Clinical Outcomes of ^{177}Lu-PSMA Radioligand Therapy in Earlier and Later Phases of Metastatic Castration-Resistant Prostate Cancer Grouped by Previous Taxane Chemotherapy

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^{177}Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy using PSMA-617 and PSMA-I&T ligands (^{177}Lu-PRLT) is an emerging treatment in metastatic castration-resistant prostate cancer (mCRPC). This retrospective study evaluates clinical outcomes of ^{177}Lu-PRLT in earlier and later phases of mCRPC grouped by previous taxane chemotherapy. **Methods:** A retrospective analysis was performed on 167 patients with mCRPC who underwent ^{177}Lu-PRLT between March 2013 and December 2016. Patients were classified as either taxane chemotherapy pretreated (T-pretreated) or naïve (T-naïve) depending on whether they had received taxane-based chemotherapy prior to ^{177}Lu-PRLT. Clinical outcome for T-pretreated and T-naïve patients was assessed by overall survival (OS), radiographic progression-free survival, and prostate-specific antigen (PSA) response rate. Univariate and multivariable analyses were performed for both T-pretreated and T-naïve patients to determine predictors of outcome. Toxicity was categorized by the Common Terminology Criteria for Adverse Events (version 4.03). **Results:** Of the 167 patients treated with ^{177}Lu-PRLT, 83 were T-pretreated and 84 were T-naïve. At baseline, T-pretreated patients had overall poorer performance status, a higher prevalence of bone metastases, higher PSA levels, lower hemoglobin levels, higher alkaline phosphatase (ALP) levels and had received more additional therapies compared with T-naïve patients. Median OS was 10.7 mo for T-pretreated patients and 27.1 mo for T-naïve patients. Median radiographic progression-free survival was 6.0 mo for T-pretreated patients and 8.8 mo for T-naïve patients. PSA response assessment was evaluable in 132 patients and seen in 25 of 62 (40%) T-pretreated patients and 40 of 70 (57%) T-naïve patients. Significant determinates of inferior OS in multivariable analysis for T-pretreated patients were poorer performance status, lower cumulative administered activity, and lower baseline hemoglobin. Higher baseline alkaline phosphatase was the only significant determinate of inferior OS in multivariable analysis for T-naïve patients. Overall ^{177}Lu-PRLT was safe, with minimal adverse effects evident during follow-up in both T-pretreated and T-naïve patients. **Conclusion:** ^{177}Lu-PRLT is a promising therapy in mCRPC, with encouraging outcomes and minimal associated toxicity seen in both our T-naïve and heavily pretreated patient cohorts.

Key Words: ^{177}Lu-PRLT; lutetium; prostate-specific membrane antigen; radioligand therapy; chemotherapy

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Prostate cancer is the most common malignancy and the second leading cause of cancer related death in men (*1*). Although androgen deprivation therapy is effective in hormone-sensitive disease, 10%–20% of patients will eventually progress under castrate levels of testosterone (*2*). Once patients develop metastatic castration-resistant prostate cancer (mCRPC), the prognosis is poor, with a survival estimate of approximately 14 mo (*2*).

Systemic chemotherapeutic options for mCRPC include docetaxel and cabazitaxel as first- and second-line agents, respectively. Although studies have demonstrated a survival benefit of 2–3 mo with these taxane-based chemotherapeutic agents compared with other therapies, not all patients can tolerate or are suitable for treatment given the associated toxicities (*3–6*). Other systemic treatment options include newer antiandrogen therapies (enzalutamide and abiraterone) and ^{223}Ra, although the results of randomized placebo controlled trials suggest these offer only a modest survival benefit (*7–11*).

By high-affinity binding to prostate-specific membrane antigen (PSMA), ^{177}Lu-labeled PSMA radioligand therapy using either PSMA-617 or PSMA-I&T ligands (^{177}Lu-PRLT) is an emerging treatment modality in mCRPC, exerting its therapeutic effect by delivering targeted ^{177}Lu β-particle radiation directly to metastatic prostate cancer cells (*12–22*). Several recent key studies have demonstrated that ^{177}Lu-PRLT has promising efficacy with minimal side effects even in patient populations heavily pretreated with multiple lines of systemic therapy (*12–18,20*). To date, however, detailed reports evaluating ^{177}Lu-PRLT outcomes in patients in earlier phases of the disease process without previous taxane-based chemotherapy are lacking and independent predictors of outcome in these patients have not yet been elucidated.

