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A single-arm, low-dose, prospective study of ^{177}Lu-EB-PSMA radioligand therapy in patients with metastatic castration-resistant prostate cancer

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ABSTRACT

We aimed to investigate the safety and therapeutic efficacy of radioligand therapy (RLT) of ^{177}Lu-EB-PSMA in patients with metastatic castration-resistant prostate cancer (mCRPC).

Methods: Thirty men with progressive mCRPC previously treated with taxane-based chemotherapy and second-generation androgen deprivati-on therapy were enrolled. All patients received up to three cycles of approximately 2.0 GBq (55 mCi) ^{177}Lu-EB-PSMA per cycle at 8-week intervals. The primary endpoint was therapeutic safety, including the changes of hematologic status, liver function, and renal function tests; the additional primary endpoint was therapeutic efficacy, including prostate-specific antigen (PSA) response and molecular imaging response; the secondary endpoints were PSA progression-free survival (PSA-PFS) and overall survival (OS). Another endpoint was patient-reported health-related quality-of-life (HRQOL).

Results: From January 2019 to December 2021, 30, 22 and 11 patients received 1, 2 and 3 cycles of ^{177}Lu-EB-PSMA RLT, respectively. During the entire follow-up period, 33.3% of patients experienced grade 3 hematological 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 mean standardized uptake value (SUVmean) was correlated with a better PSA response; higher baseline alkaline phosphatase and larger total PSMA-positive tumor volume (PSMA-VOL) were associated with worse PSA-PFS, whereas the existence of visceral metastases and PSA at baseline were significant prognosticators of worse OS. HRQOL 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 comparable PSA response and hematological toxicity with 7.4 GBq doses of ^{177}Lu-EB-PSMA 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.

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

INTRODUCTION

The treatment of metastatic castration-resistant prostate cancer (mCRPC) remains a huge challenge for uro-/oncologists. Radioligand therapy (RLT) targeting prostate-specific membrane antigen (PSMA) has attracted interest as a potential treatment modality for mCRPC. A 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 mainly based on small molecule inhibitors, such as PSMA-617 and PSMA I&T (*5,6*). Previous studies have reported no significant difference in the 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 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 down its plasma clearance rate, thereby increasing tumor accumulation and reducing the total dosage of ^{177}Lu. Hence, EB-PSMA may be an option for consideration due to the limited supply of ^{177}Lu, by which more patients may benefit from this version of ^{177}Lu-EB-PSMA. 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 treatment revealed significant decrease of ^{68}Ga-PSMA-617 uptake than ^{177}Lu-PSMA-617. However, the red

bone marrow and kidneys also showed higher ^{177}Lu-EB-PSMA uptake than ^{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)/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

Patients

Participants who met the inclusion criteria (Supplemental Information) underwent ^{68}Ga-PSMA-617 and ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) within 2 weeks before PRLT to confirm high PSMA expression, which was defined as a baseline maximum standardized uptake value (SUVmax) of most tumors (at least 80%) being significantly (≥ 1.5 times) greater than the mean standardized uptake value (SUVmean) of the normal liver, patients were excluded if they had FDG-positive tumor without corresponding PSMA uptake (*3,12*).

PET/CT Imaging

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

The images were transferred to MIM software (Version 7.1.4, MIM Software Inc., USA). The volume of interest of the tumor was segmented using PET Edge, a gradient-based segmentation algorithm with an SUV threshold of ≥ 3.0. Besides, for the segmentation of liver metastases, a threshold of 1.5 × SUVmean of the normal liver tissue was used (*14-16*). Total lesion PSMA (TLP) was calculated through the summed products of total PSMA-positive tumor volume (PSMA-VOL) × SUVmean of all tumors. Whole-body PSMA SUVmean 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 in 8-week intervals.

Hematologic status was assessed every 2 weeks after the injection of ^{177}Lu-EB-PSMA; liver function, renal function, and serum PSA values were documented every 4 weeks. Short-term follow-up ended at 10 weeks after the last cycle of PRLT. Long-term follow-up to laboratory results ended in (1) death from any cause; or (2) start of another treatment modality; or (3) the latest study visit. ^{68}Ga-PSMA-617 PET/CT reexaminations were performed one week prior to the administration of ^{177}Lu-EB-PSMA and 8 weeks after the last treatment cycle. In addition, patient-reported health-related quality-of-life (HRQOL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), which includes 30 items related to functioning and symptom scales, within 1 week before each cycle of therapy and at the 8-week final treatment session.

