

¹⁷⁷Lu-Prostate-Specific Membrane Antigen Ligand After ²²³Ra 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 ¹⁷⁷Lu-prostate-specific membrane antigen ligand (¹⁷⁷Lu-PSMA) after ²²³Ra in the ongoing noninterventional REASSURE study (²²³Ra α -Emitter Agent in Nonintervention Safety Study in mCRPC Population for Long-Term Evaluation; NCT02141438).

Results: Patients received ²²³Ra for a median of 6 injections and subsequent ¹⁷⁷Lu-PSMA for a median of 3.5 mo (\geq the fourth therapy in 69%). The median time between ²²³Ra and ¹⁷⁷Lu-PSMA treatment was 8 mo (range, 1–31 mo). Grade 3 hematologic events occurred in 9 of 26 patients (during or after ¹⁷⁷Lu-PSMA treatment in 5/9 patients; 8/9 patients had also received docetaxel). Median overall survival was 28.0 mo from the ²²³Ra start and 13.2 mo from the ¹⁷⁷Lu-PSMA start.

Conclusion: Although the small sample size precludes definitive conclusions, these preliminary data, especially the ¹⁷⁷Lu-PSMA treatment duration, suggest that the use of ¹⁷⁷Lu-PSMA after ²²³Ra is feasible in this real-world setting.

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

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The α -emitter ²²³Ra 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). ¹⁷⁷Lu-prostate-specific membrane antigen ligand (¹⁷⁷Lu-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 ²²³Ra and ¹⁷⁷Lu-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 ²²³Ra who received subsequent ¹⁷⁷Lu-PSMA.

MATERIALS AND METHODS

Patients with mCRPC involving bone and who were scheduled to receive ²²³Ra in clinical practice were included in REASSURE (²²³Ra 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 ²²³Ra treatment, and overall survival are described for patients who received the experimental drug ¹⁷⁷Lu-PSMA in compassionate-use or investigational settings after ²²³Ra. Treatment-emergent serious adverse events and drug-related adverse events were recorded during ²²³Ra treatment or up to 30 d after the last ²²³Ra dose. Grade 3 or 4 hematologic adverse events were systematically collected up to 6 mo after ²²³Ra; 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 ¹⁷⁷Lu-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 ¹⁷⁷Lu-PSMA after ²²³Ra. 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).

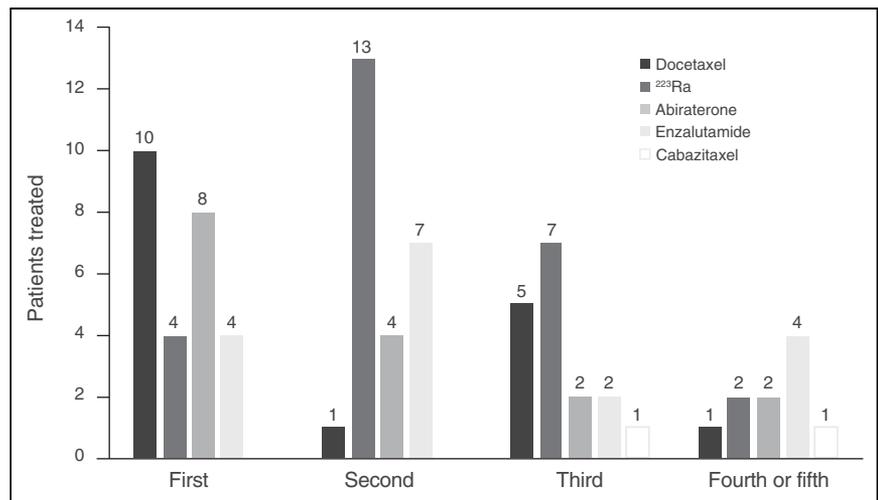


FIGURE 1. Anticancer therapies administered before ¹⁷⁷Lu-PSMA. All patients received ²²³Ra.

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
		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.

