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ORIGINAL ARTICLE

A randomised phase II trial of three dosing regimens of radium-223 in patients with bone metastatic castration-resistant prostate cancer

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Background: Radium-223 prolongs overall survival and delays symptomatic skeletal events (SSEs) in patients with metastatic castration-resistant prostate cancer (mCRPC) and bone metastases. The approved radium-223 regimen is 55 kBq/kg every 4 weeks (q4w) for six cycles (standard dose). We investigated different radium-223 regimens in patients with mCRPC.

Patients and methods: Patients were randomised 1 : 1 : 1 to radium-223 standard-dose, high-dose (88 kBq/kg q4w for six cycles) or extended-schedule arms (55 kBq/kg q4w for 12 cycles). The primary end point, SSE-free survival (SSE-FS), was compared in patients treated with a high- versus standard-dose regimen, or with a standard dose in an extended (>6 to 12 cycles) versus standard schedule (six cycles).

Results: A total of 391 patients were randomised; baseline characteristics were balanced between arms. On-treatment SSEs developed in 37/130 (28%), 42/130 (32%) and 48/131 (37%) patients in the standard-dose, high-dose and extended-schedule arms, respectively. There was no statistically significant difference in SSE-FS in the high- versus standard-dose arms [median 12.9 months versus 12.3 months; hazard ratio (HR) 1.06, 80% confidence interval (CI) 0.88—1.27, $P = 0.70$], and in the extended- versus standard-schedule arms (median 10.8 months versus 13.2 months; HR 1.26, 80% CI 0.94—1.69, $P = 0.31$). Overall survival in the three treatment arms was similar. As many as 370 (95%) patients received treatment (median of six cycles) in each arm. Grade ≥3 treatment-emergent adverse events (TEAEs) affected 34% of patients in the standard-dose, 48% in the high-dose and 53% in the extended-schedule arm, causing permanent discontinuation in 9%, 16% and 17% of patients, respectively.

Conclusion: Radium-223 high-dose or extended-schedule regimens resulted in no change in SSE-FS or other efficacy end points and were associated with more grade ≥3 TEAEs. The extended-schedule regimen (beyond six doses) could not be implemented in a large proportion of patients due to disease progression. Therefore, the standard-dose schedule remains one of the standard therapies for patients with symptomatic mCRPC.

Trial Registration: ClinicalTrials.gov NCT02023697.

Key words: bone metastases, mCRPC, radium-223 dose, safety, symptomatic skeletal events

INTRODUCTION

Radium-223 dichloride (radium-223), a bone-targeted alpha-particle therapy, is approved worldwide for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) based on the data from the pivotal phase III ALSYMPCA trial.[1,2] In the phase III trial, patients with bone pain randomly assigned to receive radium-223 at a standard dose of 55 kBq/kg every 4 weeks (q4w) and best standard of care demonstrated prolonged overall survival compared with those receiving placebo and best standard of care [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.55—0.88, $P < 0.001$] and had a significant delay in time to first on-treatment symptomatic skeletal events (SSEs; HR 0.66, 95% CI 0.52—0.83, $P = 0.00037$).[1,3]

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Radium-223 was generally well tolerated and quality of life was improved compared with patients treated in the placebo arm.[4]

Phase II studies conducted with higher doses of radium-223 in patients with mCRPC and bone metastases suggested dose-dependent effects on serum markers, increased disease control and pain relief.[5,6] Therefore, this study was designed to investigate whether the SSE-free survival (SSE-FS) and safety of radium-223 administered at a higher dose (88 kBq/kg) over six cycles, or as a standard dose (55 kBq/kg) over an extended schedule of up to 12 cycles, provided a clinical benefit when compared with a standard regimen of radium-223 in patients with mCRPC and bone metastases.

METHODS

Study design and patients

This multicentre, three-arm, randomised, open-label, phase II study investigated three dosing regimens of radium-223 in patients with mCRPC. The 1 : 1 : 1 randomisation was stratified by the number of prior chemotherapy regimens ($\leq$1 versus $>$1), total alkaline phosphatase (ALP) levels ($<$220 U/l versus $\geq$220 U/l) and worst pain score of the Brief Pain Inventory Short Form ($\leq$4 versus $>$4).

Symptomatic and asymptomatic patients $\geq$18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate and castration-resistant disease, radiographic evidence of disease progression in the bone, two or more skeletal metastases on bone scintigraphy within 8 weeks of randomisation, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, a life expectancy of $>$6 months and adequate blood and organ function were included in the study. Main exclusion criteria were a history of current visceral or central nervous system metastasis, and lymphadenopathy ($>$3 cm). Full eligibility and exclusion criteria, including treatments not permitted prior to randomisation or during the treatment period, are detailed in the supplementary Methods, available at *Annals of Oncology* online.

The protocol was approved by the institutional review boards or independent ethics committees of all participating centres. Patients provided a signed informed consent form prior to the conduct of any study-specific procedure. This study was done in accordance with Good Clinical Practice guidelines under the guiding principles detailed in the Declaration of Helsinki and in keeping with applicable local laws and regulations. This trial is registered with ClinicalTrials.gov (number NCT02023697).

