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Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial

Christopher C. Parker[a,*], *Robert E. Coleman*[b], *Oliver Sartor*[c], *Nicholas J. Vogelzang*[d], *David Bottomley*[e], *Daniel Heinrich*[f], *Svein I. Helle*[g], *Joe M. O'Sullivan*[h], *Sophie D. Fosså*[i], *Aleš Chodacki*[j], *Paweł Wiechno*[k], *John Logue*[l], *Mihalj Seke*[m], *Anders Widmark*[n], *Dag Clement Johannessen*[o], *Peter Hoskin*[p], *Nicholas D. James*[q], *Arne Solberg*[r], *Isabel Syndikus*[s], *Jan Kliment*[t], *Steffen Wedel*[u], *Sibylle Boehmer*[v], *Marcos Dall'Oglio*[w], *Lars Franzén*[x,y], *Øyvind S. Bruland*[z,aa], *Oana Petrenciuc*[bb], *Karin Staudacher*[cc], *Rui Li*[bb], *Sten Nilsson*[dd]

[a] *The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK;* [b] *University of Sheffield, Weston Park Hospital, Sheffield, UK;* [c] *Tulane Cancer Center, New Orleans, LA, USA;* [d] *Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA;* [e] *St James's University Hospital, Leeds, UK;* [f] *Akershus University Hospital, Lørenskog, Norway;* [g] *Haukeland University Hospital, Bergen, Norway;* [h] *Centre for Cancer Research and Cell Biology, Queen's University, Belfast, UK;* [i] *Radiumhospitalet, Oslo, Norway;* [j] *Hospital Kochova, Chomutov, Czech Republic;* [k] *Centrum Onkologii—Instytut im Sklodowskiej—Curie, Warsaw, Poland;* [l] *Christie Hospital, Manchester, UK;* [m] *Centrallasarettet Växjö, Växjö, Sweden;* [n] *Umeå University, Umeå, Sweden;* [o] *Ullevål University Hospital, Oslo, Norway;* [p] *Mount Vernon Hospital Cancer Centre, Middlesex, UK;* [q] *Cancer Centre, University Hospitals Birmingham NHS Trust, Birmingham, UK;* [r] *St Olavs Hospital, Trondheim, Norway;* [s] *Clatterbridge Center for Oncology, Wirral, UK;* [t] *Jessenius School of Medicine, Comenius University, University Hospital, Martin, Slovakia;* [u] *Department of Urology, Marien Hospital Herne, Ruhr—University Bochum, Herne, Germany;* [v] *Gemeinschaftspraxis, Berlin, Germany;* [w] *Hospital das Clínicas, Faculdade de Medicina da USP, Instituto do Câncer do Estado de São Paulo, Brazil;* [x] *Länssjukhuset Sundsvall-Härnösand County Hospital, Sundsvall, Sweden;* [y] *Umeå University Hospital, Umeå, Sweden;* [z] *Norwegian Radium Hospital Oslo, Norway;* [aa] *Faculty of Medicine, University of Oslo, Oslo, Norway;* [bb] *Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA;* [cc] *Bayer AS (formerly Algeta ASA), Oslo, Norway;* [dd] *Karolinska University Hospital, Stockholm, Sweden*

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Abstract

Background: In Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 versus placebo prolonged overall survival with favorable safety in castration-resistant prostate cancer patients with symptomatic bone metastases. Long-term radium-223 monitoring underlies a comprehensive safety and risk/benefit assessment.
Objective: To report updated ALSYMPCA safety, including long-term safety up to 3 yr after the first injection.
Design, setting, and participants: Safety analyses from phase 3 randomized ALSYMPCA trial included patients receiving ≥1 study-drug injection (600 radium-223 and 301 placebo). Patients (405 radium-223 and 167 placebo) entered long-term safety follow-up starting 12 wk after the last study-drug injection, to 3 yr from the first injection. Forty-eight of 405 (12%) radium-223 and 12/167 (7%) placebo patients completed follow-up, with evaluations every 2 mo for 6 mo, then every 4 mo until 3 yr.
Outcome measurements and statistical analysis: All adverse events (AEs) were collected until 12 wk after the last injection; subsequently, only treatment-related AEs were

* Corresponding author. The Royal Marsden Hospital, Academic Urology Unit, Downs Road, Sutton, Surrey SM2 5PT, UK. Tel. +44 (208) 6613425; Fax: +44 (208) 6438809.
E-mail address: chris.parker@rmh.nhs.uk (C.C. Parker).

