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A Randomized, Double-Blind, Dose-Finding, Multicenter, Phase 2 Study of Radium Chloride (Ra 223) in Patients with Bone Metastases and Castration-Resistant Prostate Cancer

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Abstract

Background: Patients with castration-resistant prostate cancer (CRPC) and bone metastases have an unmet clinical need for effective treatments that improve quality of life and survival with a favorable safety profile.
Objective: To prospectively evaluate the efficacy and safety of three different doses of radium chloride (Ra 223) in patients with CRPC and bone metastases.
Design, setting, and participants: In this phase 2 double-blind multicenter study, 122 patients were randomized to receive three injections of Ra 223 at 6-wk intervals, at doses of 25 kBq/kg ($n = 41$), 50 kBq/kg ($n = 39$), or 80 kBq/kg ($n = 42$). The study compared the proportion of patients in each dose group who had a confirmed decrease of ≥50% in baseline prostate-specific antigen (PSA) levels.
Outcome measurements and statistical analysis: Efficacy was evaluated using blood samples to measure PSA and other tumor markers, recorded skeletal-related events, and pain assessments. Safety was evaluated using adverse events (AEs), physical examination, and clinical laboratory tests. The Jonckheere-Terpstra test assessed trends between groups.
Results and limitations: The study met its primary end point with a statistically significant dose–response relationship in confirmed ≥50% PSA declines for no patients (0%) in the 25-kBq/kg dose group, two patients (6%) in the 50-kBq/kg dose group, and five patients (13%) in the 80-kBq/kg dose group ($p = 0.0297$). A ≥50% decrease in bone alkaline phosphatase levels was identified in six patients (16%), 24 patients (67%), and 25 patients (66%) in the 25-, 50-, and 80-kBq/kg dose groups, respectively ($p < 0.0001$). The most common treatment-related AEs (≥10%) occurring up to week 24 across all dose groups were diarrhea (21%), nausea (16%), and anemia (14%). No difference in incidence of hematologic events was seen among dose groups. Potential limitations include small patient numbers and differences among dose groups at baseline.
Conclusions: Ra 223 had a dose-dependent effect on serum markers of CRPC activity, suggesting that control of bone disease with Ra 223 may affect cancer-related outcomes. Ra 223 was well tolerated at all doses.
Trial registration: ClinicalTrials.gov: NCT00337155.

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1. Introduction

Bone metastases, a major cause of morbidity and mortality in patients with castration-resistant prostate cancer (CRPC) [1], are associated with pain, pathologic fracture, spinal cord compression, and decreased survival [2,3]. Current bone-targeted therapies (eg, bisphosphonates, denosumab) are primarily limited to delaying skeletal-related events (SREs), with no improvement in survival or quality of life [4–6].

Radium chloride Ra 223, a targeted α-emitter, is a calcium-mimetic, bone-seeking agent [7,8] that generates highly localized radiation zones to induce nonrepairable, double-stranded DNA breaks in metastatic cells [9–11], with minimal effects on normal tissue [12–14]. Ra 223 has demonstrated a favorable safety profile [15–17] and consistent improvement in serum biomarkers, pain, and overall survival (OS) in patients with CRPC and bone metastases [16–18]. In a phase 2 study ($n = 64$), Ra 223 significantly improved OS compared with placebo and increased prostate-specific antigen (PSA) and bone alkaline phosphatase (ALP) response rates [16,19]. In a phase 3 study ($n = 921$), Ra 223 significantly improved OS, time to first SRE, and time to PSA progression compared with placebo [18].

The current prospective study compares proportions of patients with CRPC and bone metastases showing a ≥50% PSA response across three Ra 223 doses in order to inform the dose choice for subsequent trials.

2. Patients and methods

2.1. Patients

Eligible patients had castration-resistant (hormone-refractory) prostate adenocarcinoma with serum testosterone levels ≤50 ng/dl after orchiectomy or while maintained on androgen ablation therapy. Eligibility required a baseline PSA ≥10 ng/ml with progressively rising PSA values (two consecutive increases over previous reference value), multifocal bone metastases, Eastern Cooperative Oncology Group score 0–2, life expectancy ≥6 mo, and adequate hematologic and hepatic function. Patients who received prior hormonal drug therapy had to stop flutamide, nilutamide, or cyproterone acetate ≥4 wk, and bicalutamide ≥6 wk, before Ra 223 injection, with subsequent disease progression.

Patients were excluded if they had received chemotherapy, immunotherapy, external-beam radiation therapy (EBRT), or investigational drugs within the previous 4 wk, had received systemic radiotherapy within the last year, or had visceral metastases from prostate cancer (PCa). Abdominal or pelvic lymph node involvement (≤1 cm in the short-axis diameter) was permitted. All patients provided written informed consent.

