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ORIGINAL ARTICLE

Re-treatment with radium-223: first experience from an international, open-label, phase I/II study in patients with castration-resistant prostate cancer and bone metastases

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Background: Six radium-223 injections at 4-week intervals is indicated for patients with castration-resistant prostate cancer and symptomatic bone metastases. However, patients usually develop disease progression after initial treatment. This prospective phase I/II study assessed re-treatment safety and efficacy of up to six additional radium-223 injections.

Patients and methods: Patients had castration-resistant prostate cancer and bone metastases and six initial radium-223 injections with no on-treatment bone progression; all had subsequent radiologic or clinical progression. Concomitant agents were allowed at investigator discretion, excluding chemotherapy and initiation of new abiraterone or enzalutamide. The primary endpoint was safety; additional exploratory endpoints included time to radiographic bone progression, time to total alkaline phosphatase and prostate-specific antigen progression, radiographic progression-free survival, overall survival, time to first symptomatic skeletal event (SSE), SSE-free survival, and time to pain progression.

Results: Among 44 patients, 29 (66%) received all six re-treatment injections. Median time from end of initial radium-223 treatment was 6 months. Forty-one (93%) reported ≥ 1 treatment-emergent adverse event. No grade 4–5 hematologic treatment-emergent adverse events occurred. Only one (2%) patient had radiographic bone progression; eight (18%) had radiographic soft tissue tumor progression (three lymph node and five visceral metastases). Median times to total alkaline phosphatase and prostate-specific antigen progression were not reached and 2.2 months, respectively. Median radiographic progression-free survival was 9.9 months (12.8-month maximum follow-up). Five (11%) patients died and eight (18%) experienced first SSEs. Median overall survival, time to first SSE, and SSE-free survival were not reached. Five (14%) of 36 evaluable patients (baseline worst pain score ≤ 7) had pain progression. After 2 years of follow-up, 28 (64%) patients died, and the median overall survival was 24.4 months.

Conclusions: Re-treatment with a second course of six radium-223 injections after disease progression is well tolerated, with minimal hematologic toxicity and low radiographic bone progression rates in this small study with limited follow-up. Favorable

safety and early effects on disease progression indicate that radium-223 re-treatment is feasible and warrants further evaluation in larger prospective trials.

Key words: bone metastases, injections, prostate, radium-223, re-treatment, safety

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is associated with development of bone metastases in ~90% of patients [1–3]. Radium-223 dichloride (radium-223), the first targeted alpha therapy approved for treatment of mCRPC, has a targeted effect on bone metastases, based on a dosing regimen of one injection, 55 kBq/kg, every 4 weeks for a total of six injections [4, 5].

In the phase III Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 plus best standard of care demonstrated significant improvement in overall survival (OS) [hazard ratio, 0.70; 95% CI, 0.58–0.83; $P < 0.001$] and a delay in time to first symptomatic skeletal event (SSE) (hazard ratio, 0.66; 95% CI, 0.52–0.83; $P < 0.001$) versus placebo plus best standard of care [6, 7]. Radium-223 was also associated with significant quality-of-life (QOL) benefits, including a higher percentage of patients with meaningful QOL improvement and slower QOL decline over time [6]. Radium-223 was associated with a favorable safety profile [6, 8].

Radium-223 is associated with declines in total alkaline phosphatase (tALP) levels, correlating with longer OS [6, 9]. However, tALP levels begin to rise after treatment discontinuation following six radium-223 injections, suggesting that selected patients may benefit from extended therapy. In ALSYMPCA, despite the efficacy of treatment with six radium-223 injections, patients eventually developed disease progression in bone [6]. Considering the radium-223 favorable safety profile and low myelosuppression rates, patients who tolerated and benefitted from initial treatment may tolerate and derive added benefit from re-treatment.

This phase I/II study assessed the safety of re-treatment with up to six radium-223 injections, administered at 4-week intervals, to mCRPC patients who previously received a full course (six injections) of radium-223. Additional efficacy objectives included radiographic disease progression, tALP and prostate-specific antigen (PSA) responses, OS, SSEs, and pain outcomes.

