Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study

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Summary

Background **The alpha-emitter radium-223 (^{223}Ra) is a bone-seeking radionuclide studied as a new treatment for patients with bone metastases from hormone-refractory prostate cancer. We aimed to study mature outcomes from a randomised, multicentre, phase II study of ^{223}Ra.**

Methods **Patients with hormone-refractory prostate cancer and bone pain needing external-beam radiotherapy were assigned to four intravenous injections of ^{223}Ra (50 kBq/kg, 33 patients) or placebo (31 patients), given every 4 weeks. Primary endpoints were change in bone-alkaline phosphatase (ALP) concentration and time to skeletal-related events (SREs). Secondary endpoints included toxic effects, time to prostate-specific-antigen (PSA) progression, and overall survival. All tests were done at a 5% significance level, based on intention to treat.**

Findings **Median relative change in bone-ALP during treatment was –65·6% (95% CI –69·5 to –57·7) and 9·3% (3·8–60·9) in the ^{223}Ra group and placebo groups, respectively (p<0·0001, Wilcoxon ranked-sums test). Hazard ratio for time to first SRE, adjusted for baseline covariates, was 1·75 (0·96–3·19, p=0·065, Cox regression). Haematological toxic effects did not differ significantly between two groups. No patient discontinued ^{223}Ra because of treatment toxicity. Median time to PSA progression was 26 weeks (16–39) versus 8 weeks (4–12; p=0·048) for ^{223}Ra versus placebo, respectively. Median overall survival was 65·3 weeks (48·7–∞) for ^{223}Ra and 46·4 weeks (32·1–77·4) for placebo (p=0·066, log rank). The hazard ratio for overall survival, adjusted for baseline covariates was 2·12 (1·13–3·98, p=0·020, Cox regression).**

Interpretation **^{223}Ra was well tolerated with minimum myelotoxicity, and had a significant effect on bone-ALP concentrations. Larger clinical trials are warranted to study ^{223}Ra on the prevention of SREs and on overall survival in patients with hormone-refractory prostate cancer. Bone-targeting properties of ^{223}Ra could also potentially be used for treating skeletal metastasis from other primary cancers.**

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See Reflection and Reaction page 564

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Introduction

Hormone-refractory prostate cancer has a propensity to involve the bone marrow at an early stage. Subsequently, this involvement leads to the development of symptomatic skeletal metastases with pain, spinal-cord compression, pathological fracture, and pancytopenia. Bone-targeted treatments such as bisphosphonates (eg, zoledronate) and bone-seeking radioisotopes (eg, ^{89}Sr and ethylenediaminetetramethylene phosphonate (EDTMP)-^{153}Sm) are commonly used to delay skeletal disease progression and relieve pain. Zoledronate reduces the risk of skeletal-related events, but does not extend survival.[1] The beta-emitting radioisotopes ^{89}Sr and EDTMP-^{153}Sm have been shown to improve pain control in men with symptomatic, hormone-refractory prostate cancer, with myelosuppression as their dose-limiting toxicity.[2,3]

Beta-emitting radioisotopes produce relatively low-energy radiation with a track length in tissues of up to several mm. By contrast, alpha-emitters produce high, linear energy transfer (LET) radiation with a range of less than 100 µm. Compared with ^{89}Sr and EDTMP-^{153}Sm, a bone-seeking alpha-emitter might therefore have an increased anti-tumour effect, by virtue of the densely ionising abilities of high-LET radiation, but with relative sparing of the bone marrow because of its short-track length.

Radium-223 (^{223}Ra) is a bone-seeking alpha-emitter with a half-life of 11·4 days that has been studied extensively in preclinical animal models. In mice, the biodistribution of ^{223}Ra has been shown to correspond with that of ^{89}Sr, targeting of the bony skeleton with retention of its daughter isotopes in the bone matrix.[4] Modelling of the dose deposition in relation to tumour deposits in the bone marrow suggests a substantial reduction in dose to the healthy bone marrow with ^{223}Ra compared with ^{89}Sr.[4] In a rat model of breast cancer, ^{223}Ra showed pronounced anti-tumour effects in the absence of bone marrow toxic effects.[5] After 67 days' follow-up period, two of five animals treated with at least 100 kBq/kg ^{223}Ra survived, whereas none did in the control group. In this model, treatment with bisphosphonates gave no survival benefit.

A phase I trial of one intravenous injection of ^{223}Ra was done recently in 25 patients with metastatic bone disease (15 with hormone-refractory prostate cancer, ten with

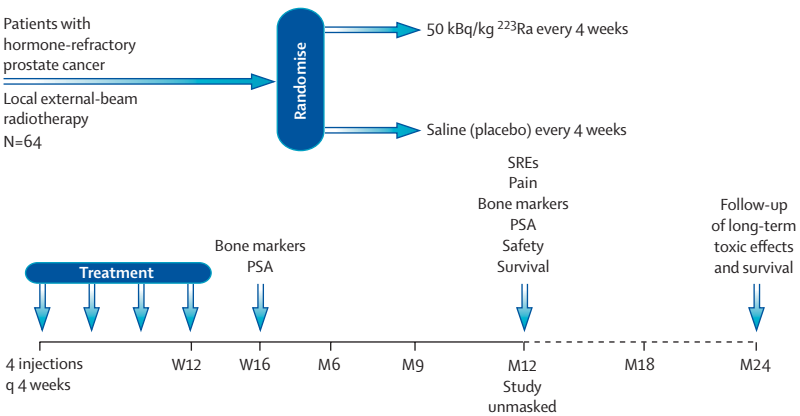

Figure 1: **Overall summary of study treatment**
W=week. M=month.

