

Outcome and Safety of Radioligand Therapy With [^{161}Tb]Tb-PSMA-617 After Re-Progression in mCRPC Patients Previously Treated With [^{177}Lu]Lu-PSMA-617

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Introduction: To enhance the effectiveness of radioligand therapy (RLT), new prostate-specific membrane antigen (PSMA) targeting radiopharmaceuticals utilizing alternative radionuclides are under active investigation. One promising alternative to the established ^{177}Lu is the use of ^{161}Tb . A key advantage of ^{161}Tb is its emission of a higher proportion of low-energy conversion and Auger electrons, which may contribute to enhanced therapeutic effectiveness. This study provides a first exploratory evaluation of the efficacy and safety of [^{161}Tb]Tb-PSMA-617 in patients with progression after [^{177}Lu]Lu-PSMA-617, aiming to generate early clinical insights.

Methods: The study included 15 patients with mCRPC, who were enrolled in the “prospective registry to assess outcome and toxicity of targeted radionuclide therapy in patients with mCRPC in clinical routine” (REALITY Study; NCT04833517). All patients had received conventional PSMA RLT using [^{177}Lu]Lu-PSMA-617, which resulted in initial biochemical response (PSA decline $\geq 50\%$), followed by a biochemical relapse, prompting the re-initiation of PSMA RLT using [^{161}Tb]Tb-PSMA-617. Patients received a median of 3 (range: 2–7) cycles with mean administered activity of 5.4 ± 1.1 GBq and mean cumulative activity of 19.2 ± 6.4 GBq [^{161}Tb]Tb-PSMA-617. Treatment response was assessed both biochemically by serum PSA levels and through molecular imaging by total lesion PSMA (TLP) on [^{68}Ga]Ga-PSMA-11 PET/CT scans. Adverse events were assessed at baseline and follow-up using the “Common Terminology Criteria for Adverse Events” (Version 5.0).

Results: [^{161}Tb]Tb-PSMA-617 RLT showed response rates of 66.7% (10/15 patients) based on biochemical assessment and 86.7% (13/15 patients) based on molecular imaging assessment. Beginning with the initiation of [^{161}Tb]Tb-PSMA-617 RLT, the median progression-free survival (PFS) was 6.4 months, and the median

overall survival (OS) was 15.5 months. In total, 6 CTCAE grade deteriorations from grade 2 to grade 3 or from grade 3 to grade 4 were observed. No discontinuation of PSMA RLT due to adverse events was reported.

Conclusions: [^{161}Tb]Tb-PSMA-617 RLT emerges as a promising treatment option, demonstrating encouraging response rates, preliminary clinical outcomes, and a favorable safety profile as second-line RLT in progressing patients who previously benefited from [^{177}Lu]Lu-PSMA-617 RLT.

Key Words: terbium-161, ^{161}Tb , lutetium-177, ^{177}Lu , PSMA, prostate cancer, mCRPC, RLT, radioligand therapy

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Globally, prostate cancer (PC) ranks among the most common malignancies of men and is associated with a substantial mortality rate.¹ One of the major challenges in the clinical management of PC is its frequent progression into metastatic castration-resistant prostate cancer (mCRPC). This advanced disease state is characterized by a poor prognosis and resistance to both surgical and pharmacological castration by androgen deprivation therapy (ADT).^{2–4} Established treatment options for metastatic castration-resistant prostate cancer (mCRPC) include androgen receptor signaling inhibitors (ARSI), taxane-based chemotherapy, bone-targeted therapy with ^{223}Ra , the use of PARP inhibitors, and prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) with [^{177}Lu]Lu-PSMA-617.^{5–10} This PSMA RLT received approval from the FDA and EMA in 2022 and 2023, respectively. Multiple studies have demonstrated the safety and efficacy of PSMA-targeted RLT.^{11–17}

However, after response and subsequent completion of therapy, most patients eventually experience disease progression in the course post-RLT. In this setting, no standardized treatment regimen is currently established. A reasonable approach is to consider re-treatment with radioligand therapy. Pilot studies suggest that rechallenging with [^{177}Lu]Lu-PSMA-617 can be effective, although response rates and progression-free survival (PFS) tend to diminish in the further course.^{18–21}