Methods

Patient eligibility

Eligible patients included men ≥ 18 years of age with pathologically confirmed CRPC, defined as castrate serum testosterone ≤ 50 ng/dl at baseline. Patients had previously completed six injections of radium-223, with no evidence of bone progression during initial treatment. Patients had either radiologic (according to adapted Prostate Cancer Working Group 2 criteria) or biochemical/clinical progression [defined as two subsequent values showing PSA increase (≥ 2 ng/ml) or substantial worsening of pain due to bone metastases (based on investigator's determination)] after initial treatment; Eastern Cooperative Oncology Group performance status ≤ 2 ; life expectancy ≥ 6 months; and adequate laboratory values (absolute neutrophil count $\geq 1.5 \times 10^9/l$, platelet count $\geq 150 \times 10^9/l$, hemoglobin ≥ 9 g/dl, total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ ULN, creatinine $\leq 1.5 \times$ ULN,

estimated glomerular filtration rate ≥ 30 ml/min/1.73 m², albumin > 25 g/l).

Patients with radium-223-related serious or grade 3 or 4 adverse events, during or after initial treatment, that did not resolve or led to treatment discontinuation were ineligible, as were patients with visceral metastases ≥ 1 cm in diameter measured ≤ 30 days from treatment start. Patients must not have received chemotherapy after their initial course of radium-223. Concomitant abiraterone (if continued from prior abiraterone treatment) and enzalutamide (if continued from prior enzalutamide treatment) were permitted, although no concomitant chemotherapy and no new abiraterone or enzalutamide treatment initiation was permitted while on the study. Other agents, including denosumab and zoledronic acid, were permitted at the investigator's discretion. Patients were > 30 days from their last dose of prior radium-223 treatment. All patients provided written informed consent.

Study design and treatment

This international, open-label, phase I/II study was conducted at 21 centers initiated in eight countries: Finland, Israel, Italy, Norway, Spain, Sweden, UK, and United States. The institutional review board at each participating center approved the study, conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, registered on clinicaltrials.gov (NCT01934790). Sample size was based on clinical and practical considerations; no statistical assumptions were made.

Enrolled patients received up to six additional doses of radium-223 (55 kBq/kg i.v.), one injection every 4 weeks. An interactive voice response system was used for patient registration, carried out within 14 days before the first dose. The first injection could not be administered earlier than 30 days from the last radium-223 dose of the initial treatment course. The planned active follow-up period was up to 2 years after the last dose of radium-223.

The primary endpoint was safety, including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory assessments, treatment-related TEAEs during active follow-up, and discontinuation due to TEAE or death. Exploratory endpoints included radiographic progression-free survival (rPFS), time to radiographic bone progression, tALP and PSA response, time to tALP and PSA progression, OS, time to pain progression, time to first SSE, and SSE-free survival.

Assessments

Patients were evaluated for adverse events at each visit before receiving radium-223. During the first dosing period (first 28 days), patients had complete blood counts weekly. Following the first dosing period, every-28-day complete blood count assessments coincided with each subsequent radium-223 injection.

Radiographic progression (soft tissue/visceral or bone) was evaluated by magnetic resonance imaging or computed tomography of the abdomen and pelvis, chest X-ray, and whole-body technetium-99 bone scans at weeks 8 and 16 during the treatment period (first 24 weeks), then at week 24 (end-of-treatment visit). rPFS was defined as time from treatment start to radiographic progression or death (any cause). If progression was detected by bone scan, a confirmatory bone scan was required ≥ 6 weeks later per Prostate Cancer Working Group 2 criteria (confirmed radiographic bone progression). tALP and PSA were assessed at baseline and day 1 of each dosing visit. tALP response was defined

