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Review

A randomized, dose–response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer ☆

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Abstract *Purpose:* To investigate the dose–response relationship and pain-relieving effect of radium-223, a highly bone-targeted alpha-pharmaceutical.
Methods: One hundred patients with castration-resistant prostate cancer (CRPC) and painful bone metastases were randomized to a single intravenous dose of 5, 25, 50 or 100 kBq/kg radium-223. The primary end-point was pain index (visual analogue scale [VAS] and analgesic use), also used to classify patients as responders or non-responders.
Results: A significant dose response for pain index was seen at week 2 ($P = .035$). At week 8 there were 40%, 63%, 56% and 71% pain responders (reduced pain and stable analgesic consumption) in the 5, 25, 50 and 100 kBq/kg groups, respectively. On the daily VAS, at week 8, pain decreased by a mean of −30, −31, −27 and −28 mm, respectively ($P = .008$, $P = .0005$, $P = .002$, and $P < .0001$) in these responders (*post-hoc* analysis). There was also a significant

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improvement in the brief pain inventory functional index for all dose-groups ($P = .04$, .01, .002 and .02, Wilcoxon signed rank test). Furthermore, a decrease in bone alkaline phosphatase in the highest dose-group was demonstrated ($P = .0067$). All doses were safe and well tolerated.

Conclusion: Pain response was seen in up to 71% of the patients with a dose response observed 2 weeks after administration. The highly tolerable side-effect profile of radium-223 previously reported was confirmed.

1. Introduction

Bone metastases, present in more than 90% of patients who die from prostate carcinoma,[1] may cause severe pain,[2] neurological symptoms, pathological bone fractures, spinal cord compression and pancytopenia with considerable impact on general suffering, reduced functional capacity and increased dependency on others.[3]

The optimal therapy should prolong survival, provide pain relief and decrease skeletal morbidity. Bone pain in prostate cancer is treated with a combination of analgesics, hormonal treatment, chemotherapy, bisphosphonates, external beam radiotherapy and beta-emitting radio-pharmaceuticals. Despite these efforts, many patients experience unrelieved pain, even when taking strong opioids.[4–8] Alternative therapies with a tolerable side-effect profile are needed to target bone metastases and improve quality of life.

Alpha-pharmaceuticals deliver high linear-energy transfer (high-LET) short-range irradiation (<100 μm), generating localised effective radiation zones with high probability of inducing double-strand DNA breaks in cancer cells, and lower surrounding tissue penetration compared with beta-emitting radiopharmaceuticals.[9] Radium-223 chloride (Alpharadin™) is a highly bone-targeted alpha-pharmaceutical[8,10] demonstrating antitumor properties in an experimental skeletal metastases model of human breast cancer cells.[11] In a phase II study, 64 prostate cancer patients with painful bone metastases were randomised to receive external radiotherapy plus either four doses of radium-223, 50 kBq/kg, or placebo, at intervals of 4 weeks. Median overall survival improved in the radium-223 group compared with placebo (65 versus 46 weeks, respectively; $P = .017$).[12,13]

This study investigated whether radium-223 could relieve pain in a dose-related manner in patients with castration-resistant prostate cancer (CRPC) and painful bone metastases, whether a pain-relieving effect occurs within each dose-group, and whether pain reduction is associated with improved functional status.

2. Patients and methods

2.1. Patients

Patients with prostate adenocarcinoma were eligible if they were castration-resistant (hormone refractory) with testosterone levels below 50 ng/dL after orchiectomy or while maintained on androgen ablation therapy. Patients were required to have bone pain with a score ⩾2 on the brief pain inventory (BPI)[14–17] and evidence of progressive disease, defined by prostate-specific antigen (PSA) level increase from baseline in two consecutive measurements at least 1 week apart with the final PSA ⩾5 ng/mL. Bone scintigraphy within 6 weeks before study drug administration ascertained multifocal osteoblastic disease and disease activity at painful sites. The main exclusion criteria were receipt of chemotherapy, immunotherapy, external radiotherapy, or an investigational agent within 4 weeks, or radiopharmaceuticals within the year before inclusion. All patients provided written informed consent.

2.2. Study design

A double-blind, randomised, dose-ranging study design was used to assess the effect of a single injection of 5, 25, 50 or 100 kBq/kg radium-223 in patients with CRPC (Fig. 1).