To enhance the effectiveness of RLT, new PSMA radiopharmaceuticals utilizing alternative radionuclides are under active investigation. One promising alternative to the established ^{177}Lu is the use of ^{161}Tb . It exhibits physical decay characteristics similar to ^{177}Lu , including comparable beta particle emission energies (^{177}Lu : 133 keV vs. ^{161}Tb :

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All procedures performed in the patients were in accordance with the ethical standards of the institutional and national research ethics committees and with the 1964 Helsinki Declaration and its later amendments. No animal studies were performed in the context of this report. The study was approved by the institutional review board (ethics committee permission number 140/17). Written and informed consent was obtained from all study participants.

All patients have given written consent to anonymized publication of any resulting data.

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TABLE 1. Patient Characteristics

Patient Characteristics	Value
Age	
Median (range)	78.1 (67–88)
Age ≥ 65 y, n (%)	15 (100)
PSA, in [ng/mL]	
Median (range)	71 (0.4–312)
ALP, in [U/L]	
Median (range)	77 (52–306)
Hemoglobin, in [g/dL]	
Median (range)	11.2 (7.2–14)
< 13 g/dL, n (%)	14 (93.3)
ECOG performance status, n (%)	
0	2 (13.3)
1	11 (73.3)
≥ 2	2 (13.3)
Sites of metastases, n (%)	
Bone	13 (86.7)
Lymph node	12 (80.0)
Liver	2 (40.0)
Other	9 (60.0)
Prior therapies, n (%)	
Prostatectomy	7 (46.7)
Radiation	14 (93.3)
ADT	13 (86.7)
ARSI	14 (93.3)
Abiraterone	0
Enzalutamide	4 (26.7)
Abiraterone and enzalutamide	10 (66.7)
Chemotherapy	11 (73.3)
Docetaxel	8 (53.3)
Cabazitaxel	0
Docetaxel and cabazitaxel	3 (20)
^{[223]Ra} Ra-dichloride	1 (6.7)
PSMA RLT	15 (100)
^{[177]Lu} Lu-PSMA-617 RLT	15 (100)
Prior PSMA RLT cycles, median (range) ¹⁷⁷ Lu	4 (2–17)
Mean activity per cycle in [GBq] (SD ±)	6.94 (± 1.0)
Mean cumulative activity in [GBq] (SD ±)	35.3 (± 27.1)

ADT indicates androgen deprivation therapy; ALP, alkaline phosphatase; ARSI, androgen receptor signaling inhibitor; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PSMA RLT, prostate-specific membrane antigen radioligand therapy.

154 keV) and a closely matched half-life (¹⁷⁷Lu: 6.647 d vs. ¹⁶¹Tb: 6.906 days). A notable advantage of ¹⁶¹Tb lies in its emission of a higher proportion of low-energy conversion and Auger electrons, which may lead to enhanced therapeutic efficacy. These electrons have an ultra-short tissue range (< 500 nm), which results in a relatively high linear energy transfer (LET) of 4–26 keV/μm. This characteristic leads to higher local dose densities, which are associated with enhanced antitumor efficacy.²² To date, ¹⁶¹Tb has demonstrated promising results in both preclinical studies and preliminary clinical reports, and recently in a first prospective phase I/II study.^{23–27} In this study, we evaluate the outcome and safety profile of [¹⁶¹Tb]Tb-PSMA-617 in patients with post-[¹⁷⁷Lu]Lu-PSMA-617 progression.