Procedures

Patients were administered a 1-minute intravenous (i.v.) injection of radium-223 55 kBq/kg q4w for up to six injections (cycles) (standard dose), or radium-223 88 kBq/kg i.v. q4w for up to six injections (cycles) (high dose) or radium-223 55 kBq/kg q4w for up to 12 injections (cycles) (extended schedule). The treatment period was the time from the initiation of treatment to 30 days after the last injection of radium-223.

The study protocol allowed concomitant use of abiraterone acetate (abiraterone), enzalutamide and bone health agents (BHAs) with radium-223. Permitted prior and concomitant treatments and reasons for treatment discontinuation are detailed in the supplementary Methods, available at *Annals of Oncology* online.

Assessments

Definition and assessment of SSEs, radiological, safety and pain assessments, and details of active follow-up are provided in the supplementary Methods, available at *Annals of Oncology* online.

Outcomes

The first co-primary study end point was to evaluate efficacy as measured by SSE-FS in the standard-dose arm versus the high-dose arm. The second co-primary study end point was evaluation of efficacy as measured by SSE-FS in the extended-schedule arm versus the standard-dose arm. Time to first or subsequent SSE was an end point in the registrational ALSYMPCA study.[1] As the time to first or subsequent SSE was considered clinically meaningful but had high censoring rates related to patients' death, a sensitivity analysis including deaths (SSE-FS) was conducted and it confirmed the benefit of radium-223 treatment. With regulatory agency agreement, SSE-FS was, therefore, viewed as a more relevant efficacy end point and thus was eventually selected as the primary end point. Patients not experiencing death or an SSE as of the database cut-off were censored at the last SSE assessment.

Secondary end points were safety and tolerability, overall survival, time to first SSE, time to radiological progression (rTTP), radiographic progression-free survival (rPFS), time to pain progression and pain improvement rate. Radiological progression definition and criteria are described in the supplementary Methods (available at *Annals of Oncology* online). Patient-reported outcomes were not evaluated due to a limited number of evaluable patients. Exploratory end points are detailed in the supplementary Methods, available at *Annals of Oncology* online.

Statistical analyses

Two comparisons of the SSE-FS primary end point were performed; the first in the intention-to-treat (ITT) population, and the second in subpopulations of patients from the selected arms (supplementary Methods, available at *Annals of Oncology* online). The first comparison evaluated SSE-FS with a start date at randomisation in the high-dose ($n = 130$) versus standard-dose ($n = 261$; data for the standard-dose arm were pooled with the first 6 months of data for patients in the extended-schedule arm) regimens (supplementary Methods, available at *Annals of Oncology* online). The second comparison evaluated SSE-FS in the extended-schedule ($n = 69$; SSE-free patients to the date of the sixth radium-223 injection who had received over six injections) versus standard-schedule radium-223 arm ($n = 84$; patients who had completed six

injections; supplementary Methods, available at *Annals of Oncology* online).

The sample size calculations are detailed in the supplementary Methods (available at *Annals of Oncology* online). Both comparisons were planned at the time of final analysis after ~135 events in patients included in comparison 1 and ~75 events following the sixth radium-223 injection in comparison 2, whichever occurred later.

The high-dose or extended-schedule regimen was declared superior to the standard-dosing regimen if the one-sided *P* value was <0.1.

Comparisons 1 and 2 were planned for overall survival, time to first SSE, rTTP and rPFS secondary end points. All end point analyses were also performed for each treatment arm. All testing was one sided with a significance level of 0.1.

Computation of HRs and time-to-event analyses are described in the supplementary Methods (available at *Annals of Oncology* online).

Safety analyses were performed in those randomised patients who had received at least one injection of radium-223 (safety population).

Data cut-off date was 15 March 2017. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patients and treatment exposure

Between 10 March 2014 and 11 August 2015, 391 patients were enrolled at 63 study centres in 16 countries (USA and non-USA) and randomly assigned to three radium-223 treatment arms (ITT population) and 370 patients received treatment (Figure 1). Baseline characteristics were generally well balanced, although the proportion of patients with a Gleason score $\geq$8 was lowest in the extended-schedule arm (Table 1). Patients had been heavily pretreated in all three