2.2. Study design

This randomized, double-blind, multicenter, phase 2 study evaluated the efficacy and safety of three Ra 223 dose regimens in patients with CRPC and bone metastases (Fig. 1). Patients were randomized with equal probability to receive three intravenous injections of Ra 223 (25, 50, or 80 kBq/kg) at 6-wk intervals. The study was unblinded after the last patient completed the week 24 assessment; follow-up visits assessed efficacy, long-term safety, and survival.

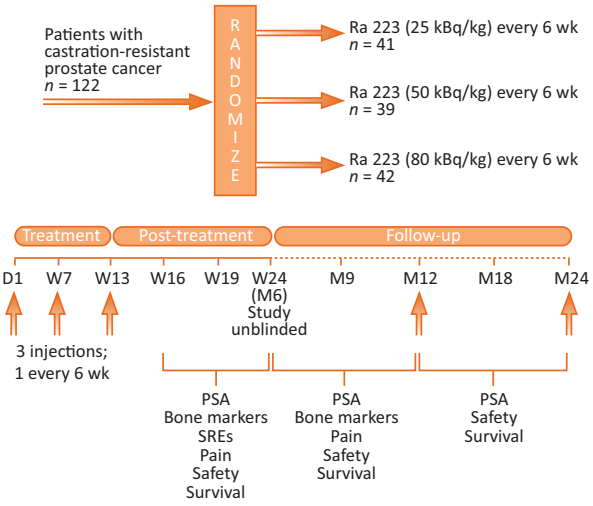

Fig. 1 – Study design. PSA = prostate-specific antigen; SRE = skeletal-related event; D = day; W = week; M = month.

The primary objective was to compare proportions of patients showing PSA response (≥50% decrease from baseline, confirmed by a second measurement ≥19 d later) on the three Ra 223 dose regimens. Secondary objectives included evaluating the effects of these regimens on bone ALP and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX-I); maximum percentage of PSA decrease from baseline; time to first SREs; pain response; correlation between bone ALP and PSA and s-CTX-I and PSA; and safety, tolerability, long-term safety, and OS.

The study was conducted in accordance with the Declaration of Helsinki and good clinical practices guidelines. The protocol was approved by an independent ethics committee at each center.

2.3. Assessments

Efficacy was evaluated on measurements made during the 24-wk blinded study period, with blood samples measuring PSA, bone ALP, and s-CTX–I evaluated in a central laboratory. Pain was measured with an index based on average pain in the last week (item 3 score on the Brief Pain Inventory [BPI] [20]) and analgesic consumption categorized using the World Health Organization analgesic ladder [21]. An adjudication committee performed pain classification before blinding was broken. SREs were defined as an increase in average pain or analgesic consumption, presence of neurologic symptoms, new pathologic bone fractures, tumor-related orthopedic surgery, EBRT or corticosteroids to relieve pain, radioisotopes to relieve new skeletal-related symptoms, chemotherapy or hormones for disease progression in the skeleton, or bisphosphonates for pain or skeletal disease progression. Survival was assessed throughout the study. Information on pain and SREs was additionally collected up to the month 12 visit (BPI) or month 24 visit (SREs).

Safety evaluations used adverse events (AEs), physical examination, and clinical laboratory tests. All AEs occurring before week 24 were reported; subsequent AEs were reported only if they were treatment-related (per investigator). AEs were graded according to Common Terminology Criteria for Adverse Events v.3.0. Long-term safety was assessed up to 24 mo.

The per-protocol (PP) population included all patients who received two or more Ra 223 injections at an interval of 6 wk ± 10 d and had two or more postbaseline PSA measurements separated by ≥19 d. Except for survival, all efficacy analyses performed on data to week 24 used the PP population. Analyses of survival and safety data, as well as of all data

from the follow-up period, used the safety population (all patients who received at least one Ra 223 injection).

2.4. Statistical analysis

Planned enrollment was 117 patients (39 patients in each dose group) to achieve 5% significance with 80% power when testing for a one-sided alternative of increasing response rate with increasing dose. The sample size accommodated a 20% dropout rate, with assumptions of PSA response rates of 50%, 35%, and 20% in the high-, middle-, and low-dose groups, respectively.

Summary statistics described values at each visit and relative change of parameters from baseline. Statistical analysis of proportions and continuous or ordinal data was conducted using a Jonckheere-Terpstra test [22] for trends between treatment groups. When trends were significant ($p < 0.05$) for the initial comparison of all groups, pairwise between-group comparisons applied the Fisher exact test. Statistical analysis of time-to-event data used the log-rank test for trends, with Kaplan-Meier estimates to determine the median and quartiles. Patients who received chemotherapy, immunotherapy, or external radiotherapy while on the study were censored from the analyses. Every attempt was made to collect survival data from patients who discontinued the study; patients were censored at the last date for which information was available to month 24.