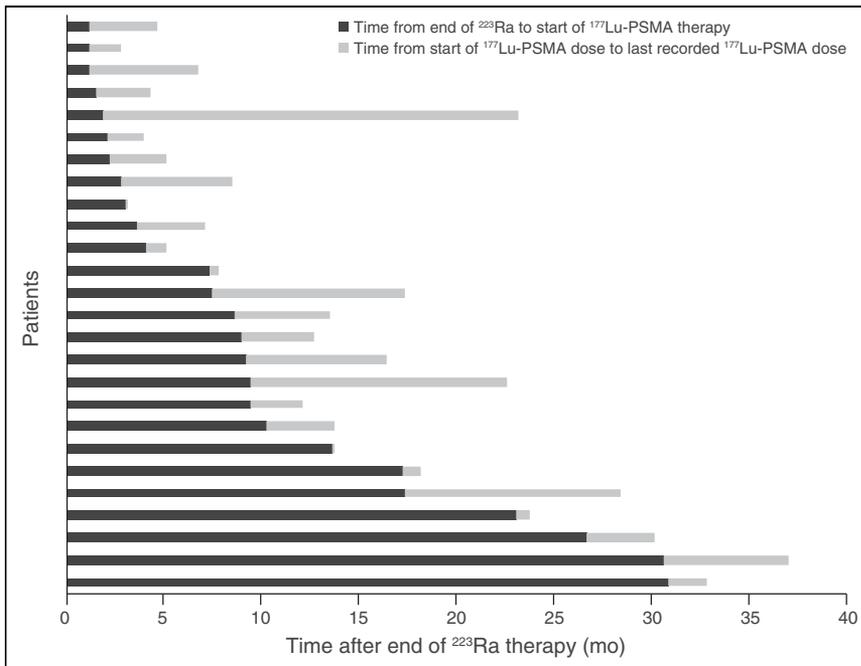


FIGURE 2. Time since end of ²²³Ra to start of ¹⁷⁷Lu-PSMA ligand and duration of ¹⁷⁷Lu-PSMA therapy.

Before starting ²²³Ra, 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 ¹⁷⁷Lu-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 ²²³Ra, 65% (17/26) had received prior docetaxel, 8% (2/26) had also received cabazitaxel between ²²³Ra and ¹⁷⁷Lu-PSMA treatment, and 50% (13/26) had received no other life-prolonging treatment between ²²³Ra and ¹⁷⁷Lu-PSMA (Fig. 1; Supplemental Fig. 1).

The median number of ²²³Ra injections was 6 (range, 1–6); 17 of 26 patients (65%) received 6 injections. The median time from the end of ²²³Ra to the start of ¹⁷⁷Lu-PSMA treatment was 8 mo (range, 1–31 mo; Fig. 2). The median duration of ¹⁷⁷Lu-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 ²²³Ra 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 ($n = 3$) ²²³Ra therapy, and 2 of 9 patients had also received cabazitaxel after ²²³Ra. The hematologic toxicities developed during or after ¹⁷⁷Lu-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 ²²³Ra therapy and 13.2 mo (95% CI, 8.4–16.2 mo) from the start of ¹⁷⁷Lu-PSMA therapy.

DISCUSSION

Although ¹⁷⁷Lu-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 ¹⁷⁷Lu-PSMA after multiple prior systemic anticancer therapies, including ²²³Ra 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 ²²³Ra and ¹⁷⁷Lu-PSMA treatment, with a median overall survival of more than 1 y from the start of ¹⁷⁷Lu-PSMA therapy. Only 3 patients had serious adverse events related to ²²³Ra, 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 ¹⁷⁷Lu-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 ¹⁷⁷Lu-PSMA

therapy was around 11 mo in 85 patients with prior ²²³Ra (7) and 16.4 mo in patients with 6–20 bone lesions treated with ²²³Ra and ¹⁷⁷Lu-PSMA (10). In another analysis, rates of grade 3 hematologic toxicity were low in patients with or without prior ²²³Ra 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 ¹⁷⁷Lu-PSMA treatment—a limitation of our study.

Additional limitations are the small sample size, reflecting the experimental status of ¹⁷⁷Lu-PSMA, and the lack of a randomized control group. Because ¹⁷⁷Lu-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 ²²³Ra 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 ²²³Ra therapy and up to 30 d after last ²²³Ra dose.
†During ²²³Ra therapy and up to 7 y after last ²²³Ra 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 ²²³Ra 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 ²²³Ra therapy; data are therefore not consistently available for patients who received ¹⁷⁷Lu-PSMA after this window.

Qualitative data are number and percentage.

The treatment duration and overall survival after ¹⁷⁷Lu-PSMA initiation indicate that its use after ²²³Ra 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 ¹⁷⁷Lu-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 ²²³Ra followed by the β -emitter ¹⁷⁷Lu-PSMA seemed feasible, based on the duration of ¹⁷⁷Lu-PSMA therapy, although definitive conclusions cannot be drawn.