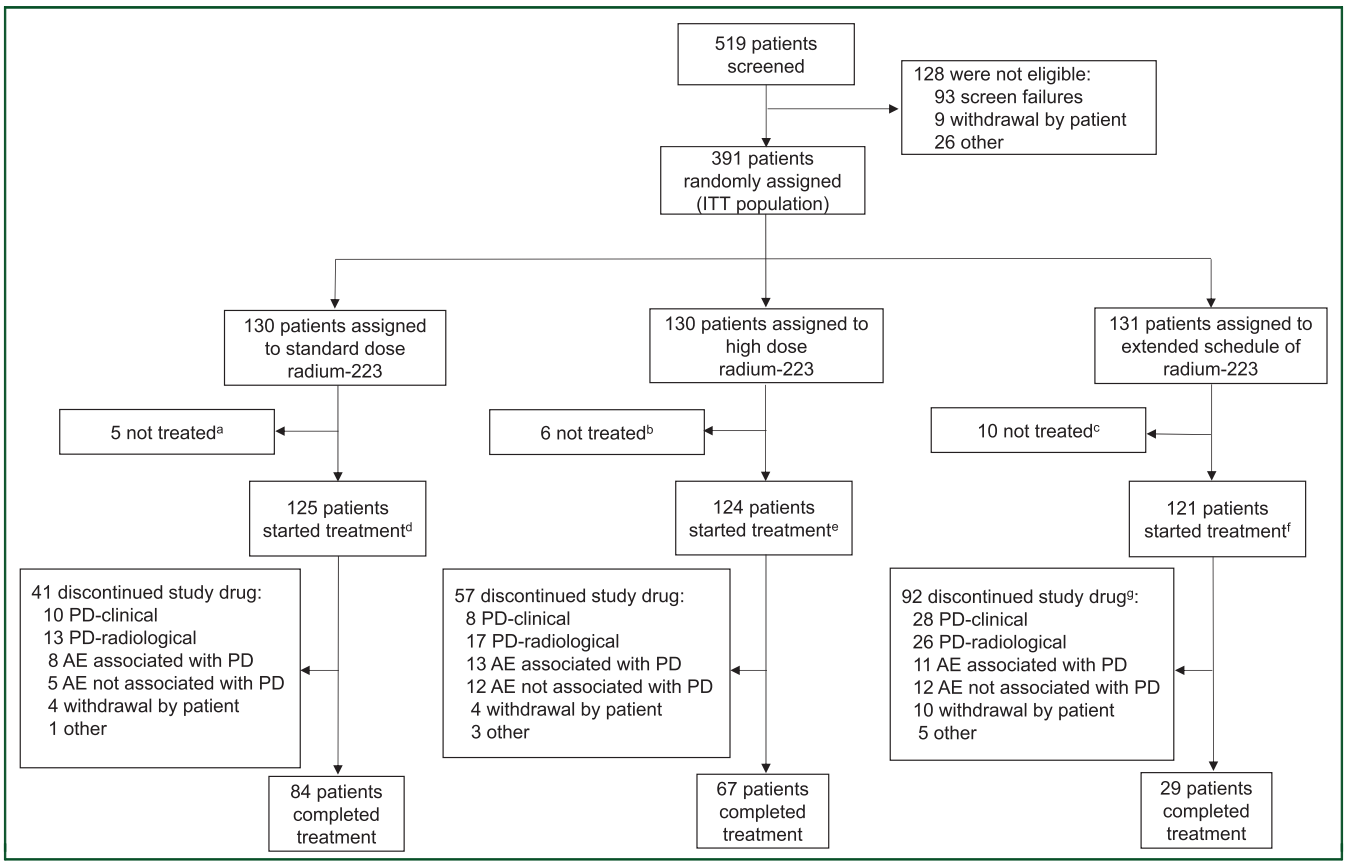

Figure 1. Trial profile.
Patients were randomly assigned to one of three radium-223 dose regimens: standard-dose radium-223, 55 kBq/kg q4w for up to six cycles; high-dose radium-223, 88 kBq/kg q4w for up to six cycles; extended-schedule radium-223, 55 kBq/kg q4w for up to 12 cycles.
AE, adverse event; ITT, intention-to-treat; PD, progressive disease.
[a] Two patients were not treated due to AEs not associated with clinical disease progression, one patient due to AE associated with clinical disease progression, one patient due to shortage of radium-223, and one patient withdrew from the study.
[b] One patient was not treated due to AE not associated with clinical disease progression, one patient due to AE associated with clinical disease progression, two patients due to progressive disease, one patient due to shortage of radium-223, and one patient due to the absence of bone metastases.
[c] Four patients were not treated due to AEs not associated with clinical disease progression, two patients due to AEs associated with clinical disease progression, two patients due to shortage of radium-223, one patient due to refusal for follow-up visits, and one patient withdrew from the study.
[d] One hundred and twenty patients subsequently entered active follow-up.
[e] One hundred and twenty patients subsequently entered active follow-up.
[f] One hundred and sixteen patients subsequently entered active follow-up.
[g] Fifty-two patients discontinued treatment prior to receiving the sixth injection of radium-223.

Table 1. Baseline characteristics (ITT population)

Characteristic	Standard-dose arm (*N* = 130)	High-dose arm (*N* = 130)	Extended-schedule arm (*N* = 131)
Race			
White	104 (80)	102 (78)	108 (82)
Age, years			
Median (range)	70.5 (51–88)	71.0 (47–87)	71.0 (48–88)
Median weight (kg)	84.0 (51–146)	80.2 (50–149)	81.8 (53–139)
Gleason score at initial diagnosis ≥8	88 (68)	82 (63)	68 (52)
Stage IV at initial diagnosis	67 (52)	63 (48)	69 (53)
Total ALP, median (range) (U/l)	128.5 (25–4130)	116.0 (42–4558)	118.0 (31–1578)
PSA, median (range) (μg/l)	76.3 (0–1755)	72.3 (0–2746)	66.4 (0–4851)
ECOG performance status			
0	48 (37)	59 (45)	49 (37)
1	78 (60)	67 (52)	77 (59)
2	4 (3)	4 (3)	5 (4)
Average WPS, median (range)	3 (0–10)	3 (0–9)	3 (0–10)
Metastatic lesions			
<6	19 (15)	22 (17)	19 (15)
6–20	52 (40)	53 (41)	52 (40)
>20	47 (36)	48 (37)	54 (41)
Superscan	12 (9)	6 (5)	6 (5)
Prior anticancer therapy[a]			
≤1 Prior regimen	13 (10)	17 (14)	21 (16)
≥2 Prior regimens	112 (90)	106 (86)	106 (84)
Any radiotherapy	96 (74)	94 (72)	99 (76)
Any prostatectomy	40 (31)	48 (37)	47 (36)
Systemic therapy[b]	130 (100)	130 (100)	130 (99)
Docetaxel	67 (52)	70 (54)	78 (60)
Cabazitaxel	19 (15)	20 (15)	19 (15)
Abiraterone	48 (37)	53 (41)	61 (47)
Enzalutamide	23 (18)	24 (19)	35 (27)
Bone health agents[c]	63 (48)	69 (53)	63 (48)
Denosumab	45 (35)	42 (32)	43 (33)
Zoledronic acid	17 (13)	23 (18)	18 (14)