In addition to the preplanned analysis, two post hoc analyses were performed. The primary end point of ≥50% PSA response was corroborated by post hoc testing against the end point of ≥30% PSA response. A sensitivity analysis was also conducted on the primary end point by excluding patients who had received EBRT or corticosteroids.

3. Results

3.1. Patient disposition

The study commenced in May 2006, and the week 24 completion date was May 2008. There were 122 patients enrolled from 21 centers in the United Kingdom, Spain, Poland, France, and Czech Republic. Patients were randomized to 25-kBq/kg ($n = 41$), 50-kBq/kg ($n = 39$), and 80-kBq/kg ($n = 42$) dose groups. All 122 patients received one or more Ra 223 injections and so composed the safety population (Fig. 2). One patient who was randomized to 50 kBq/kg, but erroneously treated with 80 kBq/kg, is included in the 80-kBq/kg dose group for all analysis. The PP population ($n = 112$) included 37, 36, and 39 patients in the 25-, 50-, and 80-kBq/kg dose groups, respectively.

3.2. Patient characteristics and cancer-related concomitant therapies

Patient baseline and disease characteristics were well balanced among treatment arms (Table 1), with no statistical difference among dose groups (Kruskal-Wallis nonparametric test or χ^2 test). PCa treatment given to ≥5% of patients during the treatment period included EBRT for 21 patients (17%), chemotherapy for 11 patients (9%), hormonal treatment for 11 patients (9%), and other treatments for 13 patients (11%).

3.3. Efficacy results: serum markers of tumor activity

The study met its primary end point with a confirmed ≥50% PSA response in no patients (0%) receiving 25 kBq/kg, two patients (6%) receiving 50 kBq/kg, and five patients (13%) receiving 80 kBq/kg at 24 wk ($p = 0.0297$ [Jonckheere-Terpstra test]) (Table 2). Pairwise comparisons between adjacent dose groups were nonsignificant ($p > 0.05$ [Fisher exact test]). Post hoc analysis confirmed a ≥30% reduction in baseline PSA in 2 patients (5%), 6 patients (17%), and 10 patients (26%) in the 25-, 50-, and 80-kBq/kg dose groups, respectively.

Five patients exhibiting ≥30% PSA response had received EBRT or corticosteroids, possibly confounding the result; two of these patients experienced a confirmed 50% PSA response. A post hoc sensitivity analysis censored all five patients from the time of receiving therapies. The Jonckheere-Terpstra results remained significant ($p = 0.046$); Kaplan-Meier curves and the log-rank test were also similar. No PSA responders received chemotherapy during the treatment period.

Figure 3A shows median relative PSA change from baseline. Median percentage changes were −14.3, −39.6, and −25.3 in the 25-, 50-, and 80-kBq/kg dose groups, respectively ($p = 0.28$ [Jonckheere-Terpstra test]).

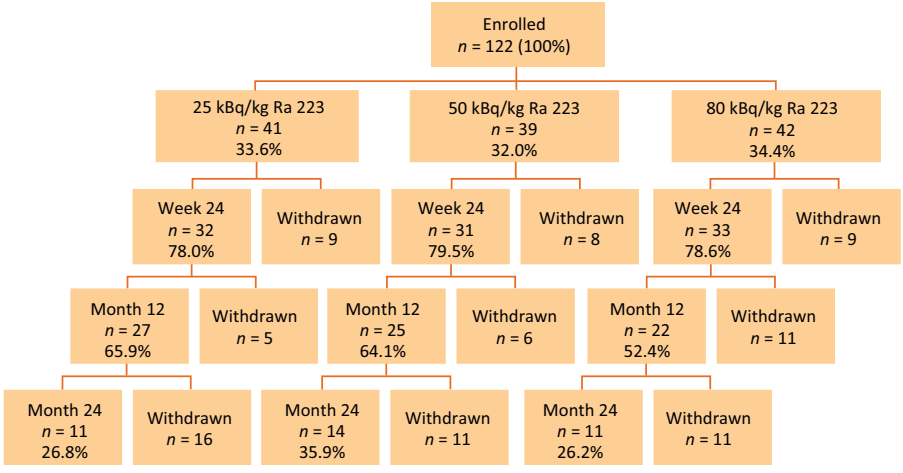

Fig. 2 – Disposition of all randomized patients (Consolidated Standards of Reporting Trials diagram).