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Long-term safety
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Follow-up

collected. Additional long-term safety was assessed by development of acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic anemia, and secondary malignancies. Data analysis used descriptive statistics.
Results and limitations: During treatment to 12 wk following the last injection, 564/600 (94%) radium-223 and 292/301 (97%) placebo patients had treatment-emergent AEs (TEAEs). Myelosuppression incidence was low. Grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia (13% vs 13%), neutropenia (2% vs 1%), and thrombocytopenia (7% vs 2%). Ninety-eight of 600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs. Long-term follow-up showed no AML, MDS, or new primary bone cancer; secondary non–treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 mo after the last injection. No other cases were observed. Limitations include short (3-yr) follow-up.
Conclusions: Final long-term safety ALSYMPCA analysis shows that radium-223 remained well tolerated, with low myelosuppression incidence and no new safety concerns.
Patient summary: Updated Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial findings show that radium-223 remained well tolerated during treatment and up to 3 yr after each patient's first injection.

1. Introduction

Radium-223 is a first-in-class targeted alpha therapy for castration-resistant prostate cancer (CRPC) and symptomatic bone metastases with minimal myelosuppressive effects [1,2]. The relatively large size of alpha particles, coupled with the high linear energy transfer of emitted particles, results in a short path length and localized area of cell destruction (<100 μm; 2–10 cell diameters), inducing predominantly nonrepairable double-stranded DNA breaks [3]. Unlike beta particles emitted from strontium-89 and samarium-153, the much shorter range of alpha particles spares hematopoietic bone marrow and produces a more tolerable safety profile.

Agents approved for use in patients with CRPC have been associated with significant toxicities. These include the taxanes docetaxel and cabazitaxel, which have a range of chemotherapy-related effects [4–6]. Beta-emitting radiopharmaceuticals such as strontium-89 and samarium-153, used for pain palliation in CRPC patients with bone metastases, are associated with significant myelosuppression [1,2,7,8].

In the phase 3 Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 plus best standard of care (BSoC), versus placebo plus BSoC, prolonged median overall survival by 3.6 mo (14.9 vs 11.3 mo; $p < 0.001$) [9]. Additionally, radium-223 was well tolerated and associated with a low incidence of grade 3 or 4 myelosuppression (radium-223 vs placebo: anemia, 13% vs 13%; neutropenia, 2% vs 1%; and thrombocytopenia, 7% vs 2%). Based on ALSYMPCA efficacy and safety results, radium-223 was approved for treatment of patients with CRPC and symptomatic bone metastases and no known visceral metastases.

Although these radium-223 safety data are reassuring, long-term safety monitoring of radium-223 is essential to provide a comprehensive safety profile, including post-treatment adverse event (AE) data, and to afford clinicians a higher level of confidence in radium-223 overall safety. This article reports radium-223 final safety data from ALSYMPCA trial. Data presented are updated from previously reported safety results [9], with additional long-term safety from 12 wk after each patient's last injection up to 3 yr after their first injection.

2. Patients and methods

2.1. Patients and study design

Complete ALSYMPCA study methods were previously reported [9,10] and are summarized here (ClinicalTrials.gov number, NCT00699751). Eligible patients had symptomatic and progressing CRPC and ≥2 bone metastases with no visceral metastases, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥6 mo, and adequate baseline hematologic, renal, and liver functions. Patients either had previous docetaxel treatment or were unsuitable for or declined docetaxel. Patients were randomized 2:1 to radium-223 50 kBq/kg (55 kBq/kg following the National Institute of Standards and Technology [NIST] update) [11] plus BSoC or placebo plus BSoC every 4 wk for 24 wk (six injections; Fig. 1). BSoC was defined as routine care provided at each center and included external beam radiation therapy for bone pain as indicated. Randomization was done with an interactive voice response system, taking into account trial stratification factors. After study unblinding, placebo patients who still met the eligibility criteria were offered radium-223 (placebo crossover patients).

The long-term safety follow-up period started 12 wk after the last study-drug injection (end of treatment) and continued until 3 yr from the first study-drug injection. During follow-up, patients were evaluated every 2 mo for 6 mo, then every 4 mo for up to 3 yr (Fig. 1).

The primary ALSYMPCA end point was overall survival; secondary end points included acute and long-term safety.

2.2. Study assessments

Safety assessments included AEs, graded according to Common Terminology Criteria for Adverse Events version 3.0. Treatment-emergent AEs (TEAEs) included all AEs that started after the first injection up to 12 wk after the last injection. Post-treatment follow-up AEs were those that started >12 wk after the last injection during long-term safety follow-up and were reported only if considered treatment related by the investigator. Additional long-term safety data were assessed by occurrence of specific diseases, including acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic

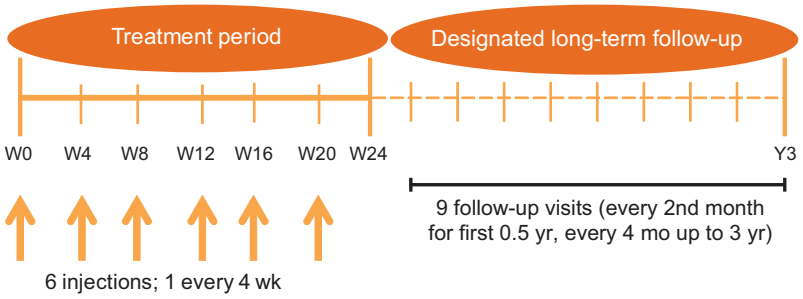

Fig. 1 – ALSYMPCA study timeline. ALSYMPCA = Alpharadin in Symptomatic Prostate Cancer; W = week; Y = year.

anemia, new primary bone cancer, and any secondary malignancies. Deaths were considered to be related (probably or possibly) or unrelated to study treatment, as judged by the investigator.

