Safety and Survival Outcomes of Lutetium-177–Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer with prior Radium-223 treatment: The RALU Study

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ABSTRACT

The RAdium LUtetium (RALU) study evaluated the feasibility of sequential alpha and beta emitter use in patients with bone-predominant metastatic castration-resistant prostate cancer. **Methods:** This pre-planned, interim, retrospective analysis investigated safety and survival outcomes with lutetium-177-PSMA ($^{177}$Lu-PSMA) in patients treated with prior radium-223 ($^{223}$Ra). **Results:** Forty-nine patients were evaluated. Patients received a median of 6 $^{223}$Ra injections; 59% of patients received ≥4 $^{177}$Lu-PSMA cycles. Most (69%) patients received ≥4 life-prolonging therapies before $^{177}$Lu-PSMA. Common Terminology Criteria for Adverse Events Grade 3–4 treatment-emergent adverse events during $^{177}$Lu-PSMA therapy and a 30-day follow-up period included anemia (18%) and thrombocytopenia (2%). Median overall survival was 12.6 (95% CI 8.8–16.1) and 31.4 months (95% CI 25.7–37.6) from starting $^{177}$Lu-PSMA or $^{223}$Ra, respectively. **Conclusions:** $^{177}$Lu-PSMA treatment was well tolerated in patients who had received prior $^{223}$Ra. $^{223}$Ra use before $^{177}$Lu-PSMA is feasible and can be considered for future assessment of optimal treatment sequence.

**Key Words:** targeted alpha therapy, radium-223, lutetium-177-PSMA, metastatic castration-resistant prostate cancer, real-world practice
INTRODUCTION

Radium-223 dichloride ($^{223}$Ra), a targeted alpha therapy with a good safety profile, improved overall survival and quality of life in patients with bone-predominant metastatic castration-resistant prostate cancer (mCRPC) (1). $^{223}$Ra therapy results in low myelosuppression rates and recent preclinical data demonstrated its transient effect on the bone marrow without long-term effects (1,2). Therefore, earlier incorporation of $^{223}$Ra in the treatment sequence may facilitate optimal build-in of life-prolonging therapies (LPTs) to improve survival outcomes.

The VISION study investigated a beta-emitter, lutetium-177-labeled prostate-specific membrane antigen ligand ($^{177}$Lu-PSMA-617) targeting PSMA-expressing cells, reporting prolonged overall survival and acceptable safety in heavily pretreated patients with mCRPC (3). Another $^{177}$Lu-PSMA radioligand ($^{177}$Lu-PSMA-I&T) was also well tolerated, with few grade $\geq$3 hematological adverse events (AEs) (4).

$^{223}$Ra and $^{177}$Lu-PSMA regulatory approval (in some countries) for patients with mCRPC, albeit in different patient populations, prompted us to investigate safety and survival outcomes of sequential $^{223}$Ra and $^{177}$Lu-PSMA. In VISION, 17.4% of patients received $^{223}$Ra therapy before $^{177}$Lu-PSMA without adversely affecting efficacy, but safety has not been reported for this subgroup (3). However, retrospective studies show using $^{223}$Ra prior to $^{177}$Lu-PSMA is feasible, with acceptable safety (5,6). Moreover, $^{177}$Lu-PSMA-617 initiation $\leq$8 weeks after $^{223}$Ra in patients with progressive bone-metastatic disease was effective, with acceptable safety (7). We analyzed interim data from the observational RAdium LUtetium (RALU) study to further evaluate safety and survival for sequential $^{223}$Ra/$^{177}$Lu-PSMA therapy in patients with mCRPC.

MATERIALS AND METHODS

RALU was a retrospective, multicenter, medical chart review study investigating the safety of $^{177}$Lu-PSMA in patients with mCRPC previously treated with $^{223}$Ra. This analysis includes patients treated in Germany. Patients were $\geq$18 years with mCRPC, and received $\geq$1 $^{223}$Ra injection and subsequently $\geq$1 $^{177}$Lu-PSMA cycle.

The retrospective observation period started at mCRPC diagnosis ending either at the last available visit or death, whichever occurred first. Pre-baseline, baseline and follow-up period definitions are shown in Figure 1.
The primary endpoint was safety of $^{177}$Lu-PSMA post-$^{223}$Ra therapy. AEs used Common Terminology Criteria for Adverse Events grading. Secondary endpoints included OS, time to next treatment, and change from baseline in serum prostate-specific antigen and alkaline phosphatase levels. AEs and grade 3–4 laboratory abnormalities were recorded as per Figure 1.

The study was conducted in accordance with relevant guidelines and regulations (Supplementary Methods).

