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ORIGINAL ARTICLE

Safety and effectiveness of the radium-223–taxane treatment sequence in patients with metastatic castration-resistant prostate cancer in a global observational study (REASSURE)

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Abstract

Background: Radium-223 and taxane chemotherapy each improve survival of patients with metastatic castration-resistant prostate cancer (mCRPC). Whether the radium-223–taxane sequence could extend survival without cumulative toxicity was explored.

Methods: The global, prospective, observational REASSURE study (NCT02141438) assessed real-world safety and effectiveness of radium-223 in patients with mCRPC.

Bertrand Tombal and Oliver Sartor should be considered joint senior authors.

Using data from the prespecified second interim analysis (data cutoff, March 20, 2019), hematologic events and overall survival (OS) were evaluated in patients who were chemotherapy-naive at radium-223 initiation and subsequently received taxane chemotherapy starting ≤90 days ("immediate") or >90 days ("delayed") after the last radium-223 dose.

Results: Following radium-223 therapy, 182 patients received docetaxel (172 [95%]) and/or cabazitaxel (44 [24%]); 34 patients (19%) received both. Seventy-three patients (40%) received immediate chemotherapy and 109 patients (60%) received delayed chemotherapy. Median time from last radium-223 dose to first taxane cycle was 3.6 months (range, 0.3–28.4). Median duration of first taxane was 3.7 months (range, 0–22.0). Fourteen patients (10 in the immediate and four in the delayed subgroup) had grade 3/4 hematologic events during taxane chemotherapy, including neutropenia in two patients in the delayed subgroup and thrombocytopenia in one patient in each subgroup. Median OS was 24.3 months from radium-223 initiation and 11.8 months from start of taxane therapy.

Conclusions: In real-world clinical practice settings, a heterogeneous population of patients who received sequential radium-223–taxane therapy had a low incidence of hematologic events, with a median survival of 1 year from taxane initiation. Thus, taxane chemotherapy is a feasible option for those who progress after radium-223.

Clinical Trial Registration: ClinicalTrials.gov identifier NCT02141438.

Plain Language Summary

- Radium-223 and chemotherapy are treatment options for metastatic prostate cancer, which increase survival but may affect production of blood cells as a side effect.
- We wanted to know what would happen if patients received chemotherapy after radium-223.
- Among the 182 men treated with radium-223 who went on to receive chemotherapy, only two men had severe side effects affecting white blood cell production (neutropenia) during chemotherapy.
- On average, the 182 men lived for 2 years after starting radium-223 and 1 year after starting chemotherapy.
- In conclusion, patients may benefit from chemotherapy after radium-223 treatment without increasing the risk of side effects.

KEYWORDS
hematologic toxicity, metastatic castration-resistant, radium-223, taxane chemotherapy, treatment sequence

INTRODUCTION

In patients with metastatic castration-resistant prostate cancer (mCRPC), the alpha-emitting radionuclide radium-223 and taxane-based chemotherapy (docetaxel or cabazitaxel) have each demonstrated overall survival (OS) benefits, with hazard ratios for death of 0.69 to 0.76 versus best standard of care in phase 3 trials.[1–3] These agents are now used in various lines and sequences within the expanding treatment options for mCRPC.

Given the different mechanisms of action of radium-223 and taxanes, sequential use of these agents may avoid cross-resistance to offer incremental survival benefit. Both radium-223 and taxanes, however, are associated with adverse events related to bone marrow suppression, including grade 3/4 thrombocytopenia in 6% of patients treated with radium-223[3,4] and grade 3/4 neutropenia in 32% to 58% of patients treated with taxanes.[1,2] Therefore, cumulative toxicity is a possible concern when these agents are used in sequence. In the phase 3 ALSYMPCA study of radium-223, 57% of patients who had

previously received a taxane had slightly increased incidences of neutropenia (7%) and thrombocytopenia (15%) compared with those who received placebo after chemotherapy (1% and 8%, respectively) and those who received radium-223 with no prior chemotherapy (2% and 6%, respectively).[5]

Using radium-223 before chemotherapy is of particular interest because it is well tolerated, maintains quality of life,[3] and is approved for use in advanced prostate cancer that has metastasized to the bone (i.e., before visceral metastases have developed). To date, there is little evidence on the safety of this sequence, although reassuringly, in an exploratory analysis of ALSYMPCA, the incidence of grade 3/4 hematologic events after initiation of subsequent chemotherapy was ≤10%.[6] We sought to support these findings in a broad population of patients treated with chemotherapy after radium-223 in real-world settings.