2.3. *Statistical analyses*

Statistical methods used in ALSYMPCA study have been described (July 2011 database lock) [9]. Data presented here include updated safety data collected for the entire study period (treatment and follow-up to 3 yr from the first study-drug injection) up to the October 2014 database lock, including the 24 placebo crossover patients who were offered radium-223 after study unblinding.

Safety analyses during the treatment period (up to 12 wk following the last study-drug injection) and long-term safety follow-up period (starting 12 wk after the last injection and continuing until 3 yr from the first study-drug injection) are presented by treatment group and summarized separately.

All patients who received radium-223 were combined (main study and placebo crossover [patients originally randomized to placebo and offered radium-223 after study unblinding]). Patient data are presented

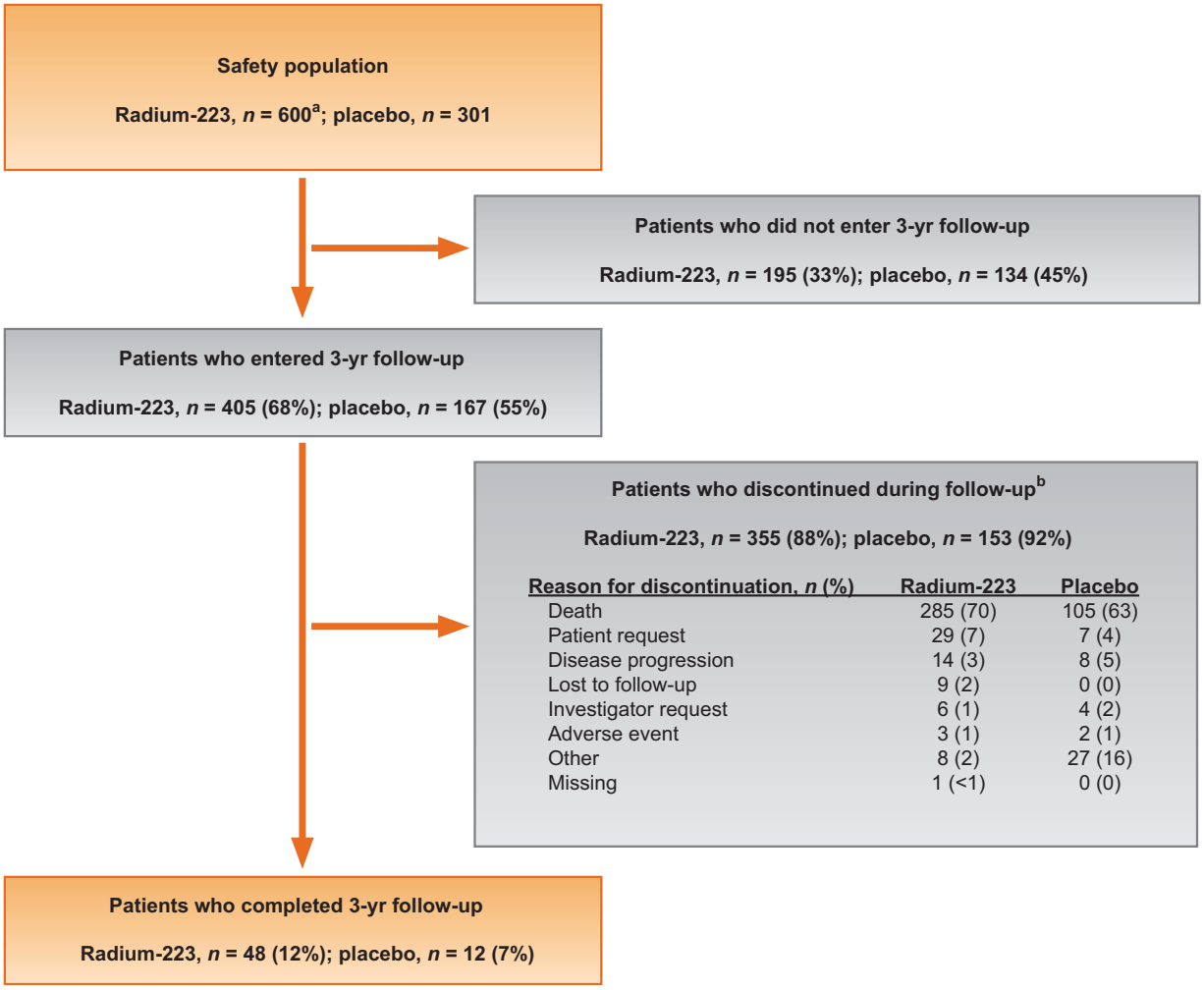

Fig. 2 – CONSORT diagram. [a] One patient in the placebo group received one injection of radium-223 (week 0) and is included in the radium-223 safety analysis. [b] Two (<1%) radium-223 and two (<1%) placebo patients' study completion pages were not received.