Panel: Definitions of SREs

- 25% increase in pain severity index compared with baseline after day 15 (during the first 16 weeks of the study, the pain increase had to be confirmed with a second assessment). Patients indicating pain severity on Brief Pain Inventory forms[8] (scale 0–10), with index defined as mean score of four questions on pain severity [worst, least, average, and current])
- Increased analgesic consumption (analgesia classified according to World Health Organization ladder for cancer pain [L0=no analgesia, L1=non-opioids, L2=weak opioids, L3=strong opioids]; increase defined as change to higher level or ≥50% increase in strong opioids, with temporary increases during first 2 weeks after first injection excluded)
- Neurological symptoms secondary to skeletal manifestations of prostate cancer
- New pathological bone fractures (vertebral and non-vertebral)
- Tumour-related orthopaedic surgical intervention
- Subsequent external-beam radiation to relieve skeletal pain
- Use of radioisotopes to relieve new skeletal-related symptoms
- Use of corticosteroids for skeletal pain palliation
- Use of chemotherapy, bisphosphonates, or hormones to treat progression of skeletal disease

breast cancer).[6] Doses of 50–250 kBq/kg were well tolerated, with grade 3 leucopenia (Common Terminology Criteria for Adverse Events [CTCAE], version 2.0) in three of 25 patients and no grade 2+ thrombocytopenia. No dose-limiting toxic effects were recorded. Gastrointestinal adverse events, most commonly diarrhoea (10 of 25 patients; highest CTCAE grade 2), were most frequent, especially in the highest dose groups. Preferential uptake was seen in skeletal metastases compared with healthy bone, with excretion mainly through the intestinal tract. Preliminary evidence of efficacy was seen with substantial reductions in serum alkaline phosphatase (ALP) concentrations and improved pain control across the dose levels.[6] Preliminary data suggested that the effect on ALP was similar across doses, and the lowest tested dose (50 kBq/kg) was selected for future studies.

In a randomised, double-blind, placebo-controlled, multicentre phase II study, we aimed to investigate the effect of repeated ^{223}Ra doses in men with symptomatic, hormone-refractory prostate cancer. Main study objectives were the efficacy of ^{223}Ra treatment with respect to the reduction in bone-specific ALP (bone-ALP) concentration, and time to occurrence of skeletal-related events (SREs).

Methods

Patients

Eligible patients had histologically or cytologically confirmed adenocarcinoma of the prostate; multiple bone metastases or one painful lesion with two consecutive rising amounts of serum prostate-specific antigen (PSA); Eastern Cooperative Oncology Group performance status 0–2; life expectancy of longer than 3 months; adequate haematological (neutrophils ≥1·5×10^9/L; platelets ≥100×10^9/L; haemoglobin >100 g/L), renal (creatinine <1·5×upper limit of normal), and hepatic (normal bilirubin [within institutional limits], aspartate aminotransferase and alanine aminotransferase <2·5×upper limit of normal) function; and bone pain needing external-beam radiotherapy. All patients had either bilateral orchidectomy or continued treatment on a luteinising-hormone-releasing-hormone agonist throughout the study. We excluded patients if they had another currently active malignant disease; had received chemotherapy, immunotherapy, or external-beam radiotherapy within the past 6 weeks; had a change in hormonal treatment within 6 weeks before study drug use, bisphosphonates within 3 months; or had any previous systemic radiotherapy with strontium, samarium, or rhenium. All patients gave written informed consent.

Procedures

Patients due to receive local-field, external-beam radiotherapy to relieve pain from bone metastases were assigned to receive either four repeated monthly injections of 50 kBq/kg ^{223}Ra (Alpharadin, Algeta ASA, Oslo, Norway) or repeated injections of saline (figure 1). ^{223}Ra was supplied to the hospitals as a ready-to-use solution for injection, with little shielding needed since the isotope is an alpha-emitter. Randomisation was done centrally with a random number generator and stratified according to study centre. For masked treatment allocation, an individual from the nuclear medicine department at every centre was responsible for study treatment preparation and labelling. Researchers remained masked to treatment allocation. Treatment lasted for 12 weeks, during which four injections were given at 4-week intervals, with the first injection given at the time of external-beam radiotherapy and no later than 7 days afterwards. External-beam radiotherapy was given to the most painful site, with appropriate margins, and to an area not exceeding 400 cm^2. Either one fraction of 8 Gy or a fractionated course of 20 Gy (4 Gy×5) over 1 week, or 30 Gy (3 Gy×10) over 2 weeks was permitted.