RESULTS

This pre-planned interim analysis included medical records from 49 patients (data cut-off, January 31, 2022) (Table 1). Before $^{177}$Lu-PSMA initiation, 31% (15/49) of patients had visceral metastases and median prostate-specific antigen and alkaline phosphatase values were 287.0 ng/ml and 142.5 U/L, respectively (Table 1). 92% (45/49) of patients received ≥1 line of taxane-based chemotherapy before $^{177}$Lu-PSMA initiation, with 51% (25/49) receiving taxane-based chemotherapy between $^{223}$Ra and $^{177}$Lu-PSMA (Table 1). Before starting $^{177}$Lu-PSMA, 63% (30/49) of patients received ≥4 LPTs (docetaxel, cabazitaxel, abiraterone, enzalutamide, and $^{223}$Ra; Table 1 and Figure 2). Most patients received chemotherapy before $^{177}$Lu-PSMA; 92% received docetaxel and 18% received cabazitaxel (Figure 2).

Median time from first $^{223}$Ra and $^{177}$Lu-PSMA dose to end of observation was 28.0 months (range 11.0–68.2) and 8.9 months (1.4–63.9), respectively. A median of 6 $^{223}$Ra injections were administered and 71% [35/49] of patients received 5–6 $^{223}$Ra injections. Median $^{223}$Ra therapy duration was 4.7 months (range 1.0–7.0). All patients received $^{177}$Lu-PSMA (PSMA-617 [67%] or PSMA-I&T [33%]) and 59% (29/49) received ≥4 $^{177}$Lu-PSMA cycles. Median $^{177}$Lu-PSMA therapy duration was 4.9 months (range 0–57.1). Median time from last $^{223}$Ra injection to first $^{177}$Lu-PSMA dose was 9.3 months (range 0.9–41.9). Overall, 51% (25/59) of patients received taxane-based chemotherapy during/after $^{223}$Ra and until 60 days before $^{177}$Lu-PSMA.

During $^{177}$Lu-PSMA, 92% (45/49) of patients experienced any grade and 41% (20/49) experienced grade 3–4 treatment-emergent AEs (Supplementary Table 1). Grade 3–4 anemia and thrombocytopenia occurred in 18% (9/49) and 2% (1/49) of patients, respectively. Grade 1–2 dry mouth occurred in 27% (13/49) of patients; none had grade 3–4 dry mouth. One patient (2%)
had grade 1–2 dry eye. Incidence of grade 3–4 laboratory abnormalities was highest for anemia (35% [17/49]) and thrombocytopenia (13% [6/49]) (Table 2). No grade 5 toxicities occurred.

Median overall survival was 12.6 months (95% CI 8.8–16.1) and 31.4 months (95% CI 25.7–37.6) from first dose of 177Lu-PSMA and 223Ra, respectively (Figure 3). During 177Lu-PSMA, 39% and 29% of patients had a ≥30% or ≥50% decline in prostate-specific antigen (best response) respectively; corresponding alkaline phosphatase decline values were 6% and 4%.

**DISCUSSION**

Randomized trials demonstrated low myelosuppression rates in patients with mCRPC receiving 223Ra or 177Lu-PSMA (1,3,8). However, chemotherapy and advanced disease affecting bone marrow function can increase myelosuppression rates in this setting (9-11). Therefore, in real-world practice, radiopharmaceutical therapy following prior chemotherapy may result in more serious hematological AEs.

177Lu-PSMA following 223Ra treatment had an acceptable safety profile. Notably, this was despite the patient population being heavily pretreated, with >90% of patients having received chemotherapy in addition to 223Ra and 177Lu-PSMA. Grade 3–4 anemia and thrombocytopenia incidences were 18% and 2%, respectively, consistent with the retrospective analysis of patients receiving the 223Ra/177Lu-PSMA sequence in the real-world REASSURE study (15% and 4%, respectively) (5). When 177Lu-PSMA was given within 8 weeks of 223Ra, the grade ≥3 anemia incidence was similar (18%), but grade ≥3 leukopenia and thrombocytopenia rates were higher than reported here (14% vs 0 and 21% vs 2%) (7).

Median overall survival from starting 177Lu-PSMA or 223Ra therapy (12.6 and 31.4 months, respectively) corresponded to that reported in REASSURE (13.2 and 28.0 months, respectively) (5). In patients with mCRPC who underwent 177Lu-PSMA therapy in the WARMTH study, overall survival was longer in patients with bone metastases receiving prior 223Ra versus those who did not (16 vs 12 months in patients with 6–20 bone lesions, p=0.038, and 11 vs 7 months in patients with diffuse involvement, p=0.034) (11).