separately to account for all patients who received radium-223 treatment and to evaluate whether the few placebo crossover patients affect the overall safety findings. Separate safety analyses were performed on the patient subset that entered the long-term safety follow-up period. Demographics, disposition, and safety variables were summarized descriptively. Data were analyzed using SAS Version 9.1.3.

3. Results

3.1. Patients

The safety population included 901 patients (600 radium-223 and 301 placebo) who received one or more study-drug injections (Fig. 2). Baseline demographics and clinical characteristics were well balanced across treatment groups (Table 1).

Median follow-up time from the first injection up to 3 yr was 13 mo (range, 0–36 mo) for radium-223 patients and 9 mo (range, 0–36 mo) for placebo patients.

3.2. Updated safety during treatment period

Overall in this updated analysis of the original ALSYMPCA study publication [9], 564/600 (94%) radium-223 and 292/301 (97%) placebo patients had one or more TEAEs during the treatment period up to 12 wk following the last injection (Table 2). Radium-223 was associated with a low incidence of myelosuppression; grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia in 13% and 13%, neutropenia in 2% and 1%, and thrombocytopenia in 7% and 2%, respectively. Grade 5 TEAEs occurred in 98/600 (16%) radium-223 and 68/301 (23%) placebo patients (Table 2); disease progression (malignant neoplasm progression) was the most frequently reported TEAE leading to death in both radium-223 and placebo groups (54/600 [9%] and 35/301 [12%], respectively).

Secondary malignancies, defined as new cancers histologically different from the primary cancer, or complications from previously existing cancer were identified in

Table 1 – Baseline demographics and clinical characteristics [a] (safety population)

	Radium-223 *N* = 600	Placebo *N* = 301	Radium-223 (main study and placebo crossover) *N* = 624
Age			
Median (IQR), yr	71 (64–76)	71 (65–77)	71 (64–76)
>75 yr, *n* (%)	169 (28)	88 (29)	176 (28)
Total ALP level, *n* (%)			
<220 U/l	345 (58)	165 (55)	345 (55)
≥220 U/l	255 (43)	136 (45)	255 (41)
Current use of bisphosphonates at study entry, yes, *n* (%)	244 (41)	120 (40)	244 (39)
Prior docetaxel use, yes, *n* (%)	347 (58)	171 (57)	347 (56)
ECOG performance status, *n* (%) [b]			
0	162 (27)	77 (26)	165 (26)
1	366 (61)	183 (61)	381 (61)
≥2	72 (12)	40 (13)	78 (13)
WHO ladder for cancer pain, *n* (%)			
0–1—no pain or mild pain; no opioid use	263 (44)	138 (46)	274 (44)
2—moderate pain, occasional opioid use	148 (25)	78 (26)	155 (25)
3—severe pain, regular daily opioid use	189 (32)	85 (28)	195 (31)
Extent of disease, *n* (%)			
<6 metastases	100 (17)	37 (12)	101 (16)
6–20 metastases	252 (42)	144 (48)	259 (42)
>20 metastases/superscan [c,d]	246 (41)	119 (40)	262 (42)
EBRT within 12 wk of screening, *n* (%)			
Yes	98 (16)	47 (16)	98 (16)
No	502 (84)	254 (84)	502 (80)
Median biochemical values (IQR) [e]			
Albumin, g/l	40 (37–43)	40 (37–43)	40 (37–43)
Total ALP, U/l	206 (104–418)	224 (124–459)	198 (103–418)
LDH, U/l	313 (223–464)	336 (232–484)	311 (221–462)
PSA, μg/l	146 (49–419)	173 (59–472)	147 (49–433)
Median hematologic values (IQR) [e]			
Hemoglobin, g/dl	12 (11–13)	12 (11–13)	12 (11–13)
Neutrophils (absolute), $\times 10^9$/l	5 (3–6)	5 (3–6)	5 (3–6)
Platelets, $\times 10^9$/l	244 (198–302)	240 (189–313)	244 (197–302)

ALP = alkaline phosphatase; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; WHO = World Health Organization.

[a] Percentages may not sum to 100% due to rounding.

[b] Value recorded at screening.

[c] Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

[d] Based on the intent-to-treat population (radium-223, *N* = 614; placebo, *N* = 307).

[e] Value recorded at week 0. If this value was missing, then the value recorded at screening was used. The normal values were as follows: albumin, 36–45 g/l; total ALP, 35–105 U/l; LDH, 115–225 U/l; PSA, 0–3.999 μg/l; hemoglobin, 13.4–17.0 g/dl; neutrophils (absolute), 2–7.5 × 10^9/l; platelets, 150–350 × 10^9/l.