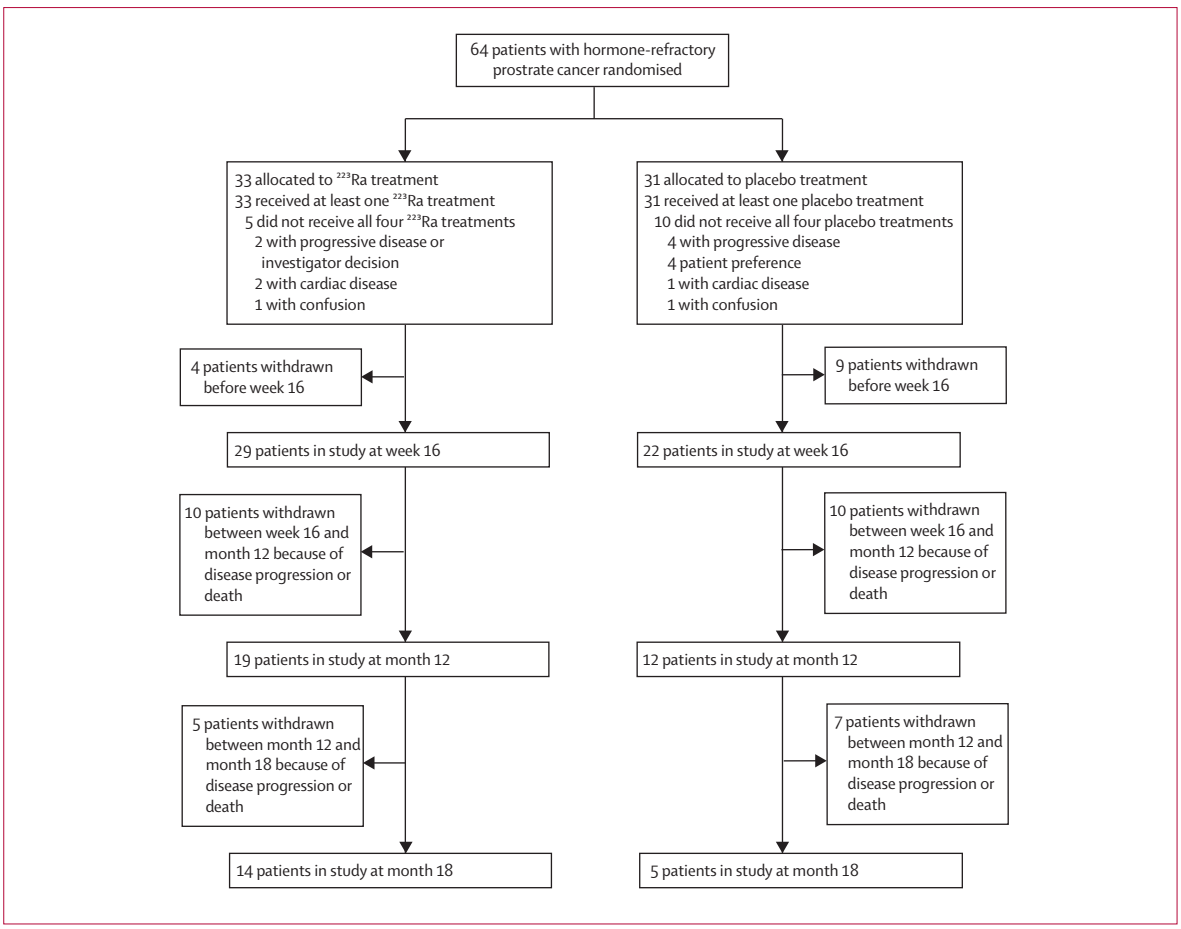

Figure 2: **Study profile**
All patients followed for survival irrespective of study status (ie, in study or withdrawn). Information on the number screened was not obtained.

Patients were monitored every 2 weeks until 4 weeks after the last injection, and then at 6, 9, and 12 months. Every visit included clinical history, concomitant medication, physical examination, pain and analgesic assessment, adverse event recording, and blood tests (including bone-ALP, PSA, full blood count, and markers of bone turnover). Patients were followed for survival and long-term toxic effects at 18 and 24 months.

Bubley described PSA-confirmed response and progression in 1999.[7] Confirmed PSA response was a 50% reduction from baseline and confirmed with a second measurement at least 4 weeks later. PSA progression was an increase of 25% from nadir in patients without a confirmed PSA response and 50% in those with a confirmed PSA response. SREs were defined as one of a specific set of events listed in the panel.

Patients who began non-study treatment (eg, hormonal therapy, external-beam radiotherapy) for progressive disease during the study were allowed to continue with the study drug and be analysed for safety. Efficacy analyses were done with and without censoring at the time of commencement of non-study treatments (corticosteroids,

	^{223}Ra (n=33)	Placebo (n=31)
Age, years	73, 73 (57–88)	72, 72 (60–84)
Haemoglobin, g/L	126, 125 (100–153)	129, 126 (99–149)
PSA, ng/mL	167, 511 (10–6000)	233, 480 (1–4002)
Bone-ALP, ng/mL	57, 121 (13–1145)	68, 132 (11–706)
Total ALP, U/L	228, 437 (80–3047)	279, 501 (51–2280)
Albumin, g/L	40, 39 (28–46)	38, 39 (30–47)
Lactate dehydrogenase (U/L)	348, 351 (154–750)	345, 426 (144–1284)
ECOG performance status		
0	9	6
1	18	20
2	6	5
Extent of disease		
<6 metastases	12	7
6–20 metastases	10	13
>20 metastases	11	11
Pain severity index	3·50, 3·88 (1·00–7·75)	4·00, 3·78 (0·75–7·75)

Data are number of patients (median, mean, range) in intention-to-treat population

Table 1: **Baseline patient characteristics**

external-beam radiotherapy, cytotoxic chemotherapy, additional radionuclides, hormones, and bisphosphonates). The study design was approved by all the research ethics committees from the study jurisdictions and centres.