Therefore, the aim of this study is to evaluate clinical outcomes and predictors of outcome in patients referred to our institution for ^{177}Lu-PRLT in earlier and later phases of mCRPC grouped by previous taxane chemotherapy.

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TABLE 1
Baseline Characteristics at Time of First ^{177}Lu-PRLT and Gleason Score/Disease Stage at Initial Diagnosis

Characteristic	T-pretreated (n = 83)	T-naïve (n = 84)	P
Age (y)	69.3 ± 8.7	70.8 ± 7.8	0.249
Karnofsky performance status			0.003
<70	16 (19%)	6 (7%)	
70	13 (16%)	7 (8%)	
80	24 (29%)	24 (29%)	
90	28 (34%)	33 (39%)	
100	2 (2%)	14 (17%)	
Metastatic disease extent			
Bone metastases	75 (90%)	66 (79%)	0.036
Nodal metastases	68 (82%)	68 (81%)	0.871
Visceral metastases (liver or lung)	20 (24%)	16 (19%)	0.428
Additional prior therapy			
Abiraterone or enzalutamide	63 (76%)	32 (38%)	<0.001
Nontaxane chemotherapy	9 (11%)	0 (0%)	NA
^{223}Ra	12 (14%)	2 (2%)	0.005
External beam radiotherapy to bone	30 (36%)	25 (30%)	0.380
Time between initial diagnosis and first ^{177}Lu-PRLT (mo)	68.8 (34.3–125.7)	72.3 (32.5–132.8)	0.813
PSA (ng/mL)	196.3 (34.1–766.1)	33.6 (4.9–106.4)	<0.001
Hematologic results			
Hemoglobin (mmol/L)	6.9 (5.9–7.9)	8.0 (7.2–8.5)	<0.001
Red blood cell count (10^6/μL)	4.0 (3.5–4.3)	4.2 (3.9–4.5)	0.002
White blood cell count (10^3/μL)	6.6 (5.0–8.1)	6.2 (5.0–7.2)	0.129
Platelet count (10^3/μL)	207 (181–265)	216 (173–259)	0.794
Renal function tests*			
Creatinine (μmol/L)	77.5 (67.8–92.0)	77.7 (68.2–92.6)	0.753
Urea (mmol/L)	7.0 (5.4–8.5)	6.3 (5.3–7.4)	0.048
eGFR (mL/min)	86.1 (70.5–100.6)	86.2 (70.0–97.8)	0.848
Liver function tests*			
Bilirubin (μmol/L)	5 (4–7)	6 (5–8)	0.016
AST (U/L)	26 (20–50)	23 (19–31)	0.044
ALT (U/L)	16 (12–24)	17 (12–24)	0.600
GGT (U/L)†	32 (22–80)	22 (17–48)	0.004
ALP (U/L)	128 (69–282)	84 (60–150)	0.007
Gleason score at initial diagnosis			0.062
≤7	19 (23%)	33 (39%)	
≥8	46 (55%)	41 (49%)	
Unknown	18 (22%)	10 (12%)	
Disease stage at initial diagnosis			
T stage			0.165
T1/2	11 (13%)	18 (21%)	
T3/4	49 (59%)	44 (52%)	
TX	23 (28%)	22 (26%)	
N stage			0.540
N0	30 (36%)	32 (38%)	
N1	25 (30%)	21 (25%)	
NX	28 (34%)	31 (37%)	
M stage			0.698
M0	35 (42%)	30 (36%)	
M1	18 (22%)	13 (15%)	
MX	30 (36%)	41 (49%)	

*Data available for 83 patients in the T-naïve group.

†Data available for 82 patients in the T-pretreated group.

NA = not applicable; eGFR = estimated glomerular filtration rate; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-glutamyl transferase.

