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Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

ABSTRACT

BACKGROUND

Radium-223 dichloride (radium-223), an alpha emitter, selectively targets bone metastases with alpha particles. We assessed the efficacy and safety of radium-223 as compared with placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases.

METHODS

In our phase 3, randomized, double-blind, placebo-controlled study, we randomly assigned 921 patients who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, to receive six injections of radium-223 (at a dose of 50 kBq per kilogram of body weight intravenously) or matching placebo; one injection was administered every 4 weeks. In addition, all patients received the best standard of care. The primary end point was overall survival. The main secondary efficacy end points included time to the first symptomatic skeletal event and various biochemical end points. A prespecified interim analysis, conducted when 314 deaths had occurred, assessed the effect of radium-223 versus placebo on survival. An updated analysis, when 528 deaths had occurred, was performed before crossover from placebo to radium-223.

RESULTS

At the interim analysis, which involved 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs. 11.2 months; hazard ratio, 0.70; 95% confidence interval [CI], 0.55 to 0.88; two-sided P=0.002). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001). Assessments of all main secondary efficacy end points also showed a benefit of radium-233 as compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer adverse events.

CONCLUSIONS

In this study, which was terminated for efficacy at the prespecified interim analysis, radium-223 improved overall survival. (Funded by Algeta and Bayer HealthCare Pharmaceuticals; ALSYMPCA ClinicalTrials.gov number, NCT00699751.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Parker at the Royal Marsden Hospital, Academic Urology Unit, Downs Rd., Sutton, Surrey SM2 5PT, United Kingdom, or at chris.parker@rmh.nhs.uk.

*Additional investigators in the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study are listed in the Supplementary Appendix, available at NEJM.org.

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More than 90% of patients with metastatic castration-resistant prostate cancer have radiologic evidence of bone metastases, which are a major cause of death, disability, decreased quality of life, and increased treatment cost among these patients.[1,2] Unlike deaths from many other types of cancer, deaths from prostate cancer are often due to bone disease and its complications.[3] Current bone-targeted therapies have not been shown to improve survival, and the benefits derived from bisphosphonates, denosumab, and existing radioisotope treatments are primarily limited to pain relief and delay of skeletal events.[4-13]

Radium-223 dichloride (radium-223) is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 μm).[14] As a bone-seeking calcium mimetic, radium-223 is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases.[15,16] The high-energy alpha-particle radiation induces mainly double-stranded DNA breaks that result in a potent and highly localized cytotoxic effect in the target areas.[10,15,17,18] The short path of the alpha particles also means that toxic effects on adjacent healthy tissue and particularly the bone marrow may be minimized.[16,19,20]

Radium-223 has been reported to have a favorable safety profile, with minimal myelotoxicity, in phase 1 and 2 studies involving patients with bone metastases.[21,22] Phase 2 studies have shown that radium-223 reduces pain and improves disease-related biomarkers (e.g., bone alkaline phosphatase and prostate-specific antigen [PSA]),[22-24] and they have suggested a survival benefit among patients with castration-resistant prostate cancer and bone metastases.[22] To evaluate the effect of radium-223 on survival, we conducted the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study, a phase 3, randomized, double-blind, multinational study comparing the efficacy and safety of radium-223 versus placebo in patients with castration-resistant prostate cancer and bone metastases.

A Quick Take animation is available at NEJM.org

METHODS

STUDY OVERSIGHT AND CONDUCT

The study was designed, conducted, and analyzed by employees of Algeta and Bayer HealthCare Pharmaceuticals, the sponsors, in collaboration with the study investigators. The blinded database was held at a third-party contract clinical research organization that provided data to the independent data and safety monitoring committee, assembled by the sponsors. After the independent data and safety monitoring committee recommended unblinding of the data, analyses were performed as defined in the statistical-analysis plan by statisticians employed by the sponsors, and the results were reviewed by the authors. The study investigators signed time-limited confidentiality agreements with the sponsors regarding publishing of the study data. Assistance in writing the first draft of the manuscript was provided by a professional medical writer paid by Bayer HealthCare Pharmaceuticals. All authors wrote the manuscript, made the decision to submit it for publication, and assume responsibility for the completeness and integrity of the data and adherence of the study to the protocol. The protocol and statistical-analysis plan are available with the full text of this article at NEJM.org.

