Original Study

Disease Characteristics and Completion of Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer Treated With Radium-223 in an International Early Access Program

Fred Saad,[1] Silke Gillessen,[2] Daniel Heinrich,[3] Daniel Keizman,[4] Joe M. O'Sullivan,[5] Sten Nilsson,[6] Kurt Miller,[7] Manfred Wirth,[8] John Reeves,[9] Monica Seger,[9] Joan Carles,[10] Axel Heidenreich[11]

Abstract

In this post hoc analysis we investigated associations between baseline characteristics and number of radium-223 injections in a phase IIIb, single-arm study in the setting of an international early access program. Patients with less advanced metastatic castration-resistant prostate cancer described by more favorable baseline characteristics were more likely to complete 5 to 6 than 1 to 4 injections and had longer overall survival.

Background: Radium-223 is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of metastatic castration-resistant prostate cancer (mCRPC). There are currently no markers for selecting patients most likely to complete radium-223 treatment. **Patients and Methods:** In this phase IIIb, international, single-arm study, patients received radium-223, 55 kBq/kg, every 4 weeks for ≤6 cycles. Primary end points were safety and overall survival. In post hoc analyses patients were grouped according to number of radium-223 injections received (1-4 or 5-6). Associations between baseline covariates and number of injections were investigated. **Results:** Of 696 eligible patients, 473 (68%) had received 5 to 6 radium-223 injections and 223 (32%) 1 to 4 injections. Patients with less pain (moderate-severe vs. none-mild, odds ratio [OR], 0.41; $P < .0001$), lower Eastern Cooperative Oncology Group performance status (≥2 vs. 0-1, OR, 0.51; $P = .0074$), lower prostate-specific antigen level (>141 μg/L vs. ≤141 μg/L, OR, 0.40; $P < .0001$), and higher hemoglobin level (<10 g/dL vs. ≥10 g/dL, OR, 0.50; $P = .0206$) were more likely to receive 5 to 6 than 1 to 4 injections. Median overall survival was not reached and was 6.3 months (95% confidence interval, 5.4-7.4) in patients who had received 5 to 6 and 1 to 4 radium-223 injections, respectively. Adverse events were less common in patients who received 5 to 6 than 1 to 4 injections; anemia was reported in 87 (18%) and 64 (29%) patients, respectively. **Conclusion:** Patients with less advanced mCRPC are more likely to receive 5 to 6 radium-223 injections and to achieve better overall survival. Consideration of baseline and disease characteristics is recommended before initiation of radium-223 treatment.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Baseline characteristics, Bone metastases, Injections, Targeted alpha therapy, Treatment completion

This study is registered at ClinicalTrials.gov, number NCT01618370 and the European Union Clinical Trials Register, EudraCT number 2012-000075-16.

[1]Department of Urology, University of Montreal Hospital Center, Montreal, Quebec, Canada
[2]Division of Cancer Sciences, University of Manchester and The Christie Hospital, Manchester, United Kingdom and Kantonsspital St Gallen, Division of Oncology/Haematology and University of Bern, Switzerland
[3]Department of Oncology, Akershus University Hospital, Lørenskog, Norway
[4]Genitourinary Oncology Service, Institute of Oncology, Meir Medical Center, Kfar-Saba, Israel
[5]Department of Clinical Oncology, The Centre for Cancer Research and Cell Biology, Queen's University Belfast and the Northern Ireland Cancer Centre, Belfast, Northern Ireland
[6]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden
[7]Department of Urology, Charité University Medicine Berlin, Berlin, Germany
[8]Department of Urology, University Hospital Carl-Gustav Carus, Dresden, Germany
[9]Pharmaceutical Division of Bayer, Whippany, NJ
[10]Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain
[11]Department of Urology, University Hospital Cologne, Cologne, Germany

Submitted: Feb 19, 2019; Revised: May 13, 2019; Accepted: May 20, 2019

Address for correspondence: Fred Saad, MD, FRCS, Department of Urology, University of Montreal Hospital Center, Pavilion R, 900, rue St-Denis, Suite R04-446, Montreal, Quebec H2X 0A9, Canada

Fax: 00 1514-412-7620; e-mail contact: fred.saad@umontreal.ca

1558-7673/© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.clgc.2019.05.012

Introduction

Radium-223, a targeted alpha therapy, accumulates within areas of increased bone turnover in bone metastases, resulting in a localized cytotoxic effect.[1-3] Radium-223 is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases.[4] Indications for the use of radium-223 might vary regarding country-specific approvals. The approved regimen is a 1-minute intravenous injection of radium-223, 55 kBq/kg, every 4 weeks (q4w) for 6 cycles.[4-6] Six cycles of radium-223 is the approved full therapeutic dose. The biological effectiveness of radionuclide therapy is dose-dependent.[7] Currently, there are no validated markers to select patients who would most likely complete all 6 cycles of radium-223 treatment.

In the phase III ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial, radium-223 with best standard of care (BSoC) compared with placebo with BSoC significantly improved overall survival, prolonged time to first symptomatic skeletal event, and improved quality of life in patients with CRPC and symptomatic bone metastases.[4,8,9] Most patients (73%) in the study completed 5 to 6 cycles of radium-223 treatment.[10] Post hoc analyses suggested that patients with more advanced disease, as shown by their poor baseline factors, were less likely to complete 5 to 6 cycles of radium-223 treatment.[10] Further analysis showed that overall survival was longer in patients who had received 5 to 6 radium-223 injections versus 5 to 6 placebo injections (hazard ratio [HR], 0.763; 95% confidence interval [CI], 0.594-0.981) whereas overall survival was similar in patients who received only 1 to 4 radium-223 versus 1 to 4 placebo injections (HR, 1.000; 95% CI, 0.755-1.324; Bayer, data on file).

In a large international early access program (iEAP), patients with CRPC and asymptomatic or symptomatic bone metastases were given early access to radium-223 at a time when other life-prolonging agents including abiraterone acetate (abiraterone) and enzalutamide were also available (unavailable during ALSYMPCA). Median overall survival in treated patients was 16 months (95% CI, 13 to not reached) and no new safety concerns were reported.[11] The objective of this post hoc analysis was to identify baseline patient and disease parameters associated with the completion of radium-223 treatment in the setting of the iEAP.

Patients and Methods

Study Design and Participants

This was a phase IIIb single-arm, prospective, interventional, open-label study of radium-223 in patients with bone-predominant metastatic CRPC (mCRPC). Study design, patients, and treatment have been previously reported in detail (summarized in the Supplemental Appendix 1 in the online version).[11]

Patients were treated with intravenous injections of radium-223, 55 kBq/kg, q4w for up to 6 cycles. The assessment period for adverse events was until 30 days after the last radium-223 injection.