Patients' pre-dosing assessments included: a 1-week diary of daily baseline pain on a 100-mm visual analogue scale (VAS), recorded analgesic consumption and complete blood count (neutrophil count $\geqslant 1.5 \times 10^9$/L; platelet count $\geqslant 100 \times 10^9$/L; haemoglobin >95 g/L). Radium-223 was administered as a sterile solution of radium-223 chloride for intravenous injection. No steroids were co-administered.

Visits were scheduled at 2, 4, 8, 12 and 16 weeks after study injection. Patients with no palliative response 8 weeks after injection could be withdrawn from the study and treated in accordance with local practice. Long-term safety and survival were monitored up to 2 years after dosing.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and the protocol was approved by ethical, regulatory and radiation protection boards.

2.3. Efficacy and safety

The radium-223 palliative effect was documented by patient self-assessment of pain using a VAS, the BPI[15] and the patient's record of analgesic consumption. Pain was measured using a pain index, derived from a

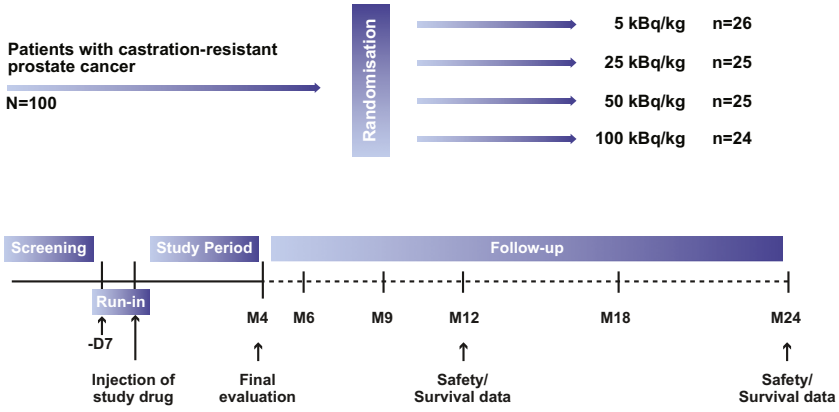

Fig. 1. Study design.

Table 1
Classification of pain index based on diary pain rating and analgesic intake.

Pain response	Pain index	Diary pain rating change from baseline	Analgesic intake compared with baseline
Complete	1	Decrease $\geqslant$90%	Stable or reduced
Marked	2	Decrease $\geqslant$50% to <90%	Stable or reduced
Moderate	3	Decrease $\geqslant$33% to <50%	Stable or reduced
Minimal	4	Decrease $\geqslant$20% to <33%	Stable or reduced
None	5	Decrease <20% or increase <20%	Stable
Pain progression	6	Increase $\geqslant$20%	Stable or increased
		Decrease <20% or increase <20%	Increased

combination of the VAS and analgesic consumption categorised according to the World Health Organization (WHO) analgesic ladder.[17] The classification (Table 1) was performed by an adjudication committee before the blind was broken. *Post-hoc*, patients were categorised as pain responders (pain index score 1–4), having no response (pain index score 5), or pain progression (pain index score 6).

The primary efficacy end-point was the pain index from baseline to weeks 2, 4, 8, 12 and 16. Secondary efficacy end-points were changed from baseline in BPI pain severity index (worst, least and average pain and pain experienced at current time), mean and sum of items 1–4, BPI functional interference index (general activity, mood, walking ability, work, relations with other people, sleep and enjoyment of life), mean and sum of items 6–12, and item 5 (pain relief from medication). Overall survival and duration of pain relief were assessed. Analyses were performed on the average of VAS data recorded over the previous 7 days, and BPI scores completed at each visit. The anticipated clinical effect of a single dose was expected to last for up to 8 weeks. Consequently, statistics focused on effects at week 8.

Safety end-points included adverse events (AEs), relative change in bone-alkaline phosphatase (ALP) and PSA, clinical laboratory tests and physical examination, all assessed at each visit. Nature and frequency of AEs and concomitant treatment were recorded throughout the 16-week posttreatment period.

2.4. Statistics

At the design stage, formal power calculation was not possible. Hence, a sample size of 100 patients (25 per dose-group) was chosen empirically. Simulations based on different assumptions regarding the distribution of pain index scores indicated that this size was reasonable.