METHODS

Study design and patients

REASSURE (NCT02141438) is an ongoing, global, prospective, single-arm, observational study of radium-223 use in real-world settings.[7,8]

Patients with mCRPC involving bone were eligible for enrollment if they were scheduled to receive radium-223 in real-world clinical practice. This post hoc analysis is limited to patients who had received no prior chemotherapy at any time before radium-223 administration and who then received taxane chemotherapy during study follow-up after radium-223 completion.

The study was performed in accordance with the principles of the Declaration of Helsinki, the International Conference of Harmonization Good Clinical Practice, and all applicable local laws and regulations. Ethics committee or institutional review board approvals were obtained according to local laws in participating countries. All patients provided written informed consent before starting treatment.

Treatment

The decision to administer radium-223 was agreed between the treating physician and the patient before enrollment. It was highly recommended that the dosage and duration of radium-223 treatment followed the approved local prescribing information. After a protocol amendment in June 2018, radium-223 could not be administered concurrently with abiraterone plus prednisone or prednisolone. Administration of a concomitant bone health agent (BHA) such as bisphosphonates or denosumab was permitted, according to local guidelines. Use of subsequent therapies after the last dose of radium-223 was at the discretion of the treating physician and patient.

End points and assessments

Details of the REASSURE study design and safety and efficacy end points have been reported previously.[7,8] In brief, for the ongoing overall study, primary outcomes are adverse events, including treatment-emergent serious adverse events and drug-related adverse events during and up to 30 days after radium-223 completion, grade 3/4 hematologic toxicities up to 6 months after the last radium-223 dose, drug-related serious adverse events after radium-223 therapy completion, and second primary malignancies. Use of life-prolonging systemic anticancer therapies (i.e., docetaxel, cabazitaxel, abiraterone plus prednisone, enzalutamide, sipuleucel-T, and/or lutetium-177 prostate-specific membrane antigen) and BHAs was recorded at baseline (start of radium-223), at each treatment visit, and at each follow-up visit until death or loss to follow-up. Therapies were defined as "prior completed" (commenced and stopped before the first radium-223 dose), "concomitant" (initiated before or during radium-223 treatment and continued during radium-223 treatment), or "subsequent" (initiated after the last dose of radium-223).

In the present analysis, the objective was to evaluate safety and OS in patients who received taxane chemotherapy after radium-223 using data from the prespecified second interim analysis.

Hematologic events associated with bone marrow suppression were assessed during study follow-up in two (potentially overlapping) time periods: (1) during and up to 6 months after the last dose of radium-223 and (2) during and up to 6 months after completion of subsequent taxane chemotherapy. In the first period, events of interest were grade 3 or 4 hematologic toxicities. In the second time period, events of interest were neutropenic fever and hemorrhage events. Events were defined using the Medical Dictionary for Regulatory Activities version 21.1, and severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Hematologic events are reported for all patients who received taxane chemotherapy after radium-223 completion and for subgroups of patients who initiated taxane chemotherapy within 90 days ("immediate") or more than 90 days ("delayed") after radium-223 completion. For patients who received both docetaxel and cabazitaxel, the chemotherapy start date was the date of the first chemotherapy dose, and the end date was the date of the last chemotherapy dose, regardless of which chemotherapy agent this was. Gaps between the end of one chemotherapy agent and start of the other were possible, and patients could receive other life-prolonging therapy between radium-223 and taxane.

OS was defined as the time from the start of radium-223 or taxane therapy to death from any cause.

Statistical analyses

All analyses were descriptive in nature. For continuous variables, summary statistics (median and range; mean and standard

deviation) were calculated. For categorical variables, frequencies and percentages were calculated. For OS, Kaplan–Meier estimates and survival curves were determined and descriptive summaries were reported.

RESULTS

Patient disposition and baseline characteristics

Patient enrollment commenced on August 20, 2014, and recruitment was completed at the end of 2017. Patients were enrolled in 189 sites in the United States, Canada, Argentina, Colombia, Mexico, Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom, and Israel.

