# A Single-Arm, Low-Dose, Prospective Study of $^{177}$Lu-EB-PSMA Radioligand Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer

Guochang Wang*[1], Jie Zang*[2], Yuanyuan Jiang*[1], Qingxing Liu[1], Huimin Sui[1], Rongxi Wang[1], Xinrong Fan†[3], Jingjing Zhang†[4–6], Zhaohui Zhu†[1], and Xiaoyuan Chen†[4–7]

*[1]Department of Nuclear Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Beijing Key Laboratory of Molecular Targeted Diagnosis and Therapy in Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; [2]Department of Nuclear Medicine, First Affiliated Hospital, Fujian Medical University, Fuzhou, China; [3]Department of Urology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; [4]Departments of Diagnostic Radiology, Surgery, Chemical Engineering, Biomolecular Engineering, and Biomedical Engineering, Yong Loo Lin School of Medicine and College of Design and Engineering, National University of Singapore, Singapore, Singapore; [5]Clinical Imaging Research Centre, Centre for Translational Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [6]Nanomedicine Translational Research Program, NUS Center for Nanomedicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; and [7]Institute of Molecular and Cell Biology, Agency for Science, Technology, and Research (A*STAR), Proteos, Singapore, Singapore*

We aimed to investigate the safety and therapeutic efficacy of radioligand therapy (RLT) of $^{177}$Lu-EB-prostate-specific membrane antigen (PSMA) in patients with metastatic castration-resistant prostate cancer. **Methods:** Thirty men with progressive metastatic castration-resistant prostate cancer previously treated with taxane-based chemotherapy and second-generation androgen deprivation therapy were enrolled. All patients received up to 3 cycles of approximately 2.0 GBq (55 mCi) of $^{177}$Lu-EB-PSMA per cycle at 8-wk intervals. The primary endpoint was therapeutic safety, including changes in hematologic status, liver function, and renal function. An additional primary endpoint was therapeutic efficacy, including prostate-specific antigen (PSA) response and molecular imaging response. The secondary endpoints were PSA progression-free survival (PFS) and overall survival (OS). Another endpoint was patient-reported health-related quality of life. **Results:** From January 2019 to December 2021, 30, 22, and 11 patients received 1, 2, or 3 cycles of $^{177}$Lu-EB-PSMA RLT, respectively. During the entire follow-up period, 33.3% of patients experienced grade 3 hematologic adverse events. Seventeen (56.7%) patients achieved a PSA reduction of at least 50%. The median PSA PFS was 4.6 mo (95% CI, 2.7–6.5 mo), and the median OS was 12.6 mo (95% CI, 8.1–17.1 mo). A higher whole-body PSMA $SUV_{mean}$ correlated with a better PSA response, higher baseline alkaline phosphatase and larger total PSMA-positive tumor volume were associated with worse PSA PFS, and the existence of visceral metastases and higher PSA value at baseline were significant prognosticators of worse OS. Health-related quality-of-life outcomes improved significantly after $^{177}$Lu-EB-PSMA RLT. **Conclusion:** RLT based on approximately 2.0 GBq of $^{177}$Lu-EB-PSMA for up to 3 cycles may achieve a PSA response and hematologic toxicity comparable to those from 7.4-GBq doses of $^{177}$Lu-PSMA-617 for up to 4–6 cycles. Further studies with more cycles of $^{177}$Lu-EB-PSMA RLT are needed to evaluate the potential benefits in terms of PFS and OS.

**Key Words:** $^{177}$Lu-EB-PSMA; radioligand therapy; metastatic castration-resistant prostate cancer (mCRPC); Evans blue; albumin binding

**J Nucl Med 2023; 64:611–617**
DOI: 10.2967/jnumed.122.264857

Treatment of metastatic castration-resistant prostate cancer (mCRPC) remains a huge challenge for urologists and oncologists. Radioligand therapy (RLT) targeting prostate-specific membrane antigen (PSMA) has attracted interest as a potential treatment modality for mCRPC. The phase 3 VISION trial demonstrated that RLT based on $^{177}$Lu-PSMA-617 plus standard care significantly extended imaging-based progression-free survival (PFS) and overall survival (OS) versus standard care alone in patients with advanced PSMA-positive mCRPC (*1*). Additionally, some phase 2 trials revealed that $^{177}$Lu-PSMA-617 therapy achieved a better serum prostate-specific antigen (PSA) response and fewer grade 3–4 adverse events in the treatment of mCRPC than cabazitaxel (*2*) and docetaxel (*3*). Given these remarkable results, PSMA-targeted radioligand therapy (PRLT) seems to be a promising treatment modality for mCRPC. On March 23, 2022, the U.S. Food and Drug Administration approved Pluvicto ($^{177}$Lu-PSMA-617; Novartis) to treat men with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy (*4*), representing a significant advance in the theranostics of prostate cancer.

Currently, PRLT is based mainly on small-molecule inhibitors, such as PSMA-617 and PSMA I&T (*5,6*). Previous studies have reported no significant difference in safety and efficacy between $^{177}$Lu-PSMA-617 and $^{177}$Lu-PSMA I&T (*7,8*). However, radiolabeled small molecules targeting PSMA are cleared quickly from the blood (*9*). Therefore, PRLT based on both PSMA-617 and PSMA I&T requires high doses, which may cause obvious systemic toxicity, require more radiation protection, and lead to a

Received Aug. 30, 2022; revision accepted Oct. 19, 2022.
For correspondence or reprints, contact Xinrong Fan (pumcfxr@126.com) or Xiaoyuan Chen (chen.shawn@nus.edu.sg).
*Contributed equally to this work.
†Contributed equally to this work.
Published online Nov. 3, 2022.