In addition to time to SREs, bone-ALP was chosen as a primary endpoint because it is used in clinical practice as a marker of disease extent and prognosis, and because a bone-targeted therapy would probably not be effective in treating hormone-refractory prostate cancer without greatly affecting bone-ALP. Secondary endpoints included safety, serum markers of bone turnover (total ALP, procollagen I N propeptide [PINP], C-terminal crosslinking telopeptide of type I collagen [S-CTX-I], and type I collagen crosslinked C-telopeptide [ICTP]), serum PSA, and overall survival.

	^{223}Ra (n=33)				Placebo (n=30*)			
	1	2	3	4	1	2	3	4
Platelets	6	0	0	0	4	0	1	0
Neutrophils	5	2	1	0	0	0	0	0
White blood cells	9	1	1	0	3	0	0	0
Haemoglobin	26	4	1	0	19	6	0	1

*One patient was not evaluable for toxic effects. Numbers in second row are toxicity graded with CTCAE version 3.0. Data are number of patients.

Table 2: **Worst grade for haematological toxic effects during treatment**

	^{223}Ra			Placebo		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Confusional State	1	0	0	0	0	0
Vomiting	0	1	0	0	0	0
Pseudomonas infection	0	0	1*	0	0	0
Exacerbated chronic obstructive airways disease	0	0	1*	0	0	0
Pneumonia	0	1	1†	0	0	0
Sepsis	0	0	1†	0	0	1‡
Dehydration	0	0	1†	0	0	0
Spinal cord compression	0	1	0	0	0	1¶
Chest pain	0	1	0	0	0	0
Myocardial infarction	0	0	1§	0	0	0
Tumour flare	0	0	1§	0	0	1
Ataxia	0	0	0	0	0	1
Subdural haematoma	0	0	0	0	0	1
Deep-vein thrombosis	0	0	0	0	1	0
Perineal pain	0	0	0	0	0	1
Bone pain	0	0	0	0	1‡	2¶
Atrial fibrillation	0	0	0	0	0	1‡
Adrenal disorder	0	0	0	0	0	1
Fall	0	0	0	0	0	1**
Cachexia	0	0	0	0	1**	0
Haemoglobin decreased	0	0	0	1	0	0
Pyrexia	0	0	0	0	1††	0
Malignant neoplasm	0	0	0	0	0	1††
Hypocalcaemia	0	0	0	0	1	0
Intestinal obstruction	0	0	0	0	0	1

Mild=transient and easily tolerated. Moderate=causes discomfort and interrupts usual activities. Severe=considerable interference with usual activities, and might be incapacitating or life threatening. *One patient had pseudomonas infection and exacerbated chronic obstructive airways disease. †One patient had pneumonia, sepsis, and dehydration. ‡One patient had atrial fibrillation, sepsis, and bone pain. ¶One patient had bone pain and spinal cord compression §One patient had myocardial infarction and tumour flare.**One patient had a fall and cachexia. ††One patient had pyrexia and malignant neoplasm. When a serious adverse event was reported more then once by the same patient, the highest intensity is listed.

Table 3: **Serious adverse events**

Statistical methods

The study was designed to have 80% power to detect an absolute difference at 5% significance level of at least 15% between treatment and control groups with respect to the mean change in bone ALP from baseline to 4 weeks after the last injection. Although medians are reported in the results and are more useful for clinicians, no standard techniques exist for calculating sample size from medians, therefore, means were used for this purpose. Sample size calculations were based on the normal distribution with the following formula and rounded up: $n=(2*SD^2*(Z_{\alpha/2}+Z_{\beta})^2/meandiff^2 + Z_{\alpha/2}/4)$ ($Z_{\alpha/2}$=value of normal distribution [1·96] for $\alpha/2$ [α=0·05], and Z_{β}=value of normal distribution [0·84] for 1-power [power=0·8]).

We planned a sample size of 60 patients (30 in each group). Patients who received at least one dose of study drug were included in the analyses, and all results were analysed by intention to treat. All tests of significance were done at the 5% significance level and no adjustment for multiplicity was done for secondary variables, since the present study was explorative in nature. We expected that the relative change of bone ALP and other variables would not be normally distributed, and would contain non-positive data, so standard transformation methods would not be possible. Therefore, we analysed the difference between groups of relative change of bone ALP and other variables by use of the Wilcoxon ranked-sums test. For the analysis of time to event, we used a log-rank test (unadjusted) and a Cox proportional hazards model (adjusted for covariates). Covariates were baseline values of albumin, ECOG performance status, haemoglobin, lactate dehydrogenase, PSA, total ALP, and age. Proportions were analysed with the Fisher's exact test. We used screening values for missing data at baseline, and a last-value-carried-forward approach for missing laboratory values. For relative change and time-to-PSA-progression, we excluded two patients in the placebo group without any post-baseline values.