The iEAP was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable local regulations. All patients provided written informed consent.

Study Assessments

Primary end points were safety and overall survival. Safety was assessed using the Common Terminology Criteria for Adverse Events version 4.03. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 17.1. Pain severity was assessed using the Brief Pain Inventory Short Form.[11]

Statistics

Safety and efficacy analyses were performed on patients who had received at least 1 dose of radium-223. In post hoc analysis, patients were grouped according to whether they had received 1 to 4 radium-223 injections or 5 to 6 injections. Survival data were summarized using Kaplan–Meier methodology.

The association between baseline covariates and the number of radium-223 injections was investigated using stepwise logistic regression analysis. Six prognostic factors were considered in the model: pain (moderate-severe vs. none-mild); Eastern Cooperative Oncology Group performance status (ECOG PS; $\geq$2 vs. 0-1); prostate-specific antigen (PSA; >141 µg/L vs. $\leq$141 µg/L); hemoglobin (<10 g/dL vs. $\geq$10 g/dL); alkaline phosphatase (ALP; $\geq$ upper limit of normal [ULN] vs. < ULN); and number of previous anticancer medications (0-1 vs. $\geq$2). In the stepwise procedure, the significance level for an effect to enter the model was set at .05. The procedure included a backward elimination step after a new effect appeared in the model: the significance level for an effect to stay in the model was also set at .05.

The association between patient characteristics and overall survival after 3 radium-223 cycles was investigated using a Cox proportional hazard model with a backward elimination procedure (exclusion at $P > .05$). Included in the model were change from baseline (<0 vs. $\geq$0) to cycle 3 for ALP, hemoglobin, and platelet levels. Overall survival after cycle 3 was investigated in patients grouped according to combinations of these prognostic risk factors.

Results

Patients

Of 696 eligible patients, 473 (68%) had received 5 to 6 radium-223 injections and 223 patients (32%) 1 to 4 injections. Reasons for treatment discontinuation are shown in Supplemental Table 1 in the online version.

Patients who had received 5 to 6 injections appeared to have more favorable baseline characteristics than those who had received 1 to 4 injections, including a lower proportion with ECOG PS $\geq$2, lower median PSA and ALP levels, and a longer time since prostate cancer diagnosis (Table 1). A higher proportion of patients who received 5 to 6 radium-223 injections were treated with concomitant abiraterone (126/473; 27%), than those who received 1 to 4 injections (30/223; 13%). The percentage of patients treated with concomitant enzalutamide was the same in patients who completed 5 to 6 (21/473; 4%) and 1 to 4 radium-223 injections (9/223; 4%). Patients with less pain, lower ECOG PS, lower PSA levels, and

Table 1 Baseline Characteristics According to Number of Radium-223 Injections Received

Characteristic	1 to 4 Radium-223 Injections (n = 223)	5 to 6 Radium-223 Injections (n = 473)
Median Age (Range), Y	72.0 (45.0-91.0)	72.0 (48.0-94.0)
ECOG PS		
0	55 (25)	206 (44)
1	123 (55)	225 (48)
≥2	45 (20)	42 (9)
Mean Pain Severity Score		
Mild	109 (49)	261 (55)
Moderate-severe	75 (34)	83 (18)
No pain	28 (13)	111 (23)
Missing	11 (5)	18 (4)
Median Alkaline Phosphatase (Range), U/L[a]	217.0 (41.0-3440.0)	133.5 (19.0-4236.0)
Median Prostate-Specific Antigen (Range), μg/L[b]	297.9 (0-9697.0)	97.0 (0-12150.0)
Median Hemoglobin (Range), g/dL	11.3 (8.4-16.3)	12.40 (9.0-18.0)
Median Time Since Prostate Cancer Diagnosis (Range), Mos[c]	59.3 (1.9-297.2)	69.6 (4.0-273.6)
Number of Previous Anticancer Medications		
0	66 (30)	163 (34)
1	56 (25)	151 (32)
2	82 (37)	135 (29)
≥3	19 (8)	24 (5)
Previous Use of Docetaxel	139 (62)	279 (59)
Previous Use of Abiraterone	102 (46)	175 (37)
Previous Use of Enzalutamide	27 (12)	29 (6)

Data are n (%) unless otherwise stated.
Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.
[a]One to 4 injections, n = 222; 5 to 6 injections, n = 472.
[b]One to 4 injections, n = 222; 5 to 6 injections, n = 471.
[c]One to 4 injections, n = 172; 5 to 6 injections, n = 380.

higher hemoglobin levels were more likely to receive 5 to 6 radium-223 injections (Table 2).

Treatment Outcome

Median follow-up was 7.5 (range, 0-20) months. Fewer deaths were recorded in patients who received 5 to 6 radium-223 injections (97/473; 21%) compared with those who received 1 to 4 injections (113/223; 51%). Median overall survival was not reached in patients who received 5 to 6 injections and was 6.3 months (95% CI, 5.4-7.4) in those who received 1 to 4 injections (Figure 1). A decline in ALP levels from baseline was detected in both groups during the first 3 injections and was greater at the end of cycle 3 (week 12) in patients who received 5 to 6 radium-223 injections than in those who received 1 to 4 injections (Figure 2).

Table 2 Baseline Covariates Associated With Receiving 5 to 6 Radium-223 Injections[a]