large financial burden. We conjugated a truncated Evans blue (EB) molecule and DOTA chelator onto PSMA-617 and labeled it with $^{177}$Lu to obtain a new radiopharmaceutical, $^{177}$Lu-EB-PSMA (*10*). EB can bind to albumin to slow its plasma clearance rate, thereby increasing tumor accumulation and reducing the total dose of $^{177}$Lu. Because of the limited supply of $^{177}$Lu, $^{177}$Lu-EB-PSMA may be an option to consider by which more patients may benefit. In a previous dosimetry study, Zang et al. demonstrated that the tumor-accumulated radioactivity of $^{177}$Lu-EB-PSMA was about 3.02-fold higher than that of $^{177}$Lu-PSMA-617, and a single low dose of $^{177}$Lu-EB-PSMA RLT revealed that the tumor uptake of $^{68}$Ga-PSMA-617 in patients was decreased more significantly than the same dose of $^{177}$Lu-PSMA-617 RLT. However, the red bone marrow and kidneys also showed higher uptake for $^{177}$Lu-EB-PSMA than for $^{177}$Lu-PSMA-617 (*9*). Subsequently, Zang et al. conducted an escalating dose study, which revealed that 2.12 ± 0.19 GBq (57.3 ± 5.1 mCi) per dose of $^{177}$Lu-EB-PSMA exhibited relatively high efficacy and acceptable side effects (*11*). All these studies suggested $^{177}$Lu-EB-PSMA to be a promising alternative radiopharmaceutical in PRLT against mCRPC.

This prospective trial was designed to further assess the safety and therapeutic efficacy of low-dose $^{177}$Lu-EB-PSMA, in doses of approximately 2.0 GBq (55 mCi) for up to 3 cycles, in patients with mCRPC.

## MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College (approval JS-2105) and was registered at ClinicalTrials.gov (NCT04996602).

### Patients

Participants who met the inclusion criteria (as stated in the supplemental materials, available at http://jnm.snmjournals.org) underwent $^{68}$Ga-PSMA-617 and $^{18}$F-FDG PET/CT within 2 wk before PRLT to confirm high PSMA expression, which was defined as most tumors' (≥80%) having a baseline $SUV_{max}$ significantly (≥1.5 times) greater than the $SUV_{mean}$ of the normal liver. Patients were excluded if they had an $^{18}$F-FDG–positive tumor without corresponding PSMA uptake (*3,12*).

### PET/CT Imaging

The $^{68}$Ga-PSMA-617 and $^{18}$F-FDG PET/CT acquisitions were performed as previously described (*13*).

The images were transferred to MIM software (version 7.1.4; MIM Software Inc.). The volume of interest for the tumor was segmented using PET Edge (MIM Software Inc.), a gradient-based segmentation algorithm with an SUV threshold of at least 3.0. For segmentation of liver metastases, a threshold of 1.5 times the $SUV_{mean}$ of the normal liver tissue was used (*14–16*). Total lesion PSMA (TLP) was calculated through the summed product of total PSMA-positive tumor volume (PSMA-VOL) times the $SUV_{mean}$ of all tumors. Whole-body PSMA $SUV_{mean}$ was calculated through dividing TLP by PSMA-VOL.

### Treatment Regimen and Follow-up

The median administered activity per cycle was 2.0 GBq (range, 1.9–2.2 GBq). The radiopharmaceutical was diluted into 100 mL of normal saline and slowly administered intravenously to the patient within 30–60 min. Before $^{177}$Lu-EB-PSMA administration, all patients accepted intravenous hydration with normal saline for 30 min, and the salivary glands were cooled with an ice pack for 30 min to minimize dry mouth syndrome. Each patient received up to 3 cycles of $^{177}$Lu-EB-PSMA RLT at 8-wk intervals.

Hematologic status was assessed every 2 wk after the injection of $^{177}$Lu-EB-PSMA; liver function, renal function, and serum PSA values were documented every 4 wk. Short-term follow-up ended at 10 wk after the last cycle of PRLT. Long-term follow-up with laboratory testing ended at the time of death from any cause, the start of another treatment modality, or the latest study visit. $^{68}$Ga-PSMA-617 PET/CT reexaminations were performed 1 wk before the administration of $^{177}$Lu-EB-PSMA and 8 wk after the last treatment cycle. In addition, patient-reported health-related quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire, which includes 30 items related to functioning and symptom scales, within 1 wk before each cycle of therapy and at the 8 wk after the final treatment session.

### Outcomes

The first primary endpoint was adverse events, which were categorized according to the Common Toxicity Criteria for Adverse Events, version 5.0 (*11*). The second primary endpoint was best PSA response based on the Prostate Cancer Clinical Trials Working group 3 guidelines, which defined a PSA decrease of at least 50% from baseline as partial response (PR), a PSA increase of at least 25% as progressive disease (PD), and a PSA increase of less than 25% or a decrease of less than 50% as stable disease. The third primary endpoint was molecular imaging response according to the adapted PET Response Criteria in Solid Tumors (PERCIST), version 1.0, and Response Evaluation Criteria in PSMA PET/CT (RECIP), version 1.0. In the former, a complete response was defined as complete disappearance of TLP from target tumors on $^{68}$Ga-PSMA-617 PET/CT compared with the baseline scan, a PR was defined as at least a 30% decrease in the TLP of target tumors without the appearance of new lesions, a PD was defined as at least a 30% increase in the TLP of target tumors or the appearance of new lesions, and stable disease was defined as a TLP increase of less than 30% or a TLP decrease of less than 30% and no appearance of new lesions (*15,17*). In RECIP, a complete response was defined as absence of any PSMA ligand uptake, PR was defined as at least a 30% decline in PSMA-VOL and no appearance of new lesions, PD was defined as at least a 20% increase in PSMA-VOL and the appearance of new lesions, and stable disease was defined as any condition but RECIP-PR or RECIP-PD (*18*).