MATERIALS AND METHODS

Patient Population

A total of 167 patients who underwent ^{177}Lu-PRLT for mCRPC between March 2013 and December 2016 at the Theranostics Center for Molecular Radiotherapy and Precision Oncology, Zentralklinik Bad Berka, were included in this retrospective analysis. All patients received ^{177}Lu-PRLT under the "compassionate use" clause of the German Medicinal Products Act (*23*), the regulations of the state authority—Government of Thuringia, and in accordance with the 1964 Declaration of Helsinki and its later amendments. All procedures related to ionizing radiation were in compliance with the regulations of the German Federal Office for Radiation Protection (*24*). The institutional review board approved this study, and all subjects signed a written informed consent form for therapy including the use of their anonymized data for research and publication purposes. The decision to undertake ^{177}Lu-PRLT was made by the urooncologists/oncologic tumor board of the referring institution. Patient selection for ^{177}Lu-PRLT was based on PSMA-avid metastatic disease confirmed on pretherapy ^{68}Ga-PSMA PET/CT imaging. In this study, patients were classified as either taxane chemotherapy pretreated (T-pretreated) or naïve (T-naïve) depending on whether they had received taxane-based chemotherapy (first- or second-line) prior to ^{177}Lu-PRLT. Administration of taxane-based chemotherapy or other systemic therapies before ^{177}Lu-PRLT was at the discretion of treating specialists, with therapy individualized depending on patient eligibility and compliance. T-naïve patients who had been previously treated with non–taxane-based cytotoxic chemotherapy before ^{177}Lu-PRLT were excluded from this analysis.

^{177}Lu-PRLT Administration

Radiolabeling of ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T as well as our administration procedure for ^{177}Lu-PRLT have been previously described (*12,17,19,25*). The number of ^{177}Lu-PRLT cycles was individualized, with repeated cycles occurring no earlier than 6 wk apart.

Data Collection

Extensive data regarding all aspects of medical history, laboratory investigations, diagnostic and therapeutic procedures, adverse effects and post–^{177}Lu-PRLT follow-up of all patients were entered into a dedicated Microsoft Access database. Relevant parameters were reviewed to determine clinical outcome, treatment response, and possible toxicity from therapy.

Treatment Effect

Treatment effect was assessed by overall survival (OS), radiographic progression-free survival (rPFS), and prostate-specific antigen (PSA) response. OS was defined as the time from the first ^{177}Lu-PRLT to the time of death from any cause. Restaging with ^{68}Ga-PSMA PET/CT was performed after every 2 cycles of ^{177}Lu-PRLT during the course of treatment in compliance with current recommendations or at an interval of 4–6 mo in the cases of stable disease or remission during the follow-up period (*26*). rPFS was defined as the time from the first ^{177}Lu-PRLT to the time of progression on molecular imaging using ^{68}Ga-PSMA PET/CT or until the time of death if progression had not been observed. Assessment of radiographic progression on ^{68}Ga-PSMA PET/CT was based on the European Organization for Research and Treatment of Cancer criteria (*27*). PSA levels were performed at baseline, immediately before each ^{177}Lu-PRLT cycle, and then at monthly intervals in the follow-up period. PSA response was defined as a maximum PSA reduction of more than 50% from baseline at any point after commencement of ^{177}Lu-PRLT.

Toxicity

Routine hematologic, renal function and liver function blood tests were performed at baseline, immediately before each ^{177}Lu-PRLT cycle, and then monthly thereafter. Treatment toxicity was categorized using the Common Terminology Criteria for Adverse Events (version 4.03), and hemoglobin, white blood cell count, platelet count, creatinine, estimated glomerular filtration rate (eGFR), and liver function including alkaline phosphatase (ALP) levels were assessed.

Statistics

Comparison of patient characteristics between T-pretreated and T-naïve patients was performed using the unpaired Student's t test, Mann–Whitney U test, χ^2 test, and Fisher's exact test. Results have been reported as frequency (%), mean ± SD, and median with 25th–75th percentiles. A 2-sided P value of less than 0.05 was considered statistically significant. Median OS and rPFS are presented as Kaplan–Meier curves. To evaluate predictors of OS and rPFS, 9 variables were subjected to univariate analysis using the Cox proportional hazards regression model with results reported as hazard ratios with 95% confidence intervals (CIs). Predictive baseline variables evaluated at the time of first ^{177}Lu-PRLT were age, performance status, time between initial diagnosis, PSA levels, presence of bone metastases, presence of visceral metastases (liver or lung), hemoglobin and ALP level. Cumulative ^{177}Lu-PRLT administered activity was also evaluated as a predictive variable. Variables with a P value of less than 0.20 in the univariate analysis were included in the multivariable analysis. Statistical analysis was performed using SPSS software (version 22; IBM).