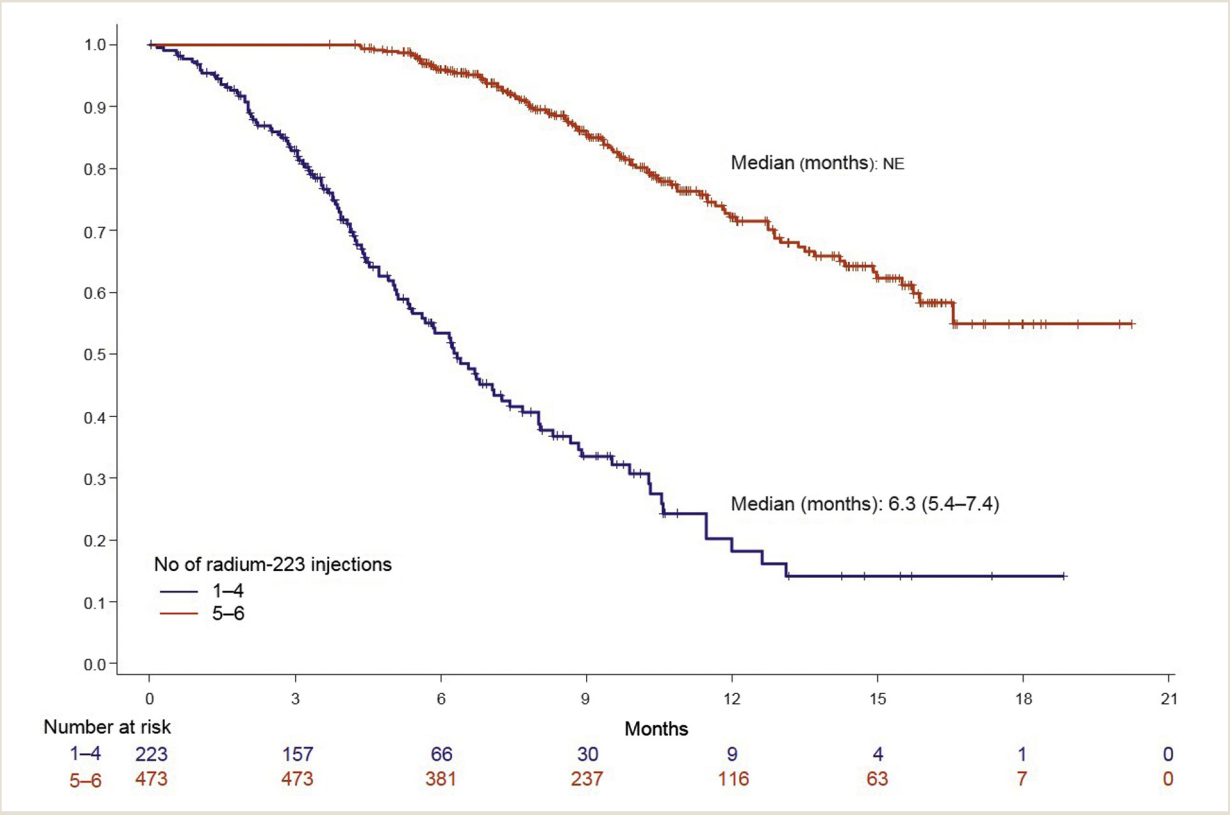
Covariates	Odds Ratio	*P*
Pain (Moderate-Severe; Ref None-Mild)	0.41	<.0001
ECOG PS (≥2; Ref 0-1)	0.51	.0074
PSA (>141 μg/L; Ref ≤141 μg/L)[b]	0.40	<.0001
Hemoglobin (<10 g/dL; Ref ≥10 g/dL)	0.50	.0206

Abbreviations: ECOG PS = Eastern Cooperative Group performance status; PSA = prostate-specific antigen; Ref = reference level.
[a]Stepwise logistic regression model for 5 to 6 radium-223 injections versus 1 to 4 radium-223 injections. Alkaline phosphatase and previous anticancer therapies were included in the analysis but were found to be nonsignificant ($P > .05$) and thus were not retained by the model.
[b]Population median (n = 696): 141 μg/L.

Safety

Treatment-emergent adverse events (TEAEs) were reported in a lower proportion of patients who received 5 to 6 radium-223 injections than 1 to 4 injections (Table 3); the most common Grade 3 or 4 TEAEs in either group included anemia (43/473; 9% and 37/223; 17%, respectively), thrombocytopenia (10/473; 2% and 14/223; 6%), bone pain (13/473; 3% and 16/223; 7%), and spinal cord compression in (7/473; 1% and 12/223; 5%). A lower proportion of patients who had received 5 to 6 injections (127/473; 27%) experienced serious adverse events of any grade than those who received only 1 to 4 injections (116/223; 52%). TEAEs considered to be treatment-related were reported in 198/473 (42%) patients who had received 5 to 6 radium-223 injections and 83/223 (37%) who had received 1 to 4 injections (see Supplemental Table 2 in the online version). These included Grade 3 or 4 anemia (15/473; 3% and 17/223; 8%) and Grade 3 or 4 thrombocytopenia (7/473; 1% and 8/223; 4%). TEAEs leading to permanent discontinuation of radium-223 were reported in 36/473 (8%) patients who received 5 to 6 injections and 108/223 (48%) who had

Figure 1 Overall Survival in Patients Grouped According to Number of Radium-223 Injections Received



Abbreviation: NE = not estimable.

received 1 to 4 injections; the most common reasons for discontinuation included general physical health deterioration (5/473; 1% and 16/223; 7%), anemia (3/473; <1% and 13/223; 6%), and thrombocytopenia (7/473; 1% and 3%; see Supplemental Table 3 in the online version). Other reasons for treatment discontinuation in patients who received 5 to 6 and 1 to 4 radium-223 injections included cardiac failure (0 and 4/223; 2%), bone pain (0 and 5/223; 2%), and spinal cord compression (1/473; <1% and 5/223; 2%). Grade 5 TEAEs were reported in 8/473 (2%) patients who had received 5 to 6 radium-223 injections and 26/223 (12%) who had received 1 to 4 injections; the most common was general physical health deterioration in one (<1%) and 11 (5%) patients, respectively. One TEAE (intestinal perforation) that led to death was considered by the investigator to be related to treatment in a patient who had received 2 radium-223 injections. One patient was reported to have a treatment-emergent Grade 3 limb abscess considered to be treatment-related after 1 radium-223 injection, the patient subsequently died during follow-up.