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

PATIENTS

Patients were eligible to participate in the study if they had histologically confirmed, progressive castration-resistant prostate cancer with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases; were receiving the best standard of care; and had received docetaxel, were not healthy enough or declined to receive it, or it was not available. Castration-resistant disease was defined as a serum testosterone level of 50 ng per deciliter or lower (≤1.7 nmol per liter) after bilateral orchiectomy or during maintenance treatment consisting of androgen-ablation therapy with a luteinizing hormone–releasing hormone agonist or polyestradiol phosphate. Patients with castration-resistant disease during maintenance treatment were required to continue that treatment throughout the study. Patients were required to have symptomatic disease with regular use of analgesic medication or treatment with external-beam radiation therapy required for cancer-related bone pain within the previous 12 weeks. Additional eligibility criteria included a baseline PSA level of 5 ng per milliliter or higher with

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evidence of progressively increasing PSA values (two consecutive increases over the previous reference value); an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a scale of 0 to 5, with 0 indicating no symptoms and full activity and higher scores indicating greater functional compromise[25]) (see the definitions of ECOG performance-status scores in the Supplementary Appendix, available at NEJM.org); a life expectancy of 6 months or longer; and adequate hematologic, renal, and liver function.

Patients were excluded if they had received chemotherapy within the previous 4 weeks or had not recovered from adverse events due to chemotherapy. Additional exclusion criteria were previous hemibody external radiotherapy, systemic radiotherapy with radioisotopes within the previous 24 weeks, a blood transfusion or use of erythropoietin-stimulating agents within the previous 4 weeks, a malignant lymphadenopathy that was more than 3 cm in the short-axis diameter, a history of or the presence of visceral metastases, and imminent or established spinal cord compression. All patients provided written informed consent.

STUDY DESIGN AND REGIMEN

Patients were stratified according to previous use or nonuse of docetaxel, baseline alkaline phosphatase level (<220 U per liter vs. ≥220 U per liter), and current use or nonuse of a bisphosphonate. They were randomly assigned in a 2:1 ratio to receive six intravenous injections of radium-223 (at a dose of 50 kBq per kilogram of body weight) or matching placebo; one injection was administered every 4 weeks (see Fig. S1A and the description of radium-223 radiation safety in the Supplementary Appendix). The best standard of care was defined as the routine care provided at each center (e.g., local external-beam radiation therapy or treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine). Chemotherapy, hemibody external radiotherapy, and other systemic radionuclides were not permitted during the period from the first injection of the study drug to 4 weeks after the last injection of the study drug. The planned follow-up period was 3 years.

The primary end point was overall survival, defined as the time from randomization to the date of death, regardless of cause. The main secondary efficacy end points were the time to an increase in the total alkaline phosphatase level (defined as an increase of ≥25% from baseline at ≥12 weeks, in patients with no decrease from baseline, or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline), a total alkaline phosphatase response (defined as a reduction of ≥30% from the baseline value, confirmed ≥4 weeks later), the time to the first symptomatic skeletal event (defined as the first use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or nonvertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention), normalization of the total alkaline phosphatase level (defined as a return to a value within the normal range at 12 weeks [confirmed by two consecutive measurements ≥2 weeks apart] in patients with total alkaline phosphatase values above the upper limit of the normal range at baseline), and the time to an increase in the PSA level (defined as a relative increase of ≥25% from the baseline level and an absolute increase of ≥2 ng per milliliter at ≥12 weeks, in patients with no decrease in the PSA level from baseline, or a relative increase of ≥25% and an absolute increase of ≥2 ng per milliliter above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline). Other secondary end points included additional efficacy end points (listed in Table S1 in the Supplementary Appendix), safety end points, and quality of life.

STUDY ASSESSMENTS

Efficacy assessments included survival status, clinically evaluated symptomatic skeletal events, and total alkaline phosphatase and PSA concentrations. Safety was assessed on the basis of adverse events, hematologic values, clinical laboratory variables, and findings on electrocardiography and physical examination. All adverse events that occurred after randomization and within 12 weeks after the last injection of the study drug were reported and evaluated for their potential relationship to the study drug. Adverse events that occurred more than 12 weeks after the final injection of the study drug were reported only if they were determined to be related to the study drug by the investigator. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire.[26]