At the prespecified second interim analysis (data cutoff: March 20, 2019; median duration of observation: 11.5 months [range 0.3–48.7]), the overall safety population included 1465 patients who received at least one dose of radium-223. Of these, 182 patients (12%) had no prior chemotherapy and received subsequent taxane chemotherapy, including 172/182 (95%) who received docetaxel and 44/182 (24%) received cabazitaxel; 34/182 (19%) received both docetaxel and cabazitaxel after radium-223. Of the 182 patients, 73 (40%) received chemotherapy within 90 days (immediate subgroup) and 109 (60%) 90 or more days (delayed subgroup) after the end of radium-223 treatment.

Most of the 182 patients (88%) had an Eastern Cooperative Oncology Group performance status of 0 or 1 at study entry. In addition, 58% had unresected primary tumors and 69% had ≥6 bone metastases identified on scintigraphy or other scans before starting radium-223 treatment. Patient demographics and baseline clinical characteristics were generally similar between the immediate and delayed subgroups (Table 1), except for the median time from diagnosis of CRPC to study entry (14 vs 8 months, respectively) and median baseline prostate-specific antigen level (66 vs 20 ng/mL).

Treatment exposure and sequencing

Most patients completed six radium-223 injections: 129/182 (71%) overall, 35/73 (48%) in the immediate subgroup, and 94/109 (86%) in the delayed subgroup. The median number of radium-223 doses administered was 6, 5, and 6, respectively, and the corresponding median duration of radium-223 treatment in each subgroup was 20, 19, and 20 weeks, respectively.

The median (range) time from the last dose of radium-223 until the start of subsequent taxane therapy was 3.6 (0.3–28.4) months overall, 1.4 (0.3–3.0) months for the immediate subgroup, and 7.3 (3.0–28.4) months for the delayed subgroup. The median (range) duration of the first subsequent taxane was 3.7 (0–22.0), 3.5 (0–22.0), and 3.7 (0–20.0) months, respectively.

Overall, 81/182 patients (45%) had completed at least one prior systemic life-prolonging therapy for mCRPC other than chemotherapy before initiation of radium-223, most commonly abiraterone plus prednisone in 48/182 patients (26%) (Figure 1A). During radium-223 treatment, 83/182 patients (46%) received at least one concomitant systemic life-prolonging therapy, primarily abiraterone plus prednisone in 50/182 patients (27%) and enzalutamide in 44/182 patients (24%) (Figure 1B). Following completion of radium-223 treatment, 61/182 patients (34%) received at least one subsequent systemic life-prolonging anticancer therapy other than taxanes, primarily enzalutamide in 45/182 patients (25%) and abiraterone plus prednisone in 21/182 patients (12%) as well as newly approved lutetium-177-prostate-specific membrane antigen (4%) (Figure 1C). Some patients received more than one prior, concomitant, or subsequent systemic anticancer therapy.

The proportions of patients who received BHAs before or with radium-223 treatment were similar (denosumab: 31% prior and 29% concomitant; zoledronic acid: 20% and 16%, respectively). After the last radium-223 dose, 5% of patients initiated denosumab and 7% initiated zoledronic acid.

Adverse events

During radium-223 therapy, 83/182 patients (46%) had ≥1 serious treatment-emergent adverse event (TEAE) or drug-related TEAE, 36/73 (49%) in the immediate subgroup and 47/109 (43%) in the delayed subgroup (Table S1). Fifteen patients (8%) had serious TEAEs (immediate subgroup 7 [10%]; delayed subgroup 8 [7%]), which resulted in permanent discontinuation of radium-223 treatment in three patients (2%, all in the immediate subgroup). Drug-related TEAEs were recorded in 71 patients (39%) overall, 30 (41%) in the immediate subgroup and 41 (38%) in the delayed subgroup. Twelve patients (7%) overall, eight (11%) in the immediate subgroup and four (4%) in the delayed subgroup, experienced grade ≥3 events. Drug-related TEAEs resulted in radium-223 discontinuation in three patients (2%) overall, all in the immediate subgroup.