The secondary endpoints were PSA PFS and OS. PSA PFS was defined as the interval from the date of patient enrollment to PSA progression, which was defined as an increase of at least 25% and at least 2 ng/mL after 12 wk (*2,12,19*). OS was defined as the interval from the date of patient enrollment to death from any cause or the last study visit (*1,15*). Another endpoint was health-related quality-of-life assessment (*2*).

## RESULTS

### Demographic and Clinical Characteristics

Thirty patients were enrolled. Data on PSA response rate and toxic side effects for the first 10 patients were previously published (*11*). The first cycle of PRLT was performed in January 2019, and the last $^{177}$Lu-EB-PSMA therapy session was in December 2021. The date of the last follow-up was August 20, 2022. In total, 22 and 11 patients received 2 and 3 cycles of $^{177}$Lu-EB-PSMA RLT, respectively. The reasons for not completing all 3 cycles as scheduled were non–tumor-related death for 1 patient (3.3%), disease progression for 5 patients (16.7%), severe side effects for 3 patients (10.0%), withdrawal from the study for 2 patients (6.6%), and quarantine measures during the novel coronavirus disease 2019 pandemic for 8 patients (26.7%). Detailed patient characteristics and flowcharts are shown in Supplemental Table 1 and Figure 1, respectively.

### Safety

All patients tolerated approximately a 2.0-GBq (55 mCi) dose of $^{177}$Lu-EB-PSMA well; there were no immediate adverse effects

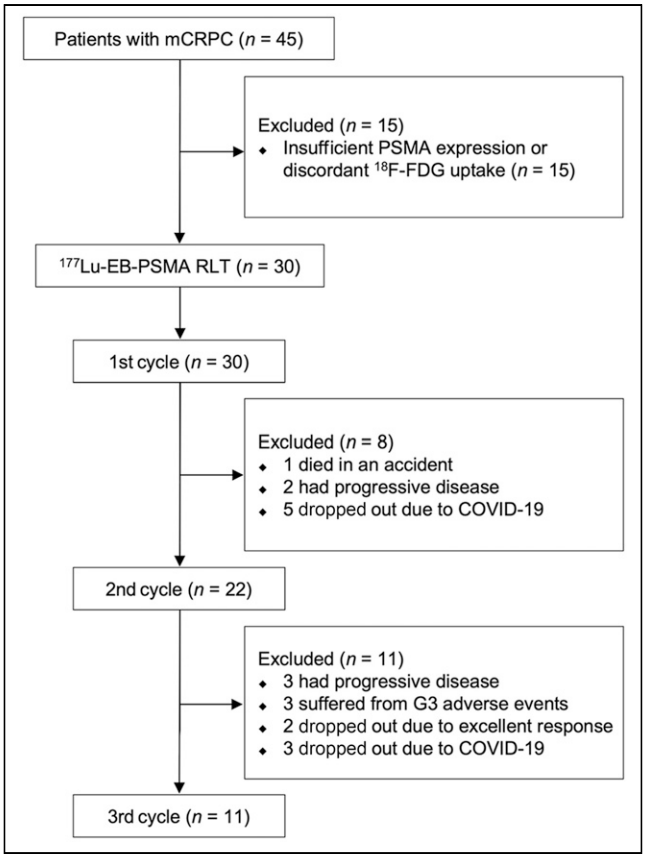


**FIGURE 1.** Flowchart of patient enrollment process and follow-up.

recorded during administration and no treatment-related deaths. One death occurred 7 wk after the first cycle of therapy because of non–treatment-related respiratory aspiration.

The most common toxic effects were fatigue, dry mouth, and nausea, which were recorded in 16 (53.3%), 12 (40.0%), and 12 (40.0%) patients, respectively. These adverse events, however, were classified as exclusively grade 1–2 and usually did not require additional interventions. In addition, 9 (30.0%) patients experienced temporary ostealgia, 3 (10.0%) patients developed mild diarrhea, and 2 (6.7%) patients reported temporary appetite loss. There were no noticeable fluctuations in liver function at any point during the entire follow-up for any enrolled patients. No patients had renal adverse events during short-term follow-up. During long-term follow-up, however, 1 patient had a grade 2 renal adverse event (increased serum creatinine) at 16 wk after the third cycle of $^{177}$Lu-EB-PSMA PRLT, 1 patient had a grade 1 renal adverse event at 18 wk after the second cycle of PRLT, and 1 patient had a grade 1 renal adverse event at 24 wk after the third cycle of PRLT.

Hematologic toxicity was the most serious side effect and caused 3 (10.0%) patients to drop out of the clinical trial. During short-term follow-up, 24 (80.0%) patients developed grade 1–2 adverse events and 9 (30.0%) patients developed grade 3 adverse events at 4–6 wk after PRLT. During long-term follow-up, 1 patient had additional grade 3 thrombocytopenia at 16 wk after the third cycle of PRLT. No patients experienced grade 4 adverse events. Details are shown in Supplemental Table 2.

### Therapeutic Response

The primary endpoint of a PSA reduction of 50% or more from baseline was achieved in 17 (56.7%; 95% CI, 37.8%–75.5%) patients over all cycles of $^{177}$Lu-EB-PSMA RLT, with 23 (76.7%; 95% CI, 60.6%–92.7%) patients showing any decline in PSA level. After the first cycle of $^{177}$Lu-EB-PSMA RLT, 10 (33.3%; 95% CI, 15.4%–51.2%) patients demonstrated at least a 50% PSA decline, with 20 (66.6%; 95% CI, 48.8%–84.6%) patients showing any decline in PSA level. Supplemental Figure 1 shows the waterfall plots of the percentage change in PSA response compared with baseline after the first cycle of $^{177}$Lu-EB-PSMA RLT and the best PSA response rate for all courses.

