Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Abiraterone acetate plus prednisone or prednisolone improves progression-free survival and overall survival in patients with metastatic castration-resistant prostate cancer. Radium-223 improves overall survival and delays the onset of symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases. We assessed concurrent treatment with abiraterone acetate plus prednisone or prednisolone and radium-223 in such patients.

Methods We did a randomised, double-blind, placebo-controlled, phase 3 trial at 165 oncology and urology centres in 19 countries. Eligible patients were aged 18 years or older, and had histologically confirmed, progressive, chemotherapy-naive, asymptomatic or mildly symptomatic castration-resistant prostate cancer and bone metastases, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 6 months, and adequate haematological, renal, and liver function. Participants were randomly assigned (1:1) according to a permuted block design (block size 4) via interactive response technology to receive up to six intravenous injections of radium-223 (55 kBq/kg) or matching placebo once every 4 weeks. All patients were also scheduled to receive oral abiraterone acetate 1000 mg once daily plus oral prednisone or prednisolone 5 mg twice daily during and after radium-223 or placebo treatment. The primary endpoint was symptomatic skeletal event-free survival, which was assessed in the intention-to-treat population. Safety analyses were done in all patients who received at least one dose of any study drug. This trial is registered with ClinicalTrials.gov, number NCT02043678. Enrolment has been completed, and follow-up is ongoing.

Findings Between March 30, 2014, and Aug 12, 2016, 806 patients were randomly assigned to receive radium-223 (n=401) or placebo (n=405) in addition to abiraterone acetate plus prednisone or prednisolone. The study was unblinded prematurely, on Nov 17, 2017, after more fractures and deaths were noted in the radium-223 group than in the placebo group (in an unplanned ad-hoc analysis), but all patients had completed radium-223 or placebo before this date. At the primary analysis (data cutoff Feb 15, 2018), 196 (49%) of 401 patients in radium-223 group had had at least one symptomatic skeletal event or died, compared with 190 (47%) of 405 patients in the placebo group (median follow-up 21·2 months [IQR 17·0–25·8]). Median symptomatic skeletal event-free survival was 22·3 months (95% CI 20·4–24·8) in the radium-223 group and 26·0 months (21·8–28·3) in the placebo group (hazard ratio 1·122 [95% CI 0·917–1·374]; p=0·2636). Fractures (any grade) occurred in 112 (29%) of 392 patients in the radium-223 group and 45 (11%) of 394 patients in the placebo group. The most common grade 3–4 treatment-emergent adverse events were hypertension (43 [11%] patients in the radium-223 group *vs* 52 [13%] patients in the placebo group), fractures (36 [9%] *vs* 12 [3%]) and increased alanine aminotransferase concentrations (34 [9%] *vs* 28 [7%]). Serious treatment-emergent adverse events occurred in 160 (41%) patients in the radium-223 group and 155 (39%) in the placebo group. Treatment-related deaths occurred in two (1%) patients in the radium-223 group (acute myocardial infarction and interstitial lung disease) and one (<1%) in the placebo group (arrhythmia).

Interpretation The addition of radium-223 to abiraterone acetate plus prednisone or prednisolone did not improve symptomatic skeletal event-free survival in patients with castration-resistant prostate cancer and bone metastases, and was associated with an increased frequency of bone fractures compared with placebo. Thus, we do not recommend use of this combination.

Funding Bayer.

Research in context

Evidence before this study

We did not do a systematic literature review before this study. Abiraterone acetate plus prednisone or prednisolone improves progression-free survival and overall survival in patients with metastatic castration-resistant prostate cancer. Radium-223 increases overall survival and decreases symptomatic skeletal events in patients with metastatic castration-resistant prostate cancer and bone metastases. Several other treatments have been approved as monotherapy for metastatic castration-resistant prostate cancer on the basis of improvements in overall survival, but little information is available about the optimal sequencing or role of combination therapy for these approved agents. In an international, early access, single-arm study, overall survival was improved a subgroup of patients who received radium-223 concomitantly with abiraterone acetate plus prednisone or prednisolone compared with those who received radium-223 alone. We aimed to assess the efficacy and safety of concurrent treatment with abiraterone acetate plus prednisone or prednisolone and radium-223 in asymptomatic or mildly symptomatic patients with chemotherapy-naive metastatic castration-resistant prostate cancer and bone metastases.

Added value of this study

To our knowledge, ERA 223 is the first randomised controlled trial to provide evidence for the efficacy and safety of the combination of two approved treatments that improve overall survival in metastatic castration-resistant prostate cancer. The study showed that the combination of abiraterone acetate plus prednisone or prednisolone and radium-223 did not improve symptomatic skeletal event-free survival or overall survival, and was associated with an increased frequency of fractures.

Implications of all the available evidence

On the basis of evidence of increased fractures and no improvement in symptomatic skeletal event-free survival or overall survival, we do not recommend the use of radium-223 in combination with abiraterone acetate and prednisone or prednisolone. As a result of our findings, the US Food and Drug Administration and the European Medicines Agency have revised prescribing recommendations for radium-223.

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Introduction

Radium-223 is a targeted alpha therapy that preferentially binds to bone metastases and induces double-stranded DNA breaks in tumour cells, osteoblasts, and osteoclasts.[1] Radium-223 is approved to treat patients with castration-resistant prostate cancer and symptomatic bone metastases. In ALSYMPCA,[2,3] radium-223 increased overall survival (hazard ratio [HR] 0·70 [95% CI 0·58–0·83]; p<0·001), delayed the onset of symptomatic skeletal events (HR 0·66 [95% CI 0·52–0·83]; p<0·001), and improved quality of life (odds ratio 1·82 [95% CI 1·21–2·74]; p=0·004) compared with placebo when added to best standard of care. Radium-223 was efficacious irrespective of previous docetaxel use,[4] and efficacy was similar in all subgroups of patients,[2] including those who were only mildly symptomatic.[5] Radium-223 was associated with fewer treatment-emergent adverse events than placebo,[2] including during long-term follow-up.[6] The safety profile and unique mechanism of action of radium-223 warrant clinical studies in combination with drugs such as docetaxel, enzalutamide, and abiraterone acetate plus prednisone or prednisolone.

Abiraterone acetate is the prodrug of abiraterone, a CYP17 inhibitor that blocks androgen synthesis in the testes, adrenal glands, and prostate cancer cells.[7] Abiraterone acetate is approved in combination with prednisone or prednisolone to treat metastatic castration-resistant prostate cancer either before or after docetaxel. In the COU-AA-302 trial[8] of patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer who had received no previous chemotherapy, abiraterone acetate plus prednisone significantly improved radiological progression-free survival, overall survival, and quality of life compared with placebo plus prednisone. In an international, early-access, open-label, single-arm phase 3b study,[9] 189 (27%) of 696 patients received radium-223 in combination with enzalutamide or abiraterone acetate plus prednisone or prednisolone, mostly after previous treatment with docetaxel. For the 154 patients who received combination therapy with radium-223 and abiraterone acetate plus prednisone or prednisolone, 82 (53%) were already receiving ongoing abiraterone acetate plus prednisone or prednisolone treatment before the first injection of radium-223. In post-hoc analyses, overall survival was longer in patients who received radium-223 in combination with either enzalutamide or abiraterone acetate plus prednisone or prednisolone than in those who received radium-223 alone; however, signficance was not reported.[9] Abiraterone acetate plus prednisone or prednisolone and radium-223 have different and potentially complementary mechanisms of action. On the basis of their individual effects in patients with metastatic castration-resistant prostate cancer, we expected that a combination of abiraterone acetate plus prednisone or prednisolone and radium-223 would improve symptomatic skeletal event-free survival to a greater extent than either agent alone. We did a placebo-controlled, phase 3 trial to assess the efficacy and safety of this combination in patients with asymptomatic or mildly symptomatic, chemotherapy-naive, castration-resistant prostate cancer and bone metastases.

