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Efficacy and Safety of Radium-223 Dichloride in Symptomatic Castration-resistant Prostate Cancer Patients With or Without Baseline Opioid Use From the Phase 3 ALSYMPCA Trial

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Abstract

Background: The phase 3 ALSYMPCA trial enrolled metastatic castration-resistant prostate cancer patients with or without baseline opioid use.
Objective: To assess the efficacy and safety of radium-223 dichloride (radium-223) versus placebo in ALSYMPCA patients by baseline opioid use.
Design, setting, and participants: Nine hundred and twenty one patients enrolled at 136 centers globally.
Intervention: Radium-223 (50 kBq/kg, intravenous injection) every 4 wk for six cycles or matching placebo, each plus best standard of care.
Outcome measurements and statistical analysis: Primary endpoint (overall survival [OS]), main secondary efficacy endpoints, and safety were evaluated by baseline opioid use. Additional analyses included time to first opioid use, time to first external beam radiation therapy for bone pain, and safety of concomitant external beam radiation therapy.
Results and limitations: At baseline, 408 (44%) patients had no pain and no analgesic use or mild pain with nonopioid therapy (World Health Organization ladder pain score 0–1 [nonopioid subgroup]), and 513 (56%) had moderate pain with occasional opioids or severe pain with regular daily opioids (World Health Organization ladder pain score 2–3 [opioid subgroup]). Radium-223 significantly prolonged OS versus placebo in nonopioid (hazard ratio [HR] = 0.70; 95% confidence interval [CI]: 0.52–0.93; $p = 0.013$) and opioid (HR = 0.68; 95% CI: 0.54–0.86; $p = 0.001$) subgroups, and significantly reduced risk of symptomatic skeletal events versus placebo, regardless of baseline opioid use (nonopioid subgroup: HR = 0.56, 95% CI: 0.39–0.82, $p = 0.002$; opioid subgroup: HR = 0.72, 95% CI: 0.53–0.98, $p = 0.038$). Time to first opioid use for bone pain was significantly delayed with radium-223 versus placebo (HR = 0.62, 95% CI: 0.46–0.85, $p = 0.002$). Adverse event incidences were similar between opioid subgroups.
Conclusions: Radium-223 versus placebo significantly prolonged OS and reduced symptomatic skeletal event risk with a favorable safety profile in castration-resistant prostate cancer patients with symptomatic bone metastases, regardless of baseline opioid use.
Patient summary: In this ALSYMPCA opioid subgroup analysis, baseline symptom levels did not appear to impact radium-223 dichloride efficacy or safety.

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1. Introduction

Radium-223 dichloride (radium-223), a first-in-class alpha-emitting radiopharmaceutical [1–3], has demonstrated survival benefits for patients with symptomatic bone metastases from castration-resistant prostate cancer (CRPC). In the randomized phase 3 ALSYMPCA study, radium-223 plus best standard of care (BSoC) versus placebo plus BSoC prolonged median overall survival (OS) by 3.6 mo (hazard ratio [HR] = 0.70; 95% confidence interval [CI]: 0.58–0.83; $p < 0.001$; median 14.9 mo vs 11.3 mo, respectively) and prolonged median time to first symptomatic skeletal event (SSE) by 5.8 mo (HR = 0.66; 95% CI: 0.52–0.83; $p < 0.001$; median 15.6 mo vs 9.8 mo, respectively) in patients with CRPC and symptomatic bone metastases [4,5]. Additionally, radium-223 had a favorable safety profile with a low myelosuppression rate [4]. ALSYMPCA results led to radium-223 approval for the treatment of CRPC patients with symptomatic bone metastases and no known visceral metastatic disease [6].

Unlike the phase 2 radium-223 dose-response pain study [7], ALSYMPCA was not designed to evaluate the effect of radium-223 on pain; the primary endpoint was OS, and all patients received BSoC during the study, including treatments to manage pain (eg, external beam radiation therapy [EBRT], analgesics) [4]. ALSYMPCA eligibility required having symptomatic disease, broadly defined to include patients with regular use of analgesic medication (non-opioid or opioid) or pain-free patients who received EBRT for cancer-related bone pain in the 12 wk before randomization [4]. At baseline, 44% of radium-223 and 45% of placebo patients had no pain or had mild pain effectively managed without need for opioids; the remaining patients (56% radium-223 and 55% placebo) required opioids at study entry [4].

The efficacy and favorable safety of radium-223 was observed in the overall ALSYMPCA population that included patients both with and without baseline opioid use. The question arises of whether the radium-223 survival advantage depended on patients' baseline symptom severity. In other words, would patients with no or minimal symptoms benefit from radium-223 as much as those with symptoms? To address this question, we assessed the efficacy and safety of radium-223 versus placebo in ALSYMPCA patients who did not require opioid therapy at baseline (ie, minimally symptomatic disease) versus those receiving opioids at baseline (ie, symptomatic disease). Additional analyses assessed the impact of radium-223 on delaying the need for opioids or EBRT for bone pain management and the safety of concomitant EBRT.

2. Patients and methods

2.1. Patients and study design

ALSYMPCA was a phase 3, randomized, double-blind, placebo-controlled study conducted at 136 centers in 19 countries to compare the efficacy and safety of radium-223 plus BSoC versus placebo plus BSoC in CRPC patients with symptomatic bone metastases. Patient eligibility criteria were previously reported [4,5,8]. Briefly, eligible patients had histologically confirmed, progressive CRPC, at least two bone metastases, no known visceral metastases, and symptomatic disease defined as regular use of nonopioid analgesics or opioid medication for cancer-related bone pain (World Health Organization [WHO] ladder pain score ≥ 1) or EBRT for cancer-related bone pain in the 12 wk prior to randomization.