Post Baseline Factors Predictive of Overall Survival

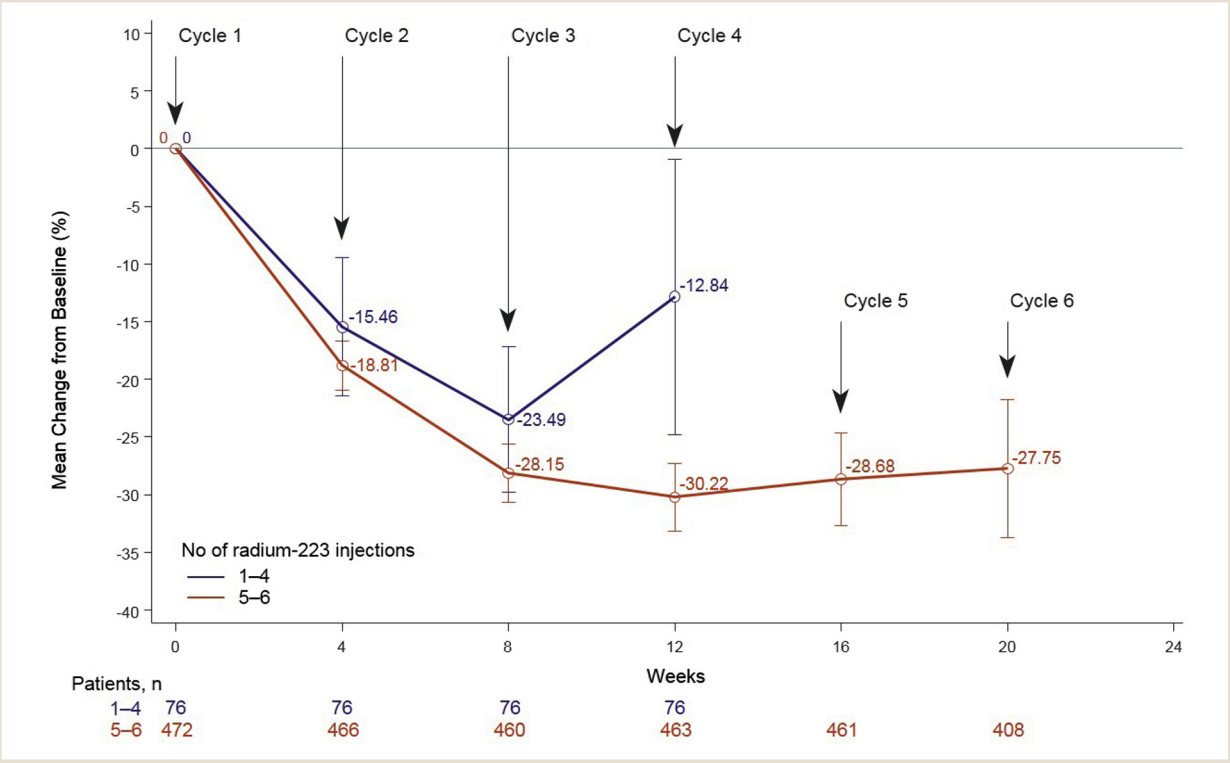
The effect of changes from baseline in ALP, hemoglobin, and platelet levels on overall survival after 3 treatment cycles was investigated in 605 patients who had received at least 3 injections of radium-223. Platelets were excluded from the Cox regression model because of nonsignificance. Changes in ALP and hemoglobin levels identified 3 patient groups associated with differing risks of death (see Supplemental Figure 1 in the online version); 65 high-risk patients (with an ALP increase and a hemoglobin decline), 358 patients at intermediate-risk (ALP increase or hemoglobin decline), and 182 at low-risk (ALP decline and hemoglobin increase). Patients in the high-risk group had shorter overall survival than those in the low-risk group (HR, 2.78; 95% CI, 1.68-4.60).

Discussion

In this iEAP, a large proportion (68%) of patients with CRPC and bone metastases received 5 to 6 injections of radium-223. The main reason for early treatment discontinuation was the emergence of adverse events associated with clinical progression. Disease progression has also been reported as the major reason (approximately 31%-62%) for early treatment discontinuation in other studies.[12-14] This might suggest that some patients might be too advanced in their disease course to complete the scheduled treatment. Better patient selection is recommended to enable patients to receive full treatment with radium-223.

A lower proportion of patients overall who had received 5 to 6 radium-223 injections experienced TEAEs than those who discontinued after 1 to 4 injections, which might be because of fewer reported adverse events associated with disease progression in patients who completed 5 to 6 injections. As might be expected from

Figure 2 Change in Total ALP From Baseline. Vertical Lines Indicate 95% CIs



Abbreviation: ALP = alkaline phosphatase.

longer exposure to radium-223, the number of patients who had drug-related TEAEs was marginally higher in patients who had received 5 to 6 injections than in those who received 1 to 4 injections.

Patients who received 5 to 6 radium-223 injections appeared to have less advanced disease, as described by their more favorable baseline characteristics, compared with those who discontinued earlier. Stepwise logistic regression analysis showed that less pain (none to mild), good ECOG PS (0-1), lower PSA (≤141 μg/L), and high hemoglobin levels (>10 g/dL), were patient factors associated with receiving 5 to 6 radium-223 injections. Similar findings were presented in exploratory analyses of an early access program (EAP) conducted in the United States and the phase III ALSYMPCA study.[10,14] Patients with bone metastases and more advanced disease in the US EAP (specifically, ≥3 previous anticancer therapies, baseline ECOG PS ≥2, lower baseline hemoglobin level) and the phase III study (higher lactate dehydrogenase and lower albumin levels, baseline ECOG PS ≥2, and higher PSA level) were less likely to receive 5 to 6 radium-223 injections. Similarly, in 2 studies in patients treated with radium-223 in a community-based setting, multivariate analyses of baseline factors also showed that those with less advanced disease were more likely to complete the scheduled treatment with radium-223.[12,13]

Our data suggest that patients who complete radium-223 treatment (5-6 injections) are more likely to have better clinical outcome (longer overall survival and a larger decline in ALP from baseline) than those who discontinue early (1-4 injections). Similar findings were reported in the ALSYMPCA study and by the US EAP, and in reports of patients treated in current clinical practice.[10,12-14] In a population-based study of patients treated with radium-223 in a single cancer center, in addition to longer overall survival, increased ALP and PSA responses were reported in patients who had completed ≥5 cycles of radium-223 compared with those who discontinued treatment earlier.[13]

As described in other studies in mCRPC,[15-17] we further modeled combinations of patient prognostic risk factors to determine their effect on overall survival. We examined factors influenced by radium-223 treatment, including changes from baseline in ALP and hemoglobin levels,[4,11] in patients who had received at least the first 3 cycles of radium-223. We identified patients with a high, intermediate, and low risk of death. Patients with an increase in ALP and a decline in hemoglobin levels at cycle 3 had the shortest overall survival time. It might be that this patient group had a poor prognosis overall, thus the validity of these (post baseline) factors in predicting radium-223 treatment benefit would require confirmation in a randomized controlled study. Alternatively, propensity score methods could be used to mimic some of the characteristics of a randomized trial by taking potential confounders into consideration.[18] The data should therefore be treated with caution with respect to making decisions on whether to stop or continue radium-223 treatment in this patient group. Decisions on continuing treatment beyond 3 injections of radium-223 might be influenced

Table 3 Treatment-Emergent Adverse Events According to Number of Radium-223 Injections Received