Table 2 – Adverse events occurring during treatment period, up to 12 wk after last injection (safety population) [a]

TEAEs *n* (%)	Radium-223 *N* = 600			Placebo *N* = 301			Radium-223 (main study and placebo crossover) *N* = 624		
	All Gr	Gr 3/4	Gr 5	All Gr	Gr 3/4	Gr 5	All Gr	Gr 3/4	Gr 5
≥1 TEAE	564 (94)	350 (58)	98 (16)	292 (97)	194 (65)	68 (23)	587 (94)	366 (59)	103 (17)
Hematologic [b]									
Anemia	187 (31)	79 (13)	0	93 (31)	39 (13)	1 (<1)	196 (31)	81 (13)	0
Neutropenia	30 (5)	13 (2)	0	3 (1)	2 (1)	0	32 (5)	15 (2)	0
Thrombocytopenia	69 (12)	39 (7)	0	17 (6)	6 (2)	0	72 (12)	42 (7)	0
Nonhematologic [b]									
Bone pain	310 (52)	132 (22)	0	192 (64)	79 (26)	0	321 (51)	136 (22)	0
Diarrhea	154 (26)	8 (1)	0	45 (15)	6 (2)	0	161 (26)	8 (1)	0
Nausea	215 (36)	10 (2)	0	102 (34)	6 (2)	0	226 (36)	10 (2)	0
Vomiting	116 (19)	10 (2)	0	41 (14)	7 (2)	0	119 (19)	10 (2)	0
Constipation	109 (18)	7 (1)	0	64 (21)	4 (1)	0	111 (18)	7 (1)	0
Fatigue	160 (27)	27 (5)	0	79 (26)	18 (6)	0	169 (27)	27 (4)	0
Peripheral edema	78 (13)	10 (2)	0	30 (10)	4 (1)	0	80 (13)	10 (2)	0
Weight decreased	73 (12)	5 (1)	0	44 (15)	5 (2)	0	75 (12)	5 (1)	0
Anorexia	109 (18)	9 (2)	0	54 (18)	2 (1)	0	113 (18)	10 (2)	0
Malignant neoplasm progression	78 (13)	14 (2)	54 (9)	46 (15)	5 (2)	35 (12)	81 (13)	15 (2)	56 (9)
Urinary tract infection	49 (8)	9 (2)	0	28 (9)	7 (2)	1 (<1)	54 (9)	9 (1)	0
Dizziness	45 (8)	2 (<1)	0	26 (9)	2 (1)	0	47 (8)	2 (<1)	0
Pyrexia	40 (7)	3 (1)	0	19 (6)	3 (1)	0	40 (6)	3 (1)	0
Spinal cord compression	25 (4)	20 (3)	1 (<1)	23 (8)	17 (6)	0	26 (4)	21 (3)	1 (<1)
Decreased appetite	36 (6)	2 (<1)	0	13 (4)	0	0	37 (6)	2 (<1)	0
Asthenia	36 (6)	6 (1)	0	18 (6)	4 (1)	0	38 (6)	6 (1)	0
Urinary retention	27 (5)	10 (2)	0	19 (6)	6 (2)	0	30 (5)	11 (2)	0
General physical health deterioration	30 (5)	11 (2)	6 (1)	21 (7)	11 (4)	2 (1)	31 (5)	11 (2)	7 (1)
Hematuria	29 (5)	7 (1)	0	16 (5)	3 (1)	0	29 (5)	7 (1)	0
Arthralgia	29 (5)	3 (1)	0	11 (4)	1 (<1)	0	29 (5)	3 (1)	0
Cough	28 (5)	0	0	11 (4)	0	0	29 (5)	0	0
Insomnia	31 (5)	0	0	17 (6)	1 (<1)	0	31 (5)	0	0
Dyspnea	49 (8)	11 (2)	1 (<1)	26 (9)	7 (2)	3 (1)	49 (8)	11 (2)	1 (<1)
Muscular weakness	9 (2)	3 (1)	0	16 (5)	6 (2)	0	11 (2)	3 (1)	0
Pathologic fracture	24 (4)	13 (2)	0	16 (5)	10 (3)	0	26 (4)	14 (2)	0
Pneumonia	21 (4)	11 (2)	4 (1)	16 (5)	7 (2)	0	22 (4)	11 (2)	4 (1)

ALSYMPCA = Alpharadin in Symptomatic Prostate Cancer; Gr = grade; TEAE = treatment-emergent adverse event.
[a] Updated from previously reported ALSYMPCA safety data.
[b] Occurring in ≥5% of patients in either study group.

both treatment groups. In the radium-223 group, one patient had carcinoma of unknown origin, one had squamous cell carcinoma, one had intestinal adenocarcinoma, and two had skin neoplasms (types unknown). In the placebo group, one patient had neoplasm of unknown origin and one had gastric cancer.