Methods

Study design and participants

The Evaluation of Radium-223 dichloride in combination with Abiraterone in castration-resistant prostate cancer study (ERA 223) was a randomised, double-blind placebo-controlled, phase 3 trial done at 165 oncology and urology centres in 19 countries (appendix pp 2–4). Medically or surgically castrated patients aged 18 years or older were eligible for inclusion in the trial if they had histologically confirmed, progressive, asymptomatic or mildly symptomatic, castration-resistant adenocarcinoma of the prostate with at least two bone metastases on bone scan and no known visceral or brain metastasis. Eligible patients had blood testosterone concentrations less than 50 ng/dL (1·7 nmol/L). Those who had not undergone orchiectomy had to have received luteinising-hormone-releasing hormone agonists or antagonists for at least 4 weeks before randomisation and had to continue this therapy throughout the study. Patients who received an anti-androgen had to have shown prostate-specific antigen progression after discontinuation of the anti-androgen before enrolment. Other eligibility criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, life expectancy of at least 6 months, and adequate haematological, renal, and liver function. Patients were excluded if they had previously received treatment with cytotoxic chemotherapy for castration-resistant prostate cancer or abiraterone acetate plus prednisone or prednisolone, if they had uncontrolled hypertension or clinically significant heart disease, or if they had previous hemibody external radiotherapy. Other types of previous external radiotherapy were allowed if patients had adequate bone marrow function. Data about specific types of radiotherapy use were not systematically collected. The full exclusion criteria are shown in the appendix (p 5).

See Online for appendix

The trial was done in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable local regulations. An independent data monitoring committee monitored study conduct and reviewed unblinded safety data. All patients provided written ,informed consent before any study-specific procedures.

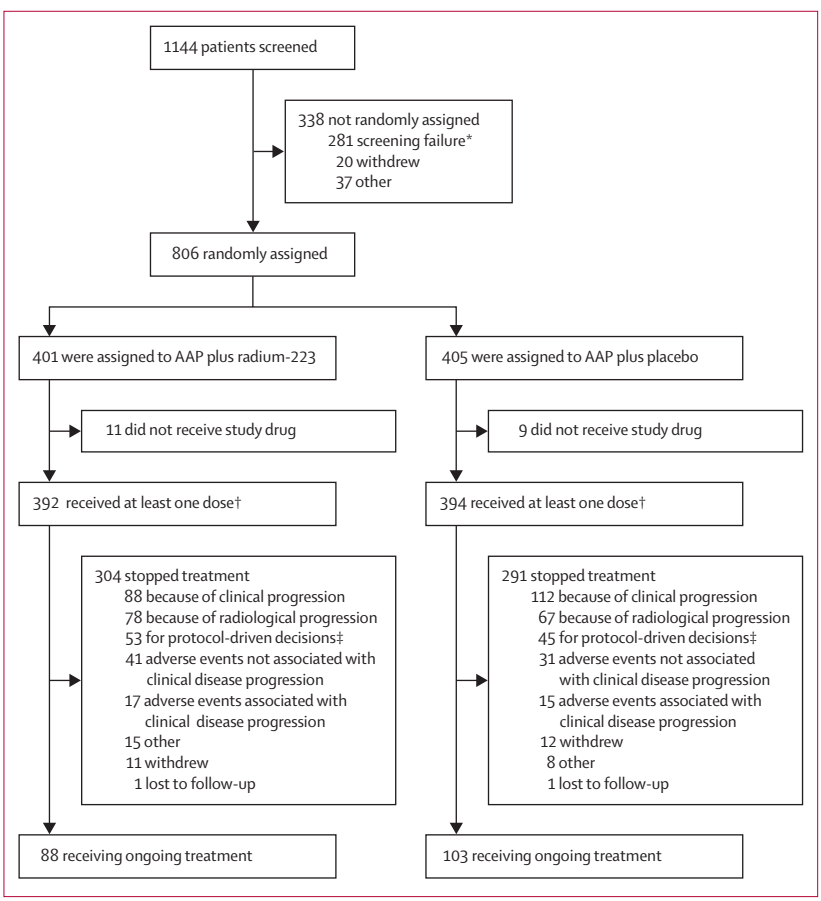

Figure 1: **Trial profile**
AAP=abiraterone acetate plus prednisone or prednisolone. *Defined as a patient who had provided informed consent but terminated the study for any reason (eg, not meeting selection criteria) before randomisation. †Two patients were randomly assigned to the placebo group, but unintentionally received one radium-223 dose during the treatment period; these patients were included in the radium-223 group in the safety population. ‡A symptomatic skeletal event occurred.

Randomisation and masking

Participants were recruited by study investigators. Eligible patients were randomly assigned (1:1) according to a permuted block design (block size 4) by use of validated interactive response technology (Almac; Souderton, PA, USA) to receive radium-223 or placebo in addition to abiraterone acetate plus prednisone or prednisolone. The study sponsor prepared the computer-generated randomisation list that was provided to the interactive response system. Randomisation was stratified by baseline use of denosumab versus bisphosphonates versus none, total alkaline phosphatase concentration (<90 U/L *vs* ≥90 U/L), and geographical region (western Europe, North America, and Australia *vs* Asia *vs* rest of world). Treating physicians, study staff, and patients were masked to treatment assignment. Patients in the placebo group received injections of colourless placebo solution that was visually indistinguishable from radium-223 solution.

Procedures

Patients were scheduled to receive up to six intravenous injections of radium-223 at a dose of 55 kBq/kg or matching placebo, with an interval of 4 weeks between injections. All patients were also scheduled to receive oral abiraterone acetate 1000 mg once daily plus oral prednisone or prednisolone 5 mg twice daily during and after the radium-223 or placebo treatment, until occurrence of a symptomatic skeletal event, which was defined as use of external beam radiotherapy to relieve skeletal symptoms, a new symptomatic pathological bone fracture, spinal cord compression, or a tumour-related orthopaedic surgical intervention. Patients with more than one event were counted only for the category of symptomatic skeletal event in which the first event

occurred. If several symptomatic skeletal events (ie, component events) occurred on the same date in one patient, the patient was counted in only one category in order of decreasing priority: spinal cord compression, then bone fracture, then orthopaedic surgery, then external beam radiotherapy. Fractures were assessed by the investigators and were reported as adverse events. A central, masked review of all fracture data was done by the co-principal investigators and a member of the study's steering committee to ensure consistent classification of pathological and non-pathological fractures (according to the presence or absence of bone metastases at the site of fracture) and correct classification of symptomatic skeletal events. Progression was documented by prostate-specific antigen concentrations according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria[10] or by radiological progression according to the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1).[11] Asymptomatic or mildly symptomatic disease was defined as a worst pain score in the previous 24 h of 3 or less on the Brief Pain Inventory-Short Form questionnaire. Radiological assessment of bone and soft-tissue progression was done centrally. Progression in soft tissue and occurrence of visceral disease were assessed by CT or MRI according to RECIST (version 1.1);[11] progression based on bone scans was defined per PCWG2 criteria.[10] Study treatment could be delayed for up to 4 weeks to allow time to recover from adverse events. If treatment was delayed for greater than 4 weeks, it had to be discontinued. Adjustment of radium-223 or placebo dose was not permitted. The dose of abiraterone acetate could be reduced no more than twice if adverse events occurred. Dose adjustments for prednisone or prednisolone were not specified in the protocol. If a patient had a symptomatic skeletal event but continued to receive clinical benefit, abiraterone acetate plus prednisone or prednisolone were continued as standard of care rather than as a study drug. If a symptomatic skeletal event occurred during the first six cycles, patients could continue radium-223 and abiraterone acetate plus prednisone or prednisolone if they continued to receive clinical benefit per investigator judgment.

