only 5 patients]. AEs that occurred in at least 2 patients are shown in Table 3. In addition, two grade 3 hematologic events were reported: 1 patient with anemia and 1 patient with neutropenia. The most frequently reported AEs were

Table 3 Adverse events that occurred in at least 2 patients

Adverse event	Radium-223 ($n = 23$)	
	All grades, *n* (%)	Grades 3/4, *n* (%)
Nausea	10 (43)	1 (4)
Diarrhea	8 (35)	0 (0)
Anorexia	3 (13)	3 (13)
Vomiting	6 (26)	0 (0)
Constipation	5 (22)	0 (0)
Fatigue	5 (22)	1 (4)
Bone pain	4 (17)	2 (9)
Musculoskeletal pain	4 (17)	0 (0)
Abdominal pain	2 (9)	0 (0)
Dyspepsia	2 (9)	0 (0)
Gait disturbance	2 (9)	0 (0)
Nasopharyngitis	2 (9)	0 (0)
Blood creatinine increased	2 (9)	0 (0)
ECOG performance status worsened	2 (9)	0 (0)
Musculoskeletal chest pain	2 (9)	0 (0)
Musculoskeletal stiffness	2 (9)	0 (0)
Anxiety	2 (9)	0 (0)
Pyrexia	2 (9)	0 (0)

No grade 5 adverse events were reported

ECOG Eastern Cooperative Oncology Group

Table 4 Nadir values for hemoglobin, white blood cell count, platelets, and neutrophils during the treatment period

Radium-223 ($n = 23$)	
Parameter	Median (min–max)
Hemoglobin (g/L)	110 (76–136)
Neutrophils (10^9/L)	1.70 (0.82–4.29)
Platelets (10^9/L)	226 (58–471)
White blood cell count (10^9/L)	3.10 (1.50–6.08)

nausea, diarrhea, anorexia, vomiting, constipation, fatigue, and bone pain. Three patients had serious AEs (nasopharyngitis [1], depression [1], and heart failure [1]) judged by the investigator to be unrelated to radium-223. The patient with heart failure died of the event before the fourth study drug injection. No patients discontinued radium-223 treatment because of AEs.

In most patients, the total white cell, absolute neutrophil, and platelet counts fell after each dose, with a nadir in the sample 3 weeks after radium-223 injection, followed by recovery (Table 4). Most of the nadir values were within normal range or grade 1 or 2. Across all hematologic parameters, the majority of values below the reference range were CTCAE grade 1, with few grade 2, and isolated grade 3 values. The biochemistry results showed no substantial trends with time. There was no pattern of change in vital sign measurements and no evidence of long-term toxicity.

Discussion

Radium-223 is the first FDA-approved alpha-emitting pharmaceutical with a potent and highly targeted antitumor effect on bone metastases [4–6]. A recent preclinical study in a mouse model of breast cancer bone metastasis showed that radium-223 increased survival and decreased biochemical markers of bone metabolism [15]. In this study, radium-223 consistently reduced uNTX-1 and bALP levels during the 16-week treatment period despite concomitant bisphosphonates, suggesting that radium-223 targets areas of increased bone metabolism caused by metastases. Although there was no control group, patients were selected because of the presence of progressive disease; in this population with stable underlying treatments, including bisphosphonates, a decrease of uNTX-1 and bALP levels over time is suggestive of a positive treatment effect.

Radium-223 treatment resulted in minimal myelotoxicity, less than that typically seen with the beta-emitting radioisotopes samarium-153 and strontium-89 [9]. There were no unexpected safety findings. Most AEs were CTCAE grade 1 or 2. Minor reversible hematologic toxicity that was not dose-limiting was observed, as reported in previous studies with radium-223.

Bone scintigraphy using technetium-99m methylene diphosphonate (^{99m}Tc-MDP) is valuable in selecting patients for radium-223 treatment because both radiotracers, radium-223 and ^{99m}Tc-MDP, have a similar calcium-mimicking affinity for the bone mineral hydroxyapatite associated with bone metastasis. However, bone scintigraphy is unreliable for assessing response to therapy, as reactive bone formation can occur during repair processes following effective antitumoral treatment and during disease progression. In contrast, FDG PET/CT directly assesses the metabolic activity of the bone metastasis itself, and sequential FDG PET/CT can provide information on the metabolic response of bone metastases to therapy, which has been correlated with patient outcome [16, 17]. A treatment effect of radium-223 was indicated by a decrease in SUV_{max} in bone metastases as assessed by FDG PET/CT.

The effects of radium-223 on bone markers, BPI score, and tumor metabolism assessed by serial FDG PET imaging provide supportive data and illustrate the effectiveness of radium-223 in treating bone metastases in patients with breast cancer and bone-dominant disease. Additional studies with radium-223 are being planned to further investigate the efficacy and safety of radium-223 in this patient population.

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Conflict of interest R. Coleman: Consultant/advisory role for Bayer HealthCare and Celgene; honoraria from Celgene and Novartis, A. K. Aksnes: Employment/leadership position for Algeta ASA and stock ownership with Algeta ASA, B. Naume: Declares no conflict of interest, C. Garcia: Consultant/advisory role for Algeta ASA, G. Jerusalem: Research funding from Algeta, M. Piccart: Consultant/advisory role for Paramour, and honoraria and research funding (to Institute Jules Bordet) from Amgen, Estella's, AstraZeneca, Bayer, Involves, MSD, Novartis, Pfizer, Sinton, Roche-Genentech, Sarnoff-Aventis, Symphogen, and Verastem, N. Vobecky: Employment/leadership position for Bayer HealthCare, M. Thuresson: Statistical consultancy for and honoraria from Algeta ASA, P. Flamen: Consultant/advisory role for Bayer HealthCare and research funding for Algeta/Bayer HealthCare.

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