Patients were randomized (2:1) to receive either six intravenous injections of radium-223 50 kBq/kg (55 kBq/kg following the National Institute of Standards and Technology update [9]) or matching placebo, one injection every 4 wk. Patients were stratified by previous docetaxel use (yes or no), baseline total alkaline phosphatase (tALP) serum level (<220 U/l or ≥220 U/l), and bisphosphonate use at study entry (yes or no). All patients received BSoC available at each center (Supplementary Table 1). The planned follow-up was 3 yr from first study-drug injection. Review boards at all participating centers approved the study, and all patients provided written informed consent. The study was registered with ClinicalTrials.gov, number NCT00699751.

2.2. Procedures

Opioids were permitted prior to and during ALSYMPCA, but were not a requirement for study entry. Investigators were free to manage bone pain during the study by starting nonopioid analgesics, or adding EBRT or opioids to pre-existing nonopioid analgesics as recommended by the WHO guidelines [10]. EBRT could be administered at any time prior to randomization or within 12 wk prior to randomization to fulfill the eligibility requirement of symptomatic disease and was allowed during the study as part of BSoC. Time to first EBRT use for bone pain was documented as a component of the secondary endpoint time to first SSE.

2.3. Opioid subgroups and study assessments

This analysis was designed to assess radium-223 efficacy and safety in the subgroups of patients who had or had not received opioids at baseline. Two subgroups were defined: the nonopioid subgroup included patients with no pain and no analgesic use (WHO ladder pain score 0) or mild pain and no opioid use (WHO ladder pain score 1) at baseline; the opioid subgroup included patients with moderate pain and occasional opioid use (WHO ladder pain score 2) or severe pain and regular daily opioid use (WHO ladder pain score 3) at baseline.

2.4. Outcomes

Patient outcomes by baseline opioid use and treatment group were evaluated for the ALSYMPCA primary endpoint (OS), main secondary efficacy endpoints, and safety. OS was defined as time from randomization to date of death, regardless of cause. Main secondary efficacy endpoints were time to first SSE (defined as first EBRT use to relieve bone pain, or occurrence of new symptomatic pathologic bone fractures [vertebral or nonvertebral], spinal cord compression, or tumor-related orthopedic surgical intervention); time to prostate-specific antigen (PSA)-level increase; time to tALP-level increase; confirmed ≥30% reduction in tALP response; and tALP normalization. The initial trial report contains a complete description of these efficacy and safety endpoints [4].

2.5. Statistical analyses

Analyses of OS by opioid subgroup and time to first EBRT use for bone pain were specified in the protocol and included in the original planned analysis. Subsequent, exploratory analyses included the main secondary efficacy endpoints by opioid subgroup, safety by opioid subgroup, time to first use of opioids, and safety with concomitant EBRT. All data were prospectively collected.

Efficacy analyses for opioid subgroups were based on the intent-to-treat (ITT) population, including all randomized patients. Safety analyses were based on the safety population, including all patients who received at least one study-drug injection. A log-rank test was used to analyze OS and main secondary efficacy endpoints of time to first SSE, time to tALP increase, and time to PSA increase. HRs were estimated using the Cox proportional hazards regression model. Both the log-rank test and the Cox model were stratified by tALP, bisphosphonate use at study entry, and prior docetaxel use. An unstratified Cox proportional hazards model was used to test the treatment by opioid subgroup interaction. Median values for time-to-event variables (OS, time to first SSE, time to tALP increase, time to PSA increase, time to first opioid use, and time to first EBRT) were assessed using the Kaplan-Meier method and censored at the last known alive date or patient assessment date, if an event had not occurred at time of analysis or the patient was lost to follow-up. tALP response and normalization were analyzed using a Cochran-Mantel-Haenszel analysis adjusting for stratification factors tALP, current bisphosphonate use, and prior docetaxel use. Safety analyses were descriptive.

Additional analyses evaluated the radium-223 effect on addition of opioids or need for EBRT. Time to first on-study opioid use was assessed in patients not receiving opioids at baseline (ie, nonopioid subgroup). Time to first EBRT use for bone pain was a component of the SSE main secondary efficacy endpoint and was assessed in the overall ALSYMPCA ITT population. Adverse events (AEs) by concomitant EBRT were analyzed in the ALSYMPCA safety population.

3. Results

3.1. Nonopioid and opioid subgroups

Of the 921 patients randomized in the ALSYMPCA ITT population, 408 (44%) had no pain and no analgesic use (WHO ladder pain score 0) or mild pain managed with nonopioid therapy (WHO ladder pain score 1) at baseline (nonopioid subgroup: radium-223, $n = 269$; placebo, $n = 139$), and 513 (56%) had moderate pain with occasional opioids (WHO ladder pain score 2) or severe pain with regular daily opioids (WHO ladder pain score 3) at baseline (opioid subgroup: radium-223, $n = 345$; placebo, $n = 168$; Fig. 1). In the nonopioid subgroup, 12 of 269 (4%) radium-223 patients and two of 139 (1%) placebo patients