The average diary pain rating was calculated, provided at least four VAS scores were available in a 7-day period (missing VAS values were replaced using LOCF). No imputation was done for other missing data. Pain relief duration was calculated by number of consecutive days pain response criteria were met. Efficacy and safety data were presented using appropriate descriptive statistics. Dose response analysis used the Jonckheere–Terpstra test for trends in ordered end-points and the Cochran–Armitage test for trend in proportions with 5% significance. A Student's *t*-test and Wilcoxon signed rank test were used for *post-hoc* analysis of changes within dose-groups.

The intent-to-treat (ITT) population included all patients who received an injection of study medication. All statistical analyses on efficacy variables used data from patients in the per protocol (PP) population,

defined as all receiving the study medication injection with a baseline average diary pain rating ⩾20 mm.

3. Results

3.1. Patient disposition and baseline characteristics

Patients were enrolled between May 2005 and December 2007 at 16 centres in Sweden, Germany, France and the United Kingdom. One hundred patients were randomized and treated (ITT population). Seven patients were excluded from PP analysis because they lacked an average diary pain rating of ⩾20 mm during the baseline period: 1, 0, 5 and 1 in the 5, 25, 50 and 100 kBq/kg groups, respectively. Seventy-eight patients completed week 16, 32 attended the 12-month follow-up and 8 completed the 24-month follow-up (Fig. 2).

The most common previous therapy was external radiotherapy, received by 61 patients overall, followed by prostatectomy in 19 patients and blood transfusion in 16 patients. Variation was wide, with no consistent differences between dose-groups that might confound results. Table 2 summarises key baseline patient characteristics.

3.2. Pain index

Table 3 presents summary statistics for pain index over time. A statistically significant dose response occurred at week 2. At week 8 there were 40%, 63%, 56% and 71% pain responders (pain index ⩽4) in the 5, 25, 50 and 100 kBq/kg groups respectively (Appendix Table A, online only), and of responders, 6/20 (30%), 8/19 (42%), 8/18 (44%) and 11/21 (52%) reached complete (pain index 1) or marked pain response (pain index 2), respectively. Up to week 8, fewer patients in higher dose-groups (50 and 100 kBq/kg) required increases in analgesia compared with lower dose-groups (Appendix Table B, online only).

Overall at week 8, mean daily diary pain decreased, on average, by 30 mm in the pain responder group, did not change in the stable response group and decreased 12 mm on average in the pain progression group. However, this group was free to increase analgesic consumption.

Mean pain relief duration was 44 days in the 50 and 100 kBq/kg groups, and 28 and 35 days in the 5 and 25 kBq/kg groups, respectively. The trends in dose response were not statistically significant ($P > .05$).

3.3. Brief pain inventory

The BPI data showed similar changes to the pain severity and functional interference indices. The Jonckheere–Terpstra test for dose response was statistically significant at week 8 for the BPI pain severity index ($P = .040$), indicating a dose-dependent treatment effect at this point.

For patients with pain response, baseline BPI pain severity index was 4.1, 4.1, 4.9 and 3.9 in the 5, 25, 50 and 100 kBq/kg dose-groups, respectively. At week 8, the mean score decreased by −1.6, −2.1, −1.9 and −1.8 in the same four dose-groups, respectively ($P = .05$, .001, .002 and .0006, Wilcoxon signed rank test).

3.4. Post-hoc analysis of pain responders

Among patients showing pain response at week 8, baseline mean daily pain was similar across dose-groups, between 40 and 48 mm. At week 8, pain decreased by a mean of −30, −31, −27 and −28 mm in the 5, 25, 50 and 100 dose-groups, respectively ($P = .008$, $P = .0005$, $P = .002$ and $P < .0001$).

Pain responders showed improvement in the BPI functional interference index for all dose-groups; the mean