The treatment period extended from initiation of treatment until 4 weeks after the last administration of abiraterone acetate plus prednisone or prednisolone as study treatment or 6 months after last administration of radium-223 or placebo (whichever occurred later), unless a new systemic anti-cancer therapy was initiated, at which point patients entered long-term follow-up. At the end of the treatment period, patients who had not had a symptomatic skeletal event plus radiological progression and had not begun a new anti-cancer therapy entered an active follow-up period. This period extended until the patient had a symptomatic skeletal event with radiological progression, initiated a new anti-cancer therapy, was unable to travel to the clinic, was lost to follow-up, or died, to a maximum of 7 years after the last dose of radium-223 or placebo. Radiological assessments (technetium-99m bone scans and CT scans) were done at

	AAP plus radium-223 group (n=401)	AAP plus placebo group (n=405)
Age (years)	71 (65–77)	71 (66–77)
Race		
White	285 (71%)	284 (70%)
Black or African American	10 (2%)	16 (4%)
Asian	79 (20%)	78 (19%)
Native American or Alaskan	1 (<1%)	1 (<1%)
Not reported	26 (6%)	26 (6%)
Gleason score at diagnosis		
<8	140 (35%)	154 (38%)
≥8	246 (61%)	233 (58%)
Missing	15 (4%)	18 (4%)
Concurrent use of denosumab or bisphosphonates	157 (39%)	172 (42%)
Alkaline phosphatase		
<90 U/L	114 (28%)	119 (29%)
≥90 U/L	284 (71%)	283 (70%)
Missing	3 (1%)	3 (1%)
Months of previous androgen deprivation therapy	34 (18–65)	34 (21–57)
ECOG performance status		
0	262 (65%)	281 (69%)
1	137 (34%)	121 (30%)
Missing	2 (<1%)	3 (1%)
BPI-SF worst pain score		
0 (asymptomatic)	195 (49%)	198 (49%)
1–3 (mildly symptomatic)	181 (45%)	174 (43%)
Missing	25 (6%)	33 (8%)
Extent of disease		
Normal or abnormal because of benign bone disease	2 (<1%)	0
<6 metastases	134 (33%)	141 (35%)
6–20 metastases	175 (44%)	181 (45%)
>20 metastases (not superscan)	71 (18%)	70 (17%)
Superscan	19 (5%)	13 (3%)
Laboratory measurements		
Prostate-specific antigen (μg/L)	30 (12–92)	31 (11–77)
Alkaline phosphatase (U/L)	129 (82–251)	121 (84–214)
Lactate dehydrogenase (U/L)	224 (185–370)	218 (180–326)
Medical history of osteoporosis	21 (5%)	9 (2%)
Previous therapy		
Docetaxel	9 (2%)	6 (1%)
Ketoconazole	8 (2%)	4 (1%)
Enzalutamide	32 (8%)	21 (5%)
Sipuleucel-T	11 (3%)	11 (3%)

Data are median (IQR) or n (%). AAP=abiraterone acetate plus prednisone or prednisolone. ECOG=Eastern Cooperative Oncology Group. BPI-SF=Brief Pain Inventory-Short Form.

Table 1: **Patient demographics and clinical characteristics (intention-to-treat population)**

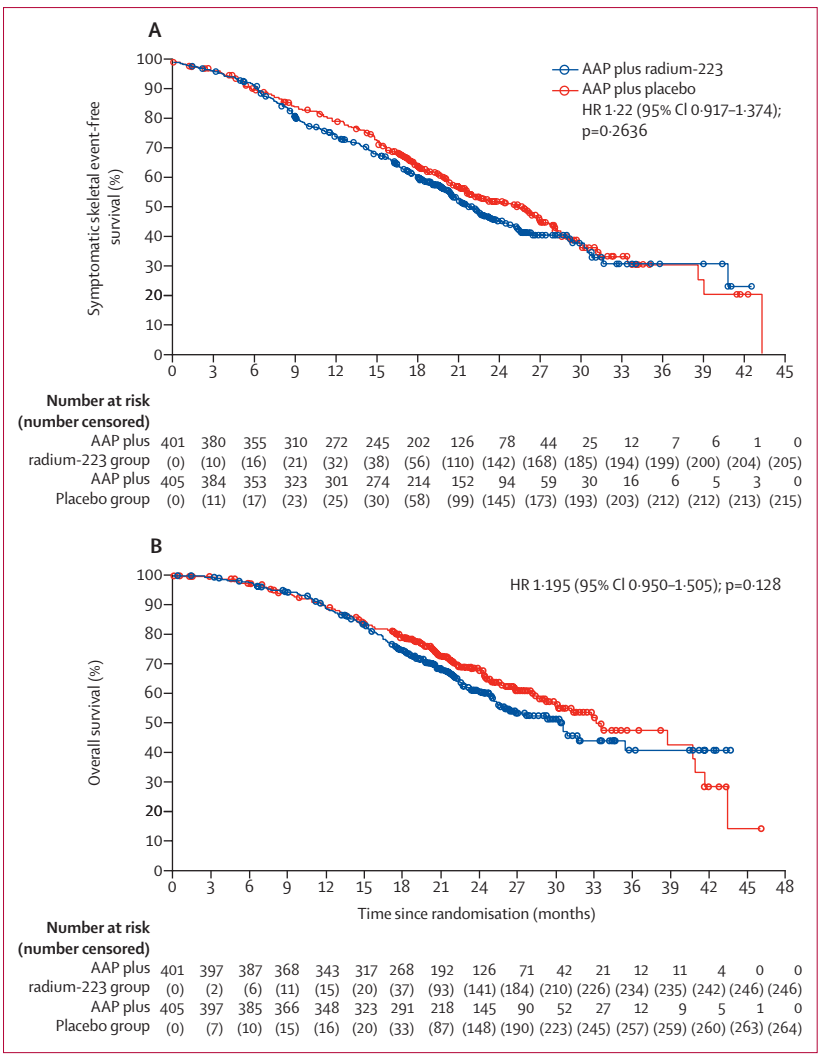

Figure 2: **Kaplan-Meier estimates of symptomatic skeletal event-free survival (A) and overall survival (B) in the intention-to-treat population**

AAP=abiraterone acetate plus prednisone or prednisolone. HR=hazard ratio.

baseline, on day 1 of cycles 3, 5, and 7, and then every 12 weeks. Patients who had a symptomatic skeletal event with radiological progression or who initiated a new anti-cancer therapy during the treatment or active follow-up periods entered a long-term follow-up period during which they were monitored every 6 months, by telephone, up to 7 years after the last dose (appendix p 6).