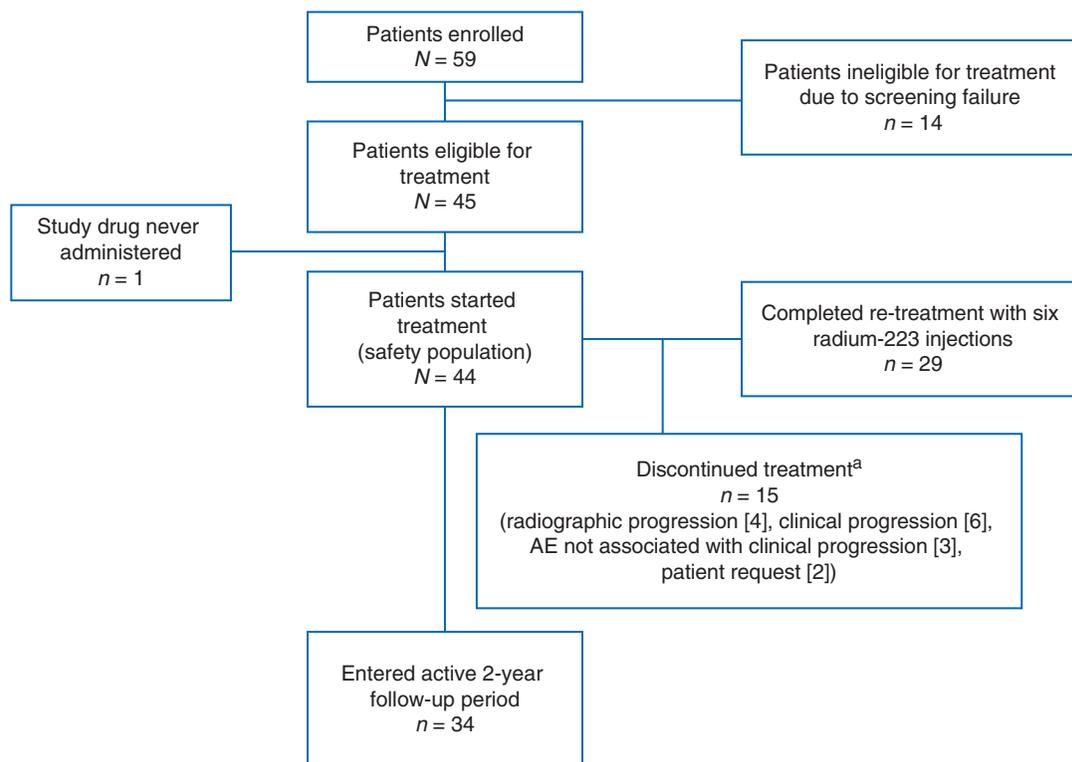


Figure 1. CONSORT diagram. ^aTypes of clinical progression leading to discontinuation were prostate-specific antigen progression ($n = 5$) and Eastern Cooperative Oncology Group performance status change ($n = 1$). The reason for discontinuation due to patient request was inability to travel to the clinic ($n = 2$).

as $\geq 30\%$ reduction from baseline; tALP progression was defined as $\geq 25\%$ increase above nadir value to at least $1.5 \times$ upper limit of normal. PSA response was defined as $\geq 30\%$ reduction from baseline, confirmed by subsequent $\geq 30\%$ reduction ≥ 4 weeks later. PSA progression was defined as $\geq 25\%$ increase above nadir value, and an increase in absolute value of ≥ 2 ng/ml above nadir. SSEs were evaluated during clinic visits and included external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fractures, spinal cord compression, and tumor-related orthopedic surgical intervention. SSE-free survival was defined as time from treatment start to first SSE or death, whichever occurred first. Pain was assessed daily using the Brief Pain Inventory-Short Form questionnaire for 7 days before day 1, dose 1 and then daily for 7 days before each 4-week assessment through week 24. Pain progression was defined as an increase in pain (according to Brief Pain Inventory-Short Form) or pain management from baseline, whichever occurred first, in evaluable patients (those with worst pain score of ≤ 7 at baseline).

Statistical analyses

This report provides study results for patients at the time of primary study completion, with a database cutoff of June 11, 2015, and OS results from up to 2 years of active follow-up from first radium-223 dose, with a database cutoff date of May 10, 2017.

All analyses reported here used the safety population, defined as all patients who received at least one study-drug dose. Statistical analyses were carried out using software package SAS version 9.3 (SAS Institute Inc., Cary, NC). All variables were analyzed by descriptive statistical methods. Baseline value was defined as the last value observed before study treatment start (cycle 1, day 1, unless otherwise specified). Durations were reported in months for baseline characteristics, patient history, and efficacy data unless otherwise specified. All efficacy analyses were considered exploratory. Time-to-event endpoints were summarized using Kaplan–Meier estimates. A Kaplan–Meier curve was generated for each

time-to-event endpoint. Categorical endpoints were summarized using frequencies and percentages.

Post hoc analysis of maximum percentage decline from baseline in tALP and PSA at 12 and 24 weeks was carried out, and waterfall plots generated.