RESULTS

Patient Population

A total of 167 patients were included: 83 were T-pretreated and 84 were T-naïve. Patient details and baseline characteristics are outlined in Table 1. At the time of first ^{177}Lu-PRLT treatment, T-pretreated patients had overall poorer performance status, higher PSA levels, higher prevalence of bone metastases, higher ALP levels, lower hemoglobin levels and had a higher prevalence of prior abiraterone/enzalutamide as well as ^{223}Ra treatment compared with T-naïve patients.

Treatment Details

The entire patient cohort received a median of 3 ^{177}Lu-PRLT cycles (range, 1–10), with an average of 6.3 GBq/cycle (range, 3.6–8.6 GBq) and a median total administered activity of 16.2 GBq (range, 3.9–56.5 GBq). ^{177}Lu-PRLT treatment details for T-pretreated and T-naïve patient groups are outlined in Table 2.

Clinical Outcomes and Treatment Response

The median follow-up duration for OS and rPFS in the entire cohort was 10.3 mo. Kaplan–Meier curves evaluated for OS and rPFS for both T-pretreated and T-naïve patients are displayed in Figure 1. The median OS was 10.7 mo (95% CI: 7.9–13.5) for T-pretreated patients and 27.1 mo (95% CI: 18.4–35.8 mo) for T-naïve patients. The median rPFS was 6.0 mo (95% CI: 3.2–8.8 mo) for T-pretreated patients and 8.8 mo (95% CI: 7.1–10.6 mo) for T-naïve patients. PSA response assessment was evaluable in 132 patients, of whom 62 were T-pretreated and 70 were T-naïve. PSA response was seen in 25 (40%) T-pretreated patients and 40 (57%) T-naïve patients. Additional treatments received after progression included further ^{177}Lu-PRLT, systemic chemotherapy, external-beam radiotherapy, and abiraterone/enzalutamide in 38 (46%), 2 (2%), 4 (5%), and 3 (4%) T-pretreated patients and in 36 (43%), 3 (4%), 2 (2%), and 16 (19%) T-naïve patients, respectively.

Univariate and Multivariable Analysis

Univariate and multivariable analyses for T-pretreated and T-naïve patients are outlined in Tables 3 and 4, respectively. In multivariable

TABLE 2
^{177}Lu-PRLT Treatment Details

Treatment details	T-pretreated (n = 83)	T-naïve (n = 84)
Median number of cycles	3 (1–3)	3 (2–4)
Average administered activity per cycle (GBq)	6.3 (5.7–6.8)	6.3 (5.7–6.7)
Median total administered activity (GBq)	15.5 (7.5–20.0)	16.3 (10.9–24.8)

analysis, significant determinates of inferior OS in T-pretreated patients were poorer performance status, lower cumulative administered activity, and lower baseline hemoglobin whereas in T-naïve patients higher baseline ALP remained the only significant determinate of inferior OS. In multivariable analysis, significant determinates of inferior rPFS in T-pretreated patients were shorter time from initial diagnosis, lower baseline hemoglobin, and higher baseline ALP whereas in T-naïve patients the presence of visceral metastases and higher baseline ALP remained significant determinates of inferior rPFS. In multivariable analysis of the entire cohort, prior taxane-based chemotherapy was not an independent predictor of OS or rPFS (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Safety

Treatment toxicity grades for T-pretreated and T-naïve patients are outlined in Table 5. Overall, ^{177}Lu-PRLT was safe, with only a minimal number of grade 3 or 4 toxicities evident during follow-up.

DISCUSSION

^{177}Lu-PRLT is a promising new treatment option for mCRPC, with several recent studies reporting high clinical efficacy and minimal associated toxicity even in patients with advanced disease heavily pretreated with multiple lines of systemic therapy (*12–18,20*). Our results support the growing evidence of good clinical efficacy of ^{177}Lu-PRLT in this patient group, with a median OS of 10.7 mo achieved in T-pretreated patients with advanced disease, most of whom had also received multiple additional treatments including enzalutamide or abiraterone. In addition, we demonstrated promising outcomes in T-naïve patients with less advanced disease achieving a median OS of 27.1 mo in our cohort. Although the T-naïve cohort only demonstrated a trend toward lower Gleason scores, it is possible that these patients also had less aggressive tumors from initial diagnosis given that T-pretreated patients had exhausted multiple additional lines of therapy in a similar time period before starting ^{177}Lu-PRLT. The overall results, however, suggest that ^{177}Lu-PRLT is a valid treatment option not only in heavily pretreated patients with mCRPC, but also in T-naïve patients with less advanced disease if deemed unsuitable for or who decline chemotherapy.