Table 1 – Baseline patient characteristics (safety population)

Variable	Ra 223 dose group		
	25 kBq/kg, *n* = 41	50 kBq/kg, *n* = 39	80 kBq/kg, *n* = 42
Age, yr			
Median	71	68	71
Interquartile range	67–76	61–75	66–75
Weight, kg			
Median	80	81	81
Interquartile range	72–87	74–96	74–91
Body mass index, kg/m^2			
Median	26.5	26.8	27.2
Interquartile range	24.9–29.0	24.6–30.0	26.0–30.0
ECOG performance status, no. (%)			
0	16 (39)	22 (56)	15 (36)
1	20 (49)	12 (31)	22 (52)
2	4 (10)	3 (8)	4 (10)
Not available	1 (2)	2 (5)	1 (2)
Extent of disease, no. (%)			
<6 metastases	13 (32)	12 (31)	11 (26)
6–20 metastases	11 (27)	15 (39)	19 (45)
>20 metastases	14 (34)	10 (26)	8 (19)
Superscan	3 (7)	2 (5)	4 (10)
Hemoglobin, g/l			
Median	125	130	128
Interquartile range	116–136	115–136	120–133
Albumin, g/l			
Median	42.5	42.0	41.4
Interquartile range	40.0–45.0	39.0–45.9	38.0–43.0
Lactate dehydrogenase, U/l			
Median	372	422	377
Interquartile range	182–427	306–643	226–548
Bone ALP, ng/ml			
Median	73.1	39.5	46.9
Interquartile range	29.1–192.0	26.11–113.5	22.0–111.8
PSA, ng/ml			
Median	147.4	96.1	128.9
Interquartile range	71.8–351.0	44.8–231.0	66.8–252.9
Pain at baseline (BPI items 1–4), no. (%)			
No	8 (20)	7 (18)	4 (10)
Yes	33 (80)	32 (82)	38 (90)
Baseline pain severity index (BPI items 1–4)[a]			
Median	1.3	2.3	3.0
Interquartile range	0.3–3.5	1.0–3.8	1.3–4.5
Use of analgesics at baseline, no. (%)			
No (WHO 0)	17 (41)	12 (31)	13 (31)
Yes (WHO 1, 2, or 3)	24 (59)	27 (69)	29 (69)
Most common (>30%) prior prostate cancer treatment registered at prestudy visit, *n* (%)[b,c]			
Antiandrogens	40 (98)	36 (92)	41 (98)
Bisphosphonates	13 (32)	16 (41)	17 (41)
Chemotherapy	13 (32)	14 (36)	11 (26)
Taxanes	8 (20)	8 (20)	8 (19)
Anthracyclines	0	1 (3)	0
Other antineoplastic agents	5 (12)	1 (3)	5 (12)
EBRT	12 (29)	17 (44)	15 (36)

ALP = alkaline phosphatase; BPI = Brief Pain Inventory; EBRT = external-beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen; WHO = World Health Organization.

[a] Values are based on 39, 38, and 42 observations in the 25-, 50-, and 80-kBq/kg dose groups, respectively.

[b] Includes past and current treatments registered at the prestudy visit.

[c] Treatment was stopped before the first injection of Ra 223.

PP population patients with ≥50% bone ALP reduction in ≤24 wk showed significant dose response between groups ($p < 0.0001$ [Jonckheere-Terpstra test]) (Table 2). Pairwise comparisons (Fisher exact test) showed significant differences in the proportion of patients with confirmed bone ALP response between the 25- and 50-kBq/kg dose groups ($p = 0.0001$, Bonferroni correction factor 3) and between the 25- and 80-kBq/kg dose groups ($p < 0.0001$, Bonferroni correction factor 3), but not between the 50- and 80-kBq/kg dose groups ($p = 1.0$, uncorrected). Figure 3B shows the median percentage change in bone ALP from baseline.

A 50% reduction in PP population baseline s-CTX-I levels occurred for one patient (3%), four patients (11%), and five

Table 2 – Proportion of patients in the per-protocol population with a confirmed prostate-specific antigen or bone alkaline phosphatase response up to week 24

Proportion of patients with a confirmed biomarker response	Ra 223 dose group[a]				Jonckheere-Terpstra test for trends
	25 kBq/kg, $n = 37$	50 kBq/kg, $n = 36$	80 kBq/kg, $n = 39$[b]	Total	
≥50% PSA response, no. (%)	0 (0)	2 (6)	5 (13)	7 (6)	$p = 0.0297$
≥30% PSA response, no. (%)[a]	2 (5)	6 (17)	10 (26)	18 (16)	$p = 0.0179$
≥50% bone ALP response, no. (%)	6 (16)	24 (67)	25 (66)	55 (50)	$p < 0.0001$

ALP = alkaline phosphatase; PSA = prostate-specific antigen.
[a] Post hoc analysis.
[b] One patient did not have a baseline bone ALP measurement.