Data are *n* (%) unless otherwise stated. Baseline characteristics in the intention-to-treat population: standard dose, radium-223 55 kBq/kg q4w for up to six cycles; high dose, radium-223 88 kBq/kg q4w for up to six cycles; extended schedule, radium-223 55 kBq/kg q4w for up to 12 cycles.

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; ITT, intension-to-treat; PSA, prostate-specific antigen; WPS, worst pain score.

[a] Some patients had received more than one prior therapy.

[b] These therapies were stopped before initiating radium-223 therapy.

[c] Any bone health agent.

treatment arms (Table 1). Over 50% of patients in each treatment arm had received prior docetaxel, 48 (37%), 53 (41%) and 61 (47%) prior abiraterone and 23 (18%), 24 (19%) and 35 (27%) prior enzalutamide in the standard-dose, high-dose and extended-schedule arms, respectively (Table 1). The study did not investigate whether the difference in the proportion of patients receiving concomitant treatment between the three arms was significant, however. Metastatic bone disease was significant in this patient population (Table 1).

A total of 34 (26%), 29 (22%) and 23 (18%) patients randomised to the standard-dose, high-dose and extended-schedule arms, respectively, were treated concomitantly with abiraterone, and 19 (15%), 16 (12%) and 21 (16%) with concomitant enzalutamide (supplementary Table S1, available at *Annals of Oncology* online). The use of BHAs was at the discretion of the investigator. The proportion of patients in each treatment arm who received concomitant denosumab, a RANK ligand inhibitor, or zoledronic acid, an intravenous bisphosphonate, is shown in supplementary Table S1, available at *Annals of Oncology* online. A total of 23 (18%) of 125, 19 (15%) of 124 and 16 (13%) of 121 patients received concomitant abiraterone and BHA treatment at baseline in the standard-dose, high-dose and extended-schedule arm, respectively, and 11 (9%), 10 (8%) and 7 (6%) received concomitant abiraterone without BHA use at baseline.

The median number of radium-223 injections for each treatment arm was six, including the extended-schedule arm (supplementary Table S2, available at *Annals of Oncology* online). A total of 41 (33%), 57 (46%) and 92 (76%) patients discontinued study drug in the standard-dose, high-dose and extended-schedule arms, with the main reasons being disease progression and adverse events (Figure 1).

Efficacy

Median SSE-FS, with a start date at the randomisation date, in the ITT patient population was 12.9 versus 12.3 months in the high-dose versus standard-dose arm (HR 1.06, 80% CI 0.88–1.27, $P = 0.70$; Figure 2A and supplementary Table S3, available at *Annals of Oncology* online; data for the standard-dose arm were pooled with the data for the first six injections for patients in the extended-schedule arm). Median SSE-FS, with a start date at the sixth injection, was 10.8 versus 13.2 months (HR 1.26, 80% CI 0.94–

1.69, $P = 0.31$) in patients in the extended-schedule arm (patients who had received >6 to 12 injections) compared with the standard-schedule arm (patients who had received six injections; Figure 2B and supplementary Table S4, available at *Annals of Oncology* online).

Overall survival was similar for patients in the high-dose versus standard-dose arm (HR 1.08, 80% CI 0.89—1.30, $P = 0.62$) or for those in the extended-schedule compared with the standard-schedule arm (HR 1.00, 80% CI 0.74—1.34, $P = 1.00$; supplementary Tables S3 and S4, available at *Annals of Oncology* online). Overall survival was 15.8 (80% CI 14.3—18.1), 16.0 (80% CI 14.7—17.2) and 14.1 (80% CI 12.1—16.5) months, respectively, in patients from the standard-dose, high-dose and extended-schedule arms (ITT analysis; Table 2 and Figure 2C). The median follow-up time for overall survival in patients in the standard-dose arm was 14.8 months, in the high-dose arm 15.1 months, and in the extended-schedule arm 13.6 months.

No notable differences were reported for time to first SSE, rPFS and rTTP, including the bone and the soft tissue rTTP, in patients in the standard-dose arm compared with the high-dose radium-223 arm (supplementary Table S3, available at *Annals of Oncology* online). Time to first SSE appeared to be longer in the standard-schedule arm compared with the extended-schedule arm (medians not reached versus 19.5 months; HR 1.55, 80% CI 1.04—2.31), although 65 (77%) and 44 (64%) patients were censored in the standard-schedule and extended-schedule arm, respectively (supplementary Table S4, available at *Annals of Oncology* online). All other end points were similar (supplementary Table S4, available at *Annals of Oncology* online).