While newer hormonal agents are more recently being introduced as first-line therapies, docetaxel as first-line chemotherapy has been the mainstay of treatment in patients with mCRPC ever since demonstration of a survival benefit in 2 landmark randomized controlled trials published in 2004 (*5,6*). In the TAX 327 and SWOG 9916 trials, median OS results of 18.9 and 17.5 mo were seen in patients receiving docetaxel treatment regimens, resulting in a survival benefit of 2–3 months compared with other treatments (*5,6*). More recent studies have reported higher median OS when investigating newer taxane-based treatment regimes in chemotherapy-naïve mCRPC patients. Published in 2017, the FIRSTANA trial compared 2 different cabazitaxel regimes to docetaxel as first-line therapy in chemotherapy-naïve mCRPC, demonstrating a similar median OS of 24–25 mo in the 3 groups (*28*). Our retrospective series demonstrates a promising median OS of 27.1 mo in T-naïve patients treated with ^{177}Lu-PRLT. In addition, 38% of patients in our T-naïve cohort had been pretreated with abiraterone or enzalutamide compared with 2% in the FIRSTANA study. While definitive conclusions cannot be made between

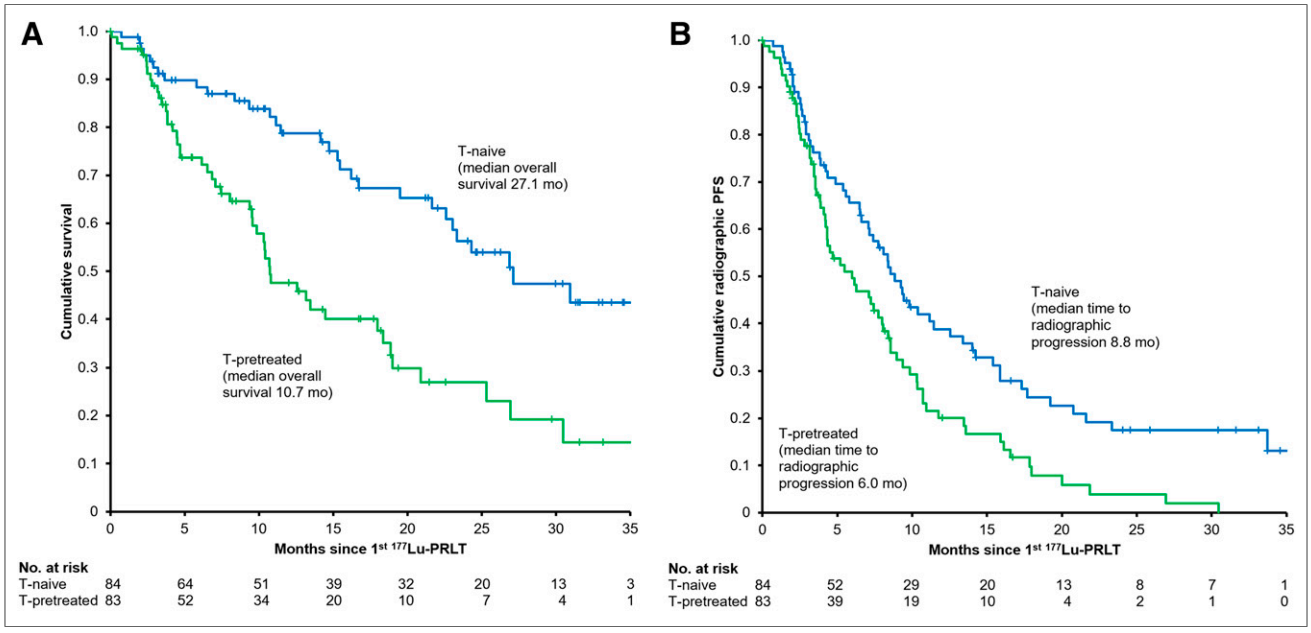

FIGURE 1. Kaplan–Meier curves for OS (A) and rPFS (B) for both T-pretreated and T-naïve patients.