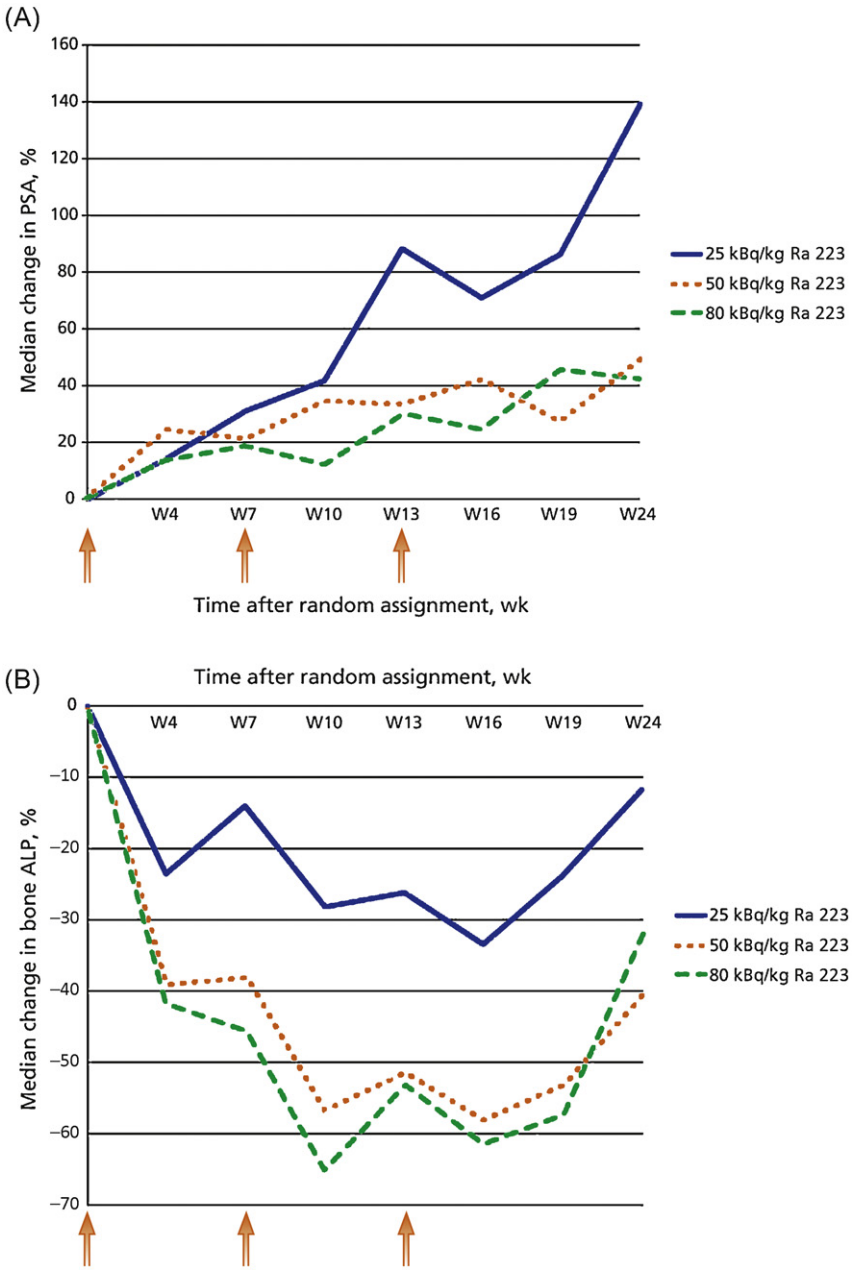

Fig. 3 – Median relative change from baseline in (A) prostate-specific antigen (PSA) and (B) bone alkaline phosphatase (ALP) for the per-protocol population. Arrows indicate the timing of each radium chloride Ra 223 injection. W = week.

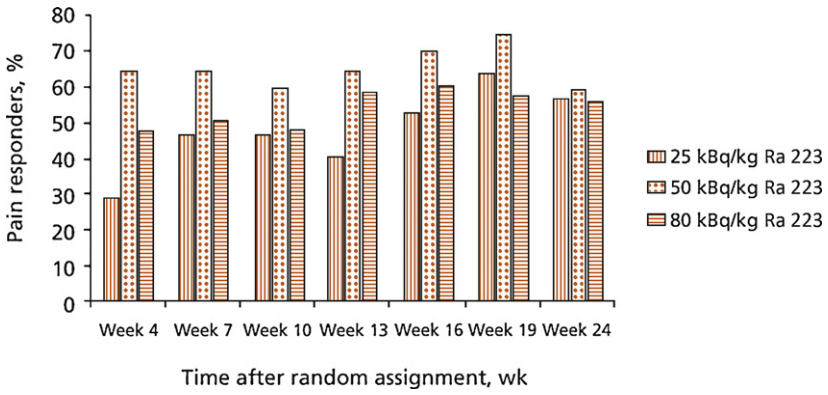

Fig. 4 – Percentage of pain responders (pain index score ≤4) by dose group for patients with pain at baseline (per-protocol population).

patients (13%) in the 25-, 50-, and 80-kBq/kg dose groups, respectively ($p = 0.16$ [Jonckheere-Terpstra test]).