During the first, second, and third observation cycles of PRLT, 27, 18, and 10 patients, respectively, underwent $^{68}$Ga-PSMA PET/CT on schedule. For adapted PERCIST, after the first cycle of treatment, 14 (51.9%) patients achieved PR, 7 (25.9%) patients had stable disease, and 6 (22.2%) patients had PD. After the second cycle of PRLT, 11 (61.1%), 4 (22.2%), and 3 (16.7%) patients had PR, stable disease, and PD, respectively. After the last cycle of PRLT, 6 (60.0%), 3 (30.0%), and 1 (10.0%) patients had PR, stable disease, and PD, respectively. Regarding RECIP, after the first cycle of PRLT, 13 (48.1%) patients achieved PR, 9 (33.3%) patients had stable disease, and 5 (18.5%) patients had PD. After the second cycle of PRLT, 10 (55.5%), 5 (27.8%), and 3 (16.7%) patients had PR, stable disease, and PD, respectively. After the third cycle of PRLT, 5 (50.0%), 4 (40.0%), and 1 (10.0%) patients had PR, stable disease, and PD, respectively.

The baseline TLP had a moderate correlation with baseline serum PSA level ($r = 0.578$, $P = 0.001$), and there was a strong association between change in (Δ) TLP and ΔPSA in patients during the matched cycle of PRLT ($r = 0.709$, $P < 0.001$). Similarly, the baseline PSMA-VOL also had a moderate correlation with baseline PSA ($r = 0.584$, $P = 0.001$), and there was a moderate association between ΔPSMA-VOL and ΔPSA in patients during the matched cycle of PRLT ($r = 0.587$, $P = 0.001$), as shown in Figures 2 and 3. A higher whole-body PSMA $SUV_{mean}$ (odds ratio, 2.085 [95% CI, 1.131–3.843]; $P = 0.009$) and higher baseline TLP (odds ratio, 1.102 [95% CI, 1.008–1.205]; $P = 0.032$) were closely associated with the best PSA response. However, multivariable analysis revealed that only a higher whole-body PSMA $SUV_{mean}$ (odds ratio, 1.977 [95% CI, 1.014–3.855]; $P = 0.043$) was predictive of the best PSA response.

### PSA PFS and OS

At a median follow-up of 23.8 mo, PSA progression occurred in all 29 (96.7%) patients (except for 1 death), and 22 (73.3%) patients had died. The median PSA PFS was 4.6 mo (95% CI, 2.7–6.5 mo), and the median OS was 12.6 mo (95% CI, 8.1–17.1 mo), as shown in Figure 4.

Univariate analysis of potential predictive factors for PSA PFS showed that higher baseline alkaline phosphatase (ALP) (hazard ratio [HR], 1.005 [95% CI, 1.001–1.008]; $P = 0.006$) and higher baseline PSMA-VOL (HR, 1.026 [95% CI, 1.003–1.083]; $P = 0.015$) were closely associated with worse PSA PFS. Multivariable analysis revealed that baseline ALP (HR, 1.006 [95% CI, 1.001–1.011]; $P = 0.010$) and baseline PSMA-VOL (HR, 1.047 [95% CI, 0.972–1.092]; $P = 0.026$) also remained predictive of PSA PFS, as shown in Figure 5.

The presence of visceral disease (HR, 0.059 [95% CI, 0.011–0.317]; $P = 0.001$), higher baseline PSA (HR, 1.003 [95% CI, 1.001–1.004]; $P = 0.001$), and higher baseline TLP (HR, 1.078 [95% CI, 1.025–1.134]; $P = 0.023$) were closely associated with worse OS. Multivariable analysis revealed that the presence of visceral disease (HR, 0.101 [95% CI, 0.024–0.437]; $P = 0.002$) and baseline PSA (HR, 1.002 [95% CI, 1.000–1.003]; $P = 0.039$) were predictive factors for OS, as shown in Figure 5.

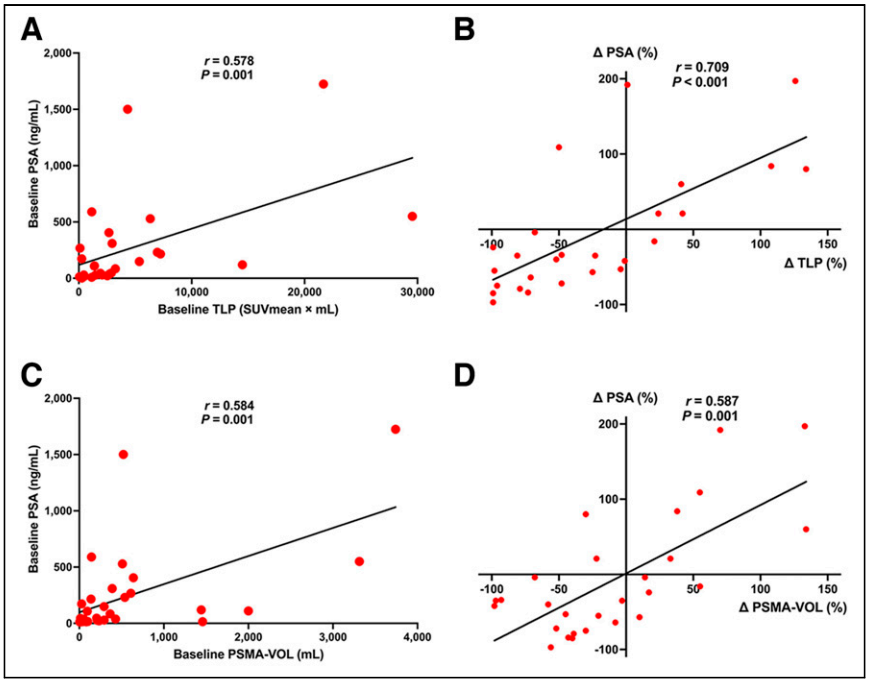


**FIGURE 2.** Correlations of baseline TLP with baseline PSA (A), ΔTLP and ΔPSA in patients during matched cycle of PRLT (B), baseline PSMA-VOL and baseline PSA (C), and ΔPSMA-VOL and ΔPSA in patients during matched cycle of PRLT (D).