Role of the funding source

This study was sponsored by Algeta ASA (Oslo, Norway) in collaboration with TFS Trial Form Support (Lund, Sweden; monitoring and database); Harrison Clinical Research (Ely, UK; monitoring); and Statisticon AB (Uppsala, Sweden; statistical advice and analysis). BB and JH are employees of Algeta. BB was involved in the study design, and BB and JH contributed to the analysis

and interpretation of the data. Algeta had no other role in the collection, analysis, or interpretation of the data. The corresponding author had full access to all the raw data and the final responsibility to submit for publication. JH, PS, and SN also had access to the raw data.

Results

64 patients were recruited in 11 centres in Sweden, Norway, and the UK between Feb 11, 2004, and May 3, 2005 (figure 2). 33 patients were assigned external-beam radiotherapy and ^{223}Ra, and 31 to external-beam radiotherapy and placebo. Table 1 shows the baseline values of bone-ALP, haemoglobin, albumin, PSA, age, extent of disease on bone scan,[9] and pain score. We recorded no significant difference in external-beam radiotherapy dose fractionation at baseline between the study groups (^{223}Ra, median 8 Gy [range 6–30]; placebo, 8 Gy [8–30]). All patients have been followed for at least 18 months (range 18–24).

All 64 patients received external-beam radiotherapy and at least one injection of study drug. 28 patients in the ^{223}Ra group and 21 in the placebo group completed all four injections of study drug. Figure 2 shows the reasons for not completing all four treatments. During treatment (from week –1 to week 16), corticosteroids were begun in 24 patients (12 ^{223}Ra, 12 placebo), anti-androgens in two ^{223}Ra patients, oestrogen in one placebo patient, and bisphosphonate in two placebo patients.

The extent of haematological toxic effects was at a minimum (table 2). Thrombocytopenia (CTCAE grade 2+) was not seen in the ^{223}Ra group but recorded in one placebo patient. We recorded grade 2+ neutropenia in three patients given ^{223}Ra and none given placebo. Neutropenia was reversible and most commonly seen during the first 4 weeks of treatment, with no evidence of cumulative myelotoxic effects recorded. We saw no substantial differences in haematological toxic effects between the two groups, and no patient discontinued ^{223}Ra because of treatment-related toxic effects.

12 serious adverse events were reported in eight patients receiving ^{223}Ra, compared with 19 serious adverse events in 14 patients receiving placebo (table 3). One patient's vomiting needed hospital care 6 h after the first ^{223}Ra injection, which was deemed related to the study drug. This patient received subsequent injections with ^{223}Ra without further vomiting. The investigators deemed that vomiting was treatment-related; but they were uncertain whether sepsis (reported in one patient in each study group) and tumour flare (one patient in the ^{223}Ra group) were treatment-related (one patient in the placebo group had tumour flare, but this was deemed not treatment-related). All other serious adverse events were deemed unrelated to treatment.

Table 4 lists adverse events that occurred in more than 15% of patients. Apart from constipation, no statistically significant difference existed between treatment groups. Constipation was mild or moderate in all but one patient.

	^{223}Ra (n=33)				Placebo (n=31)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Diarrhoea	6	3	0	9	5	5	0	10
Constipation	6	5	1	12	0	2	0	2
Vomiting	4	4	0	8	3	3	0	6
Nausea	6	3	0	9	6	3	1	10
Fatigue	3	5	0	8	7	0	0	7
Bone pain	2	7	1	10	7	7	2	16
Myalgia	3	2	0	5	3	1	0	4
Tumour flare	2	3	1	6	1	5	1	7
Anaemia	0	5	0	5	2	3	2	7

Data are number of patients. Mild=transient and easily tolerated. Moderate=causes discomfort and interrupts usual activities. Severe=considerable interference with usual activities, and might be incapacitating or life threatening.

Table 4: **Adverse events in more than 15% of study population during treatment (reported by at least nine patients)**

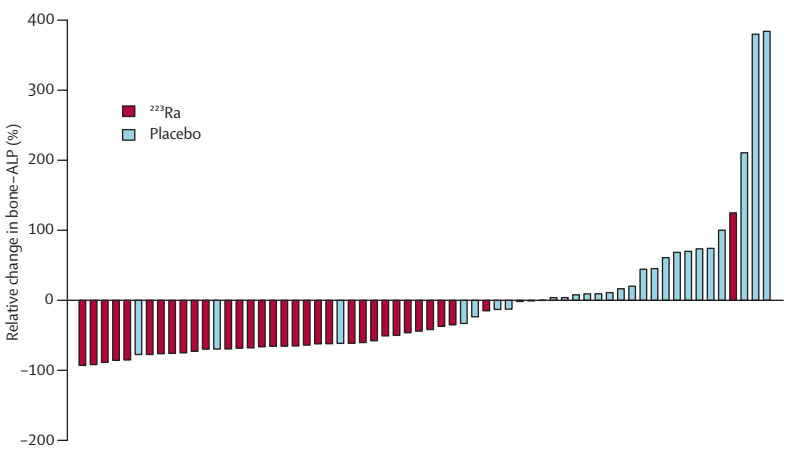

Figure 3: **Distribution of % change in serum bone-ALP from baseline to 4 weeks after last study drug**
Individual results sorted by effect size.

