^{177}Lu-Prostate-Specific Membrane Antigen Ligand After ^{223}Ra Treatment in Men with Bone-Metastatic Castration-Resistant Prostate Cancer: Real-World Clinical Experience

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We analyzed real-world clinical outcomes of sequential α-/β-emitter therapy for metastatic castration-resistant prostate cancer (mCRPC). **Methods:** We assessed safety and overall survival in 26 patients who received ^{177}Lu-prostate-specific membrane antigen ligand (^{177}Lu-PSMA) after ^{223}Ra in the ongoing noninterventional REASSURE study (^{223}Ra α-Emitter Agent in Nonintervention Safety Study in mCRPC Population for Long-Term Evaluation; NCT02141438). **Results:** Patients received ^{223}Ra for a median of 6 injections and subsequent ^{177}Lu-PSMA for a median of 3.5 mo (≥ the fourth therapy in 69%). The median time between ^{223}Ra and ^{177}Lu-PSMA treatment was 8 mo (range, 1–31 mo). Grade 3 hematologic events occurred in 9 of 26 patients (during or after ^{177}Lu-PSMA treatment in 5/9 patients; 8/9 patients had also received docetaxel). Median overall survival was 28.0 mo from the ^{223}Ra start and 13.2 mo from the ^{177}Lu-PSMA start. **Conclusion:** Although the small sample size precludes definitive conclusions, these preliminary data, especially the ^{177}Lu-PSMA treatment duration, suggest that the use of ^{177}Lu-PSMA after ^{223}Ra is feasible in this real-world setting.

Key Words: ^{177}Lu-prostate-specific membrane antigen; metastatic castration-resistant prostate cancer; ^{223}Ra; real-world evidence; treatment sequence

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The α-emitter ^{223}Ra demonstrated significantly prolonged overall survival and a favorable safety profile versus placebo in men with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 ALSYMPCA trial (*1*). ^{177}Lu-prostate-specific membrane antigen ligand (^{177}Lu-PSMA) is an investigational β-emitting radioligand with accumulating evidence of clinical efficacy and acceptable toxicity in men with advanced-stage mCRPC (*2–5*).

Early experience in patients who have received both ^{223}Ra and ^{177}Lu-PSMA indicates tolerable safety and therapeutic response with this sequence (*6–8*). We sought to add to the evidence base on sequential α-/β-emitting therapy, using data from participants in an ongoing global, prospective, observational study of ^{223}Ra who received subsequent ^{177}Lu-PSMA.

MATERIALS AND METHODS

Patients with mCRPC involving bone and who were scheduled to receive ^{223}Ra in clinical practice were included in REASSURE (^{223}Ra α-Emitter Agent in Nonintervention Safety Study in mCRPC Population for Long-Term Evaluation; NCT02141438). Primary outcomes included short-term and long-term safety. Methods and results from a previous interim analysis have been reported (*9*). This paper is based on the second prespecified interim analysis (data cutoff, March 20, 2019).

Disease characteristics, adverse events after ^{223}Ra treatment, and overall survival are described for patients who received the experimental drug ^{177}Lu-PSMA in compassionate-use or investigational settings after ^{223}Ra. Treatment-emergent serious adverse events and drug-related adverse events were recorded during ^{223}Ra treatment or up to 30 d after the last ^{223}Ra dose. Grade 3 or 4 hematologic adverse events were systematically collected up to 6 mo after ^{223}Ra; neutropenic fever or hemorrhage were recorded in patients with subsequent chemotherapy up to 6 mo after the last dose of chemotherapy. Drug-related serious adverse events continued to be recorded until the end of follow-up (maximum, 7 y). Adverse events during and after ^{177}Lu-PSMA therapy were not systematically recorded unless they met the above criteria.

The study conduct complied with the requirements of the European Medicines Agency, the U.S. Food and Drug Administration,

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applicable local laws and regulations, and International Conference on Harmonization good-clinical-practice guidance. Participants provided written informed consent, and ethics committee or institutional review board approvals were obtained according to local laws in participating countries.

RESULTS

Twenty-six patients in the United States, Germany, Austria, Italy, and Israel received ^{177}Lu-PSMA after ^{223}Ra. Their median age was 67 y, 96% (25/26) had an Eastern Cooperative Oncology Group performance status of 0 or 1, and 54% (13/24 with baseline scans) had more than 20 lesions at baseline (Table 1).