Results

Patients

Across seven countries, 59 patients were enrolled; 44 re-treated with radium-223 were included in the safety population, used for safety and efficacy analyses. A group of 29/44 (66%) patients completed re-treatment with all six planned radium-223 injections; a median of six injections (range: 1–6) were received. Reasons for premature treatment discontinuation included radiographic progression ($n = 4$), clinical progression ($n = 6$), adverse event not associated with clinical progression ($n = 3$), and patient request ($n = 2$) (Figure 1). Median time from end of initial radium-223 treatment was 6 months (range: 1.2–17.1 months). Demographics and baseline clinical characteristics are shown in Table 1; 1/44 (2%), 7/44 (16%), 6/44 (14%), and 3/44 (7%) patients had concurrent zoledronic acid, denosumab, abiraterone, and enzalutamide, respectively; those with concurrent abiraterone or enzalutamide also had prior therapy with these agents. All patients had at least two prior hormonal regimens, and 32/44 (73%) patients had prior abiraterone or enzalutamide therapy and eventually developed disease

Table 1. Demographics and baseline clinical characteristics

Parameter	Re-treatment N = 44
Age, median (range), years	71 (52–91)
ECOG PS, n (%)	
0	14 (32)
1	27 (61)
≥2 ^a	3 (7)
Extent of disease, bone metastases, n (%)	
<6	18 (41)
6–20	15 (34)
>20, not superscan	6 (14)
Superscan	5 (11)
Prior treatment, n (%)	
Docetaxel	20 (45)
Abiraterone	27 (61)
Enzalutamide	13 (30)
Bisphosphonates	5 (11)
Denosumab	21 (48)
Laboratory values, median (range)	
Hemoglobin, g/dl	12 (9–16)
Albumin, g/l	39 (32–44)
PSA, µg/l	68 (<1–2349)
LDH, U/l	203 (115–532)
tALP, U/l	85 (29–705)

^a0 patients had ECOG PS >2.

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

progression; 20/44 (45%) patients had at least one prior chemotherapy regimen.

Safety

Overall, 41/44 (93%) patients reported at least one TEAE (Table 2). No grade 4 or 5 hematologic TEAEs were reported, and no cases of myelofibrosis, aplastic anemia, or other forms of myelosuppression of any grade. The most common nonhematologic TEAEs were fatigue [12/44 (27%)], nausea [11/44 (25%)], and diarrhea [9/44 (20%)], all grades 1 or 2, except one case of grade 3 nausea.

Several ocular TEAEs were reported. Serious ocular TEAEs (uveitis and glaucoma) occurred in 2/44 (5%) patients; however, both had a history of these ocular events, diabetic retinopathy, and other risk factors. Nonserious ocular TEAEs (cataract, cataract worsening, iritis with blurred vision, uveitis, glaucoma, and photopsia) occurred in 5/44 (11%) patients. All ocular TEAEs, independent of grade, were considered unrelated to radium-223 treatment by the investigator, except one case of grade 1 photopsia.

Treatment-emergent SAEs occurred in 13/44 (30%) patients, with only one considered treatment-related (dehydration). Treatment-related TEAEs occurred in 22/44 (50%) patients; 2/44

Table 2. Treatment-emergent adverse events

	Retreatment		
	N = 44		
	All grades	Grade 3	Grade 4
Patients with ≥1 TEAE, n (%) ^a	41 (93)	18 (41)	3 (7)
Hematologic TEAEs, n (%)			
Anemia	6 (14)	2 (5)	0
Thrombocytopenia	1 (2)	1 (2)	0
Leukopenia	1 (2)	0	0
Neutropenia	0	0	0
Nonhematologic TEAEs in > 10% of patients, n (%)			
Fatigue	12 (27)	0	0
Nausea	11 (25)	1 (2)	0
Diarrhea	9 (20)	0	0
Decreased appetite	8 (18)	0	0
Arthralgia	6 (14)	0	0
Hypertension	6 (14)	5 (11)	0
Back pain	5 (11)	0	0
Fall	5 (11)	0	0
Vomiting	5 (11)	0	0

^aRecorded during treatment and up to 30 days from last injection. TEAE, treatment-emergent adverse event.

(5%) were grade 3 (anemia and thrombocytopenia), and 1/44 (2%) was grade 4 (dehydration), also the only treatment-related SAE on the study. Neutrophil, platelet, and hemoglobin values were relatively unchanged over time (Figure 2).

A treatment-related TEAE leading to dose delay or discontinuation (thrombocytopenia) occurred in 1/44 (2%) patient, and two treatment-related TEAEs leading to permanent discontinuation of study drug (fatigue and influenza-like illness) occurred in 1/44 (2%) patient. 5/44 (11%) patients died, only one during the treatment period. Causes of death were two adverse events not associated with clinical disease progression (interstitial lung disease, unknown), two cases of progressive disease, and one unknown.