Median time to pain progression was comparable between the treatment arms and pain improvement was reported in 13 of 48 (27%) patients in the standard-dose, 13 of 50 (26%) patients in the high-dose and in 16 of 43 (37%) patients in the extended-schedule arm (Table 2).

Exploratory analyses showed that prostate-specific antigen (PSA) response rates (80% CI 15%—21%) and median time to PSA progression (3.4—3.5 months) were comparable across the treatment arms (supplementary Table S5, available at *Annals of Oncology* online). ALP response rates were also comparable across treatment arms (80% CI 42%—47%); median time to ALP progression was not reached in the standard-dose and high-dose arm, and was 14.7 months (80% CI 9.6—21.0) in the extended-schedule arm (supplementary Table S5, available at *Annals of Oncology* online).

Similar rates of radiological bone and non-bone progression, the median time to radiological bone progression and the median time to progression were reported across three treatment arms (Table 2).

Safety

The most common treatment-emergent adverse events (TEAEs; >25%) in patients in the standard-dose, high-dose and extended-schedule arms (safety population; $n = 370$) were fatigue, anaemia, nausea and decreased appetite, and their incidence rates were comparable across the treatment arms (Table 3). The most common grade ≥3 adverse events (≥10%) were anaemia in 13 of 125 (10%) versus 17 of 124 (14%) versus 17 of 121 (14%) of patients in the standard-dose, high-dose and extended-schedule arms, respectively.

TEAEs leading to permanent discontinuation were reported in 13 (10%), 25 (20%) and 23 (19%) patients in the standard-dose, high-dose and extended-schedule arms, respectively. The most common grade ≥3 adverse events leading to treatment termination are detailed in supplementary Table S6, available at *Annals of Oncology* online. Serious adverse events were reported in 25 (20%) patients in the standard-dose arm, 36 (29%) in the high-dose and 37 (31%) in the extended-schedule arm. Drug-related TEAEs were reported in 73 (59%), 73 (59%), and 57 (47%) patients, respectively. Seven grade 5 TEAEs were reported (Table 3), but none were considered to be drug related.

Bone fractures were reported in 19 (15%), 27 (22%) and 23 (19%) patients in the standard-dose, high-dose and extended-schedule arms, respectively. For patients treated with or without concomitant abiraterone, differences in the incidence of fractures were seen in the radium-223 high-dose arm, where fractures were reported in five of 29 (17%) patients receiving concomitant abiraterone and 10 of 95 (11%) who did not receive concomitant abiraterone (supplementary Table S7, available at *Annals of Oncology* online). The incidence rates of fractures in patients who had or had not received concomitant abiraterone therapy in the standard-dose and extended-schedule arms or concomitant enzalutamide in the three treatment arms were similar (supplementary Table S7, available at *Annals of Oncology* online).

Post-treatment adverse events were reported in 37 (30%) patients in the standard-dose arm, 45 (36%) in the high-dose arm and 43 (36%) in the extended-schedule arm. Two grade 5 post-treatment adverse events were reported: pneumonia in a patient treated in the standard-dose arm and subdural hematoma in a patient treated in the extended-schedule arm; however, neither were considered to be drug related.

At the data cut-off date (15 March 2017), 247 deaths were reported (supplementary Table S8, available at *Annals of Oncology* online).

DISCUSSION

This study was designed to investigate efficacy end points for the three randomised radium-223 treatment arms. The study was unable to detect an improvement in SSE-FS between patients who received the standard-dose and those who received high-dose radium-223, or between patients who received six injections of standard dose and those who received more than six injections of standard dose. Notably, the median number of radium-223 injections received in each treatment arm was six and only 24% of patients completed the planned 12 injections in the extended-schedule arm.

In the current study, both asymptomatic and symptomatic patients were recruited, and prior or concomitant treatment with abiraterone or enzalutamide was allowed if

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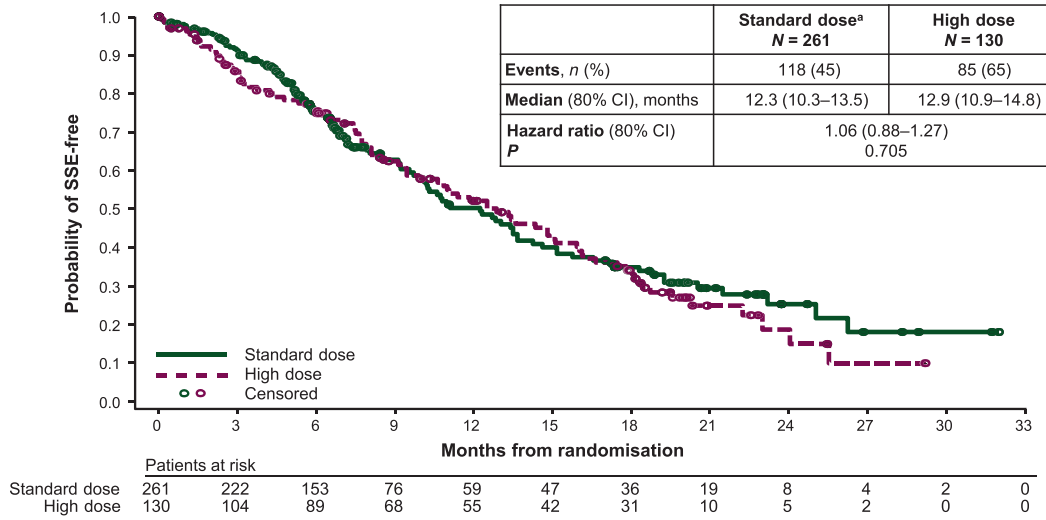