3.3. *Patients who entered long-term safety follow-up*

Of 901 patients in the ALSYMPCA safety population, 572 (405 radium-223 and 167 placebo) entered the designated 3-yr long-term safety follow-up period. Baseline demographic and clinical characteristics of those patients were generally similar across treatment groups (Table 3). During long-term safety follow-up, 185/405 (46%) radium-223 and 80/167 (48%) placebo patients had subsequent anticancer therapy following study treatment (Supplementary Table 1). The most common anticancer therapies received were abiraterone (radium-223, 92/405 [23%]; placebo, 31/167 [19%]) and docetaxel (radium-223, 92/405 [23%]; placebo, 36/167 [22%]). Radiotherapy was received by 178/405 (44%) radium-223 and 84/167 (50%) placebo patients (Supplementary Table 1).

Most patients entering follow-up had completed all six injections of study treatment (radium-223, 337/405 [83%]; placebo, 118/167 [71%]; Supplementary Table 2). The primary reason for not receiving all six injections was AEs (radium-223, 27/405 [7%]; placebo, 17/167 [10%]). Additional reasons for not receiving all six injections included investigator request (radium-223, 12/405 [3%]; placebo, 16/167 [10%]), patient request (radium-223, 15/405 [4%]; placebo, 9/167 [5%]), and other (radium-223, 14/405 [3%]; placebo, 7/167 [4%]).

All patients were followed for up to 3 yr after their first injection. The percentages of patients alive at the start of 1, 2, and 3 yr following the first treatment injection were higher for radium-223 than for placebo patients (326/405 [80%] and 118/167 [71%], 136/405 [34%] and 40/167 [24%], and 55/405 [14%] and 12/167 [7%], respectively; Supplementary Table 3).

During the 3-yr safety follow-up period, 355/405 (88%) radium-223 and 153/167 (92%) placebo patients discontinued from the study. The primary reason for discontinuation was death (radium-223, 285/405 [70%]; placebo, 105/167 [63%]); other reasons are shown in Supplementary Table 4.

Table 3 – Demographics and baseline characteristics of patients who entered 3-yr long-term safety follow-up period [a] (safety population)

	Radium-223 *n* = 405	Placebo *n* = 167	Radium-223 (main study and placebo crossover) *n* = 420
Age, median (IQR), yr	71 (64–76)	70 (65–76)	71 (64–76)
Total ALP, *n* (%)			
<220 U/l	253 (62)	114 (68)	253 (60)
≥220 U/l	152 (38)	53 (32)	152 (36)
Current bisphosphonates, yes, *n* (%)	168 (41)	73 (44)	168 (40)
Prior docetaxel, yes, *n* (%)	234 (58)	94 (56)	234 (56)
ECOG performance status, *n* (%) [b]			
0	118 (29)	54 (32)	120 (29)
1	249 (61)	100 (60)	259 (62)
2	38 (9)	13 (8)	41 (10)
WHO ladder for cancer pain, *n* (%)			
0–1—no pain or mild pain, no opioid use	190 (47)	83 (50)	199 (47)
2—moderate pain, occasional opioid use	106 (26)	47 (28)	109 (26)
3—severe pain, regular daily opioid use	109 (27)	37 (22)	112 (27)
EBRT within 12 wk of screening, yes, *n* (%)	55 (14)	20 (12)	55 (13)
Extent of disease, *n* (%)			
<6 metastases	87 (21)	29 (17)	88 (21)
6–20 metastases	173 (43)	88 (53)	177 (42)
>20 metastases/superscan	143 (35)	50 (30)	153 (36)
Median biochemical values (IQR)			
Albumin, g/l	40 (37–43)	41 (38–43)	40 (38–43)
Total ALP, U/l	159 (93–333)	164 (95–322)	157 (92–331)
LDH, U/l	272 (205–386)	300 (203–421)	270 (205–386)
PSA, μg/l	104 (40–334)	116 (36–426)	104 (40–337)
Median hematologic values (IQR)			
Hemoglobin, g/dl	13 (11–13)	13 (12–13)	13 (11–13)
Neutrophils (absolute), $\times 10^9$/l	4 (3–6)	4 (3–6)	4 (3–6)
Platelets, $\times 10^9$/l	244 (198–299)	240 (194–306)	244 (198–298)

ALP = alkaline phosphatase; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; WHO = World Health Organization.

[a] Percentages may not sum to 100% due to rounding.

[b] Value recorded at screening.

3.4. *Safety during long-term safety follow-up*

Post-treatment treatment-related AEs in patients who entered 3-yr long-term safety follow-up are presented in Table 4. Overall incidence of myelosuppression was ≤3%; nonhematologic AEs were ≤1%.