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STATISTICAL ANALYSIS

A sample of 900 patients was required to provide a statistical power of 90% to detect a hazard ratio of 0.76 for the risk of death in the radium-223 group versus the placebo group with a two-sided alpha significance level of 0.05. The final overall survival analysis would be conducted after approximately 640 deaths had occurred. One formal interim analysis was planned after approximately 50% of the deaths (i.e., 320 deaths) had occurred, to assess the effect of radium-223 on the primary end point (overall survival). As prespecified in the protocol, the Lan–DeMets alpha spending approach[27] was applied with O'Brien–Fleming stopping boundaries[28] to evaluate the difference in overall survival between the two groups. On the basis of the actual number of deaths at the time of the interim analysis (314), a two-sided alpha significance level of 0.0028 or lower was required to support early termination of the study for efficacy. An independent data and safety monitoring committee was responsible for evaluating the results of the interim analysis. On the basis of this evaluation, which showed a survival advantage with radium-223 and an acceptable safety profile, the committee recommended early discontinuation of the trial and crossover from placebo to radium-223. We report here the results of an updated descriptive analysis of the efficacy and safety data, performed when 528 deaths had occurred, before any crossover treatment with radium-223 was administered.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Radium-223 (N=614)	Placebo (N=307)
Age		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	575 (94)	290 (94)
Total alkaline phosphatase — no. (%)		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)
Any previous use of docetaxel — no. (%)		
Yes	352 (57)	174 (57)
No	262 (43)	133 (43)
ECOG performance-status score — no. (%)‡		
0	165 (27)	78 (25)
1	371 (60)	187 (61)
≥2	77 (13)	41 (13)
WHO ladder for cancer pain — no. (%)§		
1	257 (42)	137 (45)
2	151 (25)	78 (25)
3	194 (32)	90 (29)
Extent of disease — no. (%)		
<6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
>20 metastases	195 (32)	91 (30)
Superscan¶	54 (9)	30 (10)

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Table 1. (Continued.)

Characteristic	Radium-223 (N=614)	Placebo (N=307)
External-beam radiation therapy within 12 wk after screening — no. (%)		
Yes	99 (16)	48 (16)
No	515 (84)	259 (84)
Median biochemical values (range)‖		
Hemoglobin — g/dl	12.2 (8.5–15.7)	12.1 (8.5–16.4)
Albumin — g/liter	40 (24–53)	40 (23–50)
Total alkaline phosphatase — U/liter	211 (32–6431)	223 (29–4805)
Lactate dehydrogenase — U/liter	315 (76–2171)	336 (132–3856)
PSA — μg/liter	146 (3.8–6026)	173 (1.5–14500)

* Percentages may not sum to 100 due to rounding.
† Race was self-reported.
‡ The Eastern Cooperative Oncology Group (ECOG) scores the performance status of patients with respect to activities of daily living as follows: 0, fully active and able to carry out all predisease activities without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature; 2, ambulatory and up and about for more than 50% of waking hours and capable of self-care but unable to carry out work activities; 3, capable of only limited self-care and confined to a bed or chair for more than 50% of waking hours; 4, completely disabled; and 5, dead.
§ A total of 12 patients in the radium-223 group (2%) and 2 patients in the placebo group (1%) had no pain or analgesic use at baseline. A World Health Organization (WHO) score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use.
¶ Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.
‖ The normal ranges are as follows: hemoglobin, 13.4 to 17.0 g per deciliter; albumin, 36 to 45 g per liter; total alkaline phosphatase, 35 to 105 U per liter; lactate dehydrogenase, 115 to 255 U per liter; and prostate-specific antigen (PSA), 0 to 3.999 μg per liter.

The stratified log-rank test was used as the primary analysis for survival; subgroup analyses were performed to assess whether the treatment effect was consistent across subgroups. The main secondary efficacy end points were analyzed with the use of a gatekeeping procedure to control for the overall type I error rate; an end point was tested at a two-sided significance level of 0.05 only if the two-sided P value for all higher-ranking end points was 0.05 or lower. The intention-to-treat population included all randomly assigned patients, and the safety population was composed of patients who received at least one injection of a study drug.

After unblinding of the data, inconsistencies were noted between the total number of symptomatic skeletal events as reported on the case-report form and the number in the listings of adverse events. Thus, a post hoc sensitivity analysis was performed after resolution of these inconsistencies with the study sites. As shown in Figure S2 and Table S2 in the Supplementary Appendix, these inconsistencies did not affect the results of the original analysis to any meaningful degree.

RESULTS

PATIENTS AND STUDY REGIMEN

From June 2008 through February 2011, a total of 921 patients were enrolled (614 in the radium-223 group and 307 in the placebo group) at 136 study centers in 19 countries and were included in the intention-to-treat population (Fig. S1B in the Supplementary Appendix). The safety population included 901 patients (600 in the radium-223 group and 301 in the placebo group). Baseline clinical and demographic characteristics were well balanced between the study groups (Table 1). The planned interim analysis was based on data from 809 enrolled patients (541 in the radium-223 group and 268 in the placebo group) (Table S3 in the Supplementary Appendix).