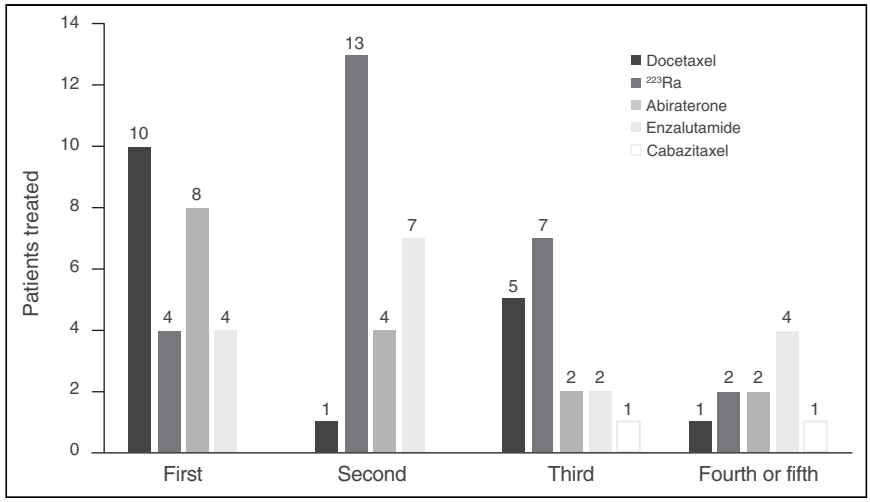

FIGURE 1. Anticancer therapies administered before ^{177}Lu–PSMA. All patients received ^{223}Ra.

TABLE 1
Baseline Disease Characteristics

Time point	Characteristic	Finding	Data
Initial diagnosis	Gleason score	≤6	3 (12)
		7	9 (35)
		8–10	12 (46)
		Unknown	2 (8)
	Stage (American Joint Committee on Cancer criteria)	I	5 (19)
		IIB	1 (4)
		III	3 (12)
		IV	13 (50)
		Missing	4 (15)
Start of ^{223}Ra therapy	Time from diagnosis of mCRPC (mo)		20 (6–48)
	Time from diagnosis of bone metastases (mo)		23 (3–40)
	Extent of disease*	<6 lesions	2 (8)
		6–20 lesions	7 (29)
		>20 lesions	11 (46)
		Superscan	2 (8)
		Missing	2 (8)
	Primary tumor status	Unresected	11 (42)
		Resected, status of residual tumor unknown	3 (12)
		R0 complete resection, all margins histologically negative	6 (23)
		R1 incomplete resection, microscopic margin involvement	5 (19)
		Missing	1 (4)
	Laboratory values	Prostate-specific antigen (ng/mL) (n = 21)	127 (8–1,319)
		Alkaline phosphatase (U/L) (n = 20)	147 (45–769)
		Lactate dehydrogenase (U/L) (n = 14)	228 (112–393)
		Hemoglobin (g/dL) (n = 23)	13 (9–15)

*Baseline scan data available for 24/26 patients.
Qualitative data are number and percentage (n = 26 unless indicated otherwise); continuous data are median and range.