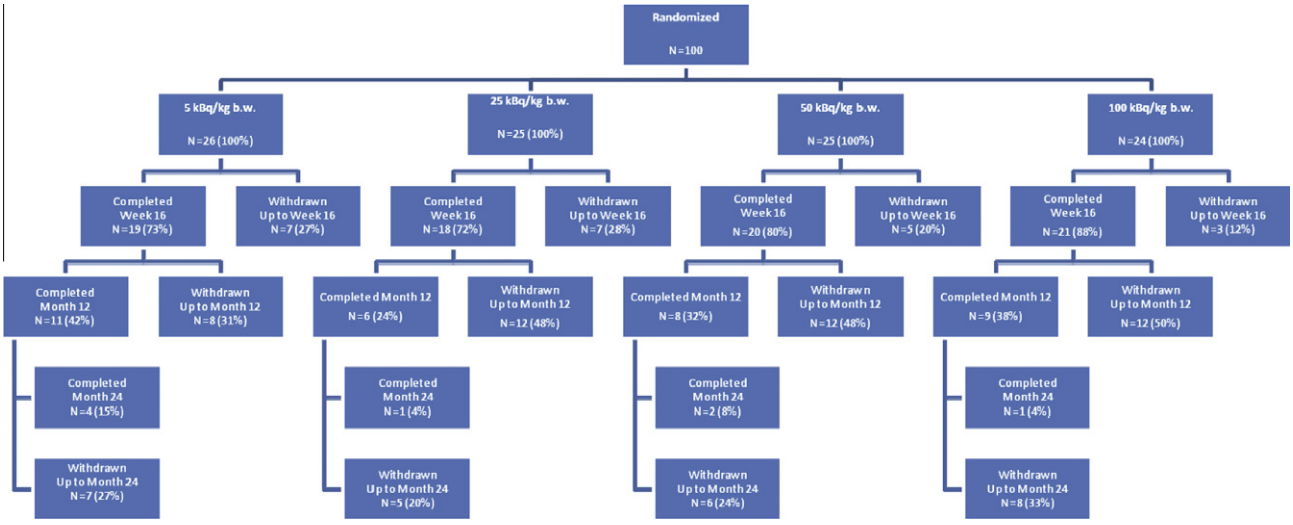

Fig. 2. Disposition of all randomised patients (CONSORT (Consolidated Standards of Reporting Trials) diagram).

Table 2
Summary of baseline characteristics (safety population).

Parameters *N*	Statistic	5 kBq/kg 26	25 kBq/kg 25	50 kBq/kg 25	100 kBq/kg 24	Total 100
Age (years)	Mean (SD)	69.7 (6.8)	69.1 (9.2)	67.4 (6.8)	69.4 (7.3)	68.9 (7.5)
	Median	72.5	70.0	67.0	71.0	70.0
	Min, max	54, 81	46, 82	56, 82	58, 81	46, 82
Haemoglobin (g/L)	Mean (SD)	120.4 (13.5)	119.3 (15.6)	127.3 (18.0)	121.1 (18.7)	122.0 (16.5)
	Median	118.5	122.0	131.0	123.5	123.0
	Min, max	96, 150	90, 142	93, 155	86, 152	86, 155
PSA (μg/L)	Mean (SD)	707.3 (1245.3)	355.8 (624.4)	357.8 (724.2)	420.3 (553.4)	466.3 (848.3)
	Median	228.2	138.5	157.1	129.5	148.6
	Min, max	6, 5548	10, 2820	6, 3662	9, 2224	6, 5548
Platelets (10^9/L)	Mean (SD)	272.9 (104.4)	255.6 (99.2)	256.9 (73.5)	247.7 (66.2)	258.5 (86.9)
	Median	265.0	248.0	250.0	238.5	244.5
	Min, max	132, 544	82, 529	108, 407	131, 390	82, 544
WBC (10^9/L)	Mean (SD)	8.47 (3.15)	7.11 (2.61)	6.61 (1.99)	7.22 (1.82)	7.36 (2.52)
	Median	8.10	6.49	6.22	7.37	6.95
	Min, max	3.4, 17.5	3.2, 13.8	3.1, 9.8	3.9, 10.4	3.1, 17.5
Bone-ALP (ng/mL)	Mean (SD)	163.4 (195.4)	167.4 (309.1)	166.3 (186.9)	246.7 (454.5)	184.7 (298.2)
	Median	88.8	71.8	98.0	124.4	96.1
	Min, max	9, 845	9, 1425	10, 828	10, 2000	9, 2000
Extent of disease (EOD)	EOD 1 (<6)	2 (9%)	5 (21%)	4 (17%)	1 (4%)	12 (13%)
	EOD 2 (6–20)	9 (41%)	9 (38%)	5 (21%)	8 (35%)	31 (33%)
	EOD 3 (>20)	9 (41%)	9 (38%)	11 (46%)	10 (44%)	39 (42%)
	EOD 4 (superscan)	2 (9%)	1 (4%)	4 (17%)	4 (17%)	11 (12%)
Time since diagnosis of bone metastases (years)	Mean (SD)	2.17 (3.46)	2.15 (2.01)	2.53 (2.38)	2.04 (2.43)	2.22 (2.60)
	Median	1.2	1.6	1.9	1.2	1.4
	Min, max	0.08, 16.5	0.04, 8.6	0.26, 11.0	0.04, 8.8	0.04, 16.5
Performance status	0	7 (28%)	2 (8%)	5 (20%)	1 (4%)	15 (15%)
	1	12 (48%)	16 (67%)	13 (52%)	14 (58%)	55 (56%)
	2	6 (24%)	6 (25%)	7 (28%)	9 (38%)	28 (29%)
Baseline VAS	Mean (SD)	41.8 (13.4)	47.7 (16.5)	41.4 (13.1)	43.4 (13.9)	43.6 (14,3)
	Median	40	46	37	45	42
	Min, Max	22, 85	24, 84	25, 68	23, 75	22, 85
WHO level of analgesia recorded at baseline	0	0	0	1 (4%)	0	1 (1%)
	1	9 (35%)	5 (20%)	5 (20%)	2 (9%)	21 (21%)
	2	6 (23%)	9 (36%)	9 (36%)	6 (26%)	30 (30%)
	3	11 (42%)	11 (44%)	10 (40%)	15 (65%)	47 (48%)
Most common previous cancer medication	Bicalutamide	20 (77%)	14 (56%)	14 (56%)	15 (63%)	63 (63%)
	Docetaxel	8 (31%)	9 (36%)	10 (40%)	9 (38%)	36 (36%)
	Leuproreline acetate	7 (27%)	7 (28%)	6 (24%)	2 (8%)	22 (22%)
	Cyproterone acetate	5 (19%)	3 (12%)	6 (24%)	5 (21%)	19 (19%)
	Gosereline	3 (12%)	7 (28%)	6 (24%)	2 (8%)	18 (18%)
	Estramustine	5 (19%)	2 (8%)	6 (24%)	4 (17%)	17 (17%)