METHODS

Patients and Ethics

The study included 15 patients with mCRPC, who were enrolled in the “prospective registry to assess outcome and toxicity of targeted radionuclide therapy in patients with

mCRPC in clinical routine” (REALITY Study; NCT04833517). All patients received conventional PSMA RLT using [¹⁷⁷Lu]Lu-PSMA-617 (median 4 cycles, range: 2–17), which resulted in initial biochemical response, as measured by prostate-specific antigen (PSA) levels and underwent a subsequent medication break after final administration. During the treatment break, which had a median duration of 9.7 months and ranged from 6.4 to 20.6 months after the final administration of [¹⁷⁷Lu]Lu-PSMA-617, all patients experienced a biochemical relapse with re-progression of disease. This recurrence prompted the re-initiation of PSMA RLT using [¹⁶¹Tb]Tb-PSMA-617. All patients had received extensive prior treatment besides earlier courses of PSMA RLT. The median interval between the first administration of [¹⁷⁷Lu]Lu-PSMA-617 and the first administration of [¹⁶¹Tb]Tb-PSMA-617 was 17.3 months, ranging from 8.0 to 84.4 months. Detailed patient characteristics are presented in Table 1. Administration of [¹⁶¹Tb]Tb-PSMA-617 was conducted on a compassionate use basis, as mandated by the German Pharmaceutical Act §13 (2b). All patients provided written informed consent after receiving comprehensive information regarding potential risks and adverse effects potentially associated with the intervention. In addition, all participants consented to the anonymized publication of study-related data, in compliance with the Declaration of Helsinki. The study protocol was approved by the local institutional review board (Ärztchamber des Saarlandes/Saarbrücken, ethics committee permission number 140/17).

Treatment Details of [¹⁶¹Tb]Tb-PSMA-617 RLT

Patients received a median of 3 (range: 2–7) cycles [¹⁶¹Tb]Tb-PSMA-617; in total 54 cycles were administered to 15 patients. The mean administered activity of ¹⁶¹Tb per cycle was 5.4 ± 1.1 GBq (range: 2.6–6.9 GBq) and the mean cumulative activity was 19.2 ± 6.4 GBq (range: 5.1–32.5 GBq). In accordance with the requirements of the German Pharmaceutical Act, PSMA RLT was administered during an inpatient stay at our institution. To mitigate potential salivary gland toxicity, all patients received external cooling of the salivary glands during administration of the radiopharmaceutical. In addition, intravenous hydration with 1000 mL 0.9% NaCl solution was initiated 30 minutes before injection and continued until 120 minutes post-injection. The individual treatment regimens for PSMA RLT are illustrated in Figure 1.

Treatment response was assessed both biochemically and through molecular imaging. Biochemical response evaluation was based on serial measurement of serum PSA levels. Progressive disease (PD) was defined as a ≥ 25% increase in PSA from baseline to follow-up.²⁸ A ≥ 50% reduction in baseline PSA levels (PSA50) was classified as partial remission (PR), whereas stable disease (SD) was defined as a change of < 50% decrease or < 25% increase. Patients achieving PR were classified as responders, whereas those exhibiting either SD or PD were considered non-responders to PSMA RLT. Molecular imaging response was assessed using [⁶⁸Ga]Ga-PSMA-11 PET/CT scans, which were performed at baseline and follow-up in all patients. On the basis of these scans, the molecular imaging biomarker total lesion PSMA (TLP), reflecting total tumor burden, was quantified.²⁹ TLP was determined using a semi-automated tumor segmentation algorithm, implemented in Syngo.Via software (Enterprise VB 40B, Siemens, Erlangen, Germany). Lesion delineation was performed using a standardized uptake value (SUV)

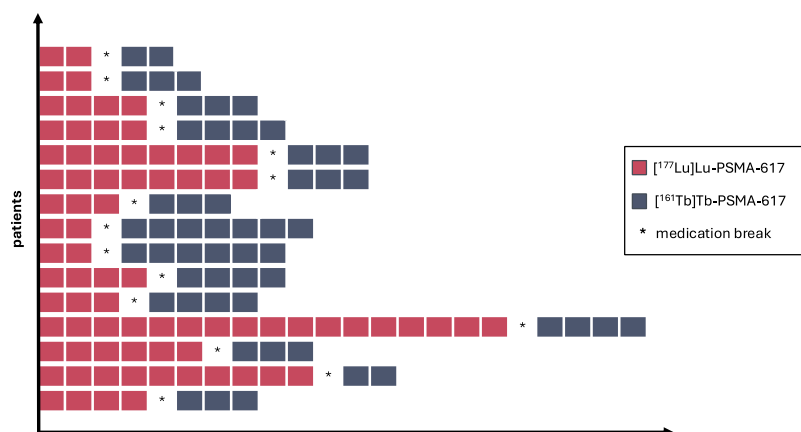


FIGURE 1. Regimen of PSMA RLT, shown for each individual patient.