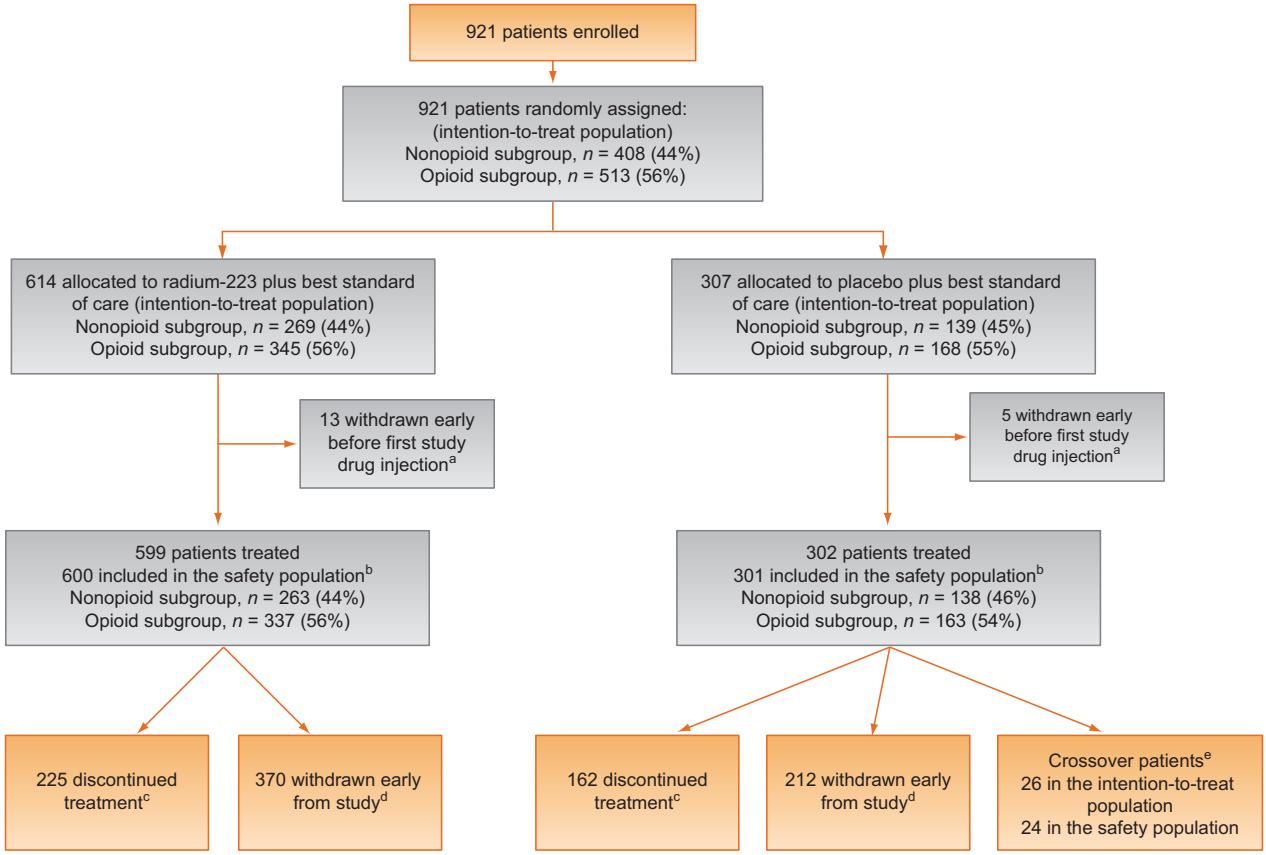

Fig. 1 – Consolidated Standards of Reporting Trials diagram.
radium-223 = radium-223 dichloride.
[a] Eighteen patients who were not being treated were withdrawn from the study before the first injection of the study drug (13 from the radium-223 group and five from the placebo group); an additional two patients received no treatment and had missing dates of withdrawal.
[b] One patient was randomly assigned to the placebo but received radium-223 at week 0; this patient is included as randomly assigned in the intention-to-treat population (placebo group) and is included in the radium-223 group for the safety population.
[c] Patients who discontinued treatment but continued to participate through follow-up were not regarded as withdrawn from the study; the study was ongoing at the time of the database lock, so patient numbers might not sum to the total number treated.
[d] Patients who withdrew before their 3-yr follow-up visit were regarded as having withdrawn early from the study; the study was ongoing at the time of the database lock, so patient numbers might not sum to the total number treated.
[e] Patients in the placebo group who received treatment with radium-223 after the study was unblinded; these patients were not regarded as having discontinued treatment or withdrawn from the study.

were completely pain free, although they met the study inclusion criteria for symptomatic disease, having received EBRT in the 12 wk prior to randomization.

3.2. Patient demographics and baseline characteristics

Demographics and baseline characteristics were generally balanced between nonopioid and opioid subgroups and the overall ALSYMPCA ITT population (Table 1). Compared with radium-223 patients who required opioids, those in the nonopioid subgroup appeared to have less advanced disease, suggested by a greater proportion with tALP values <220 U/l, lower median tALP and lactate dehydrogenase values, better performance status, and less extensive skeletal disease. Also, fewer had prior docetaxel therapy and EBRT for pain in the 12 wk prior to randomization. A similar trend was seen among placebo patients (Table 1). Irrespective of treatment allocation, the survival duration and time to first SSE were longer in minimally symptomatic (ie, WHO ladder pain score 0–1/without opioid use) than in more symptomatic patients (ie, WHO ladder pain score 2–3/with opioid use).