Use of bisphosphonates or denosumab was permitted if the patient was receiving them at baseline, but they could not be initiated during the study because of potential confounding effects on the primary outcome (a decision that was reached after discussion with health authorities before the start of the study). A full list of prohibited concomitant medications is in the appendix (p 7). Concentrations of markers of bone formation (bone alkaline phosphatase and N-terminal propeptide of type I collagen [P1NP]) and resorption (urine N-terminal cross-link telopeptides [uNTX] and serum CTX C-terminal cross-link telopeptides [βCTX]) were measured in serum and urine samples at baseline, after four cycles, after seven cycles, and at the end of treatment. We excluded end-of-treatment samples from correlative analyses to allow for identification of radium-223-specific pharmacodynamic effects. All adverse events that occurred during the treatment period were graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) and reported and assessed for their potential relationship to study treatments. Adverse events occurring after the treatment period were reported if judged to be related to study treatments by investigators.

The study was unblinded early on the recommendation of the independent data monitoring committee, because more fractures and deaths were noted in the radium-223 group than in the placebo group; the protocol was then amended on April 3, 2018, to permit initiation of bone health agents (drugs that improve bone health—specifically denosumab or bisphosphonates), to require all bone fractures and bone-associated events to be reported as adverse events or serious adverse events irrespective of the assessment of cause, and to require imaging scans diagnosing fractures to be sent for central independent review.

Health-related quality of life was assessed with the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network prostate cancer symptom index 17-item questionnaire (NCCN-FACT FPSI-17) physical disease-related symptoms subscale score measured during the treatment period.

Outcomes

The primary endpoint was symptomatic skeletal event-free survival, which was defined as the time from randomisation to first symptomatic skeletal event or death from any cause.

Secondary endpoints were overall survival (which was defined as time from randomisation to death from any cause), time to opiate use for cancer pain (time from randomisation to use of opiates), time to cytotoxic chemotherapy (time from randomisation to first use of cytotoxic chemotherapy), radiological progression-free survival (time from randomisation to radiological progression or death from any cause), time to pain, and safety.

Exploratory endpoints that we report here were prostate-specific antigen response, time to prostate-specific antigen progression, alkaline phosphatase response, time to alkaline phosphatase progression, and time to deterioration in health-related quality of life measured during the treatment period. Alkaline phosphatase and prostate-specific antigen responses were defined as 30% or greater reduction in concentrations from baseline, confirmed by a second measurement 4 or more weeks later. Prostate-specific antigen progression was defined per PCWG2 criteria.[10] Alkaline phosphatase progression

was defined as a 25% or greater increase from baseline in alkaline phosphatase concentrations after at least 12 weeks in patients without an initial decline in concentrations, or a 25% or greater increase above the nadir confirmed by a second value obtained at least 3 weeks later. Deterioration in health-related quality of life was defined as a two-point drop in the physical disease-related symptoms subscale score lasting for two consecutive assessments at least 4 weeks apart (if two consecutive assessment were available). If a second assessment was not available because the patient died, one two-point drop was counted as a deterioration.

Statistical analysis

We calculated a sample size of 800 patients on the basis of the primary endpoint. In a test based on a two-sided alpha of 0·05, 90% power, and 1:1 randomisation between the treatment groups, 389 events were required to detect a 39% increase in symptomatic skeletal event-free survival (assuming median symptomatic skeletal event-free survival of 29·2 months in the radium-223 group and 21·0 months in the placebo group). The cutoff for the primary analysis was Feb 15, 2018, but we did an unplanned ad-hoc analysis leading to study unblinding on Nov 17, 2017. For the secondary endpoint of overall survival, an interim analysis (to be done at the same time as the final symptomatic skeletal event-free survival analysis) and a final analysis (after 500 events) were planned. It was expected that 275 deaths would have occurred by the interim overall survival analysis (assuming median overall survival of 35·3 months in the placebo group).

We analysed symptomatic skeletal event-free survival and overall survival with log-rank tests stratified according to the baseline stratification factors. We censored patients who died without a previous symptomatic skeletal event and 13 weeks or longer after the last symptomatic skeletal event assessment at the last symptomatic skeletal event assessment date. Patients alive at the survival cutoff date (ie, Feb 15, 2018) were censored at the last date they were known to be alive. We calculated HR with two-sided 95% CIs for symptomatic skeletal event-free survival with a Cox regression model stratified by the same baseline stratification factors. We calculated the overall survival HR and 95% CI from a stratified Cox proportional hazards model. Alkaline phosphatase and prostate-specific antigen responses were calculated among patients with available baseline measurements. We assessed efficacy in the intention-to-treat population, comprising all randomly assigned patients. We assessed safety in the safety population, which included all randomly assigned patients who received at least one dose of any study drug.

We analysed median time to fracture with Kaplan-Meier estimates. As a supportive analysis, data were also analysed with the Fine-Gray subdistribution hazards model,[12] which includes death as a competing event and considers a patient to be at risk after death has occurred.

	AAP plus radium-223 group (n=401)	AAP plus placebo group (n=405)
Median symptomatic skeletal event-free survival, months (95% CI)	22·3 (20·4–24·8)	26·0 (21·8–28·3)
Hazard ratio (95% CI; two-sided p value)*	1·122 (0·917–1·374; p=0·2636)	..
Patients with at least one symptomatic skeletal event or death†	196 (49%)	190 (47%)
First event of external beam radiotherapy	73 (37%)	80 (42%)
First event of symptomatic pathological bone fracture	35 (18%)	17 (9%)
First event of spinal cord compression	10 (5%)	19 (10%)
First event of tumour-related orthopaedic surgical intervention	4 (2%)	1 (1%)
Death	74 (38%)	73 (38%)

Data are n (%), unless otherwise specified. AAP=abiraterone acetate plus prednisone or prednisolone. *Based on stratified Cox proportional hazards model; strata for Cox proportional hazards model and log-rank test (which was used to calculate the p value) were the baseline stratification factors of geographical region, baseline alkaline phosphatase concentration, and concurrent use of denosumab or bisphosphonates. †Patients with more than one event were counted only for the category in which the first event occurred; if multiple symptomatic skeletal events (ie, component events) occurred on the same date, the patient was counted in only one category in the order spinal cord compression, bone fracture, orthopaedic surgery, external beam radiotherapy.

Table 2: **Symptomatic skeletal event-free survival (intention-to-treat population)**

	AAP plus radium-223 group (n=401)	AAP plus placebo group (n=405)	Hazard ratio (95% CI)*
Secondary endpoints			
Overall survival, months	30·7 (25·8–NE)	33·3 (30·2–41·1)	1·195 (0·950–1·505)
Radiological progression-free survival, months			
Central review	11·2 (9·1–11·8)	12·4 (10·8–14·5)	1·152 (0·960–1·383)
Investigator review	20·0 (16·4–22·3)	19·2 (16·6–22·8)	0·971 (0·784–1·201)
Time to cytotoxic chemotherapy, months	29·5 (26·5–35·7)	28·5 (23·7–NE)	1·033 (0·816–1·308)
Time to opiate use for cancer pain, months	19·0 (14·4–23·2)	22·6 (18·0–25·7)	1·126 (0·921–1·378)
Exploratory endpoints			
Overall confirmed prostate-specific antigen response	287/396 (72%)	267/401 (67%)	..
Time to prostate-specific antigen progression, months	9·6 (8·2–10·8)	9·0 (7·9–10·1)	0·937 (0·792–1·108)
Overall confirmed alkaline phosphatase response	218/398 (55%)	104/402 (26%)	..
Time to alkaline phosphatase progression, months	7·4 (7·1–7·9)	6·8 (5·3–8·4)	1·083 (0·918–1·276)
Time to deterioration in health-related quality of life†, months	9·5 (6·9–12·0)	10·5 (8·3–13·0)	1·079 (0·865–1·345)

Data are median (95% CI) or n/N (%). AAP=abiraterone acetate plus prednisone or prednisolone. NE=not estimable. *Based on Cox proportional hazards models stratified for the baseline stratification factors of geographical region, baseline alkaline phosphatase concentration, and concurrent use of denosumab or bisphosphonates. †As reported in the safety population (n=392 for the radium-223 group and n=394 for the placebo group) based on the physical disease-related symptoms subscale score of the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network prostate cancer symptom index 17-item questionnaire, measured during the treatment period.