Overall, as of this writing, 532 of 921 patients (58%) had received all six injections of the study drug (387 patients in the radium-223 group [63%] and 145 in the placebo group [47%]). The median number of injections was six in the radium-223 group and five in the placebo group.

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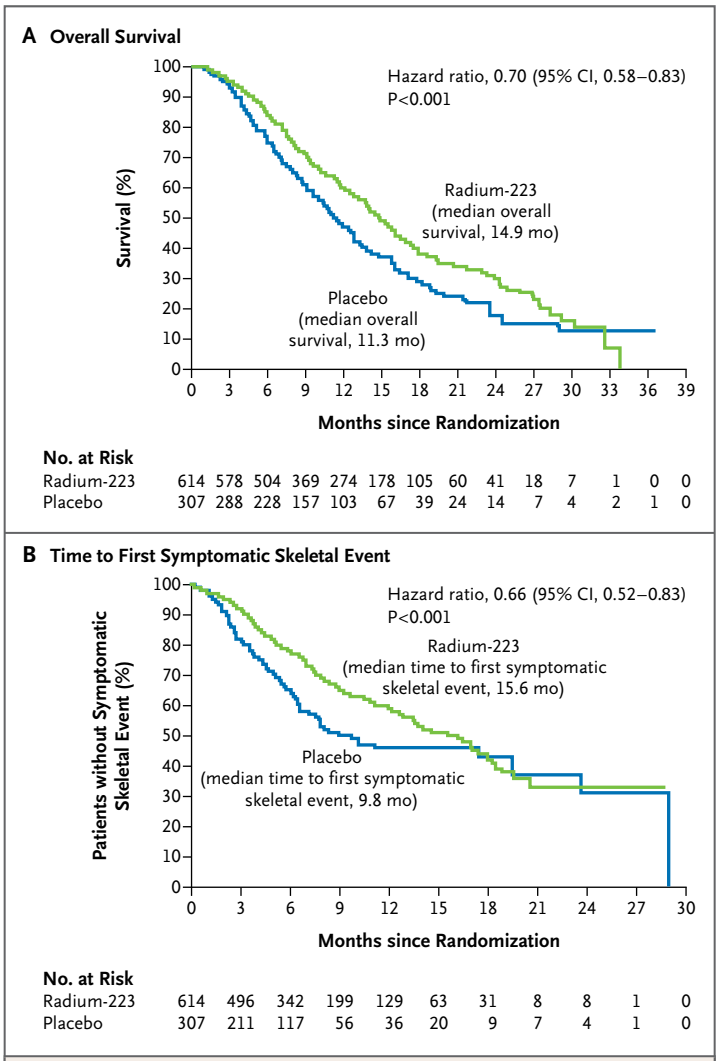

Figure 1. **Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event.**

EFFICACY

At the interim analysis, the median overall survival was 14.0 months in the radium-223 group and 11.2 months in the placebo group (Fig. S3A in the Supplementary Appendix). Radium-223, as compared with placebo, was associated with a 30% reduction in the risk of death (hazard ratio, 0.70; 95% confidence interval [CI], 0.55 to 0.88; two-sided P=0.002). In the intention-to-treat population, 314 patients died. In the radium-223 group, 191 of 541 patients died (35%), and in the placebo group, 123 of 268 patients died (46%). The effect of radium-223 on overall survival was consistent across all subgroups (Fig. S3B in the Supplementary Appendix), and radium-223, as compared with placebo, was not associated with significantly more grade 3 or 4 toxic effects (Table S4 in the Supplementary Appendix). On the basis of these data, the independent data and safety monitoring committee recommended termination of the trial.

In the updated analysis, the median overall survival was 14.9 months in the radium-223 group and 11.3 months in the placebo group (Fig. 1A). The updated analysis confirmed the 30% reduction in the risk of death among patients in the radium-223 group as compared with the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001). A total of 528 patients in the intention-to-treat population died. In the radium-223 group, 333 of 614 patients died (54%), and in the placebo group, 195 of 307 patients died (64%). The effect of radium-223 on overall survival was consistent across all subgroups (Fig. 2).

