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

Oliver Sartor1, Christian la Fougère2, Markus Essler3, Sameer Ezziddin4, Gero Kramer5, Jörg Ellinger6, Luke Nordquist7, John Sylvester8, Giovanni Paganel9, Avivit Peer10, Martin Bögemann11, Jeffrey Meltzer12, Per Sandström12, Frank Verholen13, and Daniel Y. Song14

1Tulane Cancer Center, Tulane University School of Medicine, New Orleans, Louisiana; 2Department of Nuclear Medicine and Clinical Molecular Imaging, University Hospital Tübingen, Tübingen, Germany; 3Clinic and Polyclinic for Nuclear Medicine, University Hospital Bonn, Bonn, Germany; 4Department of Nuclear Medicine, Saarland University, Homburg, Germany; 5Urology Clinic, Medical University of Vienna, Vienna, Austria; 6Clinic for Urology and Pediatric Urology, University Hospital Bonn, Bonn, Germany; 7Guam Research Network LLC, Omaha, Nebraska; 821st Century Oncology–Sarasota, Lakewood Ranch, Florida; 9Scientific Institute of Romagna for the Study and Treatment of Tumors, UOC Nuclear Medicine, Meldola, Italy; 10Rambam MC, Haifa, Israel; 11Department of Urology, University Hospital Münster, Münster, Germany; 12Bayer HealthCare, Whippany, New Jersey; 13Bayer Consumer Care, Basel, Switzerland; and 14Radiation Oncology, Johns Hopkins University, Baltimore, Maryland

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 (± 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,
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).

**TABLE 1**

Baseline Disease Characteristics

| Time point                                      | Characteristic                        | Finding | Data     |
|------------------------------------------------|---------------------------------------|---------|----------|
| Initial diagnosis                               | Gleason score                         | $\leq 6$ | 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 1. Anticancer therapies administered before $^{177}$Lu-PSMA. All patients received $^{223}$Ra.
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 treatment 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.

**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.

**TABLE 2**

| 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.
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 $\alpha$-/\(\beta\)-emitting treatments.

CONCLUSION

In this real-world population of heavily pretreated patients with mCRPC, a treatment sequence of targeted $\alpha$-therapy with $^{223}$Ra followed by the $\beta$-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 $\alpha$- and $\beta$-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-PSMA, even in heavily pretreated patients.

**IMPLICATIONS FOR PATIENT CARE:** Sequential use of $\alpha$- and $\beta$-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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