There were no reports of AML or MDS. Aplastic anemia based on bone marrow biopsy was reported in one radium-223 patient at follow-up visits 5 and 6 (16 and 20 mo from the last injection) and was considered by the investigator to be probably related to study drug. No new primary bone cancer was reported. In addition to the secondary malignancies reported during treatment, a number of secondary malignancies were reported during long-term follow-up and considered not related to study drug. In the radium-223 group, one patient had bladder cancer reported at follow-up visit 1 (3 mo after the last injection) and one had lymph node metastases of unknown origin reported at follow-up visit 6 (20 mo after the last injection). In the placebo group, one patient had squamous cell carcinoma of the left hand reported at follow-up visit 2 (6 mo after the last injection), one had adenocarcinoma of the rectum and adenocarcinoma of the sigmoid colon reported at follow-up visit 4 (12 mo after the last injection), and one had skin cancer (type unknown) reported at follow-up visits 7 and 8 (24 and 28 mo after the last injection). In the placebo crossover group, one patient had squamous cell carcinoma of the skin reported at follow-up visit 1 (3 mo after the last injection) and one had meningioma reported at follow-up visit 2 (6 mo after the last injection).

Cumulative incidence rates for hematologic and nonhematologic AEs of interest and for secondary malignancies were low (Supplementary Table 5 and Supplementary Fig. 1A–C).

3.5. *Deaths during study (treatment and safety follow-up periods)*

During the treatment period, 111/600 (19%) radium-223 and 78/301 (26%) placebo patients died (Supplementary Table 6). Deaths of two radium-223 patients were considered possibly related to study treatment: one patient who received two injections died of possible myocardial infarction or bowel ischemia 8 wk after the first injection; one patient who received one injection died of general deterioration of health with multiple organ failure within 4 wk after the first injection.

During long-term safety follow-up, a higher percentage of placebo patients than radium-223 patients died or dropped out (Supplementary Table 3). Deaths of two radium-223 patients were considered by the investigator to be related to study treatment. Both patients received all

Table 4 – Post-treatment treatment-related AEs in patients who entered 3-yr long-term safety follow-up (safety population)

	Radium-223 *n* = 405			Placebo *n* = 167			Radium-223 (main study and placebo crossover) *n* = 420		
AEs, *n* (%)	All Gr	Gr 3/4	Gr 5	All Gr	Gr 3/4	Gr 5	All Gr	Gr 3/4	Gr 5
Hematologic									
Anemia	11 (3)	5 (1)	0	5 (3)	1 (1)	0	11 (3)	5 (1)	0
Aplastic anemia	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	0
Leukopenia	2 (<1)	2 (<1)	0	0	0	0	2 (<1)	2 (<1)	0
Neutropenia	2 (<1)	2 (<1)	0	0	0	0	3 (1)	3 (1)	0
Thrombocytopenia	3 (1)	0	0	0	0	0	3 (1)	0	0
Pancytopenia	0	0	0	0	0	0	1 (<1)	1 (<1)	0
Nonhematologic									
Cardiopulmonary failure	0	0	0	1 (1)	0	1 (1)	0	0	0
Constipation [a]	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Diarrhea	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	0
Vomiting	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Nausea	0	0	0	1 (1)	0	0	0	0	0
Fatigue	1 (<1)	0	0	1 (1)	0	0	1 (<1)	0	0
General physical health deterioration	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Multiorgan failure [a]	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Pneumonia	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Weight decrease	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Anorexia	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Musculoskeletal pain	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Osteonecrosis	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Pathologic fracture	2 (<1)	1 (<1)	0	0	0	0	2 (<1)	1 (<1)	0
Dizziness	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Hematochezia	0	0	0	0	0	0	1 (<1)	0	0
Neutropenic sepsis	0	0	0	0	0	0	1 (<1)	1 (<1)	0
Femoral neck fracture	0	0	0	0	0	0	1 (<1)	1 (<1)	0

AEs = adverse events; Gr = grade.
[a] Patient died of multiorgan failure due to necrosis of the large intestine; onset of grade 5 constipation and death occurred on the same day.

six radium-223 injections. One patient died of pneumonia 8.4 mo from the last injection, and one died of multiorgan failure 18.1 mo from the last injection.

4. Discussion

Consistent with previous analyses [9,12–14], this updated final long-term safety follow-up analysis from ALSYMPCA trial in CRPC patients with symptomatic bone metastases showed that radium-223 continued to be well tolerated, with a low incidence of myelosuppression, long-term preservation of hematopoietic function, and no new safety signals.

Radium-223 compares well in safety with the hormonal therapies abiraterone and enzalutamide [15–19], but is unlike the cytotoxic chemotherapies, in which myelosuppression is the most frequent AE [20,21]. In the phase 3 TROPIC study, treatment with cabazitaxel was associated with significant myelosuppression (all grades neutropenia [94%], leukopenia [96%], anemia [97%], and thrombocytopenia [47%]) with relatively high rates of febrile neutropenia (8%) [4]. Furthermore, neutropenia frequently occurs in docetaxel-treated patients [20]. Radium-223 is also distinct from the beta-emitting radiopharmaceuticals, which are associated with significant hematologic AEs (mainly leukopenia and thrombocytopenia) [22,23].