All main secondary efficacy end points provided support for the benefit of radium-223 plus the best standard of care over placebo plus the best standard of care (Table 2). Radium-223, as compared with placebo, significantly prolonged the time to the first symptomatic skeletal event (median, 15.6 months vs. 9.8 months; hazard ratio, 0.66; 95% CI, 0.52 to 0.83; P<0.001) (Fig. 1B), the time to an increase in the total alkaline phosphatase level (hazard ratio, 0.17; 95% CI, 0.13 to 0.22; P<0.001) (Fig. S4A in the Supplementary Appendix), and the time to an increase in the PSA level (hazard ratio, 0.64; 95% CI, 0.54 to 0.77; P<0.001) (Fig. S4B in the Supplementary Appendix). Increases in the alkaline phosphatase and PSA levels, as defined in the protocol, were assessed after 12 weeks; a post hoc analysis of alkaline phosphatase and PSA levels from the start of study-drug administration is shown in Figure S4C and S4D in the Supplementary Appendix, respectively. In addition, a significantly higher proportion of patients in the radium-223 group than in the placebo group had a response according to the total alkaline phosphatase level (≥30% reduction, P<0.001) and normalization of this level (P<0.001). A 30% or greater reduction in PSA blood levels at week 12 was achieved in 16% of patients in the radium-223 group and in 6% of patients in the placebo group (P<0.001). This reduction was sustained 4 weeks after the last injection in 14% of patients in the radium-223 group and in 4% of patients in the placebo group (P<0.001).

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Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)

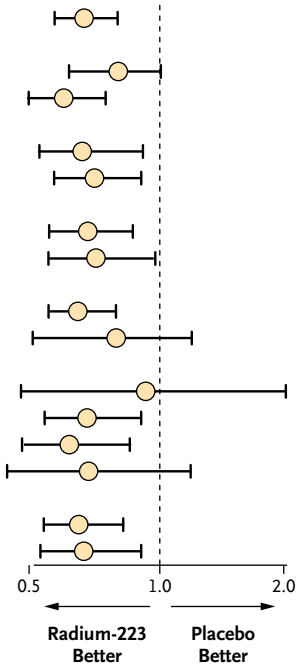

Figure 2. Subgroup Analysis of Hazard Ratios for Death in the Two Study Groups.

The Eastern Cooperative Oncology Group (ECOG) scores the performance status of patients with respect to activities of daily living as follows: 0, fully active and able to carry out all predisease activities without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature; 2, ambulatory and up and about for more than 50% of waking hours and capable of self-care but unable to carry out work activities; 3, capable of only limited self-care and confined to a bed or chair for more than 50% of waking hours; 4, completely disabled; and 5, dead. The category for use of opioids includes patients with a score of 2 or 3 on the World Health Organization "ladder" for cancer pain (a score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use). The category for nonuse of opioids includes patients without pain or opioid use at baseline and patients with a score of 1 on the WHO ladder for cancer pain. Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity. ALP denotes alkaline phosphatase, and NE not evaluated.

SAFETY

The number of patients who had adverse events after they received the study drug was consistently lower in the radium-223 group than in the placebo group for all adverse events (558 of 600 patients [93%] vs. 290 of 301 patients [96%]), grade 3 or 4 adverse events (339 patients [56%] vs. 188 patients [62%]), serious adverse events (281 patients [47%] vs. 181 patients [60%]), and study-drug discontinuation because of adverse events (99 patients [16%] vs. 62 patients [21%]).

Hematologic and nonhematologic adverse events that occurred in at least 5% of patients in either study group are shown in Table 3. Overall, no clinically meaningful differences in the frequency of grade 3 or 4 adverse events were observed between the study groups. Grade 3 febrile neutropenia was reported in one patient (<1%) in the radium-223 group and in one patient (<1%) in the placebo group. Only one grade 5 hematologic adverse event was considered to be possibly related to the study drug: thrombocytopenia in a patient in the radium-223 group, who died from pneumonia with hypoxemia, with no evidence of bleeding. For serious adverse events that occurred in at least 5% of patients in the radium-223 group or the placebo group, the respective frequencies were as follows: disease progression (11% and 12%), bone pain (10% and 16%), anemia (8% and 9%), and spinal cord compression (4% and 5%).

A significantly higher percentage of patients who received radium-223, as compared with those

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Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

* Only patients who had elevated total alkaline phosphatase levels at baseline are included.

who received placebo, had a meaningful improvement in the quality of life according to the FACT-P total score (i.e., an increase in the score of ≥10 points on a scale of 0 to 156, with higher scores indicating a better overall quality of life) during the period of study-drug administration (25% vs. 16%, P=0.02). The mean change in the FACT-P total score from baseline to week 16 significantly favored the radium-223 group, as compared with the placebo group (–2.7 vs. –6.8, P=0.006).