	^{223}Ra	Placebo	p*
Bone-ALP	–65·6% (–92·2 to 124·9)	9·3% (–77·4 to 384·1)	<0·0001
Total ALP	–46·2% (–89·3 to 102·5)	30·7% (–75·4 to 212·9)	<0·0001
PINP	–63·2% (–93·7 to 151·0)	38·3% (–72·5 to 602·8)	<0·0001
CTX-I	–31·4% (–74·3 to 143·3)	31·7% (–57·5 to 395·8)	0·002
ICTP	14·6% (–54·6 to 158·9)	43·2% (–56·3 to 242·1)	0·011

Data are median (range). *Wilcoxon ranked-sums test.

Table 5: **Relative change in serum markers of bone metabolism from baseline to 4 weeks after last study injection**

Median time to onset of constipation was 4 weeks (range 1–12) in the ^{223}Ra group, and actual time of onset from baseline was 7 and 10 weeks in the two patients in the placebo group. Unfortunately, no data for duration of constipation were available.

Median relative change in bone-ALP from baseline to 4 weeks after last study injection was –65·6% (95% CI

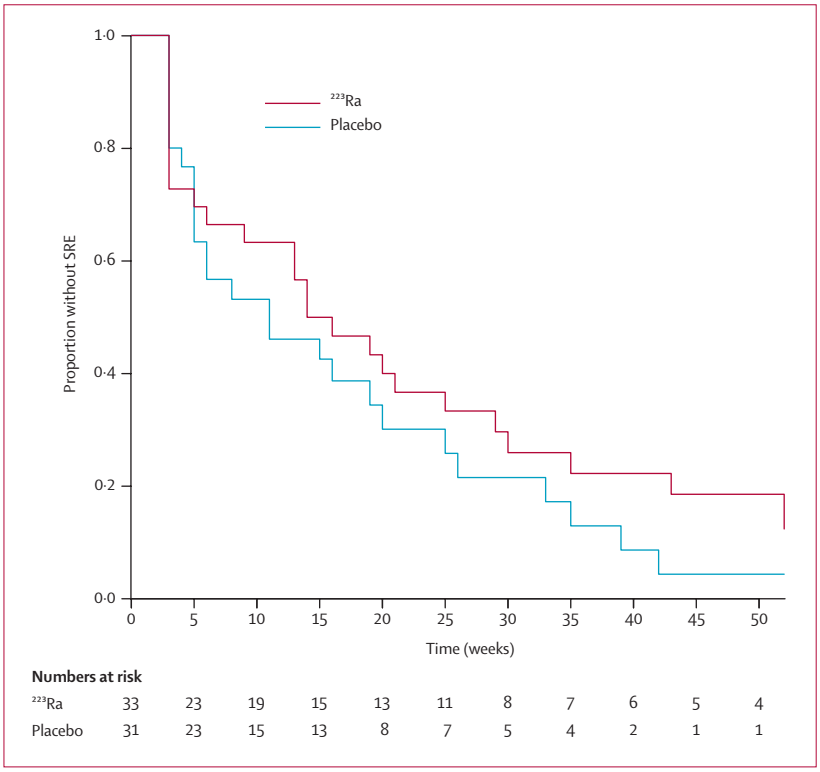

Figure 4: **Survival function of time to first SRE**

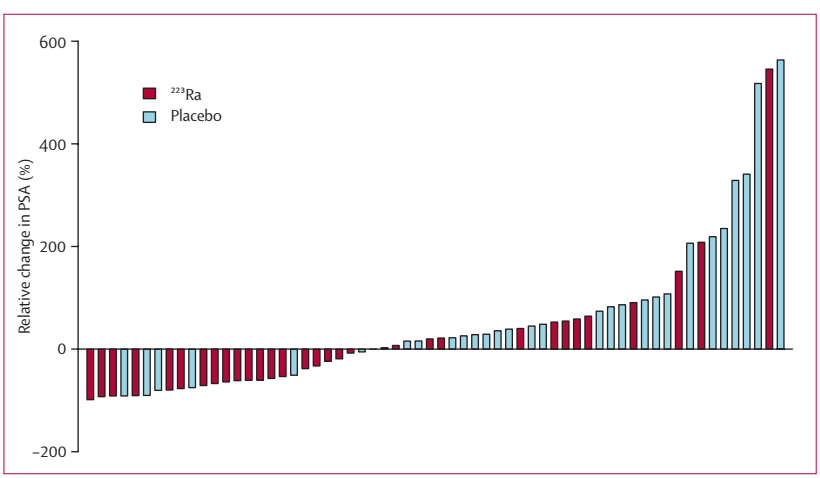

Figure 5: **Distribution of % change in serum PSA from baseline to 4 weeks after last study drug**
Individual results sorted by effect size.