Adverse Event[a]	1 to 4 Radium-223 Injections (n = 223)		5 to 6 Radium-223 Injections (n = 473)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Any	46 (21)	116 (52)	180 (38)	147 (31)
Anemia[b]	27 (12)	37 (17)	44 (9)	43 (9)
Neutropenia[c]	2 (<1)	6 (3)	6 (1)	9 (2)
Thrombocytopenia[d]	16 (7)	14 (6)	11 (2)	10 (2)
Constipation	12 (5)	3 (1)	13 (3)	3 (<1)
Diarrhea	17 (8)	2 (<1)	58 (12)	2 (<1)
Nausea	28 (13)	1 (<1)	61 (13)	1 (<1)
Vomiting	6 (3)	3 (1)	28 (6)	5 (1)
Asthenia	5 (2)	0	22 (5)	2 (<1)
Fatigue	9 (4)	8 (4)	45 (10)	5 (1)
General Physical Health Deterioration	2 (<1)	9 (4)	5 (1)	5 (1)
Pain	3 (1)	6 (3)	9 (2)	3 (<1)
Urinary Tract Infection	7 (3)	3 (1)	6 (1)	5 (1)
Weight Decreased	12 (5)	3 (1)	32 (7)	2 (<1)
Decreased Appetite	10 (4)	2 (<1)	37 (8)	1 (<1)
Arthralgia	5 (2)	2 (<1)	16 (3)	0
Back Pain	6 (3)	8 (4)	24 (5)	12 (3)
Bone Pain	26 (12)	16 (7)	53 (11)	13 (3)
Spinal Cord Compression	2 (<1)	12 (5)	1 (<1)	7 (1)
Spinal Pain	2 (<1)	5 (2)	7 (1)	1 (<1)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
[a]Data are number of patients (%) reported in ≥3% in either group during the treatment period and are ordered according to MedDRA system organ class and preferred terms. Grade 5 treatment-emergent adverse events were reported in 26 (12%) patients receiving 1 to 4 injections and 8 (2%) who received 5 to 6 radium-233 injections.
[b]Combined MedDRA preferred terms: anemia and hemoglobin decreased.
[c]Combined MedDRA preferred terms: neutropenia and neutrophil count decreased.
[d]Combined MedDRA preferred terms: thrombocytopenia and platelet count decreased.

by monitoring such factors, but should be made in consideration of wider clinical and radiological findings, as also recommended for other life-prolonging agents used in treatment of mCRPC.[19] In a retrospective analysis of radiological data from patients treated with radium-223 in 8 centers across 3 countries, the authors recommended that imaging using computed tomography should be considered after 3 and 6 injections of radium-223 to exclude extraskeletal disease progression.[20]

A limitation of the current analysis and others discussed, is the retrospective nature of the analyses, which are often performed in patient cohorts with short follow-up times and without a control arm.[12-14] In addition, in our overall survival analysis, an immortal time bias might have been introduced by the fact that patients who received 5 or 6 injections had to remain alive up to the time of the fifth or sixth injection, respectively. In contrast, patients who for whatever reason died before the fifth injection (ie, those with poor overall survival) would automatically be placed in the 1 to 4 injections group.[21] Furthermore, baseline factors identified as being associated with the completion of 5 to 6 radium-223 cycles have been shown to be markers of good prognosis in patients with mCRPC treated with other life-prolonging agents.[11,15,22-24] Thus, the finding of prolonged survival in the patients who received 5 to 6 radium-223 injections should be treated with caution because it could be because of the presence of more favorable baseline factors in this patient group. A further possible source of bias is that 38% of patients who discontinued treatment after 1 to 4 injections did so because of adverse events associated with clinical progression, thus the occurrence of such events are expected to be correlated with a shorter overall survival in this group.

Radium-223 is currently used for the treatment of patients with CRPC and symptomatic bone metastases (without visceral metastases). It might be that waiting until patients have deteriorated (with high tumor burden and increased pain) before introducing radium-223 reduces the likelihood that the patient will derive the benefit potentially associated with completing the full planned course of 6 cycles of treatment with this agent.

Conclusion

This exploratory analysis suggests that patients with less advanced disease, determined by their baseline characteristics, are more likely to receive 5 to 6 radium-223 injections. Use of radium-223 in these patients might allow the full course of 6 radium-223 injections to be administered. Careful consideration of patient and disease characteristics is recommended before treatment is initiated, and patient monitoring during the treatment course is necessary for all patients. Prospective randomized controlled studies are required to confirm the specific prognostic factors important for patient selection and monitoring during radium-223 treatment.

Clinical Practice Points

- The US Food and Drug Administration and European Medicines Agency approved regimen and dose of radium-223 for the treatment of patients with CRPC and symptomatic bone metastases is 55 kBq/kg q4w for up to 6 injections.
- Patients with less advanced disease characterized by more favorable baseline characteristics, including less pain, lower ECOG PS, lower PSA levels, and higher hemoglobin levels, were more likely to complete 5 to 6 cycles of radium-223 than those with comparatively worse baseline characteristics.
- Patients who completed 5 to 6 injections had improved overall survival compared with those who received 1 to 4 injections.
- Stratification of baseline characteristics might be useful for selecting patients for radium-223 therapy.
- Randomized control trials are required to confirm these findings.

Acknowledgments

This study was sponsored by Bayer. The iEAP study was funded by Bayer. The funder was responsible for the study design, data management and statistical analysis. Data interpretation was performed in collaboration with the study steering committee and the authors. The funder supported development of the manuscript through provision of medical writing assistance. Professor Saad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had the final responsibility for the decision to submit for publication. Dr Paul Hoban of Cancer Communications and Consultancy Ltd provided medical writing assistance, which was funded by Bayer.

Disclosure

Professor Saad has a compensated consultancy role with, and has received research funding from, Bayer, Astellas, Janssen and Sanofi; Professor Gillessen has compensated consultancy and advisory roles with AAA International, Active Biotech AB IDMC, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis, Curevac, Dendron Corporation, Ferring, Innocrin Pharmaceuticals, Janssen-Cilag, MaxiVAX SA, Millennium, Pharmaceuticals, Novartis, Orion, Pfizer, Roche, and Sanofi Aventis, and has participated in Speakers Bureaus (compensated) for Janssen and Novartis, and has a patent application for a biomarker method (WO 2009138392 A1); Dr Heinrich has received honoraria from Janssen-Cilag, Astellas, and Bayer, has compensated consultancy/advisory roles with Astellas, Bayer, and Amgen, and has had travel/accommodation expenses reimbursed from Bayer; Dr Keizman has received honoraria from and has compensated consultancy and advisory roles with Pfizer, Sanofi, Bayer, and Novartis, and has had travel/accommodation/expenses reimbursed from Pfizer and Bayer; Professor O'Sullivan has participated in advisory boards and speaker's bureaus for Bayer, Janssen, and Sanofi, and has received research funding (institute) from Bayer; Professor Nilsson has received honoraria from Bayer, Astellas, Ipsen, Sanofi-Genzyme, Novartis, Roche, and Janssen for advisory board participation and lectures; Professor Miller has received honoraria from Bayer, Janssen, and Amgen, and has compensated consultancy/advisory roles with Astellas, Astra Zeneca, Bristol-Myers Squibb, Ferring, Janssen, MSD, Novartis, Roche, and Sotio; Professor Wirth has compensated consultancy or advisory roles with ABX, Apogepha, Astellas, Amgen, Janssen-Cilag, Bayer, and MSD, and has provided expert testimony for ABX; Drs Reeves and Seger are salaried employees of Bayer; Dr Carles has a compensated consultancy role and has participated in scientific advisory boards for Johnson & Johnson, Astellas, Bayer, Amgen, Pfizer, and BMS, and has participated in speaker's bureaus for Bayer and Johnson & Johnson; Professor Heidenreich has received honoraria from Amgen, Astellas, Bayer, Dendreon, Ferring, Ipsen, Janssen, Pfizer, Sanofi, and Takeda, and has received research funding from Amgen, Astellas, and Sanofi.