	Standard dose[a] *N* = 261	High dose *N* = 130
Events, *n* (%)	118 (45)	85 (65)
Median (80% CI), months	12.3 (10.3–13.5)	12.9 (10.9–14.8)
Hazard ratio (80% CI) *P*	1.06 (0.88–1.27) 0.705	

Patients at risk

Standard dose	261	222	153	76	59	47	36	19	8	4	2	0
High dose	130	104	89	68	55	42	31	10	5	2	0	0

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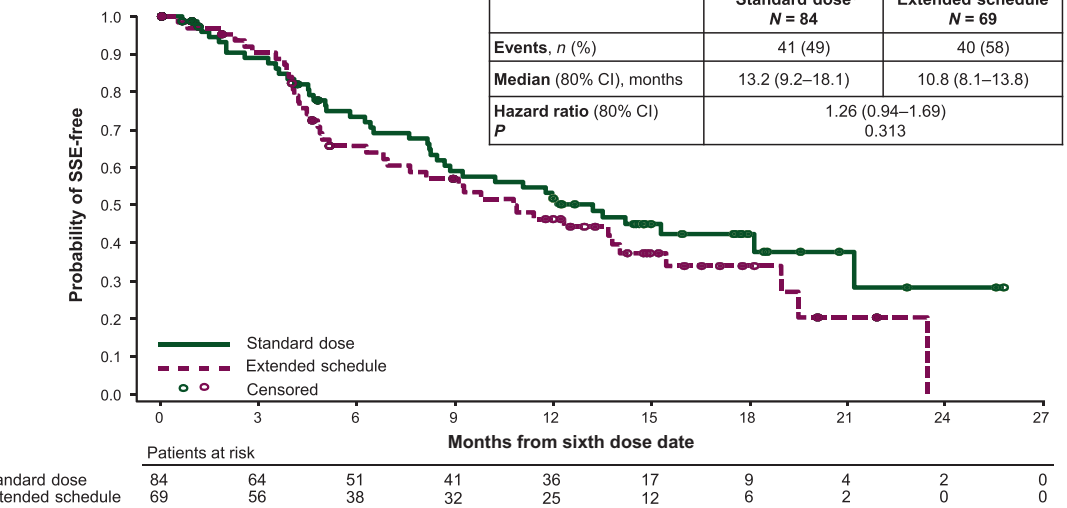

	Standard dose[b] *N* = 84	Extended schedule *N* = 69
Events, *n* (%)	41 (49)	40 (58)
Median (80% CI), months	13.2 (9.2–18.1)	10.8 (8.1–13.8)
Hazard ratio (80% CI) *P*	1.26 (0.94–1.69) 0.313	

Patients at risk

Standard dose	84	64	51	41	36	17	9	4	2	0
Extended schedule	69	56	38	32	25	12	6	2	0	0

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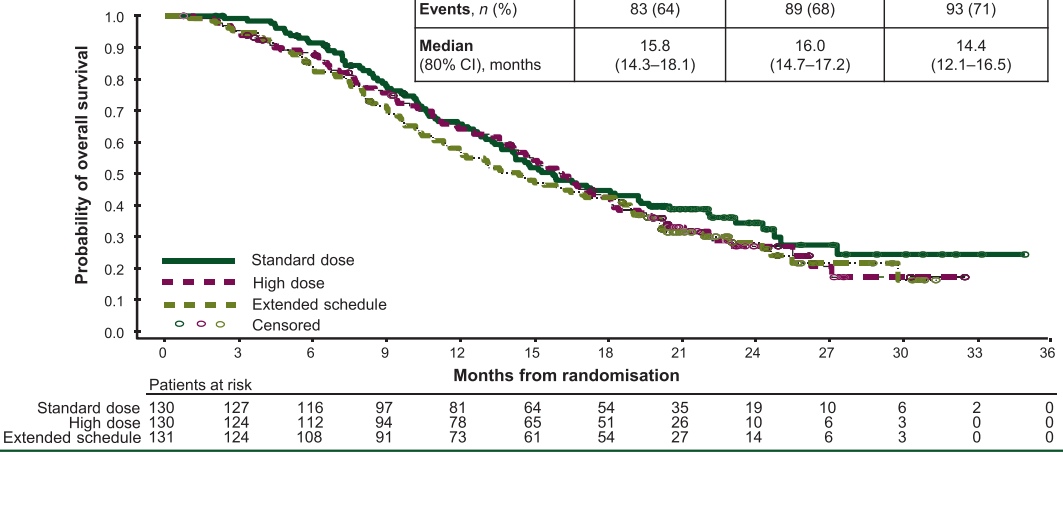

	Standard dose *N* = 130	High dose *N* = 130	Extended schedule *N* = 131
Events, *n* (%)	83 (64)	89 (68)	93 (71)
Median (80% CI), months	15.8 (14.3–18.1)	16.0 (14.7–17.2)	14.4 (12.1–16.5)