3.3. Efficacy: survival

Radium-223 significantly prolonged OS, regardless of baseline opioid use. Consistent OS benefits were seen with radium-223 treatment versus placebo in nonopioid (HR = 0.70; 95% CI: 0.52–0.93; $p = 0.013$; median 16.4 mo vs 12.8 mo, respectively) and opioid (HR = 0.68; 95% CI: 0.54–0.86; $p = 0.001$; median 13.9 mo vs 10.4 mo, respectively) subgroups (Fig. 2, A and B). The treatment by opioid subgroup interaction was not statistically significant ($p = 0.985$), indicating that there is no difference in treatment effect between the opioid and nonopioid subgroups for OS.

3.4. Efficacy: SSE and other main secondary efficacy endpoints

Radium-223 treatment significantly reduced the risk of SSEs compared with placebo, regardless of baseline opioid use (nonopioid subgroup: HR = 0.56, 95% CI: 0.39–0.82, $p = 0.002$; opioid subgroup: HR = 0.72, 95% CI: 0.53–0.98, $p = 0.038$; (Fig. 2, C and D). Additionally, all main secondary efficacy endpoints were met, regardless of baseline opioid use (Table 2).

Table 1 – Patient demographics and baseline characteristics

Characteristics[a]	Nonopioid subgroup		Opioid subgroup		ITT population	
	Radium-223 *n* = 269	Placebo *n* = 139	Radium-223 *n* = 345	Placebo *n* = 168	Radium-223 *n* = 614	Placebo *n* = 307
Age						
Median (range), yr	72 (51–90)	73 (50–89)	71 (49–88)	69 (44–94)	71 (49–90)	71 (44–94)
Total alkaline phosphatase level, *n* (%)						
<220 U/l	169 (63)	82 (59)	179 (52)	87 (52)	348 (57)	169 (55)
≥220 U/l	100 (37)	57 (41)	166 (48)	81 (48)	266 (43)	138 (45)
Current use of bisphosphonates, *n* (%)						
Yes	105 (39)	57 (41)	145 (42)	67 (40)	250 (41)	124 (40)
No	164 (61)	82 (59)	200 (58)	101 (60)	364 (59)	183 (60)
Prior use of docetaxel, *n* (%)						
Yes	139 (52)	73 (53)	213 (62)	101 (60)	352 (57)	174 (57)
No	130 (48)	66 (48)	132 (38)	67 (40)	262 (43)	133 (43)
ECOG performance status score, *n* (%)						
0	99 (37)	44 (32)	66 (19)	34 (20)	165 (27)	78 (25)
1	151 (56)	84 (60)	220 (64)	103 (61)	371 (60)	187 (61)
≥2	18 (7)	11 (8)	59 (17)	30 (18)	77 (13)	41 (13)
WHO ladder for cancer pain, *n* (%)						
0 (no pain; no opioid use)	12 (4)	2 (1)	0	0	12 (2)	2 (1)
1 (mild pain; no opioid use)	257 (96)	137 (99)	0	0	257 (42)	137 (45)
2 (moderate pain; occasional opioid use)	0	0	151 (44)	78 (46)	151 (25)	78 (25)
3 (severe pain; regular daily opioid use)	0	0	194 (56)	90 (54)	194 (32)	90 (29)
EBRT to bone ≤12 wk prior to randomization, *n* (%)	33 (12)	20 (14)	66 (19)	28 (17)	99 (16)	48 (16)
Extent of disease, *n* (%)						
<6 metastases	56 (21)	19 (14)	44 (13)	19 (11)	100 (16)	38 (12)
6-20 metastases	120 (45)	67 (48)	142 (41)	80 (48)	262 (43)	147 (48)
>20 metastases or superscan[b]	91 (34)	53 (38)	158 (46)	68 (40)	249 (41)	121 (39)
Median biochemical values (range)[c]						
Hemoglobin (g/dl)	13 (9–16)	13 (9–16)	12 (9–15)	12 (9–16)	12 (9–16)	12 (9–16)
Albumin (g/l)	40 (26–53)	40 (24–50)	40 (24–52)	40 (23–49)	40 (24–53)	40 (23–50)
Total alkaline phosphatase (U/l)	164 (32–6431)	213 (29–3225)	240 (40–2727)	235 (36–4805)	211 (32–6431)	223 (29–4805)
Lactate dehydrogenase (U/l)	280 (121–1969)	321 (138–3856)	342 (76–2171)	350 (132–2836)	315 (76–2171)	336 (132–3856)
Prostate-specific antigen (μg/l)	145 (4–5790)	165 (2–4850)	151 (4–6026)	173 (7–14500)	146 (4–6026)	173 (2–14500)

EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; radium-223 = radium-223 dichloride; WHO = World Health Organization.

[a] Percentages may not sum to 100 due to rounding.

[b] Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

[c] The normal biochemical ranges are as follows: hemoglobin, 13–17 g/dl; albumin, 36–45 g/l; total alkaline phosphatase, 35–105 U/l; lactate dehydrogenase, 115–255 U/l; and prostate-specific antigen, 0–3.999 μg/l.