Supplemental Data

Supplemental tables, figure, and appendix accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.05.012.

References

1. Bruland OS, Nilsson S, Fisher DR, Larsen RH. High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter 223Ra: adjuvant or alternative to conventional modalities? *Clin Cancer Res* 2006; 12:6250s-7s.
2. Henriksen G, Breistol K, Bruland OS, et al. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. *Cancer Res* 2002; 62:3120-5.
3. Suominen MI, Fagerlund KM, Rissanen JP, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. *Clin Cancer Res* 2017; 23:4335-46.
4. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369:213-23.
5. Zimmerman BE, Bergeron DE, Cessna JT, et al. Revision of the NIST Standard for (223)Ra: new measurements and review of 2008 data. *J Res Natl Inst Stand Technol* 2015; 120:37-57.
6. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). *Ann Oncol* 2009; 20:674-80.
7. Kassis AI. Therapeutic radionuclides: biophysical and radiobiologic principles. *Semin Nucl Med* 2008; 38:358-66.
8. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol* 2014; 15:738-46.
9. Nilsson S, Cislo P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Ann Oncol* 2016; 27:868-74.
10. Sartor O, Coleman RE, Morris MJ, et al. Baseline characteristics, number of radium-223 (Ra-223) injections, and overall survival (OS) in US Expanded Access Program (EAP) and ALSYMPCA (abstract 2530). *Eur J Cancer* 2015; 51(suppl 3): S484-5.
11. Saad F, Carles J, Gillessen S, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol* 2016; 17:1306-16.
12. McKay RR, Jacobus S, Fiorillo M, et al. Radium-223 use in clinical practice and variables associated with completion of therapy. *Clin Genitourin Cancer* 2017; 15: e289-98.
13. Parimi S, Tsang E, Alexander A, et al. A population-based study of the use of radium 223 in metastatic castration-resistant prostate cancer: factors associated with treatment completion. *Can Urol Assoc* 2017; 11:350-5.
14. Sartor O, Vogelzang NJ, Sweeney C, et al. Radium-223 safety, efficacy, and concurrent use with abiraterone or enzalutamide: first U.S. experience from an expanded access program. *Oncologist* 2018; 23:193-202.
15. Chi KN, Kheoh T, Ryan CJ, et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. *Ann Oncol* 2016; 27:454-60.
16. Meisel A, von Felten S, Vogt DR, et al. Severe neutropenia during cabazitaxel treatment is associated with survival benefit in men with metastatic castration-resistant prostate cancer (mCRPC): a post-hoc analysis of the TROPIC phase III trial. *Eur J Cancer* 2016; 56:93-100.
17. Frantellizzi V, Farcomeni A, Follacchio GA, et al. A 3-variable prognostic score (3-PS) for overall survival prediction in metastatic castration-resistant

prostate cancer treated with (223)Radium-dichloride. *Ann Nucl Med* 2018; 32:142-8.
18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46:399-424.
19. Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Ann Oncol* 2015; 26:1589-604.
20. Keizman D, Fosboel MO, Reichegger H, et al. Imaging response during therapy with radium-223 for castration-resistant prostate cancer with bone metastases-analysis of an international multicenter database. *Prostate Cancer Prostatic Dis* 2017; 20:289-93.
21. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008; 15: 492-9.
22. Azad AA, Eigl BJ, Leibowitz-Amit R, et al. Outcomes with abiraterone acetate in metastatic castration-resistant prostate cancer patients who have poor performance status. *Eur Urol* 2015; 67:441-7.
23. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 2014; 32:671-7.
24. Armstrong AJ, Garrett-Mayer E, de Wit R, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res* 2010; 16: 203-11.