Outcomes

The primary endpoint was adverse events, which were categorized according to the Common Toxicity Criteria for Adverse Events 5.0 (CTCAE 5.0) (*11*). The additional primary endpoints were best PSA response based on the Prostate Cancer Clinical Trials Working Group-3 (PCWG3) guidelines, which defined a PSA decrease ≥ 50% from baseline as partial response (PR), a PSA increase ≥ 25% as progressive disease (PD), a PSA increase < 25% or decrease < 50% as stable disease; and molecular imaging response according to the adapted PET Response Criteria in Solid Tumors (aPERCIST) 1.0 and Response Evaluation Criteria In PSMA-PET/CT (RECIP) 1.0; the former defined a complete disappearance of TLP from target tumors on ^{68}Ga-PSMA-617 PET/CT compared to the baseline scan as a complete response (CR), a decrease in the TLP of target

tumors ≥ 30% without appearance of new lesions as PR, an increase in the TLP of target tumors ≥ 30% or appearance of new lesions as PD, an increase in the TLP < 30% or decrease < 30% and no appearance of new lesions as stable disease (*15,17*); the latter defined absence of any PSMA-ligand uptake as CR, decline ≥ 30% in PSMA-VOL and no appearance of new lesions as PR, increase ≥20% in PSMA-VOL and appearance of new lesions as PD, any condition but RECIP-PR or RECIP-PD as stable disease (*18*).

The secondary endpoints were PSA-PFS and overall survival (OS). PSA-PFS was defined as the interval from the date of patient enrollment to PSA progression, defined by an increase of at least 25% and at least 2 ng/mL after 12 weeks (*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 HRQOL assessment (*2*).

RESULTS

Demographic and clinical characteristics

A total of 30 patients were enrolled in this study, data on PSA response rate and toxic side effects for the first 10 patients have been 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. A total of 22 and 11 patients received two and three cycles of ^{177}Lu-EB-PSMA RLT, respectively. The reasons for not completing all three cycles as scheduled were nontumor-related death for 1 patient (3.3%), disease progression for 5 patients (16.7%), severe side effects for 3 patients (10.0%), subjective withdrawal for 2 patients (6.6%), and quarantine measures during the novel coronavirus disease 2019 (COVID-19) pandemic for 8 patients (26.7%). Detailed patient characteristics and flow charts are shown in Supplemental Table 1 and Figure 1, respectively.

Safety

All patients tolerated approximately 2.0 GBq (55 mCi) dose of ^{177}Lu-EB-PSMA well, and there were no immediate adverse effects recorded during administration and no treatment-related deaths.

One death occurred 7 weeks after the 1st cycle of therapy due to 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 functions during the entire follow-up for all enrolled patients. No patient had no renal toxic events during short-term follow-up. During long-term follow-up, however, 1 patient had grade 2 renal toxic event (increased serum creatinine) at 16 weeks after the 3rd cycle of ^{177}Lu-EB-PSMA PRLT, and 2 patients had grade 1 renal toxic events at 18 weeks after the 2nd cycle of PRLT and 24 weeks after the 3rd cycle of PRLT, respectively.

Hematological 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 toxicity events and 9 (30.0%) patients developed grade 3 adverse events at 4-6 weeks after PRLT. During long-term follow-up, 1 patient had additional grade 3 thrombocytopenia at 16 weeks after the 3rd cycle of PRLT. Besides, no patient experienced grade 4 adverse effects. These 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 levels. After the 1st cycle of ^{177}Lu-EB-PSMA RLT, 10 (33.3%, 95% CI 15.4-51.2%) patients demonstrated a ≥ 50% PSA decline, with 20 (66.6%, 95% CI 48.8-84.6%) patients showing any decline in PSA levels. Supplemental Figure 1 shows the waterfall plots of the percent change in PSA response compared with baseline after the 1st cycle of ^{177}Lu-EB-PSMA RLT and the best PSA response rate for all courses.