TABLE 3
Univariate Analysis and Multivariable Analysis of OS and rPFS in T-Pretreated Patients

	Univariate analysis				Multivariable analysis			
	OS		rPFS		OS		rPFS	
Subgroup	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Age: >70 y	0.97 (0.55–1.72)	0.926	1.00 (0.62–1.61)	0.985	NA	NA	NA	NA
Karnofsky performance status: ≤80	2.94 (1.43–6.07)	0.003	1.56 (0.94–2.60)	0.088	2.71 (1.22–6.03)	0.015	1.41 (0.81–2.46)	0.221
Baseline PSA: >60 ng/mL	2.59 (1.28–5.26)	0.008	1.43 (0.86–2.39)	0.173	0.96 (0.44–2.10)	0.924	0.61 (0.32–1.15)	0.125
Time from diagnosis to first ^{177}Lu-PRLT treatment: >5 y	0.70 (0.40–1.23)	0.217	0.54 (0.33–0.88)	0.013	NA	NA	0.49 (0.30–0.82)	0.006
Cumulative administered activity: >16 GBq	0.32 (0.18–0.58)	<0.001	0.81 (0.50–1.30)	0.375	0.37 (0.20–0.69)	0.002	NA	NA
Bone metastases: yes	11.77 (1.61–86.20)	0.015	2.29 (0.98–5.34)	0.057	3.03 (0.38–24.15)	0.295	1.13 (0.44–2.88)	0.801
Visceral metastases: yes	2.71 (1.50–4.89)	0.001	1.55 (0.91–2.64)	0.110	1.72 (0.92–3.24)	0.090	0.97 (0.53–1.76)	0.908
Baseline hemoglobin: ≤7.5 mmol/L	4.61 (2.04–10.39)	<0.001	2.56 (1.45–4.50)	0.001	2.76 (1.11–6.89)	0.029	2.59 (1.26–5.33)	0.010
Baseline ALP: ≥220 U/L	1.84 (1.02–3.33)	0.043	2.21 (1.33–3.65)	0.002	1.20 (0.64–2.27)	0.570	2.00 (1.14–3.50)	0.015

HR = hazard ratio; NA = not applicable.
Data in parentheses are 95% CIs.

the efficacy of ^{177}Lu-PRLT compared with taxane-based chemotherapy by comparing our retrospective results to outcomes in different patient cohorts, our findings are encouraging and prospective clinical trials comparing the efficacy of ^{177}Lu-PRLT with initial taxane chemotherapy regimes in mCRPC appear warranted. Notably, high baseline ALP levels were an independent predictor of inferior OS in our T-naïve cohort treated with ^{177}Lu-PRLT, suggesting the burden of bone metastatic disease may be a particularly important factor in treatment decision making in earlier phases of the disease process.

Second-line therapeutic options following progression of mCRPC after docetaxel chemotherapy include cabazitaxel, newer hormonal agents and ^{223}Ra. OS with these agents as second-line therapies in selected patient cohorts ranges from 14 to 18 mo (*4,8,9,11*). When progression occurs following these second-line therapies, treatment options are limited. ^{177}Lu-PRLT offers an additional therapeutic option in this phase of the disease, with our results demonstrating a median OS of 10.7 mo in T-pretreated patients, most of whom had also received abiraterone or enzalutamide. While these results are comparable to outcomes in the recently published COMET-1 trial

TABLE 4
Univariate Analysis and Multivariable Analysis of OS and rPFS in T-Naïve Patients