threshold of ≥ 3 , in accordance with the protocol described by Ferdinandus.³⁰ Lesions with a volume < 0.2 mL were automatically excluded. Areas of physiological radiotracer uptake—including liver, spleen, bladder, and salivary glands—were manually excluded. Response classification was based on changes in TLP values between baseline and follow-up.

PD was defined as a $\geq 30\%$ increase in TLP, PR as a $\geq 30\%$ decrease, and SD as a change in TLP of $< 30\%$ in either direction.

Adverse Events

Adverse events were assessed at baseline and follow-up using the “Common Terminology Criteria for Adverse Events” (CTCAE v.5.0; last accessed 23.04.2025). The evaluation included hematologic toxicities—specifically anemia, leukopenia, and thrombocytopenia—based on peripheral blood cell counts. Renal function and potential nephrotoxicity were assessed using the creatinine-based estimated glomerular filtration rate (eGFR), calculated from serum creatinine levels. Non-hematologic adverse events, including xerostomia, fatigue, and nausea were evaluated using a patient-reported questionnaire.

Statistical Analysis

Descriptive statistical analyses were conducted using PRISM 10 (GraphPad Software, San Diego, USA). Survival outcomes were evaluated using the Kaplan-Meier method, defining progression-free survival (PFS) as the interval from the initiation of [¹⁶¹Tb]Tb-PSMA-617 RLT to the first occurrence of biochemical progression (as defined by PSA50), death, or the last study visit, whichever occurred first. Overall survival (OS) was defined as the time from the first administration of [¹⁶¹Tb]Tb-PSMA-617 to death from any cause or the last study visit.

RESULTS

Response assessment was based on the evaluation of changes in the biochemical biomarker PSA and the molecular imaging-derived total tumor biomarker TLP. Before the initial administration of [¹⁶¹Tb]Tb-PSMA-617, the mean baseline PSA level was 92.8 ± 89.6 ng/mL (range: 0.4–312 ng/mL). At follow-up, the mean (best) PSA value measured 32.9 ± 48.4 ng/mL (range: 0.2–172 ng/mL),

corresponding to an average PSA change (Δ PSA) of -59.2% after the initiation of [¹⁶¹Tb]Tb-PSMA-617 RLT. Similarly, the mean baseline TLP value recorded before the start of [¹⁶¹Tb]Tb-PSMA-617 RLT was 1922 ± 1818 (range: 58.3–5213), whereas the mean value at follow-up decreased to 1113 ± 1958 (range: 2.1–7703), reflecting a mean change of -51.8% . According to the biochemical PSA response, 1/15 (6.7%) patient exhibited progressive disease (PD), 4/15 (26.7%) patients showed stable disease (SD), and the majority, 10/15 (66.7%), demonstrated a partial response (PR). On the basis of the molecular imaging biomarker TLP, 1/15 (6.7%) patient was classified as PD, 1/15 (6.7%) as SD, and 13/15 (86.7%) as PR. Individual percentage changes in PSA (Δ PSA) and TLP (Δ TLP) for each patient are illustrated in Figure 2.

For the entire cohort, beginning with the initiation of [¹⁶¹Tb]Tb-PSMA-617 RLT, the median progression-free survival (PFS) was 6.4 months (range: 0.8–14.4 mo), and the median overall survival (OS) was 15.5 months (range: 3.2–26.9 mo). The corresponding survival curves are shown in Figure 3. Of note, at the time of cutoff, after a median follow-up time of 21.1 months, 8/15 patients were still alive and therefore censored in Kaplan-Meier analysis. Two exemplary patients experiencing biochemical and molecular imaging PR are presented in Figure 4.