Efficacy

Median time to radiographic bone progression was not estimable because 31/44 (70%) patients were censored; median rPFS was 9.9 months (Figure 3A and B). Maximum follow-up time for radiographic bone progression and rPFS was 12.8 months. A total of 13/44 (30%) patients experienced rPFS events; only one had confirmed radiographic bone progression. Eight had soft tissue or visceral tumor progression [three lymph node only, five visceral metastases (two liver, one lung, one liver and lung, and one adrenal)], two had radiographic progression with incomplete documentation (one had confirmed progression after data cutoff, one had bone progression at data cutoff), and two died without evidence of radiographic disease progression. Among eight patients with soft tissue or visceral tumor progression, one received concomitant hormonal therapy (abiraterone) during treatment.

Median OS was not reached at primary study completion; 5/44 (11%) patients died, and the maximum follow-up time for

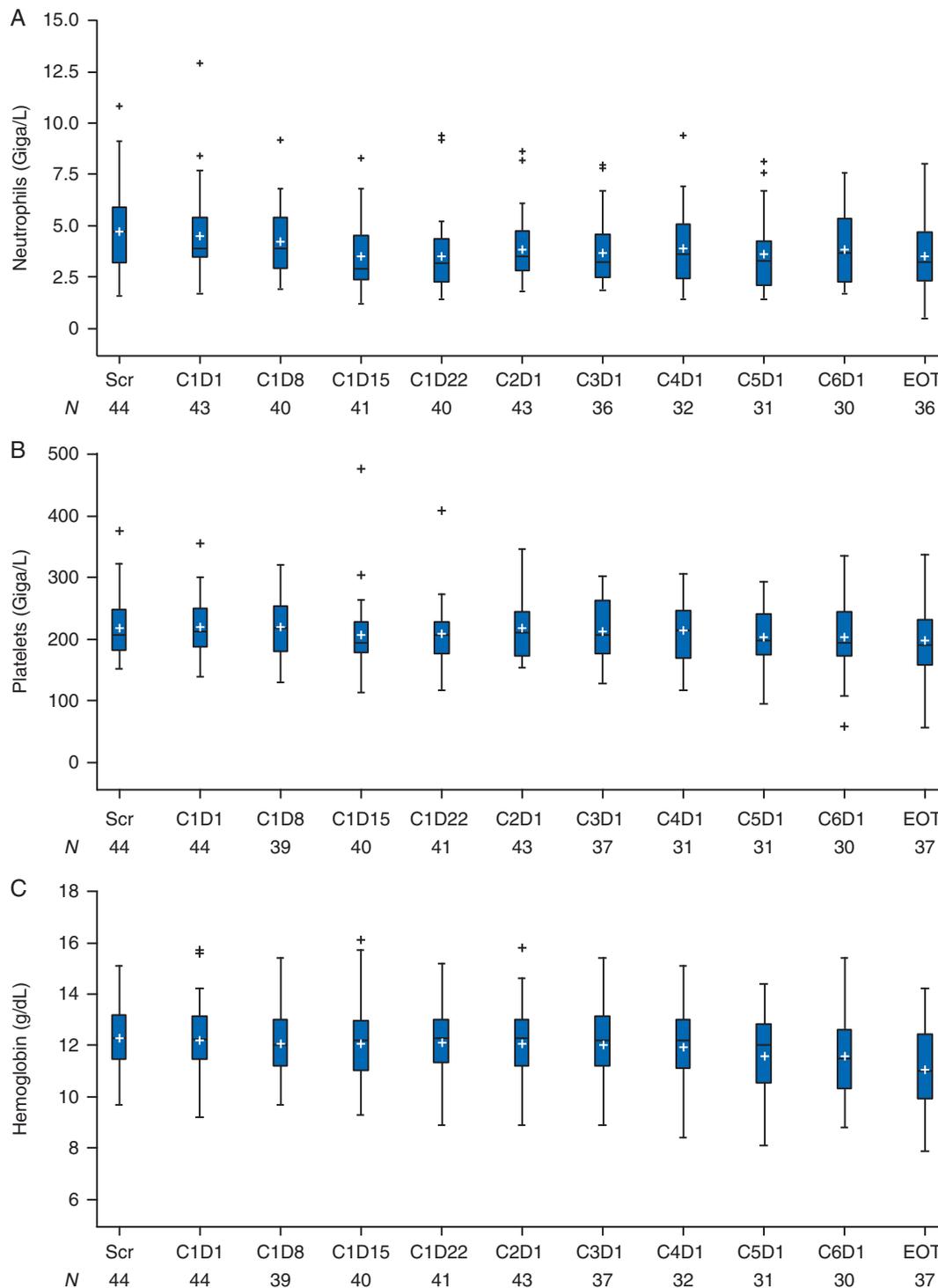


Figure 2. (A) Neutrophil, (B) platelet, and (C) hemoglobin values over time. Note: Whiskers represent maximum and minimum values within limits of 1.5 quartile ranges above and below the upper and lower quartiles. C, cycle; D, day; EOT, end of treatment; Scr, screening.