Associations between absolute values of PSA, bone ALP, and s-CTX-I were calculated using pairwise Spearman rank correlation coefficients pooled across doses. A high correlation existed between PSA and bone ALP (pooled correlation coefficients: 0.382–0.462) and between PSA and s-CTX-I (pooled correlation coefficients: 0.258–0.398).

3.4. Skeletal-related events

In total, 50 of 112 PP population patients (45%) had one or more SREs between the time of the first Ra 223 injection and week 24, with 15 patients (41%), 18 patients (50%), and 17 patients (44%) in the 25-, 50-, and 80-kBq/kg dose groups, respectively. The most frequent SREs (≥10% of patients in any dose group; $n = 112$) were pain increase (13%), analgesic consumption increase (18%), and external radiotherapy administration (11%). No notable between-group differences in nature or number of reported SREs occurred (Supplementary Table 1).

3.5. Pain

Pain index data were available for 86 of 112 patients (77%) in the PP population, of whom 66 patients (77%) had baseline pain (ie, score ≥2 on BPI item 3). The proportion of pain responders was higher in the 50-kBq/kg dose group than in the other two dose groups across time points, but not significantly (Fig. 4).

3.6. Safety

Of 122 enrolled patients, 107 patients (88%) received three scheduled Ra 223 injections: 38 patients (93%), 34 patients (87%), and 35 patients (83%) in the 25-, 50-, and 80-kBq/kg dose groups, respectively.

The safety profiles of the three doses of Ra 223 were satisfactory, with no apparent dose–response effect except for a slight trend toward an increase in gastrointestinal AEs. In total, 112 patients (92%) reported one or more AEs to week 24. Of 551 AEs reported, 145 AEs (26%) were considered treatment-related, the most common treatment-related AEs (≥10%) being diarrhea (21%), nausea (16%), and anemia (14%) (Table 3). One new treatment-related AE, bone pain in the 25-kBq/kg group, occurred during the follow-up period to month 24.

Forty serious AEs occurred to week 24 in 29 patients (24%); four of these serious AEs were attributed to Ra 223: bone pain (grade 3; $n = 1$) in the 50-kBq/kg dose group, and muscular weakness (grade 2; $n = 1$), bone pain (grade 3; $n = 1$), and constipation (grade 3; $n = 1$) in the 80-kBq/kg dose group.

Hematologic parameters did not differ between dose groups (Table 3). Median values that decreased following Ra 223 administration generally returned to baseline at the end of the 24-wk treatment period, except for hemoglobin levels, which decreased from baseline to month 24 (Fig. 5).

3.7. 24-month safety and survival

In total, 70 deaths were recorded to 24 mo after first Ra 223 injection: 26, 22, and 22 deaths in the 25-, 50-, and 80-kBq/kg dose groups, respectively. Survival analysis includes 13 additional deaths recorded later. Median times to death were 548, 569, and 604 d in the 25-, 50-, and 80-kBq/kg dose groups, respectively. No significant difference existed among dose groups in proportion of patients who died ($p = 0.31$ [Jonckheere-Terpstra test]) or in time to death ($p = 0.44$ [log-rank test]) (Fig. 6).

No acute myelogenous leukemia, myelodysplastic syndrome, or aplastic anemia occurred during the 24-mo follow-up. One patient in the 50-kBq/kg dose group developed metastatic squamous cell carcinoma of unknown origin 1 mo after the first Ra 223 injection and died 2.5 mo later; this event was not attributed to Ra 223.

4. Discussion

In this randomized phase 2 trial of Ra 223 in CRPC with bone metastases, the proportion of patients with a confirmed reduction of ≥50% PSA significantly increased with increasing doses. Pain response occurred in 29–75% of

Table 3 – Number of treatment-related adverse events and total number of hematology events reported up to week 24 by dose group and Common Toxicity Criteria safety grade (safety population)

Parameter	Ra 223 dose group											
	25 kBq/kg, *n* = 41				50 kBq/kg, *n* = 39				80 kBq/kg, *n* = 42			
CTC safety grade	1	2	3	4	1	2	3	4	1	2	3	4
Treatment-related AEs by system organ class												
Gastrointestinal disorders[a]	16	2	–	–	18	–	–	–	20	2	1	–
General disorders and administration site conditions	5	2	–	–	10	5	–	–	6	1	–	–
Blood and lymphatic system disorders[b]	1	3	–	–	–	3	3	1	2	6	1	–
Investigations[c]	–	–	2	–	3	2	1	1	–	3	–	–
Musculoskeletal and connective tissue disorders[d]	–	–	–	–	2	–	1	–	–	2	1	–
Metabolism and nutrition disorders	1	–	–	–	–	2	–	–	2	–	–	–
Nervous system disorders	–	–	–	–	2	–	–	–	–	2	–	–
Skin and subcutaneous tissue disorders	–	–	–	–	1	1	–	–	–	1	–	–
Total treatment-related AEs	23	7	2	0	36	13	5	2	30	17	3	0
Total hematology events												
White blood cell count	7	2	0	0	9	7	0	0	10	8	3	0
Neutrophils	16	0	0	0	12	7	0	0	11	8	1	0
Platelets	5	1	1	0	8	1	0	1	10	2	1	0
Hemoglobin	18	12	1	0	18	8	4	1	21	14	1	1