Grade 3 or 4 hematologic events that occurred up to 6 months after radium-223 therapy and during taxane chemotherapy were recorded in 14 patients (8%) overall, four patients (5%) in the immediate subgroup and 10 patients (9%) in the delayed subgroup. The most frequently reported event was grade 3 anemia, recorded in 6% (overall), 5% (immediate), and 6% (delayed) (Table 2). One of the four patients in the immediate subgroup had previously experienced a serious TEAE during radium-223 treatment, which was deemed to be drug-related; none of the 10 patients in the delayed subgroup had previously experienced a serious TEAE, but four patients had TEAEs during radium-223 treatment that were deemed to be drug related. All four patients in the immediate subgroup had received abiraterone plus prednisone or enzalutamide before starting radium-223 (two patients had received both abiraterone and enzalutamide), and all

TABLE 1 Baseline characteristics of patients who received radium-223 followed by chemotherapy.

Characteristic	Radium-223 followed by immediate chemotherapy[a] (*n* = 73)	Radium-223 followed by delayed chemotherapy[b] (*n* = 109)	Total (N = 182)
At initial diagnosis			
Gleason score, *n* (%)			
≤6	8 (11)	16 (15)	24 (13)
7–10	62 (85)	77 (71)	139 (76)
Stage, *n* (%)			
I–III	29 (40)	61 (56)	90 (49)
IV	26 (36)	34 (31)	60 (33)
Time to study entry			
From diagnosis of CRPC, median months (range)	*n* = 43	*n* = 61	*n* = 104
	14 (0–55)	8 (0–113)	11 (0–113)
From diagnosis of bone metastases, median months (range)	*n* = 56	*n* = 77	*n* = 133
	20 (0–77)	23 (0–202)	22 (0–202)
At start of radium-223 therapy			
Age, median (range), years	71 (57–85)	70 (54–88)	70 (54–88)
ECOG PS 0 or 1, *n* (%)	66 (90)	94 (86)	160 (88)
Extent of bone disease, *n* (%)	*n* = 67	*n* = 102	*n* = 169
Normal or benign[c]	1 (1)	2 (2)	3 (2)
<6 lesions	18 (27)	25 (25)	43 (25)
6–20 lesions	32 (48)	53 (52)	85 (50)
>20 lesions	8 (12)	18 (18)	26 (15)
Superscan	4 (6)	2 (2)	6 (4)
Primary tumor unresected, *n* (%)	41 (56)	65 (60)	106 (58)
Laboratory values, median (range)			
Alkaline phosphatase, U/L	*n* = 54	*n* = 84	*n* = 138
	113 (35–501)	103 (2–789)	106 (2–789)
Hemoglobin, g/dL	*n* = 66	*n* = 93	*n* = 159
	13 (10–15)	13 (10–15)	13 (10–15)
Lactate dehydrogenase, U/L	*n* = 27	*n* = 51	*n* = 78
	242 (150–516)	210 (3–562)	228 (3–562)
Prostate-specific antigen, ng/mL	*n* = 53	*n* = 86	*n* = 139
	66 (1–1655)	20 (0–923)	33 (0–1655)

Note: Percentages may not add up to 100% because of missing or unknown information.

Abbreviations: CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]"Immediate" refers to taxane chemotherapy initiation within 90 days after radium-223 completion.

[b]"Delayed" refers to taxane chemotherapy initiation more than 90 days after radium-223 completion.

[c]Patients had a negative bone scan but had a history of bone metastases identified on other imaging.

four patients received ≥1 dose of radium-223 concomitantly with abiraterone or enzalutamide. In the delayed subgroup, five patients received radium-223 as their first treatment for mCRPC and five received it as their second treatment following abiraterone or enzalutamide; six of the 10 patients initiated or continued to receive abiraterone or enzalutamide after radium-223 but before taxane, whereas three patients received no other treatment between radium-223 and taxane chemotherapy.

During and up to 6 months after taxane chemotherapy, the incidence of febrile neutropenia or hemorrhage events was 4% overall, 7% in the immediate subgroup and 3% in the delayed subgroup (Table 3).