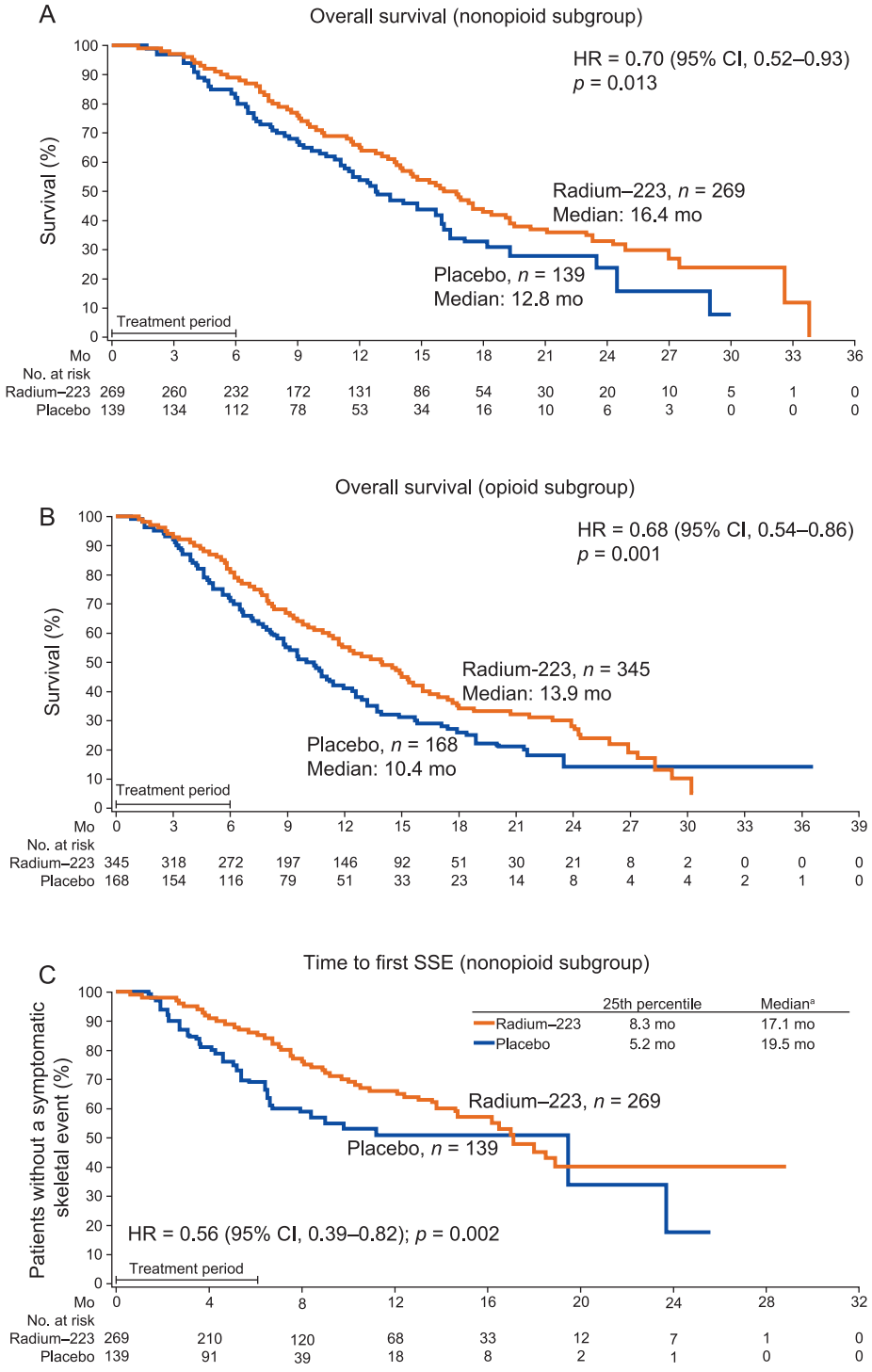

Fig. 2 – Kaplan-Meier estimates of (A, B) overall survival and (C, D) time to first symptomatic skeletal event by baseline opioid use (intent-to-treat population; *N* = 921); and (E) time to first opioid use in patients without baseline opioid use (nonopioid subgroup, *n* = 408).
CI = confidence interval; HR = hazard ratio; radium-223 = radium-223 dichloride; SSE = symptomatic skeletal event.
[a] Median time to first symptomatic skeletal event in the nonopioid subgroup was longer for placebo patients versus radium-223 patients (19.5 mo vs 17.1 mo, respectively), as few patients were left in the placebo group toward the end of the assessment period and the curves crossed before median time to first symptomatic skeletal event was reached, thus the tail end of the curves were not reliably estimated. The 25th percentile was 8.3 mo for radium-223 patients and 5.2 mo for placebo patients, indicating the treatment benefit of radium-223 during the early part of the study, when most patients were evaluable. Hazard ratio is the most appropriate statistical parameter to best interpret the treatment difference over the entire observed time frame.