Table 3: **Prespecified secondary and exploratory efficacy endpoints (intention-to-treat population)**

We did post-hoc analyses of symptomatic skeletal event-free survival, overall survival, and fracture frequency in patient subgroups, according to use of bone health agents at baseline. Multivariable analyses of overall

	AAP plus radium-223 group (n=392)	AAP plus placebo group (n=394)
Any	381 (97%)	386 (98%)
Grade 3–4 treatment-emergent adverse events	219 (56%)	206 (52%)
Grade 5 treatment-emergent adverse events	26 (7%)	20 (5%)
Any serious treatment-emergent adverse events	160 (41%)	155 (39%)
Treatment-emergent adverse event leading to dose modification	141 (36%)	123 (31%)
Treatment-emergent adverse event leading to discontinuation of radium-223 or placebo	14 (4%)	13 (3%)
Treatment-emergent adverse event leading to discontinuation of abiraterone acetate	57 (15%)	47 (12%)
Treatment-emergent adverse event leading to discontinuation of prednisone or prednisolone	55 (14%)	47 (12%)

Data are n (%). AAP=abiraterone acetate plus prednisone or prednisolone.

Table 4: **Summary of treatment-emergent adverse events (safety population)**

survival were done to adjust for baseline factors as prespecified for the primary endpoint in the statistical analysis plan: baseline albumin (below median concentration *vs* median concentration or higher), haemoglobin (below median concentration *vs* median concentration or higher), lactate dehydrogenase (below median concentration *vs* median concentration or higher), ECOG performance status (0 *vs* 1), prostate-specific antigen (below median concentration *vs* median concentration or higher), and age (<65 years *vs* ≥65 years). We also analysed fracture frequency according to subgroups with and without alkaline phosphatase flare, which was defined as a 15% or greater increase from baseline in alkaline phosphatase concentrations at week 4, followed by subsequent decreases to below the baseline concentration at week 8. Statistical analyses were done in SAS (version 9.2). This study is registered with ClinicalTrials.gov, number NCT02043678.

Role of the funding source

The study funder had roles in study design, data collection, data analysis, and data interpretation, and writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between March 30, 2014, and Aug 12, 2016, 806 patients were enrolled and randomly assigned, 401 to the radium-223 group and 405 to the placebo group (figure 1). The safety population comprised 392 patients in the radium-223 group and 394 in the placebo group (figure 1). Baseline demographic and clinical characteristics were generally similar between study groups (table 1). By November, 2017, when the study was unblinded prematurely, all patients had completed study-specified radium-223 or placebo treatment (the last radium-223 injection was given in February, 2017).

At the primary analysis, 196 (49%) patients in the radium-223 group had at least one symptomatic skeletal event or died, compared with 190 (47%) in the placebo group. Median follow-up was 21·2 months (IQR 17·0–25·8). Median symptomatic skeletal event free-survival was 22·3 months (95% CI 20·4–24·8) in the radium-223 group and 26·0 months (21·8–28·3) in the placebo group (HR 1·122 [95% CI 0·917–1·374]; p=0·2636; figure 2A; table 2). Use of external beam radiotherapy was the most frequent first symptomatic skeletal event, and was reported in 73 (37%) of 196 patients in the radium-223 group and 80 (42%) of 190 patients in the placebo group (table 2). Symptomatic pathological fracture was the first symptomatic skeletal event in 35 (18%) patients in the radium-223 group and 17 (9%) in the placebo group, whereas spinal cord compression was the first in ten (5%) patients in the radium-223 and 19 (10%) in the placebo group (table 2).

At the primary analysis (cutoff Feb 15, 2018), median follow-up for overall survival was 20·6 months (IQR 16·4–25·2) in the radium-223 group and 21·7 months (IQR 17·5–26·3) in the placebo group. 155 (39%) of 401 patients in the radium-223 group and 141 (35%) of 405 patients in the placebo group died. Median overall survival was 30·7 months (95% CI 25·8 to not estimable [NE]) in the radium-223 group and 33·3 months (30·2–41·1) in the placebo group (HR 1·195 [95% CI 0·950–1·505]; p=0·1280; figure 2B; table 3). Most patients received at least one systemic anti-cancer therapy during the follow-up period (data not shown). 23 (6%) patients in the placebo group received radium-223 during follow-up compared with two (1%) patients in the radium-223 group (appendix p 8).

Radiological progression-free survival (by central review) was 11·2 months (95% CI 9·1–11·8) in the radium-223 group and 12·4 months (10·8–14·5) in the placebo group (HR 1·152 [95% CI 0·960–1·383]; table 3).

In the radium-223 group, 347 (89%) of 392 patients received all six injections of radium-223. The overall incidence of treatment-emergent adverse events was generally similar between both groups (tables 4, 5). The most common grade 3–4 treatment-emergent adverse events were hypertension. Serious treatment-emergent adverse events occurred in 160 (41%) patients in the radium-223 group and 155 (39%) in the placebo group. Serious treatment-emergent adverse events that occurred in at least 3% of patients in either treatment group were urinary tract infection (14 [4%] patients in the radium-223 group *vs* nine [2%] in the placebo group), back pain (eight [2%] *vs* ten [3%]), pneumonia (eight [2%] *vs* ten [3%]), and traumatic fracture (11 [3%] *vs* three [1%]). Treatment-related deaths occurred in two (1%) patients in