DISCLOSURE

Oliver Sartor reports grants or fees from Amgen, Bayer, Sanofi, AstraZeneca, Dendreon, Constellation Pharmaceuticals, Advanced Accelerator Applications, Endocyte, Pfizer, Bristol Myers Squibb, Bavarian Nordic, EMD Serono, Astellas Pharma, Progenics, Blue Earth Diagnostics, Merck, Invitae, Astellas, Endocyte, Myovant Sciences, Myriad Genetics, Novartis, Clarity Pharmaceuticals, Fusion Pharmaceuticals, Isotopen Technologien, Janssen, Noxopharm, Clovis Oncology, Taiho, Noria Therapeutics, Point Biopharma, TeneoBio, Telix Pharmaceuticals, and Theragnostics. Christian la Fougère serves as a consultant/adviser for Bayer and Sanofi-Aventis. Markus Essler reports research funding from Novartis; is a consultant/adviser for Bayer, Novartis, and Ipsen; and receives travel expenses from Ipsen and Sirtex. Samer Ezzidin reports travel expenses from Ipsen. Jörg Ellinger serves as a consultant for Bayer. John Sylvester reports employment at 21st Century Oncology; research funding from Prostatak (via 21st Century Oncology); stock in Augmenix; patents, royalties, or other intellectual properties with Myriad; and honoraria from Decipher and Theragenics. John Sylvester also serves as a consultant/adviser for, receives travel expenses from, and is on the

speakers' bureau for Theragenics. Avivit Peer serves as a consultant/adviser for Pfizer, BMS, Roche, Eisai, MSD, Janssen, Astellas, Novartis, Medison, AstraZeneca, and Bayer. Jeffrey Meltzer, Per Sandström, and Frank Verhoken are employees of Bayer. Daniel Song reports research funding from Bayer, Advantagene, Bristol Myers Squibb, and BioProtect and serves as a consultant/adviser for BioProtect. This work was supported by Bayer Healthcare Pharmaceuticals Inc., Whippany, NJ, USA. No other potential conflict of interest relevant to this article was reported.

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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 ²²³Ra therapy indicated a low rate of serious adverse events and hematologic toxicities in patients who also received ¹⁷⁷Lu-PSMA, and many patients were able to receive multiple doses of ¹⁷⁷Lu-PSMA (a marker of tolerability). This sequence provides overall survival of more than 2 y from the initiation of ²²³Ra and more than 1 y from the initiation of ¹⁷⁷Lu-PSMA, 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 ²²³Ra and the duration of subsequent ¹⁷⁷Lu-PSMA; this sequence warrants further investigation.

REFERENCES

1. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213–223.

2. Sadaghiani MS, Sheikhabaei S, Werner RA, et al. A systematic review and meta-analysis of the effectiveness and toxicities of lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. *Eur Urol*. 2021;80:82–94.
3. Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with ¹⁷⁷Lu-labelled PSMA-ligands (¹⁷⁷Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging*. 2019;46:2536–2544.
4. Hofman MS, Emmett L, Sandhu SK, et al. [¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*. 2021;397:797–804.
5. Morris MJ, De Bono JS, Chi KN, et al. Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION) [abstract]. *J Clin Oncol*. 2021;39(suppl):LBS4.
6. Ahmadzadehfar H, Zimbelmann S, Yordanova A, et al. Radioligand therapy of metastatic prostate cancer using ¹⁷⁷Lu-PSMA-617 after radiation exposure to ²²³Ra-dichloride. *Oncotarget*. 2017;8:55567–55574.
7. Ahmadzadehfar H, Rahbar K, Baum RP, et al. Prior therapies as prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients treated with [¹⁷⁷Lu] Lu-PSMA-617: a WARMTH multicenter study (the 617 trial). *Eur J Nucl Med Mol Imaging*. 2021;48:113–122.
8. Ferdinandus J, Eppard E, Gaertner FC, et al. Predictors of response to radioligand therapy of metastatic castrate-resistant prostate cancer with ¹⁷⁷Lu-PSMA-617. *J Nucl Med*. 2017;58:312–319.
9. Dizdarevic S, Petersen PM, Essler M, et al. Interim analysis of the REASSURE (Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation) study: patient characteristics and safety according to prior use of chemotherapy in routine clinical practice. *Eur J Nucl Med Mol Imaging*. 2019;46:1102–1110.
10. Ahmadzadehfar H, Matern R, Baum RP, et al. The impact of the extent of the bone involvement on overall survival and toxicity in mCRPC patients receiving [¹⁷⁷Lu]Lu-PSMA-617: a WARMTH multicentre study. *Eur J Nucl Med Mol Imaging*. 2021;48:4067–4076.