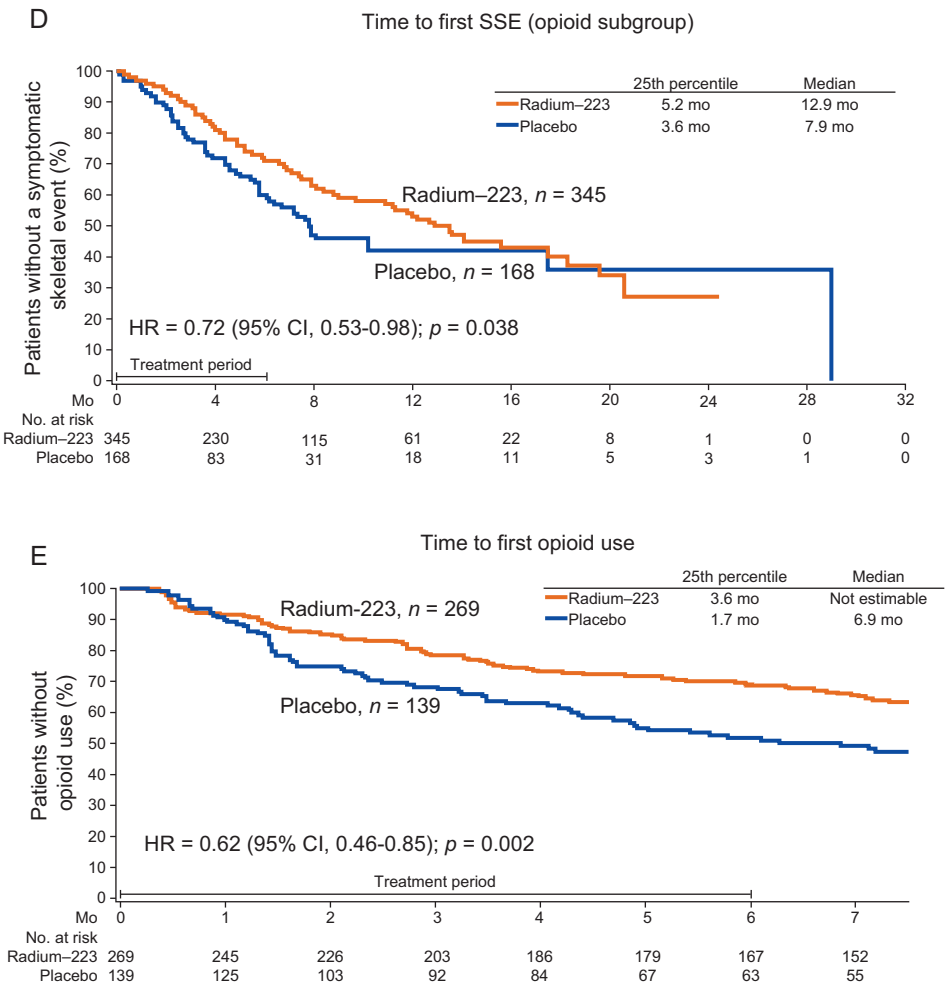

Fig. 2. (*Continued*).

3.5. *Safety*

No clinically meaningful treatment differences in the incidence of hematologic or nonhematologic AEs were observed between nonopioid and opioid subgroups (Table 3), despite the slightly higher AE incidence (all grades and Grade 3/4) in the opioid subgroup for radium-223 and placebo patients, which may reflect more advanced disease in these patients. Although rare, Grades 3/4 neutropenia and thrombocytopenia occurred more frequently in radium-223 patients versus placebo patients, regardless of opioid subgroup (nonopioid subgroup: neutropenia in 2% vs 1%, thrombocytopenia in 5% vs 1%; opioid subgroup: neutropenia in 2% vs 1%, thrombocytopenia in 7% vs 2%; Table 3).

3.6. *Radium-223 with concomitant opioids or EBRT for bone pain management*

As mentioned above, opioids and EBRT were permitted as part of BSoC for bone pain management. Time to first use of opioids for bone pain was assessed in patients not receiving baseline opioids (ie, nonopioid subgroup). During the study, opioids were required by 36% (96/269) of radium-223 patients versus 50% (70/139) of placebo patients who were not receiving opioids at baseline. Radium-223 significantly delayed time to first opioid use for bone pain versus placebo (HR = 0.62, 95% CI: 0.46–0.85, $p = 0.002$; median not estimable vs 6.9 mo, respectively; Fig. 2E).

During the study, 30% (186/614) of radium-223 patients and 34% (105/307) of placebo patients received EBRT for bone pain. Radium-223 significantly reduced the risk of needing EBRT for bone pain by 33% versus placebo (HR = 0.67, 95% CI: 0.53–0.85, $p = 0.001$; Supplementary Fig. 1). No differences were seen in the safety profile between patients who did and did not receive concomitant EBRT for bone pain during the study (Table 4). Additionally, myelosuppression rates were low regardless of concomitant EBRT.

4. Discussion

In ALSYMPCA, patients were required to have symptomatic disease to be eligible for the study; however, *symptomatic* was broadly defined, in that opioid use was not required and patients were defined as minimally symptomatic if they had regular use of any analgesic medication or if they had received EBRT in the 12 wk before randomization. This opioid subgroup analysis was conducted to determine if the radium-223 survival advantage in the overall ALSYMPCA

Table 2 – Efficacy endpoints (intent-to-treat population; *N* = 921)

	Nonopioid subgroup				Opioid subgroup			
	Radium-223 *n* = 269	Placebo *n* = 139	Hazard ratio[a] (95% CI)	*p* value[b]	Radium-223 *n* = 345	Placebo *n* = 168	Hazard ratio[a] (95% CI)	*p* value[b]
Primary endpoint								
Overall survival (mo) Median (95% CI)	16.4 (14.4–18.4)	12.8 (11.3–16.0)	0.70 (0.52–0.93)	0.013	13.9 (11.9–15.4)	10.4 (8.7–11.6)	0.68 (0.54–0.86)	0.001
Main secondary efficacy endpoints								
Patients experiencing an event, *n* (%)	77 (29)	50 (36)	0.56 (0.39–0.82)	0.002	125 (36)	66 (39)	0.72 (0.53–0.98)	0.038
Time to first SSE (mo), median (95% CI)	17.1 (14.7–NE)	19.5 (7.9–23.7)			12.9 (11.0–18.3)	7.9 (6.2–29.0)		
Patients experiencing an event, *n* (%)	44 (16)	74 (53)	0.17 (0.11–0.25)	<0.001	62 (18)	77 (46)	0.15 (0.11–0.22)	<0.001
Time to increase in tALP level (mo), median (95% CI)	7.4 (7.1–NE)	4.1 (3.6–4.3)			NE	3.7 (3.5–4.1)		
Patients experiencing an event, *n* (%)	168 (62)	94 (68)	0.68 (0.53–0.89)	0.004	220 (64)	99 (59)	0.62 (0.48–0.80)	<0.001
Time to increase in PSA level (mo), median (95% CI)	3.6 (3.5–4.0)	3.5 (3.3–3.5)			3.6 (3.5–3.9)	3.4 (3.3–3.5)		
Patients with ≥30% reduction in tALP response, *n* (%)[c]	97/225 (43)	4/102 (4)	NA	<0.001[d]	136/272 (50)	3/109 (3)	NA	<0.001[d]
Patients with normalization of tALP level, *n* (%)[e]	51/131 (39)	0/65 (0)	NA	<0.001[d]	58/190 (31)	2/75 (3)	NA	<0.001[d]