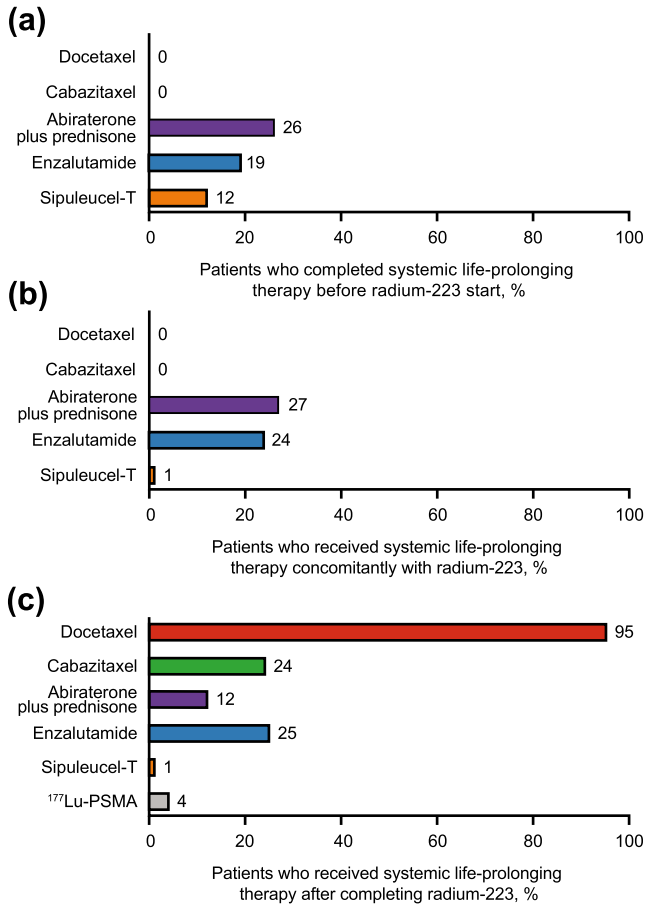

FIGURE 1 Frequency of systemic life-prolonging therapies (A) completed before start of radium-223; (B) started before or during radium-223 and continued concomitantly with radium-223; and (C) started after completion of radium-223. Patients may have received multiple therapies in each phase. ^{177}Lu-PSMA indicates lutetium-177 prostate-specific membrane antigen.

Overall survival

Median OS from the start of radium-223 treatment was 24.3 months (95% CI, 20.9–27.5) in the overall population, 16.6 months (95% CI, 13.4–17.8) in the immediate subgroup, and 30.0 months (95% CI, 26.8–32.8) in the delayed subgroup. Median OS from the start of subsequent taxane chemotherapy was 11.8 months (95% CI, 10.5–14.4) in the overall population, 11.3 months (95% CI, 8.4–13.0) in the immediate subgroup, and 14.4 months (95% CI, 10.6–17.6) in the delayed subgroup.

DISCUSSION

Given the increasing number of systemic therapies for mCRPC, which offer the possibility of several lines of life-prolonging treatments,[9–11] investigating how to sequence these agents in a safe and effective way is important. The bone-targeting mechanism of action of radium-223 provides a rationale for the use of this agent early in the treatment sequence when the disease is confined to bone, followed by a treatment with activity beyond bone, such as taxane chemotherapy, on disease progression. Furthermore, radium-223 is well tolerated and has a favorable impact on quality of life, as reported in ALSYMPCA,[3] making it a viable option for patients who wish to delay chemotherapy, because they may remain fit enough to receive chemotherapy after. Nevertheless, radium-223 and chemotherapy have some overlapping adverse events, particularly hematologic toxicities. The data collected in the REASSURE study have enabled us to evaluate the safety and effectiveness of the treatment sequence of radium-223 followed by taxane chemotherapy in real-world settings.

Among the 182 patients who received taxane chemotherapy for the first time after radium-223, the incidence of drug-related grade ≥3 adverse events during radium-223 therapy was low (7%). This finding is consistent with data from ALSYMPCA (grade 3/4 events of anemia in 13%, neutropenia in 2%, and thrombocytopenia in 7% of patients treated with radium-223),[12] and is supported by preclinical evidence that radium-223 has only a transient effect on

TABLE 2 Incidence of grade 3 or 4 hematologic events related to bone marrow suppression occurring up to 6 months after last radium-223 injection and during or up to 30 days after subsequent taxane therapy.