In this 3-yr long-term safety analysis, secondary malignancies occurred in four radium-223 patients and three placebo patients. The percentages of radium-223 and placebo patients who received anticancer medications and radiotherapies during follow-up were generally similar. A study limitation is that assessment of long-term radium-223 safety may be difficult given that many participants were treated with other anticancer therapies in combination with radium-223 during the follow-up period. Secondary malignancies induced by cancer therapies are of clinical interest, as they are a cause of morbidity and mortality in long-term cancer patients. Although secondary malignancies are uncommon, they can be a serious consequence of radiotherapy for cancer treatment [24]. None of the secondary malignancies were considered related to radium-223, and no new primary bone cancer was reported; however, another study limitation was that the follow-up was limited to 3 yr, which is a relatively short time to assess the number of treatment-induced cancers, including hematologic malignancies. Additional studies with longer follow-up times are necessary to more accurately assess the long-term safety of radium-223. Another study limitation was that AEs were reported during follow-up only if considered by the investigator to be treatment related and may therefore be under-reported. Enrollment is currently ongoing in an international, prospective, observational, single-arm study (Radium-223 Alpha Emitter Agent in Safety Study in mCRPC Population for Long-Term Evaluation) aiming to assess the incidence of second primary malignancies in CRPC patients with bone

metastases who are receiving radium-223 in routine clinical practice. Patients will be followed until 7 yr after the last radium-223 dose (NCT02141438).

Of the patients who entered long-term safety follow-up, a higher percentage of radium-223 patients compared with placebo patients were alive at the end of the 3-yr period (14% vs 7%). These results, together with the unique mechanism of action and favorable safety profile during treatment and follow-up periods, make radium-223 an important treatment option, with potential for sequencing and combination with other agents for CRPC patients.

The current safety profile of radium-223 is based on a treatment course of six injections (50 kBq/kg [55 kBq/kg following the NIST update]) [11] given at 4-wk intervals. Studies are ongoing with higher-dose or extended-dose radium-223 regimens (NCT02023697) and combination with other agents (NCT02034552 [radium-223 + abiraterone or enzalutamide], NCT02043678 [radium-223 + abiraterone + prednisone/prednisolone], NCT01106353 [radium-223 + docetaxel]). Results from a phase 1/2 international, multicenter, prospective study in a highly selected population of patients with CRPC and bone metastases who were retreated with six additional radium-223 doses (NCT01934790) showed that retreatment with radium-223 was well tolerated, with minimal hematologic toxicity [25]. Results from these studies will further contribute to our understanding of the overall safety and efficacy of radium-223.

5. Conclusions

This updated final long-term safety follow-up ALSYMPCA analysis shows that radium-223 is well tolerated in CRPC patients with symptomatic bone metastases, with minimal nonhematologic AEs, a low incidence of myelosuppression with long-term preservation of hematopoietic function, and no new safety signals.

5.1. Future perspectives

The safety of radium-223 combined with the unique mechanism of action and prolongation of overall survival suggests the possibility of combining it with other agents. Additionally, earlier radium-223 use in patients with a low bone disease burden has the potential advantage of allowing patients to receive the recommended dosing regimen of six injections and to sequence this agent with subsequent therapies. Clinicians should consider using the most efficacious and safest agents early in treatment, thereby affording the possibility of allowing patients to better tolerate subsequent therapies and achieve maximum survival benefit. These updated ALSYMPCA safety data provide support for using radium-223 treatment earlier in the disease course, thus ensuring that patients achieve the full six injections of radium-223, the regimen associated with longer overall survival.

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, Sartor, Heinrich, Hoskin, Kliment, Bruland, Nilsson.
Acquisition of data: Parker, Vogelzang, Heinrich, O'Sullivan, Fosså, Wiechno, Logue, Hoskin, Solberg, Syndikus, Kliment, Wedel, Boehmer, Petrenciuc, Staudacher, Nilsson.
Analysis and interpretation of data: Parker, Coleman, Sartor, Vogelzang, Heinrich, O'Sullivan, Chodacki, Wiechno, Widmark, Kliment, Wedel, Dall'Oglio, Bruland, Petrenciuc, Staudacher, Li, Nilsson.
Drafting of the manuscript: Parker, Coleman, Sartor, Vogelzang, Kliment, Nilsson.
Critical revision of the manuscript for important intellectual content: Parker, Coleman, Sartor, Vogelzang, Heinrich, O'Sullivan, Widmark, Johannessen, Hoskin, James, Solberg, Syndikus, Kliment, Wedel, Boehmer, Dall'Oglio, Franzén, Bruland, Petrenciuc, Nilsson.
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Appendix A. Supplementary data

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