### Quality of Life

We summarized the health-related quality-of-life scores, as shown in Supplemental Table 3. The baseline assessment was completed by all 30 participants. Subsequently, 29, 21, and 11 men completed the same assessments after 1, 2, and 3 cycles of $^{177}$Lu-EB-PSMA RLT, respectively.

Overall, physical functioning and global health status improved significantly after 2 cycles of PRLT, and the mean pain severity score decreased from baseline. After the first cycle of $^{177}$Lu-EB-PSMA RLT, there was a transient increase in fatigue and appetite loss scores, but no statistically significant difference was found between baseline and cycles 2 or 3.

## DISCUSSION

We conducted a clinical study to verify the safety and therapeutic efficacy of $^{177}$Lu-EB-PSMA at approximately 2.0 GBq (55 mCi) per cycle in a 30-person cohort with mCRPC. Our study exhibited a 50% or higher PSA decline from baseline in 56.7% of patients undergoing $^{177}$Lu-EB-PSMA RLT, as well as exhibiting significantly improved health-related quality-of-life scores, whereas a high rate of hematologic toxicity was also observed.

Sartor et al. conducted a phase 3 trial to assess the efficacy and safety of $^{177}$Lu-PSMA-617 RLT (7.4 GBq every 6 wk for 4–6 cycles) in patients with mCRPC and reported that adverse events of grade 3 or above occurred in 52.7% of patients (*1*). Another clinical trial (TheraP), conducted by Hofman et al., compared $^{177}$Lu-PSMA-617 (6.0–8.5 GBq

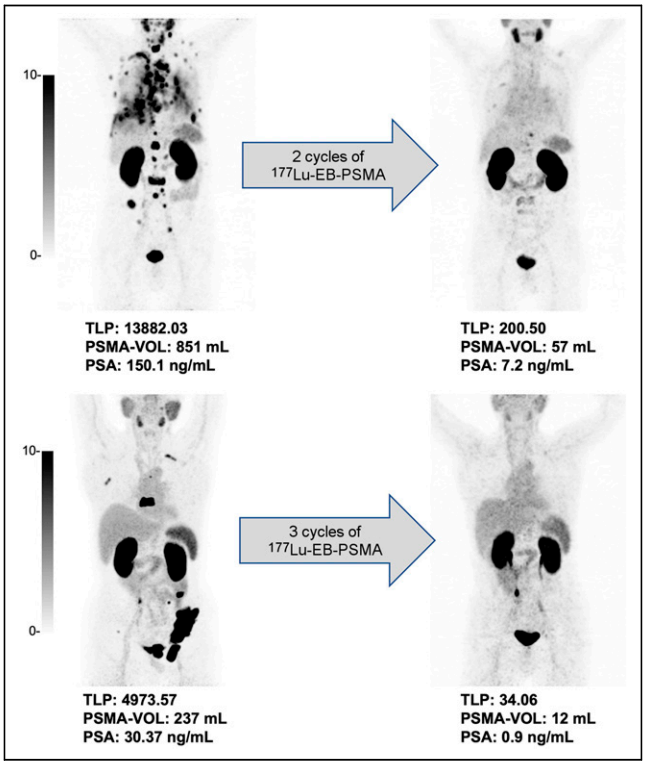


**FIGURE 3.** Representative molecular imaging and PSA responses in 2 patients before and 8 wk after $^{177}$Lu-EB-PSMA therapy.