Hematologic events related to bone marrow suppression occurring during taxane chemotherapy, No. (%)	Radium-223 followed by immediate chemotherapy[a] (*n* = 73)		Radium-223 followed by delayed chemotherapy[b] (*n* = 109)		Total (*N* = 182)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any	4 (5)	0	9 (8)	1 (1)	13 (7)	1 (1)
Leukopenia	0	0	0	0	0	0
Neutropenia	0	0	1 (1)	1 (1)	1 (1)	1 (1)
Pancytopenia	0	0	0	0	0	0
Thrombocytopenia	1 (1)	0	1 (1)	0	2 (1)	0
Anemia	4 (5)	0	7 (6)	0	11 (6)	0

[a]"Immediate" refers to taxane chemotherapy initiation within 90 days after radium-223 completion.

[b]"Delayed" refers to taxane chemotherapy initiation more than 90 days after radium-223 completion.

TABLE 3 Incidence of febrile neutropenia or hemorrhage events during and up to 6 months after completion of taxane chemotherapy.

Febrile neutropenia or hemorrhage event during or up to 6 months after taxane chemotherapy (MedDRA preferred term), No. (%)	Radium-223 followed by immediate chemotherapy[a] (*n* = 73)	Radium-223 followed by delayed chemotherapy[b] (*n* = 109)	Total (N = 182)
Patients with ≥1 event	5 (7)	3 (3)	8 (4)
Febrile neutropenia	1 (1)	1 (1)	2 (1)
Hematochezia	2 (3)	0	2 (1)
Rectal hemorrhage	0	1 (1)	1 (<1)
Hematuria	0	1 (1)	1 (<1)
Epistaxis	3 (4)	0	3 (2)

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

[a]"Immediate" refers to taxane chemotherapy initiation within 90 days after radium-223 completion.

[b]"Delayed" refers to taxane chemotherapy initiation more than 90 days after radium-223 completion.

hematopoietic stem cells, with no long-term myelotoxicity.[13] In our analysis, among patients who received taxane chemotherapy during follow-up, the incidence of grade 3/4 hematologic adverse events related to bone marrow suppression was also low, at 8%, and grade 3/4 neutropenia and thrombocytopenia were reported in only two patients (1%) each. Hematologic toxicities did not accumulate with sequential therapy, regardless of whether the taxane was initiated immediately following the completion of radium-223 treatment or after a delay of 3 months or more. Furthermore, of the 83 patients who experienced serious or drug-related TEAEs during radium-223 therapy, only five had hematologic adverse events during taxane chemotherapy, whereas the nine other patients who had hematologic events during taxane therapy had not previously experienced serious or drug-related TEAEs during radium-223 treatment, suggesting that occurrence of hematologic adverse events on taxane therapy is not related to TEAEs during radium-223 treatment. These findings are consistent with the results from an exploratory analysis of the phase 3 ALSYMPCA trial in patients who received chemotherapy (primarily docetaxel) after radium-223 treatment[6]; in that analysis, approximately 10% of patients had grade 3/4 hematologic laboratory abnormalities up to 18 months after the first chemotherapy cycle.[6] Other prospective observational studies and retrospective analyses in patients with mCRPC provide evidence of the favorable safety profile of radium-223 in real-world settings, with a generally low incidence of myelosuppression.[14–19]

Notably, the 182 patients in our analysis received taxane chemotherapy for 3.7 months on average, which equates to six 3-weekly cycles. For context, although patients received up to 10 cycles of docetaxel as first-line therapy in the pivotal TAX-327 study,[1] in the exploratory ALSYMPCA analysis, the median duration of first post-radium-223 chemotherapy was 4.6 months[6]; in addition, in a real-world analysis of US electronic health records, the median duration of docetaxel therapy for mCRPC was 4.1 months in the second line and 3.8 months in the third line.[20] In the REASSURE study, patients could have received more than one line of life-prolonging treatment for mCRPC before radium-223 and so they might have been receiving docetaxel as a fourth or later line of treatment. Thus, the duration of docetaxel treatment compares favorably with other real-world settings and indicates that some patients are able to tolerate chemotherapy after radium-223 treatment.