AE = adverse event; CTC = Common Toxicity Criteria.
[a] One case of grade 3 constipation was reported in the 80-kBq/kg group.
[b] All reported grade 3 or 4 AEs were classified as anemia.
[c] One case each of grade 3 decreased hemoglobin or platelet counts occurred in the 25-kBq/kg group; decreased hemoglobin (grade 3) and decreased platelet counts (grade 4) occurred in the 50-kBq/kg group.
[d] All reported grade 3 AEs were classified as bone pain.

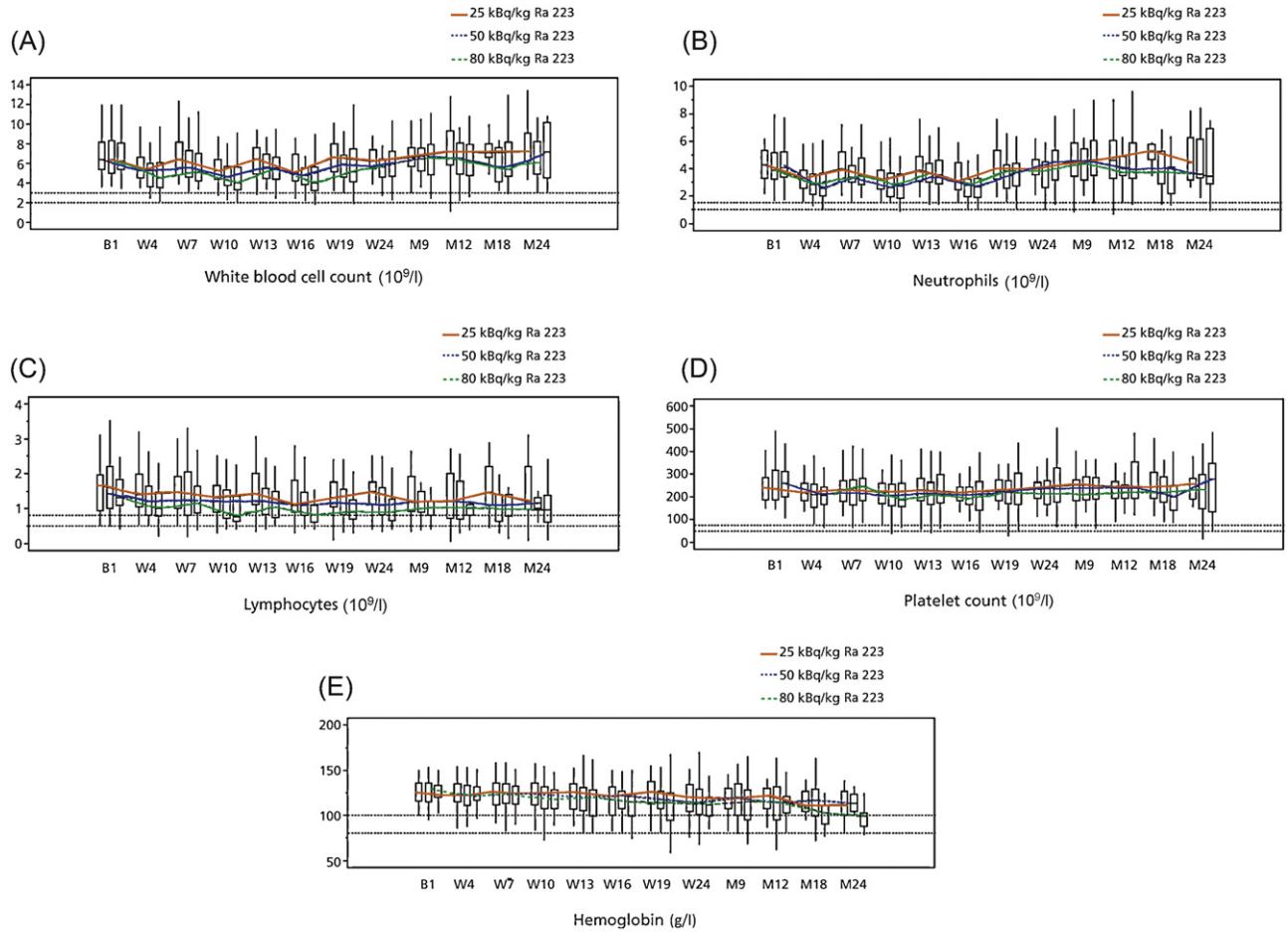

Fig. 5 – Median hematologic values over time by dose group for (A) white blood cells, (B) neutrophils, (C) lymphocytes, (D) platelets, and (E) hemoglobin. The dotted line represents the value of grade 2 and 3 Common Terminology Criteria for Adverse Events. B = baseline; W = week; M = month.