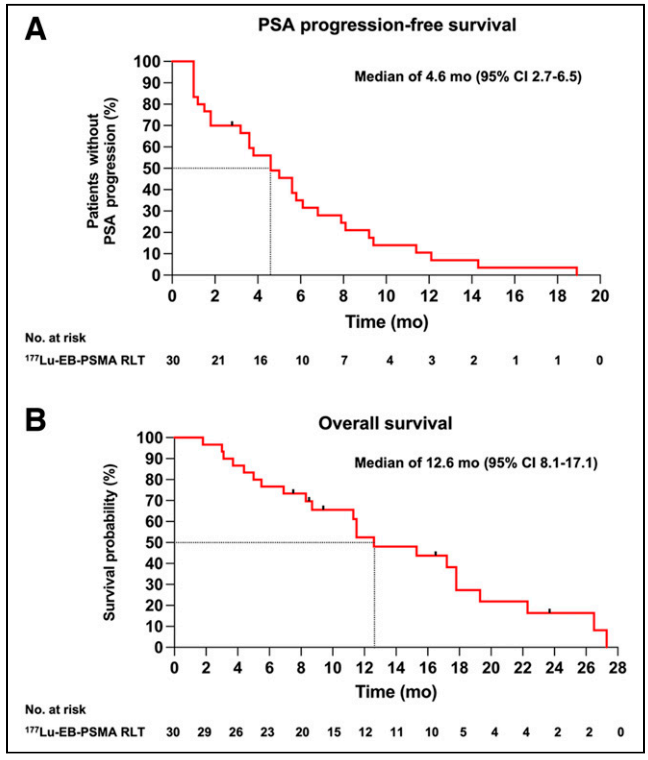


**FIGURE 4.** Kaplan–Meier curves of PSA PFS (A) and OS (B).

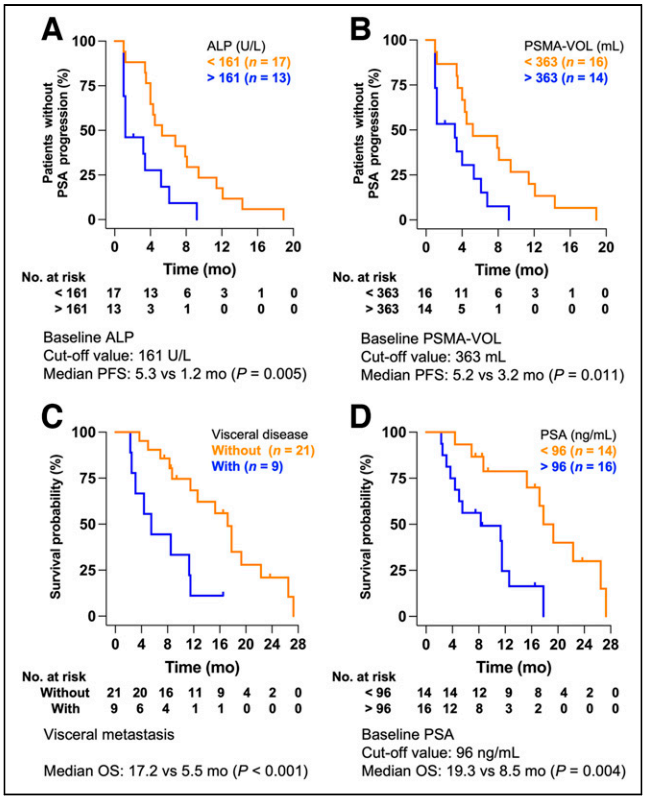


**FIGURE 5.** Kaplan–Meier curves of PSA PFS and OS using log-rank comparison. Patients with higher baseline ALP (A) and larger baseline PSMA-VOL (B) showed worse PSA PFS. Patients with visceral metastasis (C) and higher baseline PSA (D) showed worse OS.

every 6 wk for up to 6 cycles) with cabazitaxel in patients with mCRPC and showed that 32 of 98 (32.7%) patients had grade 3–4 adverse events in the $^{177}$Lu-PSMA-617 group (*2*). Previous studies have confirmed that the kidney- and red bone marrow–accumulated radioactivities of $^{177}$Lu-EB-PSMA were about 6.51-fold and 6.13-fold higher, respectively, than those of $^{177}$Lu-PSMA-617. On the basis of the dosimetry of $^{177}$Lu-EB-PSMA to red bone marrow and kidneys, as well as the respective maximum tolerated doses of 2 Gy and 23–29 Gy (*9,20*), respectively, similar mCRPC patients can accept up to 5–6 cycles of $^{177}$Lu-EB-PSMA RLT with approximately 2.0 GBq (55 mCi) per cycle. In our study, no renal adverse event was observed during short-term follow-up, and 3 grade 1–2 adverse events occurred at long-term follow-up. Importantly, 33.3% of patients had grade 3 hematologic events within up to 3 cycles of PRLT, which was comparable to 7.4-GBq (200 mCi) doses of $^{177}$Lu-PSMA-617 for up to 4–6 cycles; this result suggests that future studies with larger samples and more cycles (≥4) of treatment must be carefully performed.

Regarding PSA response, the clinical trial conducted by Sartor et al. reported a PSA decrease of at least 50% in 177 of 385 (46.0%) patients (*1*). A systematic review also reported that approximately 46.0% of mCRPC patients achieved a PSA decrease of at least 50% after at least 1 cycle of RLT ($^{177}$Lu-PSMA-617 or $^{177}$Lu-PSMA-I&T) (*21*). It is encouraging that $^{177}$Lu-EB-PSMA at a third or fourth of the dose of $^{177}$Lu-PSMA-617 can achieve a comparable best PSA response rate (56.7%). A previous study reported that more PRLT cycles may be associated with a higher proportion of patients who achieve the best PSA responses (*21*). In this study, we performed an average of only 2 cycles of PRLT, which may reduce the real therapeutic efficacy of $^{177}$Lu-EB-PSMA. In addition, the median PSA PFS and OS in our study were 4.6 mo (95% CI, 2.7–6.5 mo) and 12.6 mo (95% CI, 8.1–17.1 mo), respectively. Hofman et al. (*12*) revealed a median PSA PFS of 7.6 mo (95% CI, 6.3–9.0 mo) and a median OS of 13.5 mo (95% CI, 10.4–22.7 mo) in their $^{177}$Lu-PSMA trial ($^{177}$Lu-PSMA-617, 7.4 GBq every 6 wk for up to 4 cycles). Satapathy et al. compared $^{177}$Lu-PSMA-617 (6.0–7.4 GBq every 8 wk for up to 4 cycles) with docetaxel in patients with mCRPC and reported a median PFS of 4.0 mo (95% CI, 1.8–6.2 mo) (*3*). In addition, Sartor et al. revealed a median OS of 15.3 mo (*1*). Quite a few studies confirmed that prior chemotherapy and visceral metastasis correlated with worse time-to-event outcomes after PRLT (*22–24*). In our study, all patients received chemotherapy before PRLT, and 30.0% of patients were diagnosed with visceral metastasis, which may partly contribute to relatively shorter PSA PFS and OS. Another important reason may be that some patients did not complete their established treatment plans because of the coronavirus disease 2019 pandemic. Of course, these speculations need to be further confirmed in subsequent studies.