Patients at risk

Standard dose	130	127	116	97	81	64	54	35	19	10	6	2	0
High dose	130	124	112	94	78	65	51	26	10	6	3	0	0
Extended schedule	131	124	108	91	73	61	54	27	14	6	3	0	0

Table 2. Summary of efficacy (ITT population)

Parameter	Standard-dose arm (*N* = 130)	High-dose arm (*N* = 130)	Extended-schedule arm (*N* = 131)
Primary end point			
SSE-FS			
Events, *n* (%)	80 (62)	85 (65)	92 (70)
Death	43 (33)	43 (33)	44 (34)
SSEs	37 (28)	42 (32)	48 (37)
Bone fracture	4 (3)	9 (7)	10 (8)
EBRT	29 (22)	22 (17)	32 (24)
Orthopaedic surgery	0	1 (<1)	0
Spinal cord compression	4 (3)	10 (8)	6 (5)
Median (80% CI), months	13.1 (11.0—14.6)	12.9 (10.9—14.8)	9.6 (9.0—10.9)
Secondary end points			
Overall survival			
Events, *n* (%)	83 (64)	89 (68)	93 (71)
Median (80% CI), months	15.8 (14.3—18.1)	16.0 (14.7—17.2)	14.4 (12.1—16.5)
rPFS			
Events, *n* (%)	77 (59)	77 (59)	90 (69)
Median (80% CI), months	6.3 (5.1—7.2)	7.5 (5.9—8.6)	6.1 (5.2—6.6)
rTTP			
Events, *n* (%)	66 (51)	63 (48)	67 (51)
Median (80% CI), months	6.2 (5.9—7.1)	8.7 (6.2—9.7)	6.6 (6.0—8.7)
Time to radiological bone progression			
Events, *n* (%)	28 (22)	27 (21)	24 (18)
Median (80% CI), months	17.4 (14.6—NR)	14.5 (11.3—15.7)	15.1 (14.4—NR)
Time to radiological soft tissue/visceral progression			
Events, *n* (%)	52 (40)	52 (40)	50 (38)
Median (80% CI), months	9.0 (7.1—22.9)	10.7 (9.1—11.5)	9.5 (8.4—12.6)
Time to first SSE			
Events, *n* (%)	37 (28)	42 (32)	48 (37)
Median (80% CI), months	NR (26.3—NR)	24.1 (18.0—NR)	18.8 (15.1—25.6)
Time to pain progression			
Events, *n* (%)	32 (29)	31 (27)	46 (43)
Median (80% CI), months	NR (8.9—NR)[a]	NR (9.4—NR)[b]	10.1 (8.8—11.8)[c]
Pain improvement rate, *n* (%)	13 (27)[d]	13 (26)[e]	16 (37)[f]

Data are *n* (%) unless otherwise stated. Efficacy in the intention-to-treat population: standard dose, radium-223 55 kBq/kg q4w for up to six cycles; high dose, radium-223 88 kBq/kg q4w for up to six cycles; extended schedule, radium-223 55 kBq/kg q4w for up to 12 cycles.

CI, confidence interval; EBRT, external beam radiation therapy; ITT, intention-to-treat; NR, not reached; rPFS, radiological progression-free survival; rTTP, time to radiological progression; SSEs, symptomatic skeletal events; SSE-FS, SSE-free survival.

[a] Calculated in 110 patients.
[b] Calculated in 113 patients.
[c] Calculated in 108 patients.
[d] Calculated out of 48 patients.
[e] Calculated out of 50 patients.
[f] Calculated out of 43 patients.

the treatment was ongoing at baseline or was introduced during the study. This is in contrast to patients treated in the ALSYMPCA study, where only symptomatic patients were recruited and abiraterone and enzalutamide were unavailable, although the proportion of patients with prior treatment with docetaxel was similar for the two studies (52% versus 57% in the ALSYMPCA study).[1] Nevertheless, patient baseline characteristics were generally balanced across the treatment arms and comparable with those reported for patients treated with radium-223 in current clinical practice.[7,8]

No notable differences between the high-dose arm and the standard-dose arm, or between the extended-schedule arm and the standard-dose arm were found for overall survival, rTTP and rPFS (secondary end points). However, this study lacked statistical power to detect the difference in treatment effects using only randomised patients from the standard-dose and high-dose arms for comparison 1, and all randomised patients from the standard-dose and extended-schedule arms for comparison 2. Overall survival in the standard-dose treatment arm was comparable to that reported in the radium-223 arm of the ALSYMPCA study and

Figure 2. Kaplan—Meier analysis (ITT population and selected subpopulations).
(A) SSE-free survival in patients in the radium-223 high-dose versus standard-dose arms (ITT population). (B) SSE-free survival in patients in the radium-223 extended-schedule arm (over six cycles) versus standard-schedule arm (six cycles). The comparison was performed in selected patient subpopulations. Patients who had completed less than six cycles were excluded from the analysis. SSE-FS was calculated from the sixth injection of radium-223. (C) Overall survival in the standard-dose arm, high-dose arm and extended-schedule arm (ITT population).

CI, confidence interval; ITT, intention-to-treat; SSE-FS, symptomatic skeletal event-free survival.

[a] Data for the standard-dose arm were those from the standard-dose arm pooled with the first 6 months of data from patients in the extended-schedule arm. Data from patients who had received seven or more radium-223 injections were excluded from the analysis.
[b] Patients in the standard-dose arm who completed 6 injections of 55 kBq/kg radium-223 (standard schedule).