	Univariate analysis				Multivariable analysis*			
	OS		rPFS		OS		rPFS	
Subgroup	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Age: >70 y	1.23 (0.59–2.53)	0.584	0.68 (0.41–1.14)	0.142	NA	NA	0.71 (0.42–1.21)	0.212
Karnofsky performance status: ≤80	2.05 (0.99–4.26)	0.055	0.83 (0.49–1.39)	0.477	0.60 (0.22–1.66)	0.326	NA	NA
Baseline PSA: >60 ng/mL	2.40 (1.16–4.98)	0.019	1.88 (1.09–3.24)	0.024	1.41 (0.50–4.00)	0.521	1.01 (0.50–2.03)	0.977
Time from diagnosis to first ^{177}Lu-PRLT treatment: >5 y	0.42 (0.20–0.86)	0.018	0.59 (0.35–0.98)	0.040	0.72 (0.32–1.65)	0.439	0.71 (0.42–1.21)	0.205
Cumulative administered activity: >16 GBq	0.42 (0.21–0.86)	0.017	0.89 (0.53–1.49)	0.658	0.44 (0.18–1.10)	0.080	NA	NA
Bone metastases: yes	3.46 (1.05–11.42)	0.041	1.49 (0.77–2.86)	0.235	2.51 (0.70–8.97)	0.156	NA	NA
Visceral metastases: yes	1.56 (0.69–3.52)	0.285	2.08 (1.13–3.82)	0.018	NA	NA	2.30 (1.23–4.33)	0.009
Baseline hemoglobin: ≤7.5 mmol/L	2.96 (1.45–6.05)	0.003	1.76 (1.03–3.02)	0.039	1.22 (0.44–3.37)	0.706	1.28 (0.70–2.32)	0.428
Baseline ALP*: ≥220 U/L	12.93 (4.98–33.60)	<0.001	4.03 (2.03–7.98)	<0.001	11.7 (2.92–47.15)	0.001	3.87 (1.55–9.70)	0.004

*Data available for 83 patients.
HR = hazard ratio; NA = not applicable.
Data in parentheses are 95% CIs.

TABLE 5
Baseline Toxicity Grade Before ^{177}Lu-PRLT and Worst Toxicity Grade Achieved After ^{177}Lu-PRLT

Organ system	T-pretreated (n = 83)		T-naïve (n = 84)	
	Before ^{177}Lu-PRLT	After ^{177}Lu-PRLT	Before ^{177}Lu-PRLT	After ^{177}Lu-PRLT
Hematologic toxicity				
Anemia				
All grades	77 (93%)	80 (96%)	65 (77%)	82 (98%)
Grade 3 or 4	3 (4%)	7 (8%)	0 (0%)	1 (1%)
Leukocytopenia				
All grades	10 (12%)	25 (30%)	8 (10%)	22 (26%)
Grade 3 or 4	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Thrombocytopenia				
All grades	11 (13%)	30 (36%)	10 (12%)	22 (26%)
Grade 3 or 4	1 (1%)	3 (4%)	0 (0%)	1 (1%)
Renal toxicity*				
Creatinine				
All grades	16 (19%)	21 (25%)	9 (11%)	20 (24%)
Grade 3 or 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
eGFR				
All grades	17 (20%)	22 (27%)	9 (11%)	20 (24%)
Grade 3 or 4	2 (2%)	2 (2%)	1 (1%)	2 (2%)
Hepatic toxicity*				
Bilirubin				
All grades	1 (1%)	4 (5%)	2 (2%)	3 (4%)
Grade 3 or 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AST				
All grades	19 (23%)	33 (40%)	8 (10%)	15 (18%)
Grade 3 or 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ALT				
All grades	2 (2%)	10 (12%)	2 (2%)	4 (5%)
Grade 3 or 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
GGT†				
All grades	24 (29%)	31 (38%)	13 (16%)	20 (24%)
Grade 3 or 4	4 (5%)	10 (12%)	0 (0%)	3 (4%)
ALP				
All grades	41 (49%)	50 (60%)	22 (27%)	30 (36%)
Grade 3 or 4	5 (6%)	9 (11%)	4 (5%)	8 (10%)

*Baseline data available for 83 patients in the T-naïve group.
†Data available for 82 patients in the T-pretreated group.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ-glutamyl transferase.

where a median OS of 11.0 mo was reported in taxane- and abiraterone-pretreated patients treated with the kinase inhibitor cabozantinib, the vast majority (88%) of patients in COMET-1 had Eastern Cooperative Oncology Group performance status of 0 or 1 and there appeared to be fewer patients with Gleason scores of 8 or greater, suggesting that our T-pretreated cohort possibly had more advanced and aggressive disease (*29*). Therefore, our results lend support to recent evidence suggesting that ^{177}Lu-PRLT remains a promising therapeutic option in these treatment-refractory patients with advanced disease (*30*), particularly given that best supportive care is the typically recommended management in this late phase of the disease (*3*). In our study, independent predictors of inferior OS with ^{177}Lu-PRLT in this patient group were lower cumulative administered activity, lower baseline hemoglobin levels and poorer performance status highlighting the need to consider radiation dosimetry, laboratory results and overall patient condition in a personalized nuclear medicine treatment model in patients with advanced cancer. It is important to recognize that other predictors such as PSA doubling time, change in bone scan index, and lactate dehydrogenase may also be useful, although these were

not all routinely available in our study population and were therefore unable to be assessed as independent predictors.