survival analysis was 15.5 months (Figure 3C). At the end of the 2-year active follow-up period, 28/44 (64%) patients died and median OS was 24.4 months, with a maximum follow-up time of 36.4 months from first radium-223 dose.

At primary study completion, median time to first SSE was not reached; 8/44 (18%) patients experienced first SSEs [6/44 (14%) with external beam radiation therapy for bone pain and 2/44

(5%) with pathologic fracture] (Figure 3D). Median SSE-free survival was also not reached; 10/44 (23%) patients experienced an SSE or died before an SSE (Figure 3E). Maximum follow-up time for SSE and SSE-free survival was 14.1 months.

Among patients evaluable for pain progression (i.e. baseline worst pain score ≤ 7), 5/36 (14%) experienced pain progression. Median time to pain progression was not reached (Figure 3F).

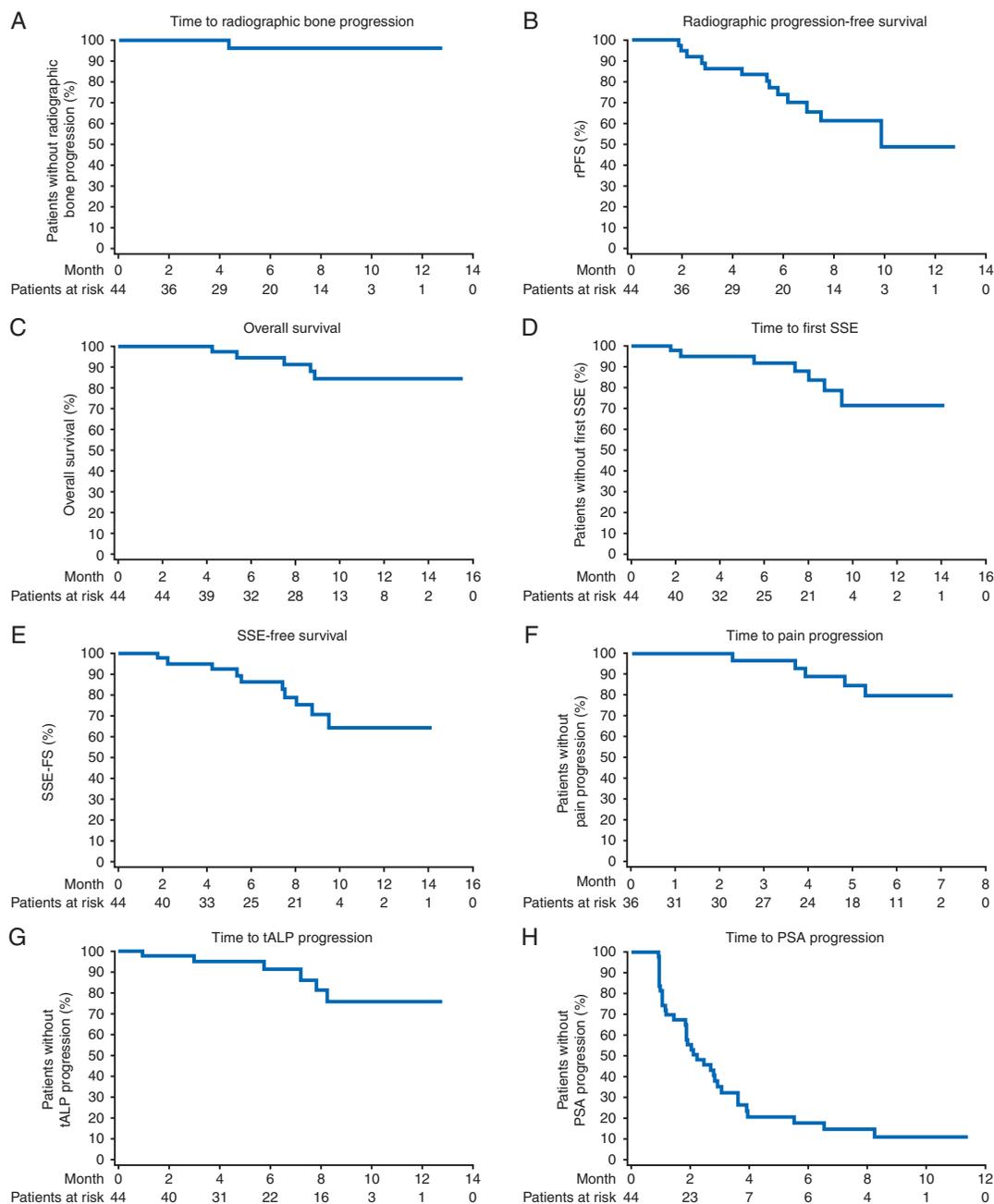


Figure 3. Kaplan–Meier analysis of (A) time to radiographic bone progression, (B) radiographic progression-free survival (rPFS), (C) overall survival, (D) time to first symptomatic skeletal event (SSE), (E) symptomatic skeletal event-free survival (SSE-FS), (F) time to pain progression, (G) time to total alkaline phosphatase (tALP) progression, and (H) time to prostate-specific antigen (PSA) progression.

Median time to tALP progression was not reached, and median time to PSA progression was 2.2 months (Figure 3G and H). Maximum follow-up times for tALP and PSA progression were 12.8 and 11.4 months, respectively. tALP and PSA maximum percentage declines from baseline at weeks 12 and 24 are shown in Figure 4. The majority of patients had a tALP decline from baseline at weeks 12 and 24, whereas few had a PSA decline. tALP and PSA response rates are shown in Table 3. Response rates at week 12 were 39% (13/33) for tALP and 6% (2/32) for PSA. At 24 weeks, response rates were 31% (11/36) for tALP and 0% for PSA.

Discussion

The approved radium-223 dose regimen of 55 kBq/kg every 4 weeks for a total of six injections was based on the phase III ALSYMPCA trial. Despite being a proven effective regimen, six radium-223 doses may not represent the optimal treatment duration. Long-term and in-depth hematologic safety analyses from ALSYMPCA further support the favorable radium-223 safety profile and suggest its possible use beyond six injections [8, 10].

Whether treatment beyond the approved six injections could be safely administered to extend the radium-223 clinical benefit