Table 3. Treatment-emergent adverse events (safety population)

TEAE[a]	Standard-dose arm (*N* = 125)		High-dose arm (*N* = 124)		Extended-schedule arm (*N* = 121)	
	Any grade	Grade ≥3[b]	Any grade	Grade ≥3[c]	Any grade	Grade ≥3[d]
Any	118 (94)	43 (34)	119 (96)	59 (48)	116 (96)	64 (53)
Haematological						
Anaemia	31 (25)	13 (10)	34 (27)	17 (14)	31 (26)	17 (14)
Thrombocytopenia	7 (6)	2 (2)	13 (10)	8 (6)	11 (9)	6 (5)
Neutropenia	2 (2)	2 (2)	11 (9)	5 (4)	5 (4)	0 (0)
Neutrophil count decreased	3 (2)	2 (2)	9 (7)	4 (3)	3 (2)	1 (<1)
Non-haematological						
Fatigue	39 (31)	4 (3)	37 (30)	0 (0)	35 (29)	3 (2)
Nausea	31 (25)	1 (<1)	29 (23)	1 (<1)	28 (23)	1 (<1)
Decreased appetite	31 (25)	1 (<1)	24 (19)	1 (<1)	26 (21)	1 (<1)
Diarrhoea	26 (21)	1 (<1)	28 (23)	1 (<1)	26 (21)	0 (0)
Bone pain	26 (21)	9 (7)	19 (15)	4 (3)	28 (23)	4 (3)
Back pain	20 (16)	2 (2)	19 (15)	4 (3)	25 (21)	5 (4)
Constipation	21 (17)	2 (2)	10 (8)	0 (0)	18 (15)	0 (0)
Arthralgia	20 (16)	4 (3)	18 (15)	2 (2)	19 (16)	2 (2)
Weight decreased	12 (10)	1 (<1)	6 (5)	0 (0)	19 (16)	1 (<1)
Vomiting	12 (10)	0 (0)	15 (12)	0 (0)	17 (14)	1 (<1)
Asthenia	12 (10)	3 (2)	9 (7)	1 (<1)	17 (14)	5 (4)
Pain in extremity	13 (10)	1 (<1)	9 (7)	1 (<1)	12 (10)	2 (2)
Spinal cord compression	2 (2)	1 (<1)	7 (6)	7 (6)	4 (3)	4 (3)
Hypertension	6 (5)	4 (3)	5 (4)	4 (3)	6 (5)	6 (5)

Data are *n* (%). TEAEs in the safety population: standard dose, radium-223 55 kBq/kg q4w for up to six cycles; high dose, radium-223 88 kBq/kg q4w for up to six cycles; extended schedule, radium-22, 55 kBq/kg q4w for up to 12 cycles.

NCI-CTCAE, National Cancer Institute Common Terminology Criteria Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE(s), treatment-emergent adverse event(s).

[a] Shown are MedDRA-preferred terms ordered by any NCI-CTCAE grade in ≥10% of patients, and those with CTCAE grade ≥3 occurring in ≥3% of patients in any treatment arm.

[b] One grade 5 event due to general physical health deterioration.

[c] Two grade 5 events are febrile neutropenia and general physical health deterioration.

[d] Four grade 5 events are general physical health deterioration, myocardial infarction, subdural haematoma and urosepsis.

the international and US-expanded access programmes.[1,7,8] Time to first SSE appears to be shorter in the extended-schedule arm than in the standard-schedule arm (HR 1.55, 80% CI 1.04—2.31), although a high number of patients in each arm were censored (64% versus 77%) and some of these patients were asymptomatic.

The safety profile for radium-223 in this study was comparable with other studies with no new safety concerns reported.[1,5—7] Grade ≥3 TEAEs were more frequently reported in patients treated in the high-dose and extended-schedule arms and more permanent treatment discontinuations were reported in these arms compared with the standard-dose arm. No reported drug-related TEAEs leading to death were reported.

A small retrospective study has recently shown that radium-223 treatment significantly improved ALP responses and the time to ALP progression in the presence of mutations leading to homologous recombination deficiency in tumours from patients with mCRPC and bone metastases. This novel synthetic lethality hypothesis warrants further validation in prospective studies.[9]

In summary, the current study supports six injections of standard-dose radium-223 as the optimal regimen for patients with mCRPC and bone metastases.

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Novartis, Pfizer, Roche and Sanofi; and is unremunerated director and Chair of ANZUP Cancer Trials Group. BW and LT are employed by Bayer. VJW is employed by Bayer and declares stock ownership from Bayer and Merck Serono. MH declares fees for consultancy and advisory roles from AstraZeneca, Pfizer and Genentech; research funding from AstraZeneca, Pfizer, Genentech and Bayer; and holds patent 'Systems and methods for tissue imaging' (US 8,185,186), and pending and filed patent applications (EP 08745653.9; CA 2683805; US 13/362,500; 224990/10-016P2/311733; 11764665.4-1464; 11764656.2-1464). ER and RJE declare no conflicts of interest.

DATA SHARING STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, timepoint and process of data access.

As such, 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 United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on 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 will take all necessary measures to ensure that patient privacy is safeguarded.

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