	AAP plus radium-223 group (n=392)				AAP plus placebo group (n=394)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Back pain*	110 (28%)	23 (6%)	0	0	104 (26%)	16 (4%)	0	0
Fatigue	85 (22%)	4 (1%)	0	0	73 (19%)	6 (2%)	0	0
Arthralgia	76 (19%)	4 (1%)	0	0	70 (18%)	5 (1%)	0	0
Fracture†	67 (17%)	35 (9%)	1 (<1%)	0	25 (6%)	12 (3%)	0	0
Hypertension	16 (4%)	43 (11%)	0	0	26 (7%)	51 (13%)	1 (<1%)	0
Increased alanine aminotransferase	35 (9%)	29 (7%)	5 (1%)	0	31 (8%)	28 (7%)	0	0
Constipation	55 (14%)	1 (<1%)	0	0	72 (18%)	0	0	0
Diarrhoea	61 (16%)	4 (1%)	0	0	53 (13%)	7 (2%)	0	0
Nausea	65 (17%)	1 (<1%)	0	0	58 (15%)	1 (<1%)	0	0
Increased aspartate aminotransferase	42 (11%)	18 (5%)	1 (<1%)	0	37 (9%)	16 (4%)	0	0
Peripheral oedema	49 (13%)	2 (1%)	0	0	61 (15%)	0	0	0
Anaemia	33 (8%)	24 (6%)	0	0	35 (9%)	11 (3%)	0	0
Bone pain	40 (10%)	9 (2%)	0	0	46 (12%)	8 (2%)	0	0
Pain in extremity	43 (11%)	2 (1%)	0	0	50 (13%)	0	0	0
Fall	51 (13%)	4 (1%)	0	0	37 (9%)	2 (1%)	0	0
Decreased appetite	51 (13%)	2 (1%)	0	0	36 (9%)	2 (1%)	0	0
Musculoskeletal pain	37 (9%)	4 (1%)	0	0	43 (11%)	0	0	0
Hypokalaemia	30 (8%)	9 (2%)	0	0	29 (7%)	10 (3%)	0	0
Asthenia	32 (8%)	2 (1%)	0	0	39 (10%)	3 (1%)	0	0
Urinary tract infection	29 (7%)	15 (4%)	0	0	23 (6%)	8 (2%)	1 (<1%)	0
Hot flush	23 (6%)	0	0	0	49 (12%)	0	0	0
Vomiting	34 (9%)	3 (1%)	1 (<1%)	0	28 (7%)	4 (1%)	0	0
Dizziness*	38 (10%)	1 (<1%)	0	0	29 (7%)	0	0	0
Pneumonia	5 (1%)	6 (2%)	1 (<1%)	0	2 (1%)	11 (3%)	0	1 (<1%)
General deterioration of physical health	1 (<1%)	3 (1%)	0	6 (2%)	2 (1%)	1 (<1%)	0	7 (2%)
Syncope	1 (<1%)	9 (2%)	0	0	1 (<1%)	8 (2%)	0	0
Diabetes mellitus	6 (2%)	8 (2%)	0	0	7 (2%)	7 (2%)	0	0
Hyponatraemia	1 (<1%)	6 (2%)	2 (1%)	0	2 (1%)	6 (2%)	1 (<1%)	0
Pulmonary embolism	0	10 (3%)	1 (<1%)	0	0	3 (1%)	1 (<1%)	0
Spinal cord compression‡	2 (1%)	3 (1%)	0	0	5 (1%)	9 (2%)	2 (1%)	0
Atrial fibrillation	10 (3%)	5 (1%)	0	0	12 (3%)	6 (2%)	0	0
Hyperglycaemia	12 (3%)	1 (<1%)	0	0	9 (2%)	8 (2%)	2 (1%)	0
Cataract	5 (1%)	3 (1%)	0	0	2 (1%)	5 (1%)	0	0
Haematuria	21 (5%)	5 (1%)	0	0	14 (4%)	3 (1%)	0	0
Decreased lymphocyte count	0	5 (1%)	1 (<1%)	0	0	2 (1%)	0	0
Urosepsis	0	1 (<1%)	0	0	1 (<1%)	4 (1%)	2 (1%)	1 (<1%)
Acute myocardial infarction	0	2 (1%)	0	2 (1%)	0	1 (<1%)	2 (1%)	0
Increased blood alkaline phosphatase	4 (1%)	4 (1%)	0	0	8 (2%)	2 (1%)	1 (<1%)	0
Hydronephrosis	0	2 (1%)	0	0	0	5 (1%)	0	0
Muscular weakness	20 (5%)	6 (2%)	0	0	28 (7%)	1 (<1%)	0	0
Decreased platelet count	8 (2%)	3 (1%)	3 (1%)	0	2 (1%)	1 (<1%)	0	0
Spinal pain§	17 (4%)	4 (1%)	0	0	18 (5%)	3 (1%)	0	0
Hypotension	5 (1%)	3 (1%)	0	0	8 (2%)	3 (1%)	0	0
Pelvic pain§	7 (2%)	3 (1%)	0	0	13 (3%)	3 (1%)	0	0
Sciatica	5 (1%)	3 (1%)	0	0	9 (2%)	3 (1%)	0	0
Sepsis	1 (<1%)	0	0	2 (1%)	0	0	2 (1%)	2 (1%)
Urinary retention	7 (2%)	4 (1%)	0	0	7 (2%)	2 (1%)	0	0

(Table 5 continues on next page)

	AAP plus radium-223 group (n=392)				AAP plus placebo group (n=394)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Dehydration	3 (1%)	5 (1%)	0	0	0	0	0	0
Increased γ-glutamyl transferase	0	2 (1%)	0	0	4 (1%)	3 (1%)	0	0
Neutropenia	4 (1%)	3 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Osteonecrosis of jaw	5 (1%)	3 (1%)	0	0	4 (1%)	2 (1%)	0	0
Presyncope	4 (1%)	5 (1%)	0	0	0	0	0	0
Thrombocytopenia	5 (1%)	2 (1%)	3 (1%)	0	3 (1%)	0	0	0
Cellulitis	2 (1%)	1 (<1%)	0	0	2 (1%)	3 (1%)	0	0
Hypophosphataemia	2 (1%)	2 (1%)	0	0	2 (1%)	2 (1%)	0	0
Pyrexia*	24 (6%)	2 (1%)	0	0	24 (6%)	2 (1%)	0	0
Squamous cell carcinoma of skin	4 (1%)	2 (1%)	0	0	5 (1%)	2 (1%)	0	0
Tooth infection	5 (1%)	3 (1%)	0	0	8 (2%)	1 (<1%)	0	0
Multiple organ dysfunction syndrome	0	0	0	2 (1%)	0	0	0	0
Myocardial infarction	0	0	0	2 (1%)	1 (<1%)	0	0	0
Arrhythmia	1 (<1%)	1 (<1%)	0	0	0	0	0	1 (<1%)
Aortic dissection	0	0	0	1 (<1%)	0	0	1 (<1%)	0
Aspiration pneumonia	0	0	0	0	0	0	0	1 (<1%)
Bronchial carcinoma	0	0	0	1 (<1%)	0	0	0	0
Cardiac arrest	0	0	0	1 (<1%)	0	0	0	1 (<1%)
Cardiac disorder	0	0	0	1 (<1%)	0	0	0	0
Cardiorespiratory arrest	0	0	0	1 (<1%)	0	0	0	0
Disseminated intravascular coagulation	0	0	0	0	0	0	0	1 (<1%)
Fungal encephalitis	0	0	0	1 (<1%)	0	0	0	0
Interstitial lung disease	0	0	0	1 (<1%)	0	0	0	0
Intracranial haemorrhage	0	0	0	0	0	0	0	1 (<1%)
Malignant lung neoplasm	0	0	0	0	0	0	0	1 (<1%)
Mobility decreased	1 (<1%)	0	0	1 (<1%)	0	0	0	0
Pulmonary sepsis	0	0	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Respiratory failure	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Staphylococcal infection	0	0	0	0	1 (<1%)	0	0	1 (<1%)
Sudden death	0	0	0	0	0	0	0	2 (1%)
Ventricular fibrillation	0	0	0	1 (<1%)	0	0	0	0
Wound infection	2 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0

Data are n (%). Grade 1–2 treatment-emergent adverse events that occurred in 10% or more of patients in either group are shown; grade 3–4 treatment-emergent adverse events that occurred in 1% or more of patients in the overall population are shown; and all grade 5 events are shown. All grade 3–5 treatment-emergent adverse events are shown in the appendix (pp 9–14). AAP=abiraterone acetate plus prednisone or prednisolone. *Grade of severity missing for one patient in the placebo group. †Compound term for treatment-emergent events listed under the following Medical Dictionary for Regulatory Activities (version 21.0) preferred terms: femoral neck, femur, humerus, lumbar vertebral, osteoporotic, pathological, radius, rib, spinal compression, stress, thoracic vertebral, tooth, traumatic, and ulna fracture; grade of severity missing for one patient in the placebo group. ‡Grade of severity missing for two patients in the radium-223 group. §Grade of severity missing for one patient in the radium-223 group.