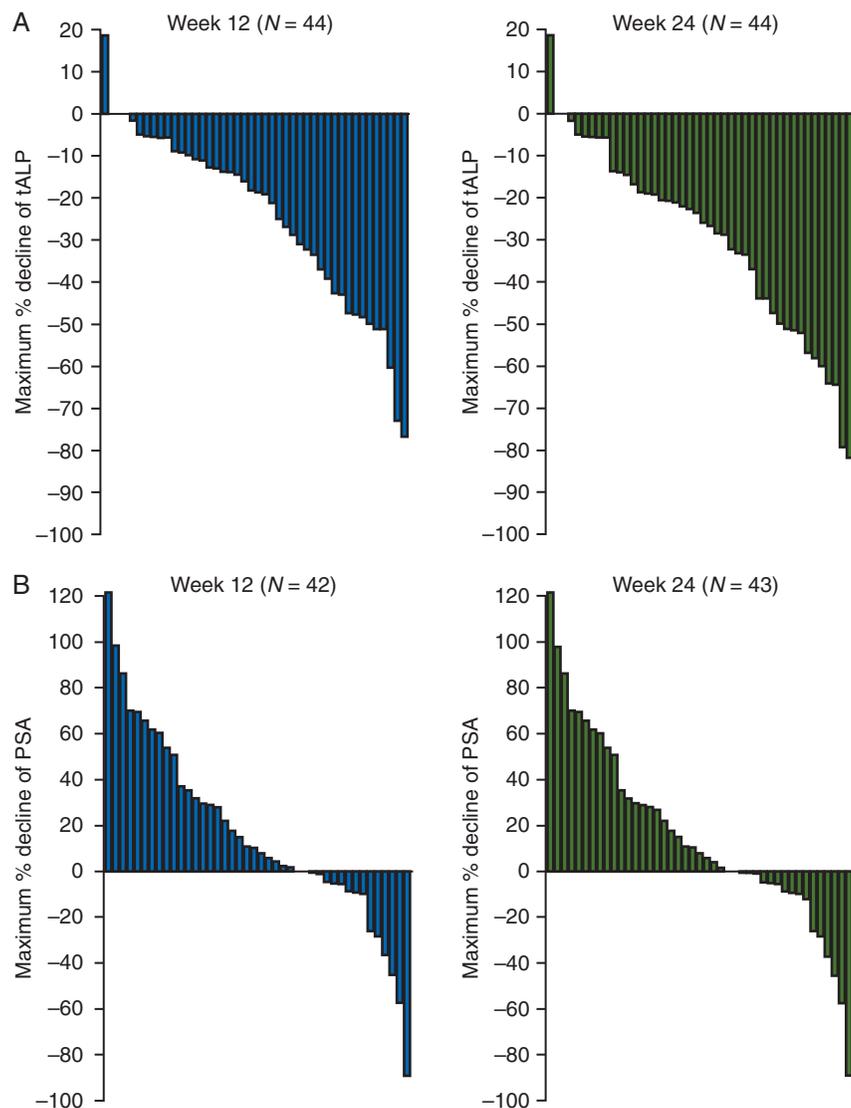


Figure 4. (A) Total alkaline phosphatase (tALP) and (B) prostate-specific antigen (PSA) maximum percentage decline from baseline.

has potential clinical importance. This is the first trial designed and executed for a specific population of interest: patients who derived a clinical benefit from six initial injections, most having had several lines of prior therapy, with 45% having had prior docetaxel and all having had at least two prior hormonal agents. Notably, in addition to meeting the inclusion criterion of disease progression, 73% had failed prior abiraterone or enzalutamide treatment.

In this trial on re-treatment with six additional radium-223 injections after disease progression, the possibility of cumulative hematopoietic toxicity was particularly relevant; however, hematologic toxicity was minimal with no cumulative toxicity. Several ocular TEAEs were observed, although considered unrelated to radium-223 treatment by the investigators and sponsor (except one case of grade 1 photopsia). Overall, no marked alterations in TEAE incidence were observed, versus ALSYMPCA [6].

Although in ALSYMPCA tALP began to rise again shortly after completion of six radium-223 injections, in this study tALP declined from baseline with re-treatment, suggesting continued

evidence of radium-223 biologic effects. Furthermore, based on tALP response rate and low incidence of clinical events (i.e., SSE and radiographic bone progression), as well as favorable median OS of 24.4 months at the end of the 2-year active follow-up period, we hypothesize that re-treatment with radium-223 is efficacious in selected patients. Further clinical trials are warranted.

Study limitations include the single-arm design and the small, selected patient population. All patients had tolerated initial radium-223 treatment well, with no disease progression in bone during that treatment, but with progression afterward. This analysis represents limited follow-up time at primary study completion. Remaining data from the planned 2-year active follow-up period will be published subsequently.