This study’s strength is underlined by broad inclusion criteria and high-quality data with few missing datapoints. Accordingly, we could effectively evaluate 177Lu-PSMA safety in patients with a history of 223Ra therapy who received chemotherapy, before or after 223Ra treatment.
Nevertheless, a retrospective study design may have contributed to patient selection bias due to pre-set outcomes of interest. Other limitations include retrospective AE grading, and lack of ascertainment of $^{177}$Lu-PSMA doses and schedules and comparisons to non-$^{223}$Ra pretreated patients. Despite small patient numbers, patients were managed and treated in German high volume Nuclear Medicine Centers with extensive $^{223}$Ra and $^{177}$Lu-PSMA experience.

CONCLUSION

This retrospective cohort study demonstrates that, for patients with bone predominant mCRPC receiving $^{223}$Ra in routine care, subsequent $^{177}$Lu-PSMA treatment was clinically feasible and well tolerated, with limited myelosuppression. Survival outcomes reflected previous reports. Therefore, in patients with bone-predominant mCRPC, $^{223}$Ra use before $^{177}$Lu-PSMA can be considered in future assessments of optimal treatment sequence of LPTs.

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DISCLOSURE

KR reports honoraria: Advanced Accelerator Applications (AAA), Bayer; consultancy/advisory: ABX GmbH, ABX-CRO, Bayer, AAA. MEs reports consultancy/advisory: Bayer, AAA, Ipsen; travel expenses: Ipsen. MEi reports stocks/other ownership interests: Novartis, Telix Pharmaceuticals; consultancy/advisory: Blue Earth Diagnostics, ABX Advanced biochemical compounds, Janssen Oncology, Telix Pharmaceuticals, Novartis; research funding: Siemens, ABX Advanced biochemical compounds, Blue Earth Diagnostics, Bayer; patent application: rhPSMA; travel expenses: Bayer Schering Pharma. CF reports consultancy/advisory: Novartis, EUSA-Pharma, Ipsen, Oncodesign, Sirtex Medical; research funding: Oncovision. VP reports honoraria: AAA, consultancy/advisory: Bayer; research funding: Ipsen. WPF reports honoraria: Parexel, AAA; consultancy/advisory: Janssen, Calyx, Bayer; research funding: SOFIE. PR is an employee of Porterhouse Group AG Paracelsus Kliniken. EH reports no disclosures. HD reports consultancy/advisory: Bayer, Ipsen, Eisai AG. RAB reports honoraria: Eisai AG; consultancy/advisory: Bayer. KP reports a Junior Clinician Scientist Stipend of the University Medicine Essen Clinician Scientist Academy (sponsor: Faculty of Medicine and Deutsche Forschungsgemeinschaft); research funding: Bayer. MK, PS and FV are employees of Bayer. OS reports consultancy/advisory: Bayer, Sanofi, AstraZeneca, Dendreon, Constellation Pharmaceuticals, AAA, Pfizer, Bristol-Myers Squibb, Bavarian Nordic, EMD Serono, Astellas Pharma, Progenics, Blue Earth Diagnostics, Myovant Sciences, Myriad Genetics, Novartis, Clarity Pharmaceuticals, Fusion Pharmaceuticals, Isotopen Technologien, Janssen, Noxopharm, Clovis Oncology, Noria Therapeutics, Point Biopharma, TeneoBio, Telix Pharmaceuticals, Theragnostics; travel expenses: Bayer, Johnson & Johnson, Sanofi, AstraZeneca, Progenics; expert testimony: Sanofi; stocks/other ownership interests: Lilly, GlaxoSmithKline, Abbvie, Cardinal Health, United Health Group, PSMA Therapeutics, Clarity Pharmaceuticals, Noria Therapeutics, Clovis Oncology; research funding: Bayer, Sanofi, Endocyte, Merck, InVitae, Constellation Pharmaceuticals, AAA, AstraZeneca, Dendreon, SOTIO, Janssen, Progenics. No other potential conflicts of interest relevant to this article exist.
KEY POINTS

Objective: To investigate if it is safe to use $^{177}$Lu-PSMA to treat patients with mCRPC if they have previously received $^{223}$Ra.

Findings: Low rates of overall and hematological AEs indicate an acceptable safety profile for this treatment sequence. Median OS was 12.6 and 31.4 months from first dose of $^{177}$Lu-PSMA and $^{223}$Ra, respectively, and 39% of patients had a $\geq$30% decline in prostate-specific antigen.