DISCUSSION

In this phase 3 study, radium-223 significantly prolonged overall survival in patients who had castration-resistant prostate cancer and bone metastases, with a 30% reduction in the risk of death, as compared with placebo. In the updated analysis, the median survival was longer among patients who received radium-223 than among those who received placebo, by 3.6 months. All main secondary efficacy end points were significant and favored treatment with radium-223, including the clinically defined end point of the time to the first symptomatic skeletal event, which was significantly prolonged among patients who received radium-223. Whereas other trials included asymptomatic fractures — detected by means of periodic radiologic review — as skeletal events, in this study, only symptomatic pathologic bone fractures were included as symptomatic skeletal events.

The highly targeted nature of radium-223, with alpha particles of short range (<100 μm), minimizes myelosuppression and has limited effects on normal tissue. The overall incidence of adverse events was consistently lower in the radium-223 group than in the placebo group for adverse events of all grades, grade 3 or 4 adverse events, and serious adverse events. The number of patients who discontinued the study drug because of adverse events was also lower in the radium-223 group. No clinically meaningful differences in the frequency of hematologic adverse events were observed between the study groups.

A distinctive feature of the study was the liberal definition of the best standard of care permitted with both study drugs (radium-223 and placebo); this allowed patients to be treated with standard therapies chosen by the treating physician. Consequently, findings from this study may be generalizable to routine clinical practice, since the control group consisted of patients who received placebo with the best standard of care. The study also has high external validity because it used liberal inclusion criteria that are representative of the general population of patients with castration-resistant prostate cancer. One limitation was the exclusion of patients with visceral metastases, which may occur in up to 25% of patients with castration-resistant prostate cancer.[1,29]

Many patients with castration-resistant prostate cancer and bone metastases do not receive docetaxel because they are too frail (ECOG performance-status score >2), they have coexisting conditions that preclude its use, or they simply decline treatment. Our study addressed this important group by including patients who were not

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Table 3. Adverse Events That Occurred in at Least 5% of Patients in Either Study Group in the Safety Population.

Adverse Event	Radium-223 (N=600)				Placebo (N=301)			
	All Grades	Grade 3	Grade 4	Grade 5*	All Grades	Grade 3	Grade 4	Grade 5*
	number of patients (percent)							
Hematologic								
Anemia	187 (31)	65 (11)	11 (2)	0	92 (31)	37 (12)	2 (1)	1 (<1)
Thrombocytopenia	69 (12)	20 (3)	18 (3)	1 (<1)	17 (6)	5 (2)	1 (<1)	0
Neutropenia	30 (5)	9 (2)	4 (1)	0	3 (1)	2 (1)	0	0
Nonhematologic								
Constipation	108 (18)	6 (1)	0	0	64 (21)	4 (1)	0	0
Diarrhea	151 (25)	9 (2)	0	0	45 (15)	5 (2)	0	0
Nausea	213 (36)	10 (2)	0	0	104 (35)	5 (2)	0	0
Vomiting	111 (18)	10 (2)	0	0	41 (14)	7 (2)	0	0
Asthenia	35 (6)	5 (1)	0	0	18 (6)	4 (1)	0	0
Fatigue	154 (26)	21 (4)	3 (1)	0	77 (26)	16 (5)	2 (1)	0
Deterioration in general physical health	27 (4)	9 (2)	2 (<1)	5 (1)	21 (7)	8 (3)	2 (1)	2 (1)
Peripheral edema	76 (13)	10 (2)	0	0	30 (10)	3 (1)	1 (<1)	0
Pyrexia	38 (6)	3 (1)	0	0	19 (6)	3 (1)	0	0
Pneumonia	18 (3)	9 (2)	0	4 (1)	16 (5)	5 (2)	2 (1)	0
Urinary tract infection	47 (8)	7 (1)	0	0	28 (9)	4 (1)	1 (<1)	1 (<1)
Weight loss	69 (12)	4 (1)	0	0	44 (15)	5 (2)	0	0
Anorexia	102 (17)	9 (2)	0	0	55 (18)	2 (1)	0	0
Decreased appetite	35 (6)	2 (<1)	0	0	13 (4)	0	0	0
Bone pain	300 (50)	120 (20)	5 (1)	0	187 (62)	74 (25)	3 (1)	0
Muscular weakness	9 (2)	2 (<1)	1 (<1)	0	17 (6)	6 (2)	0	0
Pathologic fracture	22 (4)	13 (2)	0	0	15 (5)	8 (3)	1 (<1)	0
Progression of malignant neoplasm	77 (13)	9 (2)	4 (1)	55 (9)	44 (15)	4 (1)	1 (<1)	33 (11)
Dizziness	43 (7)	2 (<1)	0	0	26 (9)	2 (1)	0	0
Spinal cord compression	25 (4)	14 (2)	6 (1)	1 (<1)	23 (8)	16 (5)	1 (<1)	0
Insomnia	27 (4)	0	0	0	21 (7)	1 (<1)	0	0
Hematuria	30 (5)	7 (1)	0	0	15 (5)	3 (1)	0	0
Urinary retention	25 (4)	9 (2)	0	0	18 (6)	6 (2)	0	0
Dyspnea	49 (8)	10 (2)	1 (<1)	1 (<1)	26 (9)	7 (2)	0	3 (1)