Abbreviations: ALP, alkaline phosphatase; PSA, prostate-specific antigen; SD, standard deviation; VAS, visual analogue scale; WBC, white blood count; WHO, World Health Organization.

decreased by −1.6, −1.8, −2.1 and −1.1 ($P = .04$, .01, .002, and .02, Wilcoxon signed rank test) in the 5, 25, 50 and 100 kBq/kg dose-groups, respectively.

3.5. Adverse events

Almost all (97%) patients reported at least one AE during the study. Approximately half reported at least one serious AE. No trend existed with increasing dose in number, nature or seriousness of reported events (Table 4). The most frequently reported non-haematological AEs across all dose-groups were nausea, fatigue, vomiting, diarrhoea, constipation, bone pain, urinary tract infection and peripheral oedema. No differences occurred between dose-groups (Appendix Table C, online version only). The most frequent AE with an outcome of death was disease progression.

3.6. Biomarker safety evaluations

Median per cent changes in bone-ALP are shown in Fig. 3. Changes from baseline were statistically

Table 3
Pain index (PP population). Data presented as number of patients, mean (standard deviation) and median (minimum, maximum).

N	Dose-group				Jonckheere–Terpstra test for trends
	5 kBq/kg	25 kBq/kg	50 kBq/kg	100 kBq/kg	
	26	24	20	23	
Week 2	25	23	20	23	$P = .035$
	4.8 (1.4)	4.1 (1.8)	3.9 (1.4)	3.9 (1.6)	
	5.0 (2,6)	5.0 (1,6)	4.0 (1,6)	5.0 (1,6)	
Week 4	26	22	19	22	$P = .123$
	4.0 (1.8)	3.9 (1.9)	3.6 (1.6)	3.3 (1.8)	
	3.5 (1,6)	4.0 (1,6)	4.0 (1,6)	3.0 (1,6)	
Week 8	20	19	18	21	$P = .103$
	4.2 (1.8)	3.6 (2.0)	3.8 (1.9)	3.1 (1.7)	
	5.0 (1,6)	3.0 (1,6)	4.0 (1,6)	2.0 (1,6)	
Week 12	20	18	17	20	$P = .717$
	3.9 (2.2)	3.6 (2.3)	4.6 (1.8)	3.8 (1.8)	
	4.0 (1,6)	3.5 (1,6)	5.0 (1,6)	3.0 (2,6)	
Week 16	16	16	16	17	$P = .598$
	4.3 (2.1)	3.1 (2.0)	4.2 (2.0)	3.4 (2.1)	
	5.5 (1,6)	2.0 (1,6)	5.0 (1,6)	2.0 (1,6)	

Abbreviation: PP, per protocol.