–69·5 to –57·7) in the ^{223}Ra group and 9·3% (3·8–60·9) in the placebo group (p<0·0001, Wilcoxon ranked-sums test). Figure 3 shows distribution of the change in bone-ALP. Table 5 shows median relative change in bone-ALP and the other serum markers of bone metabolism. Compared with the placebo group, the ^{223}Ra group had a significant reduction in all five markers (bone-ALP, total-ALP, PINP, CTX-I, and ICTP).

Median time to first SRE was 14 weeks (95% CI 9–30) in the ^{223}Ra group and 11 weeks (5–25) in the placebo group (p=0·257, log rank; figure 4). Hazard ratio for time to first SRE adjusted for baseline covariates was 1·75 (95% CI 0·96–3·19, p=0·065, Cox regression) where the placebo group is the reference. By week 16, 17 patients in the ^{223}Ra group had 34 SREs in total, compared with 18 patients who had 44 SREs in the placebo group (p=0·625, Fisher's exact test). If we excluded pain and analgesic consumption from the SRE definitions, six patients in the ^{223}Ra group had nine SREs in total, compared with 11 patients in the placebo group who had 21 SREs (p=0·159). By week 52, 26 patients in each group had had at least one SRE.

Median relative change in PSA from baseline to 4 weeks after last study injection was –23·8% (range –98·6 to 545·6) in the ^{223}Ra group and 44·9% (–91·3 to 563·5) in the placebo group (p=0·003, Wilcoxon ranked-sums test; figure 5). A confirmed PSA response of more than 50% was seen in 11 of 31 patients assigned ^{223}Ra and five of 28 assigned placebo (p=0·153, Fisher's exact test). Median time to PSA progression was 26 weeks (95% CI 16–39) for ^{223}Ra compared with 8 weeks (4–12) for placebo (p=0·048, log rank).

Censoring for concomitant treatment that might affect PSA did not change the overall results, since most treatments were started after the PSA endpoints were reached (PSA response or progression). After censoring of concomitant treatments, nine patients who were assigned ^{223}Ra showed a confirmed PSA response of at least 50% compared with two assigned placebo (p=0·045, Fisher's exact test). The three censored patients in the placebo group and two in the experimental group with confirmed 50% PSA response had all started corticosteroids. Median time to PSA progression remained at 26 weeks for ^{223}Ra-treated patients compared with 8 weeks for placebo (p=0·040, log rank).

Median overall survival was 65·3 weeks (95% CI 48·7–∞) for ^{223}Ra and 46·4 weeks (32·1–77·4) weeks for placebo (p=0·066, log rank; figure 6). Hazard ratio for survival adjusted for baseline covariates was 2·12 (95% CI 1·13–3·98, p=0·020, Cox regression), indicating an increased risk of death in the placebo group. At 18 months' follow-up, 15 patients assigned ^{223}Ra survived compared with eight assigned placebo.

Discussion

In our randomised study of patients with symptomatic, hormone-refractory prostate cancer, ^{223}Ra was well tolerated with little or no myelotoxic effect, and showed promising evidence of efficacy. One primary endpoint was met, with a significant effect on bone-ALP 4 weeks after last treatment. Efficacy data in this small study suggested a potential beneficial effect of ^{223}Ra on SRE risk, time to PSA progression, and overall survival. The good toxicity profile seen for ^{223}Ra will allow future studies to use increased doses and extended treatment periods.

This study shows promising evidence for the safety and tolerability of ^{223}Ra 50 kBq/kg at 4 weekly intervals.

The lack of haematological toxic effects contrasts with those in previous studies of beta-emitting radioisotopes in the treatment of hormone-refractory prostate cancer. For example, ^{89}Sr was studied in a trial of similar design (n=126),[10] in which grade 2+ thrombocytopenia was seen in 41 (61%) of 67 patients assigned ^{89}Sr versus six (10%) of 58 assigned placebo. Notably, grade 4 thrombocytopenia was seen in seven (10%) patients in the ^{89}Sr group versus one (2%) in the placebo group. ^{89}Sr was shown to significantly reduce alkaline phosphatase and PSA concentrations, but no effect was seen on overall survival. On the basis of the present study, ^{223}Ra at 50 kBq/kg given every 4 weeks seems to be at least as effective as conventional radioisotopes, but with fewer haematological toxic effects. This result supports the hypothesis that, compared with beta-emitters such as ^{89}Sr and HEDP-^{153}Sm, the short-range, high LET alpha radiation from ^{223}Ra has an increased anti-tumour effect, with relative sparing of the bone marrow.[11] Since myelosuppressive chemotherapy is now a standard treatment for hormone-refractory prostate cancer and pancytopenia is a feature of progressive disease, this result represents a major advantage for the future development of ^{223}Ra. Docetaxel is the standard first-line chemotherapy for hormone-refractory prostate cancer.[12] In view of the favourable toxicity profile of ^{223}Ra in the present trial, combination therapy with docetaxel could be considered, either sequentially or concurrently. Furthermore, whereas ^{89}Sr and HEDP-^{153}Sm are used for pain palliation, and repeat treatment is not possible until bone-marrow recovery, the toxicity profile of ^{223}Ra will allow repeat treatment of asymptomatic patients and could have a disease-modifying effect.