A course of six injections is the approved label dosing regimen. Experience beyond six injections is limited, although a recently published case describes treatment of an mCRPC patient with 18 radium-223 injections, which was tolerated with continued disease control through the third treatment cycle [11]. This study suggests that up to 12 injections may be safe and may afford

Table 3. tALP and PSA response rates

	Retreatment N = 44
tALP, n/N ^a (% response) ^b	
12 weeks	13/33 (39)
24 weeks	11/36 (31)
Any time before database cutoff ^c	19/44 (43)
PSA, n/N ^a (% response) ^b	
12 weeks	2/32 (6)
24 weeks	0/36 (0)
Any time before database cutoff ^c	4/44 (9)

^an/N = patients with response/patients with valid laboratory assessment.

^btALP and PSA response defined as $\geq 30\%$ decline from baseline. PSA response confirmed by a subsequent PSA value ≥ 4 weeks later.

^cN = safety population; patients with no valid postbaseline laboratory assessment were counted as nonresponders; database cutoff was June 11, 2015.

PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

continued therapeutic efficacy and clinical benefit. This finding may be important to consider when investigating radium-223 in other cancer types and earlier in the disease course.

Conclusions

Re-treatment with a second course of six radium-223 injections after disease progression is well tolerated, with minimal hematologic toxicity and low rates of radiographic bone progression in this small study of selected patients; however, these safety data represent only early toxicity because of limited follow-up. Favorable safety and preliminary results on disease progression, tALP response, OS, SSEs, and pain indicate that re-treatment with radium-223 is feasible and should be studied in larger prospective trials. An ongoing study will further evaluate higher radium-223 dosing and longer treatment duration (NCT02023697).

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