In the overall REASSURE study population (*n* = 1465), median OS was 15.6 months; however, the study included a wide range of patients, including many who did not live long enough to receive subsequent therapies. In the subgroup of 182 patients who lived long enough to receive taxane chemotherapy after radium-223, median OS was approximately 2 years from the start of radium-223 treatment and 1 year from the start of the first taxane chemotherapy. Median OS from the start of radium-223 treatment differed markedly between the immediate and delayed subgroups (16.6 vs 30.0 months, with nonoverlapping CIs), which likely reflects differences in underlying disease biology between the subgroups: patients with aggressive disease, with poor prognosis at baseline (as indicated by baseline prostate-specific antigen values of 66 vs 20 ng/mL in the immediate vs delayed subgroups), would generally have an urgent need for new lines of treatment and would therefore be included in the immediate subgroup. Once patients initiated taxane chemotherapy, the median OS was relatively similar between the subgroups (11.3 vs 14.4 months, with overlapping CIs).

Taken together, these findings suggest that, in patients with bone-dominant disease who are treated with radium-223 and remain fit enough to receive chemotherapy afterward, this sequence is tolerable and feasible. This sequence may be of particular interest after prior use of doublets containing androgen receptor (AR)–targeted agents (abiraterone acetate, apalutamide, darolutamide, or enzalutamide) and androgen deprivation therapy in the metastatic hormone-sensitive, nonmetastatic castration-resistant, or metastatic castration-resistant settings, offering patients treatment with three different mechanisms of action to avoid cross-resistance. In addition to sequential use, there is interest in combination therapy involving radium-223. The ERA-223 study indicated increased risk of fracture when abiraterone acetate and radium-223 were used together

versus abiraterone alone,[21] resulting in regulatory restrictions on this combination.[22,23] However, other studies and meta-analyses indicate that the combination of radium-223 and AR-targeted therapy is effective, and the risk of fracture can be reduced by concomitant use of BHAs such as denosumab or zoledronic acid.[24–31] The ongoing phase 3 PEACE III study (NCT02194842) will assess the efficacy and safety of radium-223 combined with enzalutamide. Furthermore, the phase 3 DORA study (NCT03574571) is being conducted to assess the combination of radium-223 with docetaxel; this combination was found to be well tolerated and have enhanced antitumor activity versus the individual components in a phase 1/2a study.[32] Several early-phase studies have indicated good tolerability and promising antitumor efficacy with the use of radium-223 in combination with poly (ADP-ribose) polymerase inhibitors, such as niraparib or olaparib, or immuno-oncology agents, such as atezolizumab or sipuleucel-T.[33–36]

Observational real-world studies have limitations, including a heterogeneous patient population, diversity of treatments and treatment sequences, and inconsistencies in data collection during follow-up. For the current analysis, only 182 of the 1465 patients enrolled in the REASSURE study met the criteria of treatment with radium-223 followed by taxane chemotherapy, and the median duration of observation was less than 1 year at the time of the planned interim analysis. Nevertheless, the REASSURE study is the largest prospective study of real-world data on radium-223, providing a good reflection of global clinical practice.

In conclusion, in this real-world study of patients with bone-dominant mCRPC treated with radium-223 who remain fit for subsequent taxane chemotherapy, this sequence appears to be viable with an acceptable safety profile without accumulation of hematologic toxicity, regardless of the interval between radium-223 and taxane chemotherapy (immediate or delayed).

AUTHOR CONTRIBUTIONS

Celestia S. Higano: Conceptualization, investigation, methodology, resources, writing – original draft, and writing – review and editing. **Sabina Dizdarevic**: Investigation, resources, and writing – review and editing. **John Logue**: Investigation, resources, and writing – review and editing. **Timothy Richardson**: Investigation, resources, and writing – review and editing. **Saby George**: Investigation, resources, and writing – review and editing. **Igle de Jong**: Investigation, resources, and writing – review and editing. **Jeffrey J. Tomaszewski**: Investigation, resources, and writing – review and editing. **Fred Saad**: Investigation, resources, and writing – review and editing. **Kurt Miller**: Investigation, resources, and writing – review and editing. **Jeffrey Meltzer**: Formal analysis and writing – review and editing. **Per Sandström**: Conceptualization, formal analysis, methodology, project administration, resources, writing – original draft, and writing – review and editing. **Frank Verholen**: Conceptualization, methodology, and writing – review and editing. **Bertrand Tombal**: Conceptualization, investigation, methodology, resources, and writing – review and editing. **Oliver Sartor**: Conceptualization, investigation, methodology, resources, and writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing." This pertains to scope, time point and process of data access. As such, Bayer commits to sharing on request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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