* Only one grade 5 hematologic adverse event was considered to be possibly related to the study drug: thrombocytopenia in one patient in the radium-223 group.

thought to be eligible to receive chemotherapy or who chose not to receive it. It is possible that some of these men could have received chemotherapy at other institutions or in other studies; however, at least 20 to 40% of patients with castration-resistant prostate cancer and bone metastases never receive chemotherapy,[30-32] so our study addresses an important unmet need in a population that is not served by current therapies.

The treatment of prostate cancer has evolved since the trial began, with new data on the use of cabazitaxel,[29] abiraterone,[33] and enzalutamide[34] in patients who have received docetaxel. The excellent safety profile of radium-223 and the nonover-

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lapping mechanism of action make radium-223 potentially suitable for use either sequentially or in combination with these other agents. A phase 1–2 trial of radium-223 combined with docetaxel in patients with castration-resistant prostate cancer and bone metastases is currently ongoing (ClinicalTrials.gov number, NCT01106352).

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APPENDIX

The authors' full names, academic degrees, and affiliations are as follows: Royal Marsden National Health Service Foundation Trust and Institute of Cancer Research, Sutton (Christopher Parker, M.D.), Centre for Cancer Research and Cell Biology, Queen's University, Belfast (Joe M. O'Sullivan, M.D.), Christie Hospital, Manchester (John Logue, F.R.C.R.), Mount Vernon Hospital Cancer Centre, Northwood (Peter Hoskin, M.D.), St. James's University Hospital, Leeds (David Bottomley, F.R.C.R.), Cancer Research UK Clinical Trials Unit, School of Cancer Sciences, Birmingham (Nicholas D. James, M.D., Ph.D.), Clatterbridge Center for Oncology, Wirral (Isabel Syndikus, F.R.C.R.), and Weston Park Hospital, Sheffield (Robert Coleman, M.D.) — all in the United Kingdom; Karolinska University Hospital, Stockholm (Sten Nilsson, M.D., Ph.D.), Centrallasarettet Växjö, Växjö (Mihalj Seke, M.D.), Umeå University (Anders Widmark, M.D., Ph.D.) and Umeå University Hospital (Lars Franzén, M.D., Ph.D.), Umeå, and Länssjukhuset Sundsvall-Härnösand County Hospital, Sundsvall (L.F.) — all in Sweden; Akershus University Hospital, Lørenskog (Daniel Heinrich, M.D.), Haukeland University Hospital, Bergen (Svein Inge Helle, M.D., Ph.D.), Radiumhospitalet (Sophie D. Fosså, M.D., Ph.D.), Ullevål University Hospital (Dag Clement Johannessen, M.D.), Algeta (Charles Gillies O'Bryan-Tear, M.R.C.P., Karin Staudacher, M.Sc.), and Norwegian Radium Hospital and Faculty of Medicine, University of Oslo (Øyvind S. Bruland, M.D., Ph.D.), Oslo, and St. Olavs Hospital, Trondheim (Arne Solberg, M.D., Ph.D.) — all in Norway; Hospital Kochova, Chomutov, Czech Republic (Aleš Chodacki, M.D.); Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland (Paweł Wiechno, M.D., Ph.D.); Jessenius School of Medicine, University Hospital, Martin, Slovakia (Jan Kliment, M.D.); Ortenau Klinikum Offenburg-Gengenbach, Klinik für Urologie und Kinderurologie, Offenburg (Steffen Wedel, M.D.), and Gemeinschaftspraxis, Berlin (Sibylle Boehmer, Dipl.Med.) — both in Germany; Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Instituto do Câncer do Estado de São Paulo, São Paulo (Marcos Dall'Oglio, M.D., Ph.D.); Comprehensive Cancer Centers of Nevada, Las Vegas (Nicholas J. Vogelzang, M.D.); Bayer HealthCare Pharmaceuticals, Montville, NJ (Jose Garcia-Vargas, M.D., Minghua Shan, Ph.D.); and Tulane Cancer Center, New Orleans (Oliver Sartor, M.D.).