CI = confidence interval; NA = not applicable; NE = not estimable; PSA = prostate-specific antigen; radium-223 = radium-223 dichloride; SSE = symptomatic skeletal event; tALP = total alkaline phosphatase.
[a] Hazard ratio (radium-223: placebo) is from a Cox proportional hazards model stratified by tALP, current use of bisphosphonates, and prior use of docetaxel.
[b] Unless otherwise noted, the *p* value is from the log-rank test stratified by tALP, current use of bisphosphonates, and prior use of docetaxel.
[c] *n* value is the number of patients with a confirmed tALP response/the total number of patients with nonmissing tALP values. A ≥30% reduction was defined relative to the baseline value, and was confirmed by a second tALP value approximately 4 or more wk later.
[d] *p* value is from a Cochran-Mantel-Haenszel test adjusted for the stratification factors tALP, current use of bisphosphonates, and prior use of docetaxel.
[e] *n* value is the number of patients with an elevated baseline tALP that normalized on study/the total number of patients with an elevated baseline tALP.

Table 3 – Adverse events (AEs) by opioid subgroup (safety population; *N* = 901)

No. of patients with an AE, *n* (%)	Nonopioid subgroup						Opioid subgroup					
	Radium-223 *n* = 263			Placebo *n* = 138			Radium-223 *n* = 337			Placebo *n* = 163		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hematologic AEs[a]												
Anemia[b]	69 (26)	26 (10)	4 (2)	38 (28)	14 (10)	0	118 (35)	39 (12)	7 (2)	54 (33)	23 (14)	2 (1)
Leukopenia	12 (5)	4 (2)	0	0	0	0	13 (4)	3 (1)	1 (<1)	1 (1)	1 (1)	0
Neutropenia	11 (4)	4 (2)	1 (<1)	1 (1)	1 (1)	0	19 (6)	5 (1)	3 (1)	2 (1)	1 (1)	0
Thrombocytopenia[c]	27 (10)	9 (3)	5 (2)	6 (4)	2 (1)	0	42 (12)	11 (3)	13 (4)	11 (7)	3 (2)	1 (1)
Nonhematologic AEs[d]												
Constipation	46 (17)	2 (1)	0	26 (19)	0	0	62 (18)	4 (1)	0	38 (23)	4 (2)	0
Diarrhea	70 (27)	3 (1)	0	27 (20)	4 (3)	0	81 (24)	6 (2)	0	18 (11)	1 (1)	0
Nausea	79 (30)	4 (2)	0	39 (28)	2 (1)	0	134 (40)	6 (2)	0	65 (40)	3 (2)	0
Vomiting	42 (16)	5 (2)	0	15 (11)	3 (2)	0	69 (20)	5 (1)	0	26 (16)	4 (2)	0
Fatigue	63 (24)	5 (2)	2 (1)	33 (24)	7 (5)	1 (1)	91 (27)	16 (5)	1 (<1)	44 (27)	9 (6)	1 (1)
Peripheral edema	26 (10)	2 (1)	0	14 (10)	1 (1)	0	50 (15)	8 (2)	0	16 (10)	2 (1)	1 (1)
Weight decreased	25 (10)	3 (1)	0	19 (14)	1 (1)	0	44 (13)	1 (<1)	0	25 (15)	4 (2)	0
Anorexia	38 (14)	4 (2)	0	25 (18)	2 (1)	0	64 (19)	5 (1)	0	30 (18)	0	0
Bone pain	111 (42)	35 (13)	2 (1)	82 (59)	26 (19)	1 (1)	189 (56)	85 (25)	3 (1)	105 (64)	48 (29)	2 (1)
Malignant neoplasm progression[e]	25 (10)	2 (1)	1 (<1)	13 (9)	2 (1)	0	52 (15)	7 (2)	3 (1)	31 (19)	2 (1)	1 (1)

radium-223 = radium-223 dichloride.
[a] All grades occurring in ≥5% of patients in either treatment subgroup.
[b] Grade 5 anemia occurred in one (1%) patient in the placebo group (nonopioid subgroup).
[c] Grade 5 thrombocytopenia occurred in one (<1%) patient in the radium-223 group (nonopioid subgroup); this was considered possibly drug related by the investigator, and the patient died from pneumonia with no evidence of bleeding.
[d] All grades occurring in ≥15% of patients in either treatment subgroup.
[e] Grade 5 malignant neoplasm progression occurred in 17 (7%) patients in the radium-223 group and eight (6%) patients in the placebo group (nonopioid subgroup) and in 38 (11%) patients in the radium-223 group and 25 (15%) patients in the placebo group (opioid subgroup).