We analyzed the possible predictors of treatment response and prognosis and found that whole-body PSMA $SUV_{mean}$ was an independent predictor of the best PSA response, and this was confirmed by some previous studies (*14,25,26*). At present, most clinical trials on PRLT use PSMA PET/CT to screen participants, and the $SUV_{max}$ of the tumor is the most common evaluation parameter. However, whole-body PSMA $SUV_{mean}$ may be more suitable than $SUV_{max}$ to assess the heterogeneity of PSMA expression in mCRPC patients. In addition, a previous dosimetry study demonstrated that whole-body PSMA $SUV_{mean}$ was associated with the average absorbed radiation dose and therapeutic response (*27*). Hence, we suggest that whole-body PSMA $SUV_{mean}$ may be a better biomarker for guiding enrollment screening in future studies. A higher baseline ALP and larger PSMA-VOL correlated with worse PSA PFS, as is consistent with other studies (*14,28*). A higher ALP and larger PSMA-VOL indicate a higher tumor burden, especially bone metastases. Therefore, it is biologically plausible that ALP and PSMA-VOL are significant prognosticators of PSA PFS. Finally, visceral metastasis and baseline PSA were negative predictive factors for OS, as also agrees with previous studies (*22,29–32*). All these findings are valuable in guiding future PRLT.

In this study, the molecular imaging response was assessed by $^{68}$Ga-PSMA-617 PET/CT based on adapted PERCIST and RECIP. We observed that baseline TLP and PSMA-VOL had a moderate correlation with baseline PSA. In addition, we found a strong correlation between ΔTLP and ΔPSA and a moderate association between ΔPSMA-VOL and ΔPSA in patients during the matched cycle of PRLT. Recently, some researchers confirmed that evaluating PSMA response with PET had value even better than that of RECIST and the adapted Prostate Cancer Clinical Trials Working Group 3 Criteria (*33–35*). In our study, some parameters derived from PSMA PET, such as whole-body PSMA $SUV_{mean}$ and PSMA-VOL, also correlated significantly with therapeutic response evaluation and PSA PFS. Hence, we believe that PSMA PET should be used not only for screening patients based on the inclusion criteria but also for restaging disease during the course of PRLT to standardize PSMA-driven response assessments in patients with mCRPC.

Our study had some limitations. The most notable issue was the limited number of participants and treatment cycles. In particular, more than half the patients did not complete the established 3 cycles of treatment for various reasons. The second limitation is the lack of a control group for standard RLT with $^{177}$Lu-PSMA-617, as comparing the therapeutic value of $^{177}$Lu-EB-PSMA with the published literature might lead to some bias. Larger studies are needed to validate these results.

Even so, this prospective study demonstrated the potential value of $^{177}$Lu-EB-PSMA in the treatment of mCRPC. In other words, it is feasible to reduce the dose of each injection and optimize the use of $^{177}$Lu by improving the internal pharmacokinetics of the therapeutic drug, although the resulting systemic toxicity should be closely monitored.

## CONCLUSION

Our study demonstrated that $^{177}$Lu-EB-PSMA may be an alternative radiopharmaceutical in the therapy of mCRPC. A low dose (~2.0 GBq) of $^{177}$Lu-EB-PSMA for up to 3 cycles may reach a PSA response rate and hematologic toxicity comparable to those from 7.4 GBq per cycle of $^{177}$Lu-PSMA-617 for up to 4–6 cycles. In our study, shorter PFS and OS may be attributed partly to fewer cycles of $^{177}$Lu-EB-PSMA RLT. Further studies with increased numbers of patients and more cycles of treatment are warranted.

## DISCLOSURE

This study was supported by the Chinese Academy of Medical Science Innovation Fund for Medical Sciences (2021-I2 M-1-016, 2022-I2 M-2-002), the Beijing Natural Science Foundation (M22035), the National Natural Science Foundation of China (81871392), the National University of Singapore Start-up Grant (NUHSRO/2020/133/Startup/08), and the National Research Foundation, Singapore, and National Medical Research Council, Singapore, under their NMRC Centre Grant Program (CG21APR1005). No other potential conflict of interest relevant to this article was reported.

**KEY POINTS**

**QUESTION:** Is RLT based on a low dose of $^{177}$Lu-EB-PSMA safe and efficacious?

**PERTINENT FINDINGS:** A 2.0-GBq (55 mCi) dose of $^{177}$Lu-EB-PSMA for up to 3 cycles achieved acceptable side effects and therapeutic response.

**IMPLICATIONS FOR PATIENT CARE:** RLT based on low-dose $^{177}$Lu-EB-PSMA may be a promising therapeutic option for patients with mCRPC.