rPFS was superior in T-naïve patients compared with T-pretreated patients (8.8 vs. 6.0 mo), likely reflecting the more aggressive and advanced nature of the disease in the T-pretreated cohort. In T-naïve patients, the presence of visceral metastatic disease and higher baseline ALP levels were significant independent predictors of inferior rPFS in keeping with our clinical experience of patients with liver or lung metastatic disease or extensive bone metastatic disease being at higher risk for early disease progression. Although the rPFS results in this study are shorter than those previously reported by our institution, this is explainable by the use of molecular imaging criteria in the current study being more sensitive in detecting disease progression than the RECIST 1.1 used in our prior analysis (*17*). Our use of molecular imaging response criteria also makes comparison of rPFS results with other studies difficult given most have used RECIST-based criteria. Our PSA response rates appear comparable to the results of taxane-based chemotherapy trials (*4–6,28*). This also lends support to the high clinical efficacy of ^{177}Lu-PRLT, although relying on PSA as a primary measure of disease burden and treatment response may be imperfect given that dedifferentiated disease can be associated with minimal PSA elevation despite maintaining high PSMA expression (*17*).

Our results demonstrate minimal toxicity of ^{177}Lu-PRLT with grade 3 or 4 anemia, leukocytopenia, and thrombocytopenia seen in only 3%, 1%, and 2% of additional patients in the entire cohort, respectively. Notably, these minimal hematologic toxicities are overall lower than those seen with first- and second-line taxane-based chemotherapeutic agents (*4–6,28*). In particular, the rate of grade 3 or 4 leukocytopenia appears dramatically less with ^{177}Lu-PRLT potentially translating to a lower risk of treatment-related complications such as neutropenic septicemia with possible lethal outcomes (*4–6,28*). Furthermore, only 1 additional patient in the entire cohort achieved grade 3 renal toxicity as measured by eGFR. This patient had normal renal function before ^{177}Lu-PRLT, but suffered coexistent hypercalcemic nephropathy in the setting of extensive osteoblastic metastases, which was established as the cause for deterioration in renal function. The minimal hematologic and renal toxicity associated with ^{177}Lu-PRLT in this study is in keeping with prior results from our institution as well as other centers, providing further evidence for the safety of ^{177}Lu-PRLT even in patients with advanced disease (*13,17,18*).

Limitations of our study include its retrospective design and the heterogeneous nature of both patient cohorts including the prior treatments received. However, this analysis provides detailed outcomes of patients referred to our center in a real-world clinical setting and, therefore, we believe the findings are highly relevant to current clinical practice. The univariate/multivariable analysis is also likely to be limited by the small sample size in each cohort, which resulted in higher uncertainty in estimated HR for T-pretreated patients with bone metastases and T-naïve patients with high baseline ALP. In addition, there is possible bias introduced when using cumulative administered activity as a predictor of OS since patients who respond well to initial therapy are more likely to live longer and receive further ^{177}Lu-PRLT cycles. In our study, rPFS was based on European Organization for Research and Treatment of Cancer molecular imaging criteria, although these have not been validated for use with ^{68}Ga-PSMA PET/CT. Nevertheless, given that RECIST- and bone scan–based criteria have major limitations in assessing disease response in patients with extensive bone metastases, our results remain meaningful despite the absence of established clinical guidelines in this regard (*31*). Furthermore, PET-based molecular imaging forms the cornerstone of assessing suitability for radionuclide treatment and may be a preferred method of response assessment according to the principles of theranostics. Our PSA response assessment criteria of greater than 50% was based on prior guidelines (*32*) to allow comparison with earlier studies, although we note that recent evidence suggests using a lower PSA percentage decline may be a more optimal measure of ^{177}Lu-PRLT response (*30*).

CONCLUSION

^{177}Lu-PRLT is a promising therapy in mCRPC with encouraging outcomes and minimal associated toxicity seen in both our T-naïve and heavily pretreated patient cohorts. Prospective clinical trials investigating ^{177}Lu-PRLT in direct comparison to currently recommended treatments in mCRPC are warranted to establish its rightful place in the treatment algorithm of the respective clinical management guidelines.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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