Table 4
Adverse event profile (safety population).

N	Dose-group				Overall
	5 kBq/kg	25 kBq/kg	50 kBq/kg	100 kBq/kg	
	26	25	25	24	100
Number of patients					
With at least one AE	26	23	25	23	97
With at least one related AE	13	14	14	16	57
With at least one SAE	15	16	10	8	49
With at least one AE leading to withdrawal	0	1	0	0	1
Died in 16-week post-treatment period	4	6	1	2	13
Number of adverse events					
Number of AEs	166	140	135	123	564
Number of related AEs	25	29	30	44	128
Number of SAEs	33	38	14	16	101

Abbreviations: AE, adverse event; SAE, serious adverse event.

significant only in the 100 kBq/kg dose-group at weeks 4 and 8 ($P < .0001$ and $P = .0067$, Wilcoxon signed rank test). PSA levels increased in all dose-groups, from baseline to week 16.

3.7. Haematological safety

Haematological events were generally mild (Table 5). Clinical laboratory tests showed slightly greater reductions in platelet counts, white blood cell counts and neutrophils in the two highest dose-groups. These tended to occur in the first 2 weeks after injection, subsequently returning to baseline levels. The most frequent haematological AEs (reported by >10% across all dose-groups) were anaemia (11%) and haemoglobin decrease (15%), with no obvious differences between dose-groups.

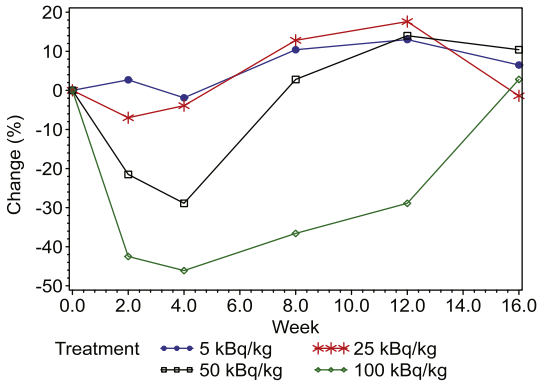

Fig. 3. Bone-alkaline phosphatase (ALP): median percentage change from baseline (safety set).

3.8. Other treatment

Forty-one patients had at least one concomitant therapy during the study, most commonly blood transfusion (23 patients) and external radiotherapy (26 patients) during the entire 16-week period; however, only five of 26 patients received external radiotherapy while still included in the study. The other 21 of 26 patients received external radiotherapy after they went off the study due to pain progression (pain level 6). Of the 26 patients, only two in the 100 kBq/kg group (8%) had external radiotherapy (compared with eight patients in each of 5, 25 and 50 kBq/kg dose-groups).

3.9. Twenty four-month safety and survival

During 24-month follow-up, no new diagnoses of AML, MDS, aplastic anaemia or primary bone cancer were observed across groups. At 24 months, 62 patients had died. Median survival was 50 weeks (range: 3–110 weeks) and did not differ between dose-groups.

4. Discussion

This is the first clinical study focusing on the pain-relieving effect of an alpha-pharmaceutical. Up to 71% of these patients with metastatic CRPC had a pain response at week 8 after a single radium-223 injection, accompanied by significant improvement in activities on the BPI functional scale. The pain-relieving effect was present at 2 weeks, and mean duration in responders was approximately 50 days. The safety profile was good—only 5 transient grade 4 events.

Since radium-223 was not an "add-on" to standard palliative care, it was considered unethical to randomise patients with advanced CRPC and pain to placebo control. When the trial was designed, the 5 kBq/kg radium-223 was thought to be similar to a placebo dose; however, it had some pain-relieving effects compared to baseline values, and occasionally this dose had a transient mild effect on neutrophils. It was therefore not a placebo dose, although a degree of placebo response cannot be excluded with such subjective measures as pain. However, external radiotherapy experience shows that doses needed for pain relief are generally low.[18,19] A higher dose may be required to achieve an antitumor effect; pain-relieving effects occurred in all four dose-groups, but a significant effect on bone-ALP only with the highest dose, emphasising the importance of distinguishing the radium-223 pain-relieving effect from its antitumor effect.