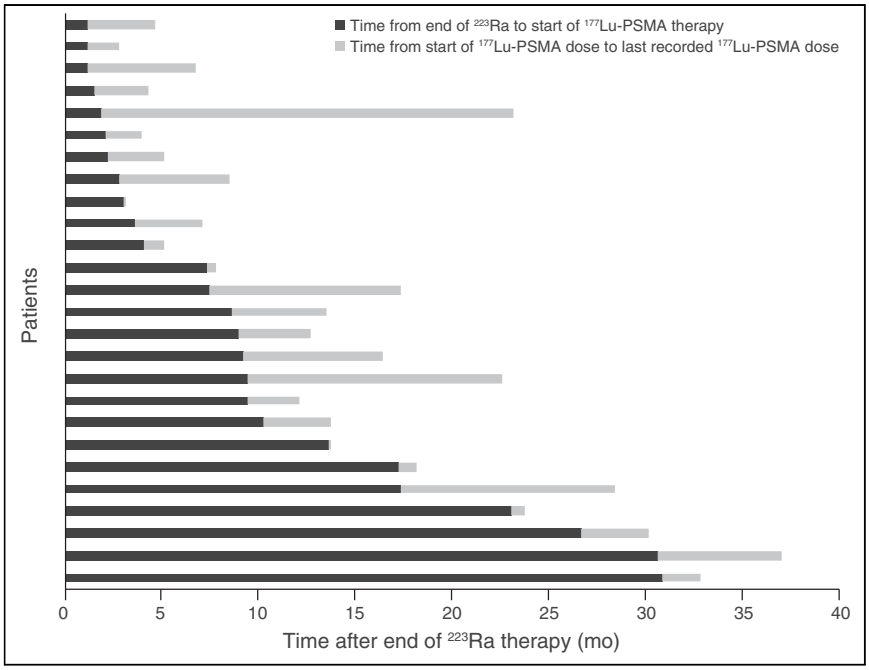

FIGURE 2. Time since end of ^{223}Ra to start of ^{177}Lu-PSMA ligand and duration of ^{177}Lu-PSMA therapy.

Before starting ^{223}Ra, 85% of patients (22/26) received at least 1 life-prolonging systemic anticancer therapy (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org), including androgen receptor–targeted therapy (enzalutamide and/or abiraterone acetate) in 65% (17/26) and docetaxel in 42% (11/26).

Before starting ^{177}Lu-PSMA, 92% of patients (24/26) had received at least 2 life-prolonging therapies, 69% (18/26) had received at least 3 therapies, 8% (2/26) had received only ^{223}Ra, 65% (17/26) had received prior docetaxel, 8% (2/26) had also received cabazitaxel between ^{223}Ra and ^{177}Lu-PSMA treatment, and 50% (13/26) had received no other life-prolonging treatment between ^{223}Ra and ^{177}Lu-PSMA (Fig. 1; Supplemental Fig. 1).

The median number of ^{223}Ra injections was 6 (range, 1–6); 17 of 26 patients (65%) received 6 injections. The median time from the end of ^{223}Ra to the start of ^{177}Lu-PSMA treatment was 8 mo (range, 1–31 mo; Fig. 2). The median duration of ^{177}Lu-PSMA treatment was 3.5 mo (range, 0.5–21.2 mo; Fig. 2).

Fifteen patients (58%) experienced treatment-emergent drug-related adverse events during ^{223}Ra treatment (Table 2). Nine patients (35%) had grade 3 hematologic toxicities (Table 3); 8 of 9 patients had previously received docetaxel, before ($n = 5$) or after ($n = 3$) ^{223}Ra therapy, and 2 of 9 patients had also received cabazitaxel after ^{223}Ra. The hematologic toxicities developed during or after ^{177}Lu-PSMA treatment in 5 patients (6 events). No grade 4 hematologic events were recorded.

Median overall survival was 28.0 mo (95% CI, 19.5–32.7 mo) from the start of ^{223}Ra therapy and 13.2 mo (95% CI, 8.4–16.2 mo) from the start of ^{177}Lu-PSMA therapy.

DISCUSSION

Although ^{177}Lu-PSMA is not yet approved for patients with mCRPC, patients are increasingly receiving this investigational treatment in clinical trials or compassionate-use programs. Most patients receive ^{177}Lu-PSMA after multiple prior systemic anticancer therapies, including ^{223}Ra in some cases, as recorded in the REASSURE study. This subgroup analysis of REASSURE, which reflects real-world clinical practice, adds to the evidence for the feasibility of sequential ^{223}Ra and ^{177}Lu-PSMA treatment, with a median overall survival of more than 1 y from the start of ^{177}Lu-PSMA therapy. Only 3 patients had serious adverse events related to ^{223}Ra, and the reported (albeit incompletely) incidence of grade 3 hematologic events was acceptable, mostly consisting of anemia, which may be partially explained by increasing disease burden. Furthermore, the treatment duration for ^{177}Lu-PSMA (median, 3.5 mo) indicates that several patients were able to receive multiple cycles, even though most patients had received at least 3 prior life-prolonging therapies, including taxane chemotherapy.