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REFERENCES

1. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.
2. Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004;350:1655-64.
3. Lange PH, Vessella RL. Mechanisms, hypotheses and questions regarding prostate cancer micrometastases to bone. Cancer Metastasis Rev 1998-1999;17:331-6.
4. Lipton A. Implications of bone metastases and the benefits of bone-targeted therapy. Semin Oncol 2010;37:Suppl 2:S15-S29.
5. Adami S. Bisphosphonates in prostate carcinoma. Cancer 1997;80:Suppl:1674-9.
6. Silberstein EB. Systemic radiopharmaceutical therapy of painful osteoblastic metastases. Semin Radiat Oncol 2000;10:240-9.
7. Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 2009;27:1564-71.
8. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, double-blind study. Lancet 2011;377:813-22.
9. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol 2005;6:392-400.
10. Lewington VJ. Bone-seeking radionuclides for therapy. J Nucl Med 2005;46:Suppl 1:38S-47S.
11. Sartor O. Potential synergistic implications for stromal-targeted radiopharmaceuticals in bone-metastatic prostate cancer. Asian J Androl 2011;13:366-8.
12. Sartor O, Bruland O. Stromal targeted therapies in prostate and renal cancer: new concepts and knowledge. Clin Genitourin Cancer 2011;9:1-2.
13. Sartor O, Goeckeler W, Bruland O. Stromal targeted therapy in bone metastatic prostate cancer: promise delivered. Asian J Androl 2011;13:783-4.
14. Bruland ØS, Nilsson S, Fisher DR, Larsen RH. High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter 223Ra: adjuvant or alternative to conventional modalities? Clin Cancer Res 2006;12:6250s-6257s.
15. Henriksen G, Breistøl K, Bruland ØS, Fodstad Ø, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. Cancer Res 2002;62:3120-5.
16. Henriksen G, Fisher DR, Roeske JC, Bruland ØS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med 2003;44:252-9.
17. Liepe K. Alpharadin, a 223Ra-based alpha-particle-emitting pharmaceutical for the treatment of bone metastases in patients with cancer. Curr Opin Investig Drugs 2009;10:1346-58.
18. McDevitt MR, Sgouros G, Finn RD, et al. Radioimmunotherapy with alpha-emitting nuclides. Eur J Nucl Med 1998;25:1341-51.
19. Kerr C. (223)Ra targets skeletal metastases and spares normal tissue. Lancet Oncol 2002;3:453.
20. Li Y, Russell PJ, Allen BJ. Targeted alpha-therapy for control of micrometastatic prostate cancer. Expert Rev Anticancer Ther 2004;4:459-68.
21. Nilsson S, Larsen RH, Fosså SD, et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. Clin Cancer Res 2005;11:4451-9.
22. Nilsson S, Franzén L, Parker C, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol 2007;8:587-94.
23. Parker CC, Pascoe S, Chodacki A, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra-223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol 2013;63:189-97.
24. Nilsson S, Strang P, Aksnes AK, et al. 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. Eur J Cancer 2012;48:678-86.
25. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
26. Cella D, Nichol MB, Eton D, et al. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy–Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health 2009;12:124-9.
27. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
28. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
29. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-54.
30. Perlroth DJ, Thompson SF, Luna Y, et al. Timing is everything: time to ADT and chemotherapy initiation for treatment of metastatic prostate cancer (mPC). Presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, February 2–4, 2012 (poster).
31. Perlroth DJ, Thompson SF, Mozaffari E, et al. Treating people right: who goes untreated with systemic therapy for metastatic prostate cancer (mPC)? Presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, February 2–4, 2012 (poster).
32. Harris V, Lloyd K, Forsey S, Rogers P, Roche M, Parker C. A population-based study of prostate cancer chemotherapy. Clin Oncol (R Coll Radiol) 2011;23:706-8.
33. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.
34. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-97.

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