The majority of documented adverse events were classified as mild or moderate in severity (CTCAE grade 1 or 2), whereas higher-grade events (CTCAE grade 3 or 4) were infrequently observed. A detailed overview of the CTCAE gradings is provided in Figure 5. In detail, 6 CTCAE grade deteriorations from grade 2 to grade 3 or from grade 3 to grade 4 were observed. Specifically, 2 cases of post-therapeutic anemia classified as CTCAE grade 3 and 4 (prior [¹⁶¹Tb]Tb-PSMA-617 RLT both grade 2), respectively, were documented. Furthermore, 4 cases of post-therapeutic renal impairment classified as CTCAE grade 3 were recorded, all presented CTCAE grade 2 pre-therapeutically. In addition, 3 cases of CTCAE grade 3 (1 anemia, 2 renal impairment) remained stable. No discontinuation of PSMA RLT due to adverse events was reported.

DISCUSSION

¹⁶¹Tb is an increasingly discussed radionuclide for use in RLT.^{31–33} By emitting a higher proportion of Auger and

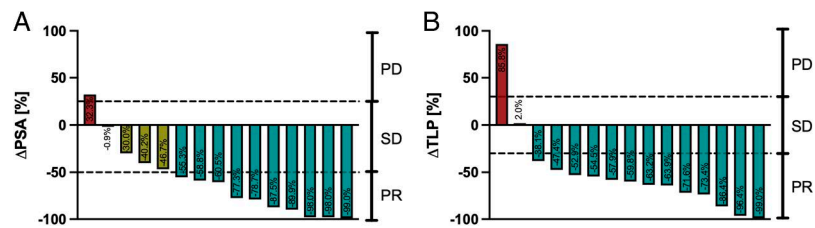


FIGURE 2. Individual (A) Δ PSA (%) and (B) Δ TLP (%) of each patient after initiation of [¹⁶¹Tb]Tb-PSMA-617 RLT.

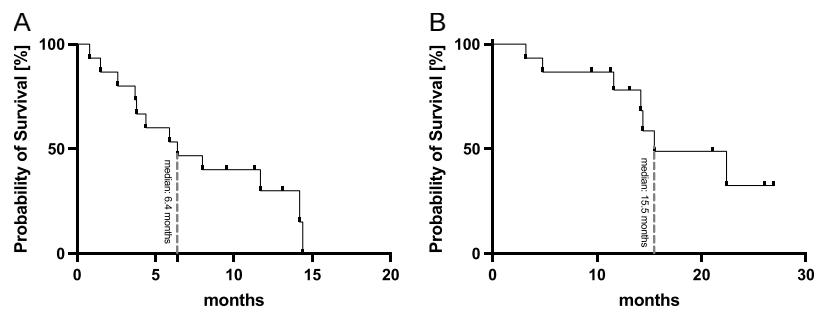


FIGURE 3. Kaplan-Meier curves for the entire cohort, presenting progression-free survival (A) and overall survival (B).