Implications for routine clinical practice: Introduction of $^{223}$Ra early in the treatment sequence in patients with bone-predominant mCRPC and subsequent treatment with $^{177}$Lu-PSMA is feasible, well tolerated, and effective.
### TABLE 1. Baseline characteristics before starting $^{177}$Lu-PSMA

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Patients N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range) years</strong></td>
<td>72 (57–83)</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group performance status (baseline)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1</td>
<td>36 (73)</td>
</tr>
<tr>
<td>2</td>
<td>13 (27)</td>
</tr>
<tr>
<td>3–4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/mL), median (range)</td>
<td>287.0 (20–12,229)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L), median (range)</td>
<td>142.5 (48–730)</td>
</tr>
<tr>
<td>Visceral metastatic disease</td>
<td>15 (31)</td>
</tr>
<tr>
<td>≥4 life-prolonging therapies$^a$</td>
<td>30 (61)</td>
</tr>
<tr>
<td>Novel antiandrogen therapies</td>
<td></td>
</tr>
<tr>
<td>Abiraterone</td>
<td>39 (80)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>33 (67)</td>
</tr>
<tr>
<td>Abiraterone and enzalutamide</td>
<td>33 (67)</td>
</tr>
<tr>
<td>Number of any taxane-based chemotherapy lines$^b$</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (8)</td>
</tr>
<tr>
<td>1</td>
<td>35 (71)</td>
</tr>
<tr>
<td>≥2</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>45 (92)</td>
</tr>
<tr>
<td>Number of cycles$^c$</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>10 (20)</td>
</tr>
<tr>
<td>≥5</td>
<td>26 (53)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Number of cycles$^c$</td>
<td></td>
</tr>
<tr>
<td>1–4 cycles</td>
<td>0 (0)</td>
</tr>
<tr>
<td>≥5 cycles</td>
<td>5 (10)</td>
</tr>
<tr>
<td><strong>Taxane-based chemotherapy between $^{223}$Ra and $^{177}$Lu-PSMA$^d$</strong></td>
<td>25 (51)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise stated

$^a$Docetaxel, cabazitaxel, abiraterone, enzalutamide, $^{223}$Ra

$^b$Chemotherapies with same start date ±15 days are counted as one line

$^c$Not available for some pts

$^d$After last $^{223}$Ra dose and 60 days before $^{177}$Lu-PSMA
TABLE 2. Incidence of grade 3–4 laboratory abnormalities measured from $^{177}$Lu-PSMA start to 90 days after last dose

<table>
<thead>
<tr>
<th>Laboratory abnormalities</th>
<th>Patients (N)</th>
<th>Incidence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>49</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>47</td>
<td>6 (13)$^a$</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>49</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>49</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

$^a$4/6 had low platelets at baseline, with further reductions at follow-up (1 had chemotherapy prior to $^{177}$Lu-PSMA); 1/6 had normal platelets at baseline, with reductions seen after chemotherapy and at follow-up; 1/6 had normal platelets at baseline, with a reduction at follow up
Figure 1. RALU study design

*From $^{177}$Lu-PSMA start to 90 days after last dose
†From $^{177}$Lu-PSMA start to 30 days after last dose

AEs, adverse events; d, days; ALP, alkaline phosphatase; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; SAEs, serious adverse events
FIGURE 2. Use of life-prolonging therapies

*Chemotherapy was not used concomitantly with \(^{177}\text{Lu}-\text{PSMA}\)
FIGURE 3. Kaplan-Meier plots for overall survival calculated from the first $^{177}$Lu-PSMA (A) and $^{223}$Ra (B) dose

CI, confidence interval; Mo, months; n, number of evaluable patients
REFERENCES


Graphical Abstract

Safety and Effectiveness of Lutetium-177-Prostate-Specific Membrane Antigen (177Lu-PSMA) Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Previously Treated with Radium-223 (223Ra): The RALU Study

Primary objective: the safety of sequential 223Ra/177Lu-PSMA therapy

- 49 patients with bone predominant mCRPC
- Median 9.3 mo between treatments (Range, 0.9–41.9 mo)
- ≥4 life prolonging therapies: 61% of patients

Overall survival from first 223Ra injection
Median 31.4 mo

Overall survival from first 177Lu-PSMA injection
Median 12.6 mo

In patients with bone-predominant disease 223Ra before 177Lu-PSMA treatment was clinically feasible and well tolerated, with a similar survival outcome to those reported in previous studies.

177Lu-PSMA used after 223Ra has acceptable toxicity and low myelosuppression rates

Grade 3–4 TEAEs
41%

Grade 3–4 laboratory abnormalities
- Hemoglobin: 35%
- Platelet count: 13%
- Neutrophils: 2%
- AST: 4%