Supplemental Appendix 1

Methods

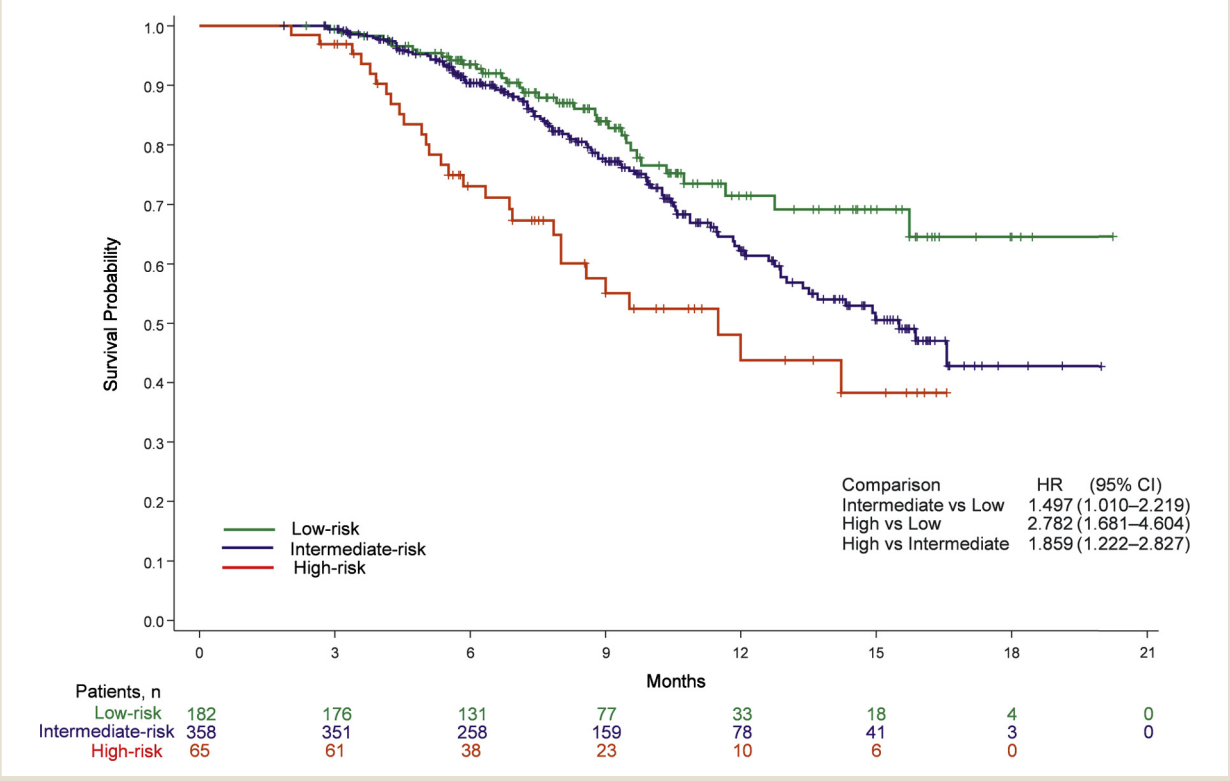
Study Design, Patients, and Treatment

This was a phase IIIb single-arm, prospective, interventional, open-label study of radium-223 in patients with bone-predominant metastatic castration-resistant prostate cancer (mCRPC). Study design and patient inclusion and exclusion criteria and treatment have been previously reported in detail.[1]

Briefly, enrolled patients were aged 18 years or older with histologically or cytologically confirmed progressive bone-predominant mCRPC with 2 or more skeletal metastases on imaging (with no restriction as to whether they were symptomatic or asymptomatic) with no lung, liver, or brain metastasis (lymph node-only metastases not exceeding 6 cm were allowed).

Patients were treated with intravenous injections of radium-223, 55 kBq/kg, every 4 weeks for up to 6 cycles. The study assessment period was until 30 days after the last radium-223 injection. Concomitant treatment with abiraterone and enzalutamide was permitted. Patients who had not undergone bilateral orchiectomy received luteinizing hormone-releasing hormone analogues throughout. Supportive care was provided in accordance with local institutional guidelines.

Supplemental Figure 1 **Overall Survival in Patients Grouped According to Prognostic Factors and Completing at Least 3 Cycles of Radium-223. Only Patients Who Completed 3 Cycles Are Included in the Analysis. Prognostic Risk Factors Were ALP and Hemoglobin Levels at Cycle 3. Patients Were Grouped Into 1 of 3 Risk Groups: Patients in the High-Risk Group Had 2 Risk Factors (ALP Increase and Hemoglobin Decline); Patients in the Intermediate-Risk Group Had 1 Risk Factor (ALP Increase or Hemoglobin Decline) and Patients in the Low-Risk Group Had No Risk Factors (No ALP Increase and No Hemoglobin Decline)**



Abbreviations: ALP = alkaline phosphatase; HR = hazard ratio.

Baseline Characteristics and Number of Radium-223 Injections

Supplemental Table 1 Patient Disposition According to Number of Radium-223 Injections

	1 to 4 Radium-223 Injections (n = 223)	5 to 6 Radium-223 Injections (n = 473)
Completed Treatment	0	403 (85)
Discontinued Study Treatment	223 (100)	70 (15)
Reasons for Discontinuing Treatment		
AE Associated With Clinical Disease Progression	84 (38)	25 (5)
AE Not Associated With Clinical Disease Progression	43 (19)	20 (4)
Progression	58 (26)	13 (3)
PSA Progression	3 (1)	1 (<1)
Death	4 (2)	4 (<1)
Lost to Follow-up	1 (<1)	0
Patient Withdrawal	27 (12)	5 (1)
Other	3 (1)[a]	2 (<1)

Data are n (%).
Abbreviations: AE = adverse event; PSA = prostate-specific antigen.
[a]Includes 2 patients reported as having completed cycle 6 of radium-223, but information on dose was incomplete in some previous cycles from these patients.

Supplemental Table 2 Treatment-Related Adverse Events According to Number of Radium-223 Injections Received

	1 to 4 Radium-223 Injections (n = 223)			5 to 6 Radium-223 Injections (n = 473)		
Adverse Event[a]	**Grade 1 or 2**	**Grade 3 or 4**	**Grade 5**	**Grade 1 or 2**	**Grade 3 or 4**	**Grade 5**
Any	43 (19)	39 (17)	1 (<1)	151 (32)	47 (10)	0
Anemia[b]	12 (5)	17 (8)	0	24 (5)	15 (3)	0
Thrombocytopenia[c]	13 (6)	8 (4)	0	9 (2)	7 (1)	0
Diarrhea	13 (6)	2 (<1)	0	46 (10)	1 (<1)	0
Intestinal Perforation	0	0	1 (<1)	0	0	0
Nausea	15 (7)	1 (<1)	0	46 (10)	0	0
Vomiting	4 (2)	1 (<1)	0	19 (4)	4 (<1)	0
Fatigue	5 (2)	2 (<1)	0	27 (6)	2 (<1)	0
Weight Decreased	1 (<1)	0	0	18 (4)	0	0
Decreased Appetite	4 (2)	0	0	21 (4)	0	0
Bone Pain	10 (4)	2 (<1)	0	22 (5)	3 (<1)	0

Data are n (%) reported in ≥3% and all Grade 5 in either group.
Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
[a]Reported as MedDRA preferred terms during the treatment period.
[b]Combined MedDRA preferred terms: anemia and hemoglobin decreased.
[c]Combined MedDRA preferred terms: thrombocytopenia and platelet count decreased.