Table 5: **Treatment-emergent adverse events (safety population)**

the radium-223 group (one acute myocardial infarction and one interstitial lung disease) and one (<1%) patient in the placebo group (arrhythmia).

The greatest difference in adverse events between treatment groups was in the incidence of fractures (table 5). Treatment-emergent fractures occurred in 103 (26%) of 392 patients in the radium-223 group and 38 (10%) of 394 patients in the placebo group (table 5). Grade 1 fractures (asymptomatic) occurred in 23 (6%) patients in the radium-223 group versus 12 (3%) patients in the placebo group, and grade 2 fractures (symptomatic but non-displaced) occurred in 44 (11%) versus 13 (3%). When events reported during the post-treatment follow-up period were included, fractures occurred in 112 (29%) patients in the radium-223 group and 45 (11%) in the placebo group (table 6). Median time to fracture was 31·7 months (95% CI 27·6–NE) in the radium-223 group but could not be estimated in the placebo group

(HR 3·135 [95% CI 2·206–4·455]; appendix p 15). Results were similar with a subdistribution hazard model that included death as a competing event (HR 3·043 [95% CI 2·171–4·266]; data not shown). Fractures first occurred before or on the date of the last study treatment in 100 (89%) of 112 patients in the radium-223 group and 35 (78%) of 45 in the placebo group. Most fractures were outside sites of bone metastases in both treatment groups (table 6). Among 76 patients with one or more independently assessed fractures in the radium-223 group, 60 (79%) occurred at a skeletal site with no bone metastasis, and osteoporotic fractures were the most common type of fracture in this group (table 6). The difference between groups was greatest in the incidence of osteoporotic fractures (table 6). The most frequent cause of death in both treatment groups was progressive disease (109 [72%] of 151 deaths in the radium-223 group and 102 [73%] of 140 deaths in the placebo group). Most patients who died had not experienced a fracture (109 [72%] in the radium-223 group and 121 [86%] in the placebo group; table 6).

In post-hoc analyses, use of bone health agents at baseline was substantially less common in patients who had a fracture than in those who had not in both groups (appendix p 16). In patients taking bone health agents, 24 (15%) of 157 patients in the radium-223 group and 11 (7%) of 169 in the placebo group experienced a fracture. The corresponding figures in patients not taking bone health agents were 88 (37%) of 235 and 34 (15%) of 225, respectively.

Time to deterioration in health-related quality of life was 1 month less in the radium-223 group than in the placebo group (table 3). 218 (55%) of 398 patients in the radium-223 group and 104 (26%) of 402 in the placebo group had a confirmed alkaline phosphatase response. The corresponding proportions for prostate-specific antigen response were 287 (72%) of 396 and 267 (67%) of 401 in the radium-223 and placebo groups, respectively.

In post-hoc analyses, the HR for symptomatic skeletal event-free survival for the radium-223 versus placebo groups was 0·932 (95% CI 0·666–1·306) in patients taking bone health agents and 1·252 (0·971–1·615) in those not taking bone health agents ($p_{interaction}$ 0·1219; appendix p 19). The corresponding HRs for overall survival were 1·128 (0·781–1·629) and 1·238 (0·920–1·665; $p_{interaction}$ 0·5628; appendix p 18). After adjustment for baseline factors in a multivariable analysis, the HR for overall survival was 1·06 (95% CI 0·837–1·351; appendix p 19).

A post-hoc analysis showed that 35 (9%) of 392 patients in the radium-223 group and 41 (10%) of 394 in the placebo group had alkaline phosphatase flares. In the radium-223 group, six (17%) of 35 patients with flares in alkaline phosphatase concentrations had fractures, compared with 102 (30%) of 343 patients without flares in concentrations. In the placebo group, three (7%) of 41 patients with flares in alkaline phosphatase concentrations had fractures, compared with 41 (12%) of 329 patients without flares (two-sided $p_{interaction}$ 0·7917).

After four treatment cycles, bone alkaline phosphatase concentrations were reduced from baseline by 50% in the radium-223 group and by 14% in the placebo group, whereas P1NP concentrations were reduced by 74% in

	AAP plus radium-223 group (n=392)	AAP plus placebo group (n=394)
Fractures		
Patients with at least one fracture by investigator assessment	112 (29%)	45 (11%)
Time to first fracture		
<6 months	45 (11%)	11 (3%)
6 to <12 months	46 (12%)	15 (4%)
12 to <24 months	19 (5%)	16 (4%)
≥24 months	2 (1%)	3 (1%)
Patients with independently reviewed fracture imaging scans	80 (20%)	27 (7%)
Patients with at least one fracture confirmed by independent assessment	76 (19%)	23 (6%)
Bone metastasis at site of fracture	20/76 (26%)	6/23 (26%)
New bone lesion	15/76 (20%)	5/23 (22%)
Old bone lesion	6/76 (8%)	1/23 (4%)
No bone metastasis at site of fracture	60/76 (79%)	17/23 (74%)
Type of fracture		
Pathological	19/76 (25%)	6/23 (26%)
Traumatic	27/76 (36%)	13/23 (57%)
Osteoporotic	37/76 (49%)	4/23 (17%)
Indeterminate	1/76 (1%)	0
Deaths		
n	151 (39%)	140 (36%)
Cause of death		
Progressive disease	109 (28%)	102 (26%)
Adverse event associated with clinical progression	13 (3%)	12 (3%)
Adverse event not associated with clinical progression	13 (3%)	12 (3%)
Unknown	8 (2%)	5 (1%)
Other	8 (2%)*	9 (2%)†
Relationship between fracture and death		
Death with no previous fracture	109 (28%)	121 (31%)
Death with previous symptomatic skeletal event fracture	23 (6%)	9 (2%)
Death with previous non-symptomatic skeletal event fracture	25 (6%)	12 (3%)

Data are n (%) or n/N (%). Patients with more than one fracture were counted in all relevant categories. AAP=abiraterone acetate plus prednisone or prednisolone. *Burn injury, colorectal cancer, gastrointestinal bleeding, heart failure and pneumonitis, pneumonia, pulmonary embolism, septic shock, and unrelated to cancer. †Brain tumour of unknown origin, cardiac event, cardiopulmonary arrest, clinical deterioration with no connection to oncological history, general deterioration and pulmonary embolism, myocardial infarction and circulatory arrest, non-ST-elevation myocardial infarction, sepsis, and stroke and pneumonia.

Table 6: **Summary of fractures and deaths (safety population)**

the radium-223 group and by 49% in the placebo group (appendix p 20). Reductions in all markers were significantly greater in the radium-223 group than in the placebo group (appendix p 20).

Discussion

In this double-blind, randomised, placebo-controlled, phase 3 trial, concurrent treatment with radium-223 and abiraterone acetate plus prednisone or prednisolone did not improve symptomatic skeletal event-free survival in patients with castration-resistant prostate cancer with bone metastases. Overall survival did not differ significantly between groups, but concurrent treatment with abiraterone acetate plus prednisone or prednisolone and radium-223 was associated with increased fracture risk.