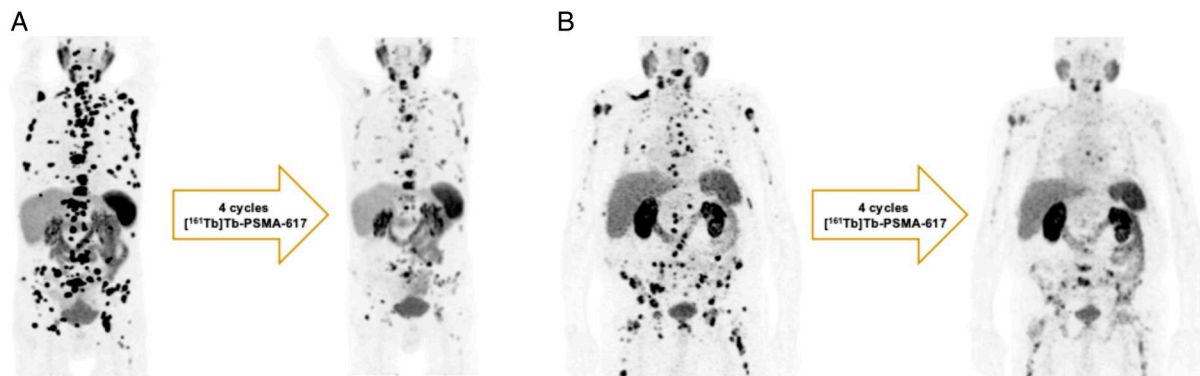


FIGURE 4. Maximum intensity projections of [⁶⁸Ga]Ga-PSMA-11 PET/CT images from 2 representative patients exhibiting partial remission (PR) after treatment with [¹⁶¹Tb]Tb-PSMA-617.

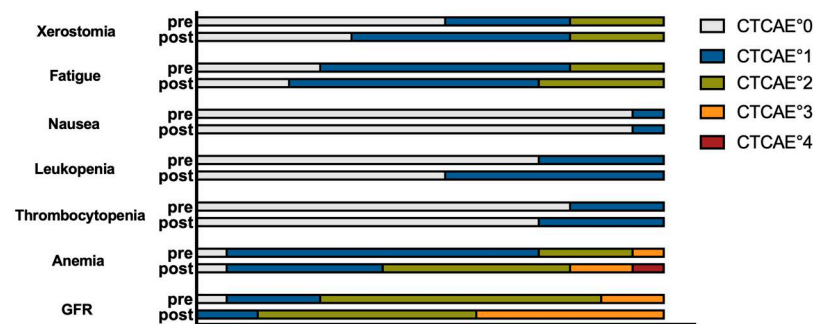


FIGURE 5. Record of adverse events, according to the CTCAE grading system (Version 5.0).

conversion electrons ^{161}Tb provides considerable advantages over the established radionuclide ^{177}Lu . This study is to the best of our knowledge the first dedicated investigation on ^{161}Tb Tb-PSMA-617 RLT as second-line RLT after post ^{177}Lu Lu-PSMA-617 progression occurred.

On the basis of our data, ^{161}Tb Tb-PSMA-617 RLT emerges as a promising treatment option, demonstrating encouraging response rates, clinical outcomes, and a favorable safety profile. Given the lack of standardized treatment recommendations in current guidelines after ^{177}Lu Lu-PSMA-617 RLT, therapy with ^{161}Tb Tb-PSMA-617 may offer an alternative in this context. In a recent pilot study conducted by our group involving a heterogeneous cohort with different clinical settings receiving ^{161}Tb Tb-PSMA-617 after conventional RLT, the best response (PSA50 response rate: 60%) was observed in the subgroup of patients who experienced post-RLT progression after responding to ^{177}Lu Lu-PSMA-617 RLT.²⁷ This observation provided the rationale for the present dedicated study focusing on a cohort of mCRPC patients showing post-RLT progression after the initially successful application of ^{177}Lu Lu-PSMA-617 RLT. Subsequently, as second-line RLT applied ^{161}Tb Tb-PSMA-617 confirmed promising response rates, 66.7% (10/15 patients) based on biochemical assessment (PSA50) and even 86.7% (13/15 patients) based on molecular imaging assessment by PSMA PET/CT. A repeated RLT with the same radiopharmaceutical of ^{177}Lu Lu-PSMA-617 (rechallenge RLT) might also provide a conservative treatment option in this setting with satisfying outcome. For ^{177}Lu Lu-PSMA-617 rechallenge a wide range of response rate was reported.^{18–21,34} Recently, Seifert et al³⁴ reported a response rate of 37.1% for ^{177}Lu Lu-PSMA-617 rechallenge in a multicenter study involving 63 patients. A recent study by our group observed a higher response rate of 57.4% in a cohort of 47 patients.²⁷ These 2 studies represent the largest to date on this topic; however, both reported lower response rates compared with those observed with ^{161}Tb Tb-PSMA-617 in the present study, which underlines the potential of ^{161}Tb Tb-PSMA-617 RLT. The encouraging antitumor effect of ^{161}Tb Tb-PSMA-617 is further supported by dosimetric simulations and calculations being superior to ^{177}Lu -based RLT.^{23,35,36} The observed outcomes, with a median PFS of 6.4 months and a median OS of 15.5 months, seem promising—particularly considering that, at the time of analysis, with a median follow-up of 21.1 months, more than half of the patients (53.3%) were still alive. However, due to the small sample size ($n = 15$) and the relatively high proportion of censored observations, the results should be interpreted as initial exploratory findings. This also helps to explain why our earlier study on ^{177}Lu Lu-PSMA-617 rechallenge reported a higher median OS of 22.7 months.¹⁸ Longer follow-up periods are necessary to allow for more robust survival comparisons. Although investigations of ^{177}Lu Lu-PSMA-617 rechallenge reported a median PFS of 8.7 months,¹⁸ our findings on ^{161}Tb Tb-PSMA-617 RLT demonstrated a median PFS of 6.4 months. This minor difference may be linked to the relatively small cohort of patients treated with ^{161}Tb Tb-PSMA-617. Larger, ideally prospective studies are recommended, and a multicenter approach seems well-suited to ensure robust external validity and broader applicability of the findings. Our pilot experience provides a rational basis for a direct comparison of ^{161}Tb Tb-PSMA-617 versus ^{177}Lu Lu-PSMA-617 as a second-line RLT in future prospective studies. Preliminary