Table 4 – Adverse events (AEs) by concomitant external beam radiation therapy (EBRT) use (safety population; *N* = 901)

	With concomitant EBRT				Without concomitant EBRT			
	Radium-223 *n* = 227		Placebo *n* = 140		Radium-223 *n* = 373		Placebo *n* = 161	
Patients with AEs, *n* (%)	All grades	Grades 3–4	All grades	Grades 3–4	All grades	Grades 3–4	All grades	Grades 3–4
Hematologic AEs (all grades occurring in ≥5% of patients in either treatment subgroup)								
Anemia	77 (34)	27 (12)	51 (36)	21 (15)	110 (29)	50 (13)	41 (25)	19 (12)
Leukopenia	7 (3)	2 (1)	0 (0)	0 (0)	18 (5)	6 (2)	1 (1)	1 (1)
Neutropenia	14 (6)	5 (2)	1 (1)	1 (1)	16 (4)	8 (2)	2 (1)	1 (1)
Thrombocytopenia	27 (12)	13 (6)	8 (6)	2 (1)	42 (11)	26 (7)	9 (6)	4 (2)
Nonhematologic AEs (all grades occurring in ≥15% of patients in either treatment subgroup)								
Constipation	54 (24)	4 (2)	35 (25)	1 (1)	54 (14)	2 (1)	29 (18)	3 (2)
Diarrhea	71 (31)	1 (0)	26 (19)	3 (2)	80 (21)	8 (2)	19 (12)	2 (1)
Nausea	98 (43)	8 (4)	61 (44)	3 (2)	115 (31)	2 (1)	43 (27)	2 (1)
Vomiting	56 (25)	4 (2)	26 (19)	4 (3)	55 (15)	6 (2)	15 (9)	3 (2)
Fatigue	67 (30)	10 (4)	24 (17)	3 (2)	87 (23)	14 (4)	53 (33)	15 (9)
Weight decreased	33 (15)	2 (1)	20 (14)	2 (1)	36 (10)	2 (1)	24 (15)	3 (2)
Anorexia	31 (14)	2 (1)	30 (21)	0 (0)	71 (19)	7 (2)	25 (16)	2 (1)
Bone pain	158 (70)	80 (35)	103 (74)	48 (34)	142 (38)	45 (12)	84 (52)	29 (18)
Malignant neoplasm progression	31 (14)	14 (6)	17 (12)	9 (6)	46 (12)	22 (6)	27 (17)	14 (9)

radium-223 = radium-223 dichloride.

population depended on the patient's baseline symptom level.

At study entry, 44% of radium-223 patients and 45% of placebo patients were minimally symptomatic, with no pain or mild pain and no opioid use; of these, 4% of radium-223 patients and 1% of placebo patients were completely pain free at study entry. Radium-223 versus placebo significantly prolonged OS, reduced risk of initial SSE, and improved biochemical markers with a favorable safety profile in ALSYMPCA patients, regardless of baseline opioid use. For both radium-223 and placebo patients, minimally symptomatic patients (ie, WHO ladder pain score 0–1/without opioid use) had longer OS than patients with more symptomatic disease (ie, WHO ladder pain score 2–3/with opioid use). Results from these opioid subgroup analyses showed that radium-223 is effective and well tolerated in both minimally symptomatic nonopioid patients (WHO ladder pain score 0–1) and those with more advanced symptomatic disease who required opioid therapy (WHO ladder pain score 2–3), suggesting that appropriate timing of radium-223 treatment should not be based on symptom severity.

During ALSYMPCA, radium-223 treatment significantly delayed time to first opioid use and reduced the risk of needing EBRT for bone pain. Importantly, ALSYMPCA was not designed to evaluate the effect of radium-223 on pain; any observed pain response or lack thereof should not be considered a reason to stop radium-223 treatment. In fact, 63% of ALSYMPCA patients in the radium-223 group were able to receive all six injections of radium-223 [4], the recommended course stated in approved radium-223 labeling. It is worth noting that concomitant EBRT had no effect on AE incidence or severity; as part of BSoC, EBRT may be used as needed to manage pain in patients undergoing radium-223 therapy. Using radium-223 earlier in the disease course, when patients are minimally symptomatic, may optimize treatment outcome and allow sequencing or combination use with other life-prolonging therapies. Additionally, radium-223 treatment has been shown to reduce hospitalization costs versus placebo [11]. Exploratory analyses from an international expanded access program with radium-223 (*n* = 696; included CRPC patients with symptomatic or asymptomatic bone metastases) showed that low or no pain at baseline was prognostic for prolonged survival, and that radium-223 combined with abiraterone acetate and/or enzalutamide was generally well tolerated [12–14]. Randomized trials are ongoing to prospectively evaluate radium-223 combined with abiraterone acetate and enzalutamide in asymptomatic or mildly symptomatic metastatic CRPC patients (NCT02043678; NCT02034552).

5. Conclusions

Radium-223 compared with placebo improved OS and reduced the risk of initial SSE with a favorable safety profile in patients with CRPC and symptomatic bone metastases, regardless of baseline opioid use. These results show that radium-223 is effective and well tolerated in both minimally symptomatic nonopioid patients (WHO ladder pain score 0–1) and patients with more advanced symptomatic disease who required opioid therapy (WHO ladder pain score 2–3) at baseline. This suggests that symptom severity should not be the basis for determining appropriate timing of radium-223 treatment.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.06.002.

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