In the previously reported ALSYMPCA study,[2,3,6] radium-223 was associated with significant improvements in overall survival (which was maintained at long-term follow-up), time to symptomatic skeletal events, and quality of life in patients with castration-resistant prostate cancer and bone metastases who previously had either received docetaxel or were not candidates for docetaxel treatment. In addition to more extensive previous treatment, patients in ALSYMPCA had a greater disease burden, more disease-related symptoms, and higher alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen concentrations than did patients in our trial.[2] Although our results show that radium-223 should not be administered in combination with abiraterone acetate plus prednisone or prednisolone, radium-223 remains a treatment option for patients with bone-dominant, metastatic castration-resistant prostate cancer and disease progression after other appropriate therapies.

The cause of the higher number of deaths in the radium-223 group is unknown. The final analysis of overall survival will be done after 500 events have been recorded. At this interim analysis, 211 (73%) of the 291 deaths in the safety population were due to progressive disease. The proportion of patients with a prostate-specific antigen response and time to prostate-specific antigen progression were similar in both groups. Fractures are associated with increased mortality in various clinical settings.[13,14] However, in our trial, most of the patients who died in both groups had not had a previous fracture. Minor imbalances in baseline factors could have contributed to the higher number of deaths in the radium-223 group compared with the placebo group. Consistent with this finding, the HR for overall survival was smaller in a post-hoc multivariable analysis that adjusted for baseline factors than in the primary analysis.

Notably, fewer patients in radium-223 group had spinal cord compression than in the placebo group. However, subgroup analyses of these patients would probably not be informative because of the small number of events.

Patients with prostate cancer are at risk of both pathological and osteoporotic fractures.[13,15] Bone metastases are the root cause of pathological fractures.[16,17] Various factors contribute to the risk of osteoporotic fractures, including older age, increased falls, and the adverse effects of androgen deprivation therapy, prednisone, and other drugs on bone.[15,18–21] Osteoporotic fractures were the most common type of fracture in the radium-223 group and, of all fracture types, differed the most between the study groups. These findings suggest that radium-223 could contribute to the risk of osteoporotic fractures in patients with prostate cancer. Non-clinical studies are underway to better characterise the effects of radium-223 on bone quality. Clinical practice guidelines recommend screening and intervention to prevent osteoporotic fractures, and guidelines also recommend the use of bone health agents to reduce skeletal morbidity in patients with castration-resistant prostate cancer and bone metastases.[22,23] The finding that use of bone health agents was associated with decreased fracture frequency in both groups in our study shows the importance of the use of these drugs to prevent skeletal morbidity in patients with metastatic castration-resistant prostate cancer.

As a randomised controlled trial, a limitation of our study is that patients were selected on the basis of specific eligibility criteria (including the exclusion of patients with visceral metastases). Therefore the results might not be generalisable to routine clinical practice. Another limitation is that bone mineral density was not assessed at baseline or during the study. Typical osteoblastic bone metastases from prostate cancer are characterised by increased bone mineral density and, accordingly, bone mineral density is not a reliable predictor of risk for osteoporotic fracture in this context. Our clinical trial is the first to provide data for a combination of therapies with overall survival benefit in metastatic castration-resistant prostate cancer. Randomised phase 3 trials of radium-223 in combination with enzalutamide (NCT02194842) and docetaxel (NCT03574571) are underway, as are numerous other studies of novel therapeutic combinations in metastatic castration-resistant prostate cancer. The results of our trial reinforce the importance of randomised controlled trials to critically assess the efficacy and safety of combination therapy.

In summary, the addition of radium-223 to abiraterone acetate plus prednisone or prednisolone did not decrease the risk of symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases, and increased the risk of clinical fractures compared with treatment with abiraterone acetate and prednisone or prednisolone alone. Thus, we do not recommend use of radium-223 in combination with abiraterone acetate plus prednisone or prednisolone.

Contributors

MS, CP, FS, KM, BT, QSN, MB, VM, JMP, LEZ, OK, GK, NM, WCN, FN, ER, AH, YK, and CH were investigators and participated in study conduct. MS, AZ, MT, JS, VW, and CH designed the study. AZ, HK, MT, and JS analysed the data. All authors interpreted data and reviewed and approved the final Article.

Declaration of interests

MS reports personal fees from Amgen, Astellas, Bayer, Clovis, Gilead, Janssen, Lilly, Novartis, and Pfizer, and institutional fees for contracted clinical research from Amgen, Bayer, Clovis, Gilead, Janssen, and Lilly. CP reports personal fees from AAA and Janssen, and grants and personal fees from Bayer. FS reports grants, personal fees, and non-financial support from Bayer, Janssen, Astellas, Amgen, AstraZeneca, and Pfizer. KM reports personal fees from Janssen, Bayer, Amgen, Novartis, Bristol-Myers Squibb, Ferring, Merck, Pfizer, Roche, and MSD, and grants from Novartis. BT reports personal fees and non-financial support from Bayer, Janssen, Sanofi, and Amgen, and grants, personal fees, and non-financial support from Astellas and Ferring. QSN reports non-financial support from Bayer, personal fees from Boehringer Ingelheim, Celgene, Novartis, AstraZeneca, and MSD, and grants from Bristol-Myers Squibb and Pierre-Fabre. MB reports personal fees from Bayer, Janssen, Amgen, Pfizer, Ipsen, Eisai, Bristol-Myers Squibb, MSD, Sanofi, and AstraZeneca. VM reports personal fees and non-financial support from Bayer, Janssen, Sanofi, and Astellas. JMP reports personal fees and non-financial support from Bayer, Astellas, Beigene, Novartis, and Roche, and grants, personal fees, and non-financial support from Bristol-Myers Squibb, VCN Biopharma, MSD, Pfizer, and Janssen. OK reports grants, personal fees, and non-financial support from Bayer, Novartis, Bristol-Myers Squibb, and Ono, and personal fees and non-financial support from Pfizer and Chugai. GK reports grants, personal, fees and non-financial support from Bayer, BMS, Ono, MSD, and Chugai, personal fees from Novartis, and personal fees and non-financial support from Pfizer. NM reports grants from Janssen and Bayer. ER reports personal fees from Bayer. AH reports grants and personal fees from Astellas and Ipsen, and personal fees from Amgen, Bayer, Ferring, Janssen, and Pfizer. CH reports grants from Aptevo, Aragon, Astellas, AstraZeneca, Bayer, Dendreon, Emergent, Genentech, Roche, Medivation, Millennium, Sanofi, and Pfizer, and personal fees from Churchill, Clovis, Dendreon, Endocyte, Ferring, Janssen, Medivation, MorphoSys, Orion, and Pfizer. AZ, HK, MT, JS, and VW are employed by Bayer. LEZ, WCN, FN, and YK declare no competing interests.

Data sharing

Availability of the data underlying this publication will be based on Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations' and the Pharmaceutical Research and Manufacturers of America's Principles for responsible clinical trial data sharing, which pertains to the scope, timing, and process of data access. Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and EU as necessary for legitimate research. This policy applies to data for new medicines and indications that have been approved by the EU and US regulatory agencies on or after Jan 1, 2014. Interested researchers can request access to anonymised patient-level data and supporting documents from clinical studies to do further research that could help to advance medical science or improve patient care. Information about the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer takes all necessary measures to ensure that patient privacy is safeguarded.

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