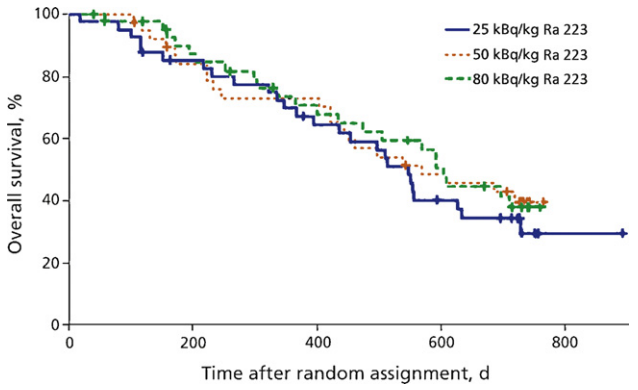

Fig. 6 – Overall survival of patients receiving three injections of radium chloride Ra 223 at doses of 25, 50, or 80 kBq/kg (safety population); $p = 0.44$ (log-rank) between groups for time to death.

patients with baseline pain, with a trend toward greater response in the 50-kBq/kg dose group. SREs occurred in each dose group, with no notable between-group differences in the nature of SREs or number of patients with SREs.

Serum biomarkers, such as PSA and bone ALP, are commonly used as early efficacy markers in CRPC and bone metastases. Often, bone ALP rather than PSA is used as a trial end point [23]; this concept was reinforced in the TAX327 trial retrospective analysis, in which ALP normalization at 90 d occurred in 26% of patients receiving docetaxel or mitoxantrone and correlated with better survival, independent of ≥30% PSA declines [24]. The current study showed a ≥50% decrease in baseline bone ALP in 16%, 67%, and 66% of patients in the 25-, 50-, and 80-kBq/kg dose groups, respectively ($p < 0.0001$ [Jonckheere-Terpstra test]).

A ≥30% PSA decline from baseline has been shown to correlate more closely with survival than the earlier ≥50% standard [25,26]. Post hoc analysis of patients achieving 30% PSA reduction reveals a significant dose response ($p = 0.0179$ [Jonckheere-Terpstra test]). However, PSA may not be the best predictor of response. A phase 3 study of sipuleucel-T in CRPC showed encouraging survival improvement but minimal PSA response [27].

This study supports the safety and tolerability of Ra 223 to the highest dose level (80 kBq/kg). The AE profile was consistent with expectations for advanced PCa, with no clear dose–toxicity relationship in treatment-related AEs or hematologic event pattern.

Potential limitations of the study include the small patient numbers and, hence, limited statistical power, as well as differences among dose groups at baseline in extent of disease, pain, and use of analgesics. However, patients were randomized to the three dose groups, so any differences at baseline were random. In addition, the inclusion of pain as an SRE may be a confounding factor, as pain is not now an accepted SRE.

To explore further the clinical potential of Ra 223 (50 kBq/kg every 4 wk) in CRPC and bone metastases, a randomized, double-blind, placebo-controlled, phase 3 survival study (ALSYMPCA; NCT00699751) was undertaken worldwide. At interim analysis, ALSYMPCA met its primary end point of significantly improving OS. Based on an Independent Data Monitoring Committee recommendation, the study stopped early, and placebo group patients were offered Ra 223 [18].

5. Conclusions

Ra 223, a targeted α-emitter, was well tolerated at all dose levels and had a dose-dependent effect on serum levels of PSA and bone ALP in patients with CRPC and bone metastases. These findings suggest that control of bone disease with Ra 223 may affect cancer-related outcomes.

Prior presentation: Presented in part at the 15th Congress of the European Cancer Organization in Berlin, Germany, September 20–24, 2009, and at the National Cancer Research Institute annual meeting in Birmingham, UK, October 4–7, 2009.

Author contributions: Christopher C. Parker had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Parker, O'Bryan-Tear.
Acquisition of data: Parker, Pascoe, Chodacki, O'Sullivan, Germá, Hoskin.
Analysis and interpretation of data: Parker, O'Bryan-Tear, Haider.
Drafting of the manuscript: Parker, Pascoe, Chodacki, O'Sullivan, Germá, O'Bryan-Tear, Haider, Hoskin.
Critical revision of the manuscript for important intellectual content: Parker.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2012.09.008.

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