Supplemental Table 3 Treatment-Emergent Adverse Events Leading to Permeant Discontinuation According to Number of Radium-223 Injections Received

	1 to 4 Radium-223 Injections (n = 223)			5 to 6 Radium-223 Injections (n = 473)		
Adverse Event	**Grade 1 or 2**	**Grade 3 or 4**	**Grade 5**	**Grade 1 or 2**	**Grade 3 or 4**	**Grade 5**
Any	21 (9)	77 (35)	10 (4)	7 (1)	27 (6)	2 (<1)
Blood and Lymphatic Disorders						
Anemia[a]	5 (2)	8 (4)	0	2 (<1)	1 (<1)	0
Neutropenia[b]	0	2 (<1)	0	0	2 (<1)	0
Pancytopenia	0	3 (1)	0	0	1 (<1)	0
Thrombocytopenia[c]	2 (<1)	11 (5)	0	2 (<1)	5 (1)	0
Cardiac Disorders						
Cardiac failure	0	4 (2)	0	0	0	0
Congestive cardiac failure	0	1 (<1)	0	0	0	0
Myocardial infarction	0	0	1 (<1)	0	0	0
Eye Disorders						
Blindness	1 (<1)	0	0	0	0	0
Diplopia	0	1 (<1)	0	0	0	0
Gastrointestinal Disorders						
Upper abdominal pain	0	1 (<1)	0	0	0	0
Constipation	0	0	0	1 (<1)	0	0
Diarrhea	0	0	0	1 (<1)	0	0
Dysphagia	0	1 (<1)	0	0	0	0
Gastric hemorrhage	0	0	0	0	1 (<1)	0
Intestinal perforation	0	1 (<1)	0	0	0	0
Nausea	1 (<1)	0	0	1 (<1)	0	0
Vomiting	0	1 (<1)	0	0	0	0
General Disorders and Administration Site Conditions						
Asthenia	1 (<1)	0	0	0	0	0
Chest pain	0	1 (<1)	0	0	0	0
Fatigue	0	0	0	1 (<1)	0	0
General physical health deterioration	1 (<1)	8 (4)	7 (3)	3 (<1)	2 (<1)	0
Malaise	2 (<1)	0	0	0	0	0
Pain	1 (<1)	0	0	0	0	0
Sudden death	0	0	1 (<1)	0	0	0
Hepatobiliary Disorders						
Jaundice	0	1 (<1)	0	0	0	0
Infections and Infestations						
Limb abscess	0	1 (<1)	0	0	0	0
Bacterial arthritis	0	2 (<1)	0	0	0	0
Meningitis	0	1 (<1)	0	0	0	0
Pelvic infection	0	1 (<1)	0	0	0	0
Pneumonia	0	1 (<1)	0	0	1 (<1)	0

Baseline Characteristics and Number of Radium-223 Injections

Supplemental Table 3 Continued

Adverse Event	1 to 4 Radium-223 Injections (n = 223)			5 to 6 Radium-223 Injections (n = 473)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
Post procedural infection	1 (<1)	0	0	0	0	0
Acute pyelonephritis	0	0	0	0	1 (<1)	0
Sepsis	0	1 (<1)	0	0	0	0
Urosepsis	0	2 (<1)	0	0	0	0
Injury, Poisoning, and Procedural Complications						
Cervical vertebral fracture	0	0	0	0	1 (<1)	0
Femoral neck fracture	0	0	0	0	1 (<1)	0
Fibular fracture	0	0	0	0	1 (<1)	0
Hip fracture	0	1 (<1)	0	0	0	0
Spinal compression fracture	1 (<1)	0	0	0	0	0
Spinal fracture	0	1 (<1)	0	0	0	0
Subdural hemorrhage	0	0	0	0	1 (<1)	0
Tibia fracture	0	0	0	0	1 (<1)	0
Investigations						
Bronchial aspiration	0	0	0	0	1 (<1)	0
PSA increased	0	1 (<1)	0	0	0	0
White blood cell count decreased	1 (<1)	0	0	0	0	0
Metabolism, and Nutrition Disorders						
Decreased appetite	0	1 (<1)	0	1 (<1)	0	0
Hypercalcemia	1 (<1)	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders						
Back pain	0	2 (<1)	0	0	1 (<1)	0
Bone pain	4 (2)	1 (<1)	0	0	0	0
Fracture pain	0	1 (<1)	0	0	0	0
Musculoskeletal chest pain	1 (<1)	0	0	0	0	0
Osteonecrosis of the jaw	0	0	0	0	1 (<1)	0
Spinal column stenosis	0	1 (<1)	0	0	0	0
Spinal pain	1 (<1)	1 (<1)	0	0	1 (<1)	0
Neoplasms, Malignant and Unspecified[a]						
Bladder transitional cell carcinoma	0	0	0	0	1 (<1)	0
Cancer pain	0	0	0	0	1 (<1)	0
Metastatic pain	0	1 (<1)	0	0	0	0
Tumor pain	1 (<1)	1 (<1)	0	0	0	0
Nervous System, Disorders						
Aphasia	0	1 (<1)	0	0	0	0

Supplemental Table 3 Continued

Adverse Event	1 to 4 Radium-223 Injections (n = 223)			5 to 6 Radium-223 Injections (n = 473)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
Cerebrovascular accident	0	1 (<1)	0	0	0	0
Dizziness	0	1 (<1)	0	0	0	0
Epilepsy	0	0	0	0	1 (<1)	0
Headache	1 (<1)	0	0	0	0	0
Hemiparesis	0	0	0	0	1 (<1)	0
Ischemic stroke	0	1 (<1)	0	0	0	0
Metabolic encephalopathy	0	0	0	0	1 (<1)	0
Paraplegia	0	1 (<1)	0	0	0	0
Peripheral motor neuropathy	0	1 (<1)	0	0	0	0
Peripheral sensory neuropathy	0	1 (<1)	0	0	0	0
Spinal cord compression	1 (<1)	4 (2)	0	0	1 (<1)	0
Subarachnoid hemorrhage	0	0	0	0	1 (<1)	0
Trigeminal neuralgia	0	1 (<1)	0	0	1 (<1)	0
Renal and Urinary Disorders						
Hydronephrosis	0	0	0	0	1 (<1)	0
Renal failure	0	1 (<1)	0	0	0	0
Acute renal failure	0	1 (<1)	0	0	0	0
Urinary tract obstruction	0	0	0	0	1 (<1)	0
Respiratory, Thoracic, and Mediastinal Disorders						
Pleural effusion	0	0	0	0	0	1 (<1)
Pneumonitis	1 (<1)	0	0	0	0	0
Pneumothorax	0	1 (<1)	0	0	0	0
Pulmonary embolism	0	2 (<1)	0	0	0	0
Respiratory failure	0	1 (<1)	1 (<1)	0	0	0
Vascular Disorder						
Hypotension	0	0	0	0	0	1 (<1)

Data are number of patients (%) and are ordered according to MedDRA system organ class and preferred terms.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PSA = prostate-specific antigen.
[a]Combined MedDRA preferred terms: anemia and hemoglobin decreased.
[b]Combined MedDRA preferred terms: neutropenia and neutrophil count decreased.
[c]Combined MedDRA preferred terms: thrombocytopenia and platelet count decreased.
[d]Including cysts and polyps.

Supplemental Reference

1. Saad F, Carles J, Gillessen S, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol* 2016; 17:1306-16.