In this study, radium-223 had no effect on PSA levels. This is not surprising considering only a single injection was administered; multiple radium-223 50 kBq/kg injections have normalised PSA levels in this patient population.[12] Additionally, the effect of a single radium-223 injection on reducing bone-ALP observed here has also been demonstrated with multiple injections.[12] ALP normalisation correlated with improved survival, independent of PSA declines, in patients with CRPC and bone metastases treated with docetaxel or mitoxantrone.[20]

Table 5
Haematological parameters: occurrence of each CTCAE grade. Safety set; all patients/dose levels; number and percentage of patients.

Parameter	CTCAE grade			
	0–1	2	3	4
Posttreatment period (weeks 0–16)				
Haemoglobin	66 (66)	26 (26)	7 (7)	1 (1)
White blood cells	87 (87)	12 (12)	1 (1)	0
Platelets	92 (92)	2 (2)	4 (4)	2 (2)
Neutrophils	85 (90)	6 (6)	1 (1)	2 (2)

Abbreviation: CTCAE, common terminology criteria for adverse events.

Approximately 30–40% of patients in each dose-group received prior treatment with docetaxel. Although a low percentage versus current standards, it is consistent with treatment practices of participating centers during the study.

The pattern of analgesic use should also be considered. Reduction of regular analgesic medication would not be expected, even with a pain decrease after radium-223, since patients are reluctant to reduce their analgesic medication unless it produces marked side-effects. This may explain the minority of patients across all dose-groups reporting decreased analgesic consumption. Importantly, the improvement in responders' pain scores was not achieved by a greater increase in analgesic use. The lower percentage of patients in the 100 kBq/kg dose-group requiring external radiotherapy also supports the trend toward a more beneficial effect of the highest radium-223 doses.

Even in the highest dose-group, 29% did not respond to the single dose of radium-223. Pain continued to be a problem in these patients despite dose escalations of opioids. In fact, their pain relief was less pronounced than that from radium-223 in responders, perhaps because of insufficient analgesic doses, suboptimal analgesic choice or infrequent patient contact. However, the refractory pain might also be due to different pain mechanisms. In external beam radiotherapy studies, the highest attainable response is often of the magnitude of 60–80% of patients treated. New non-clinical data indicate that bone pain not only is nociceptive, but in early stages has neuropathic components, partially refractory to opioids.[2,21] In vivo models demonstrate that sensory and sympathetic neurons are present within the bone marrow, mineralised bone and periosteum; sensory fibres in these tissues play a role in generating and maintaining bone cancer pain.[2,21] Indirectly, a neuropathic component is also demonstrated in animal models, as drugs such as gabapentin, normally used for neuropathic pain, attenuate bone pain.[2,21]

Pain response was seen in up to 71% of patients treated with a single dose of radium-223, with a dose response already observed at 2 weeks and continued to 8 weeks after administration. The highly tolerable side-effect profile of radium-223, previously reported, was confirmed. There was no evidence of long-term toxicity during the 24-month follow-up. The 50 and 100 kBq/kg doses appear to be safe, well tolerated and effective, with positive effects on both pain and bone-ALP.

Drop-outs constitute a possible source of bias in the study. The main point of evaluation was at week 8. At that time, there were 6, 5, 4 and 2 drop-outs in the 5, 25, 50 and 100 kBq/kg dose-groups, respectively, with more drop-outs in the lower dose-groups ($6 + 5 = 11$). Since it is plausible that the drop-outs were patients who had more pain problems, the consequence is that the drop-out rate favoured the lower dose-groups. As patients with more pain left the study, the mean pain was consequently reduced.

In order to explore further the clinical potential of radium-223 in men with CRPC and symptomatic bone metastases, a randomised, double-blind, placebo-controlled phase III survival study (ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer); NCT00699751) was undertaken worldwide. In a preplanned interim analysis, ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) met its primary end-point of significantly improving OS (overall survival). Based on the recommendation of the Independent Data Monitoring Committee, the study was stopped and patients in the placebo group offered treatment with radium-223.

5. Role of the funding source

The study was sponsored and funded by Algeta ASA. The sponsor wrote the study protocol in collaboration with the investigators and was responsible for quality assurance in accordance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP). In collaboration with the investigators, the sponsor made the decision to submit the manuscript for publication.

Conflict of interest statement

Consultant or advisory role: Sten Nilsson, Peter Strang and Øyvind Bruland. Minor stock ownership: Øyvind Bruland. Employment or leadership position: Anne-Kirsti Aksnes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.12.023.

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