The 13-mo median overall survival in our analysis is consistent with a retrospective multicenter study in which median overall survival from the start of ^{177}Lu-PSMA therapy was around 11 mo in 85 patients with prior ^{223}Ra (*7*) and 16.4 mo in patients with 6–20 bone lesions treated with ^{223}Ra and ^{177}Lu-PSMA (*10*). In another analysis, rates of grade 3 hematologic toxicity were low in patients with or without prior ^{223}Ra therapy (anemia, 1/20 [5%] vs. 3/29 [10%]; thrombocytopenia, 1/20 [5%] vs. 2/29 [7%]) (*6*), a result that again supports our findings, although we did not systematically assess hematologic toxicity in all patients during ^{177}Lu-PSMA treatment—a limitation of our study.

Additional limitations are the small sample size, reflecting the experimental status of ^{177}Lu-PSMA, and the lack of a randomized control group. Because ^{177}Lu-PSMA is still an investigational agent, treatment was likely undertaken in academic settings (e.g., university hospital cancer centers); it is therefore unknown whether the findings can be extrapolated to real-world community settings.

TABLE 2
Adverse Events During and After ^{223}Ra Treatment

Adverse event	Incidence ($n = 26$)
Drug-related	
Treatment-emergent*	15 (58%)
Serious†	3 (12%)
Bone-associated events	6 (23%)
Fractures	2 (8%)
Bone disorders‡	4 (15%)

*During ^{223}Ra therapy and up to 30 d after last ^{223}Ra dose.
†During ^{223}Ra therapy and up to 7 y after last ^{223}Ra dose.
‡Excluding congenital disorders and fractures, according to *Medical Dictionary for Regulatory Activities,* version 21.1 (https://www.meddra.org/).
Qualitative data are number and percentage.

TABLE 3
Grade 3 Hematologic Adverse Events After Start of ^{223}Ra Therapy*

Patients with events†	Incidence (n = 26)		
	Overall	Starting before ^{177}Lu-PSMA treatment	Starting during or after ^{177}Lu-PSMA treatment‡
Any	9 (35%)	5 (19%)	5 (19%)
Leukopenia	0	0	0
Neutropenia	0	0	0
Pancytopenia	1 (4%)	0	1 (4%)
Thrombocytopenia	3 (12%)	2 (8%)	1 (4%)
Anemia	6 (23%)	3 (12%)	4 (15%)

*No grade ≥4 events were recorded.
†Patients may have had >1 event at different times; these patients are counted only once in "Any" row and "Overall" column.
‡Grade 3/4 hematologic toxicity data were systematically recorded only up to 6 mo after completion of ^{223}Ra therapy; data are therefore not consistently available for patients who received ^{177}Lu-PSMA after this window.
Qualitative data are number and percentage.

The treatment duration and overall survival after ^{177}Lu-PSMA initiation indicate that its use after ^{223}Ra in heavily pretreated mCRPC patients is feasible, but interpretation is hindered by lack of a comparator arm, and possibly only the fittest patients were selected for ^{177}Lu-PSMA treatment. Nevertheless, this interim analysis of an ongoing real-world study provides clinically meaningful evidence in patients with mCRPC who successfully received sequential α-/β-emitting treatments.

CONCLUSION

In this real-world population of heavily pretreated patients with mCRPC, a treatment sequence of targeted α-therapy with ^{223}Ra followed by the β-emitter ^{177}Lu-PSMA seemed feasible, based on the duration of ^{177}Lu-PSMA therapy, although definitive conclusions cannot be drawn.

DISCLOSURE

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KEY POINTS

QUESTION: Is it feasible to treat men with mCRPC with sequential α- and β-emitting therapies?

PERTINENT FINDINGS: Subgroup analysis of a global observational study of ^{223}Ra therapy indicated a low rate of serious adverse events and hematologic toxicities in patients who also received ^{177}Lu-PSMA, and many patients were able to receive multiple doses of ^{177}Lu-PSMA (a marker of tolerability). This sequence provides overall survival of more than 2 y from the initiation of ^{223}Ra and more than 1 y from the initiation of ^{177}Lu-PMSA, even in heavily pretreated patients.

IMPLICATIONS FOR PATIENT CARE: Sequential use of α- and β-emitters appears to be feasible in selected patients, on the basis of the known safety profile of ^{223}Ra and the duration of subsequent ^{177}Lu-PSMA; this sequence warrants further investigation.

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