data also suggest ^{161}Tb Tb-PSMA-617 as possible escalating treatment for mCRPC progressing under ongoing ^{177}Lu Lu-PSMA-617^{23,37} or as an alternative to RLT with an alpha emitter.^{38–40} Furthermore, ^{161}Tb Tb-PSMA as initial RLT regimen also merits evaluation. In this context, the recently published single-center, single-arm phase 1/2 study by Buteau et al²⁶ reported encouraging antitumor effect of ^{161}Tb Tb-PSMA-I&T in 30 mCRPC patients undergoing their initial RLT. The study demonstrated a median PSA-based progression-free survival of 9.0 months, a PSA50 response rate of 70%, and a PSA90 response rate of 40%. Buteau and colleagues observed few grade 3 adverse events, with no treatment-related deaths, dose reductions, or therapy discontinuations due to toxicity.

This is in line with our results regarding adverse events. The safety profile of ^{161}Tb Tb-PSMA-617 also seemed comparable to that of established ^{177}Lu Lu-PSMA-617 therapy, with only a limited number of grade 3/4 (CTCAE) cases of anemia and renal impairment observed, and no treatment discontinuations due to toxicity.^{13,16} It is important to note that post-RLT adverse events may, in part, reflect disease progression rather than being solely attributable to the treatment.

This study has several limitations. Primarily, the monocentric design and the small sample size limit the generalizability of the results. Larger studies, preferably with prospective designs, are warranted to substantiate these findings, as previously noted. A further limitation is the lack of an internal control group, which restricts comparison with other treatment strategies, for example, rechallenge approaches. Because of the lack of a control group, the outcomes reported in this study are descriptive in nature and should therefore be interpreted accordingly. In addition, it is important to note that the cohort exclusively included mCRPC patients who had previously responded to ^{177}Lu Lu-PSMA-617 therapy, potentially exerting a selection bias towards biologically favorable disease. Consequently, the results may not be applicable to patients with different clinical backgrounds, such as those who were RLT-naïve, non-responsive to initial RLT, or who received alternative RLT regimens. Therefore, the findings should not be generalized and instead only regarded as an initial step for future investigations.

CONCLUSIONS

^{161}Tb Tb-PSMA-617 RLT emerges as a promising treatment option, demonstrating encouraging response rates, preliminary clinical outcomes, and a favorable safety profile as second-line RLT in progressing patients who previously benefited from ^{177}Lu Lu-PSMA-617 RLT. Future studies, ideally in a prospective, multicenter setting are warranted.

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