## REFERENCES

1. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385:1091–1103.
2. Hofman MS, Emmett L, Sandhu S, et al. [$^{177}$Lu]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.
3. Satapathy S, Mittal BR, Sood A, et al. $^{177}$Lu-PSMA-617 versus docetaxel in chemotherapy-naive metastatic castration-resistant prostate cancer: a randomized, controlled, phase 2 non-inferiority trial. *Eur J Nucl Med Mol Imaging.* 2022;49:1754–1764.
4. Mullard A. FDA approves first PSMA-targeted radiopharmaceutical. *Nat Rev Drug Discov.* 2022;21:327.
5. Benešová M, Schafer M, Bauder-Wust U, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56:914–920.
6. Weineisen M, Schottelius M, Simecek J, et al. $^{68}$Ga- and $^{177}$Lu-labeled PSMA I&T: optimization of a PSMA-targeted theranostic concept and first proof-of-concept human studies. *J Nucl Med.* 2015;56:1169–1176.
7. Schuchardt C, Zhang J, Kulkarni HR, Chen X, Muller D, Baum RP. Prostate-specific membrane antigen radioligand therapy using $^{177}$Lu-PSMA I&T and $^{177}$Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: comparison of safety, biodistribution, and dosimetry. *J Nucl Med.* 2022;63:1199–1207.
8. Hartrampf PE, Weinzierl FX, Buck AK, et al. Matched-pair analysis of [$^{177}$Lu]Lu-PSMA I&T and [$^{177}$Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2022;49:3269–3276.
9. Zang J, Fan X, Wang H, et al. First-in-human study of $^{177}$Lu-EB-PSMA-617 in patients with metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2019;46:148–158.
10. Wang Z, Tian R, Niu G, et al. Single low-dose injection of Evans blue modified PSMA-617 radioligand therapy eliminates prostate-specific membrane antigen positive tumors. *Bioconjug Chem.* 2018;29:3213–3221.
11. Zang J, Liu Q, Sui H, et al. $^{177}$Lu-EB-PSMA radioligand therapy with escalating doses in patients with metastatic castration-resistant prostate cancer. *J Nucl Med.* 2020;61:1772–1778.
12. Hofman MS, Violet J, Hicks RJ, et al. [$^{177}$Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* 2018;19:825–833.
13. Wang G, Zhou M, Zang J, et al. A pilot study of $^{68}$Ga-PSMA-617 PET/CT imaging and $^{177}$Lu-EB-PSMA-617 radioligand therapy in patients with adenoid cystic carcinoma. *EJNMMI Res.* 2022;12:52.
14. Ferdinandus J, Violet J, Sandhu S, et al. Prognostic biomarkers in men with metastatic castration-resistant prostate cancer receiving [$^{177}$Lu]-PSMA-617. *Eur J Nucl Med Mol Imaging.* 2020;47:2322–2327.
15. Rosar F, Wenner F, Khreish F, et al. Early molecular imaging response assessment based on determination of total viable tumor burden in [$^{68}$Ga]Ga-PSMA-11 PET/CT independently predicts overall survival in [$^{177}$Lu]Lu-PSMA-617 radioligand therapy. *Eur J Nucl Med Mol Imaging.* 2022;49:1584–1594.
16. Werner-Wasik M, Nelson AD, Choi W, et al. What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. *Int J Radiat Oncol Biol Phys.* 2012;82:1164–1171.
17. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50(suppl 1):122S–150S.
18. Gafita A, Rauscher I, Weber M, et al. Novel framework for treatment response evaluation using PSMA PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP 1.0): an international multicenter study. *J Nucl Med.* 2022;63:1651–1658.
19. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34:1402–1418.
20. Zhang J, Wang H, Jacobson O, et al. Safety, pharmacokinetics, and dosimetry of a long-acting radiolabeled somatostatin analog $^{177}$Lu-DOTA-EB-TATE in patients with advanced metastatic neuroendocrine tumors. *J Nucl Med.* 2018;59:1699–1705.
21. Sadaghiani MS, Sheikhbahaei 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.
22. Kessel K, Seifert R, Schafers M, et al. Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving $^{177}$Lu-PSMA-617. *Theranostics.* 2019;9:4841–4848.
23. 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 [$^{177}$Lu]Lu-PSMA-617: a WARMTH multicentre study. *Eur J Nucl Med Mol Imaging.* 2021;48:4067–4076.
24. 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 [$^{177}$Lu]Lu-PSMA-617. A WARMTH multicenter study (the 617 trial). *Eur J Nucl Med Mol Imaging.* 2021;48:113–122.
25. Pathmanandavel S, Crumbaker M, Yam AO, et al. $^{177}$Lu-PSMA-617 and idronoxil in men with end-stage metastatic castration-resistant prostate cancer (LuPIN): patient

outcomes and predictors of treatment response in a phase I/II trial. *J Nucl Med.* 2022;63:560–566.
26. Kuo P, Hesterman J, Rahbar K, et al. [$^{68}$Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [$^{177}$Lu]Lu-PSMA-617 in patients with mCRPC: a VISION substudy [abstract]. *J Clin Oncol.* 2022;40:5002.
27. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of $^{177}$Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019;60:517–523.
28. Fizazi K, Massard C, Smith M, et al. Bone-related parameters are the main prognostic factors for overall survival in men with bone metastases from castration-resistant prostate cancer. *Eur Urol.* 2015;68:42–50.
29. Heck MM, Tauber R, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with $^{177}$Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. *Eur Urol.* 2019;75:920–926.
30. Barber TW, Singh A, Kulkarni HR, Niepsch K, Billah B, Baum RP. Clinical outcomes of $^{177}$Lu-PSMA radioligand therapy in earlier and later phases of metastatic castration-resistant prostate cancer grouped by previous taxane chemotherapy. *J Nucl Med.* 2019;60:955–962.
31. Seifert R, Kessel K, Schlack K, et al. PSMA PET total tumor volume predicts outcome of patients with advanced prostate cancer receiving [$^{177}$Lu]Lu-PSMA-617 radioligand therapy in a bicentric analysis. *Eur J Nucl Med Mol Imaging.* 2021;48:1200–1210.
32. Seifert R, Herrmann K, Kleesiek J, et al. Semiautomatically quantified tumor volume using $^{68}$Ga-PSMA-11 PET as a biomarker for survival in patients with advanced prostate cancer. *J Nucl Med.* 2020;61:1786–1792.
33. Grubmüller B, Senn D, Kramer G, et al. Response assessment using $^{68}$Ga-PSMA ligand PET in patients undergoing $^{177}$Lu-PSMA radioligand therapy for metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2019;46:1063–1072.
34. Michalski K, Klein C, Brueggemann T, Meyer PT, Jilg CA, Ruf J. Assessing response to [$^{177}$Lu]PSMA radioligand therapy using modified PSMA PET progression criteria. *J Nucl Med.* 2021;62:1741–1746.
35. Gafita A, Rauscher I, Fendler WP, et al. Measuring response in metastatic castration-resistant prostate cancer using PSMA PET/CT: comparison of RECIST 1.1, aPCWG3, aPERCIST, PPP, and RECIP 1.0 criteria. *Eur J Nucl Med Mol Imaging.* 2022;49:4271–4281.