For non-haematological toxic effects, constipation was the only adverse event seen substantially more often in the ^{223}Ra group than in the placebo group, for which the explanation is unclear. Constipation was mild or moderate in all but one patient, and no clear temporal relation was recorded with study drug treatment. Notably, the phase I study[6] showed that ^{223}Ra was associated with diarrhoea and not constipation.

A significant benefit for ^{223}Ra was recorded with respect to all serum bone markers. These endpoints are not in themselves clinically meaningful, but suggest that ^{223}Ra has a real biological effect on bone metabolism. Favourable trends were seen in all PSA endpoints, including a significant effect on time to PSA progression, which is consistent with the hypothesis that effective treatment of bone metastases can substantially delay overall disease progression in hormone-refractory prostate cancer.

Interpretation of the clinically meaningful endpoints is restricted by the sample size, and by the fact that all patients received external-beam radiotherapy at baseline. Too few SREs were recorded for firm conclusions to be drawn regarding the clinical effectiveness of ^{223}Ra. However, in the pivotal trial of zoledronate,[13] the proportion of patients having an SRE fell from 44% to 33%, a relative reduction of 25%.

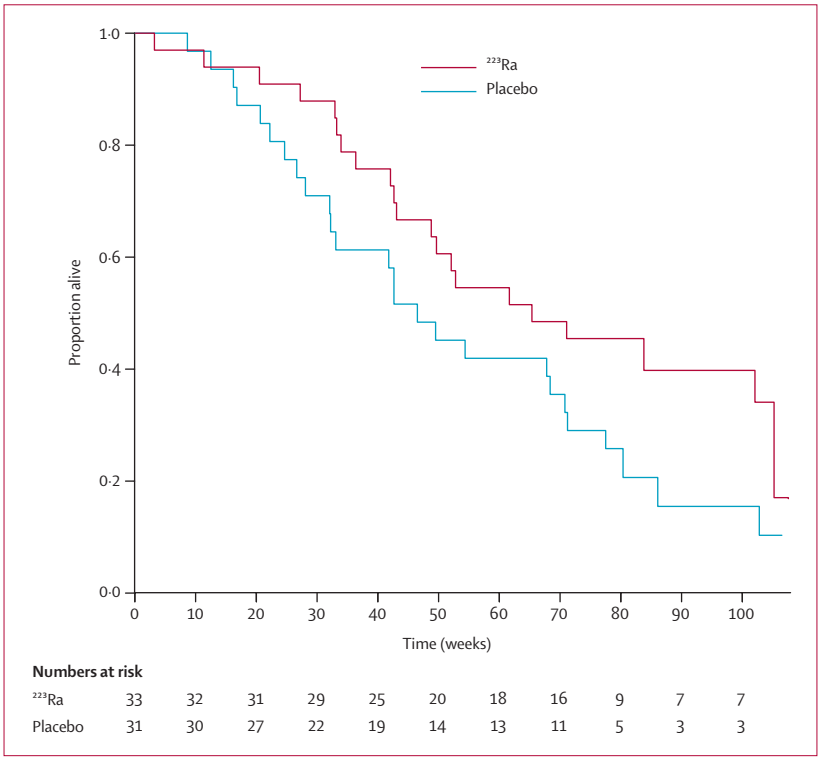

Figure 6: **Overall survival**

The overall survival data in this study of only 64 patients should be interpreted with caution. The effects of known baseline prognostic factors on time to SRE, time to PSA progression, and overall survival time have been tested using a Cox proportional hazards model, which, if anything, increased rather than decreased the treatment effect of ^{223}Ra. Furthermore, our small randomised trial is the third to show a significant advantage in overall survival for radioisotope treatment in hormone-refractory prostate cancer.[14,15] Thus, the survival benefit of ^{223}Ra in this trial could be a genuine treatment effect. However, the benefits of ^{223}Ra could be due to an imbalance in important but unknown baseline characteristics (eg, doubling time of pretreatment PSA). Efficacy data might also be confounded by concomitant use of other anticancer treatments. However, the main results remain unaltered or strengthened after patients were censored at the time of receiving concomitant treatments. Therefore the benefits of ^{223}Ra seen in this study are unlikely to be explained by concomitant treatments. Further studies of ^{223}Ra should explore the potential for escalation of dose and for increased duration of treatment by more than four injections. The bone-targeting properties of ^{223}Ra could also be applicable to the treatment of skeletal metastasis from other primary cancers.

Contributors

ØB, PS, BB, JY, and SN contributed to study design. SN, LF, CP, CT, RB, JT, BL, UP, DJ, MS, KP, JY, and MG contributed to data collection. ØB, CP, BB, JH, PS, and SN had access to the raw data, and contributed to analysis and interpretation of the data. CP wrote the first draft of the manuscript and had final editorial control. All authors contributed to revision of the manuscript.

Conflicts of interest

CP, ØB, and PS are external consultants of Algeta ASA, Norway (sponsors of the study and manufacturers of ^{223}Ra). BB and JH are employees of Algeta ASA. ØB, LF, BB, and JH own stock or options in Algeta ASA. CP received payment from Algeta ASA for writing the manuscript. No other conflict of interest has been declared.

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