During the 3 observation cycles of PRLT, 27, 18, and 10 patients underwent ^{68}Ga-PSMA

PET/CT on schedule, respectively. For aPERCIST criteria, after the 1st 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 2nd cycle of PRLT, 11 (61.1%), 4 (22.2%), and 3 (16.7%) patients showed PR, stable disease, and PD, respectively. After the last cycle of PRLT, 6 (60.0%), 3 (30.0%), and 1 (10.0%) patients showed PR, stable disease, and PD, respectively. Regarding RECIP criteria, after the 1st 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 2nd cycle of PRLT, 10 (55.5%), 5 (27.8%), and 3 (16.7%) patients showed PR, stable disease, and PD, respectively. After the 3rd cycle of PRLT, 5 (50.0%), 4 (40.0%), and 1 (10.0%) patients showed PR, stable disease, and PD, respectively.

The baseline TLP revealed a moderate correlation with baseline serum PSA level (r = 0.578, P = 0.001), and there was a strong association between ΔTLP and ΔPSA in patients during the matched cycle of PRLT (r = 0.709, P < 0.001). Similarly, the baseline PSMA-VOL also depicted 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 SUVmean (odds ratio [OR], 2.085 [95% CI, 1.131-3.843]; P = 0.009) and higher baseline TLP (OR, 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 SUVmean (OR, 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 months, PSA progression occurred in all 29 (96.7%) patients (except for one death), and 22 (73.3%) patients had died. The median PSA-PFS was 4.6 months (95% CI 2.7-6.5), and the median OS was 12.6 months (95% CI 8.1-17.1), 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 (hazard ratio [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 (hazard ratio [HR], 0.059 [95% CI, 0.011-0.317]; *P* = 0.001), higher baseline PSA (hazard ratio [HR], 1.003 [95% CI, 1.001-1.004]; *P* = 0.001), and higher baseline TLP (hazard ratio [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 (hazard ratio [HR], 1.002 [95% CI, 1.000-1.003]; *P* = 0.039) were predictive factors for OS, as shown in FIGURE 5.

Quality of Life

We summarized the HRQOL 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 1-3 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 1st 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 2-3.

DISCUSSION

In this study, we conducted a clinical study to verify the safety and therapeutic efficacy of ^{177}Lu-EB-PSMA in 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 ^{177}Lu-EB-PSMA RLT, and significantly improved HRQOL scores, whereas 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 weeks for 4 to 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 conducted by

Hofman *et al.* compared ^{177}Lu-PSMA-617 (6.0-8.5 GBq, every 6 weeks for up to 6 cycles) with cabazitaxel (TheraP) in patients with mCRPC and showed that 32 of 98 (32.7%) patients suffered from grade 3-4 adverse events in the ^{177}Lu-PSMA-617 group (*2*). Previous studies have confirmed that the kidneys and red bone marrow accumulated radioactivities of ^{177}Lu-EB-PSMA were about 6.51-fold and 6.13-fold higher than those of ^{177}Lu-PSMA-617, respectively. Based on dosimetry of ^{177}Lu-EB-PSMA to red bone marrow and kidneys, as well as the respective maximum tolerated dose of 2 Gy and 23-29 Gy (*9,20*), 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 toxic event was observed during short-term follow-up, and 3 grade 1-2 toxic events occurred at long-term follow-up. Importantly, 33.3% patients had grade 3 hematological events within up to 3 cycles of PRLT, which was comparable with 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 or more) of treatment must be carefully preformed.

Regarding PSA response, the clinical trial conducted by Sartor *et al.* reported a PSA decrease ≥ 50% in 177/385 (46.0%) patients (*1*). A systematic review also reported that approximately 46.0% of CRPC patients achieved a PSA decrease ≥ 50% after at least one cycle of RLT (^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T) (*21*). It is encouraging that ^{177}Lu-EB-PSMA at 1/3-1/4 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 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 months (95% CI 2.7-6.5) and 12.6 months (95% CI 8.1-17.1), respectively. Hofman *et al.* revealed a median PSA-PFS of 7.6 months (95% CI 6.3–9.0) and a median OS of 13.5 months (95% CI 10.4-22.7) in their Lu-PSMA trial (^{177}Lu-PSMA-617, 7.4 GBq, every 6 weeks for up to 4 cycles). Satapathy *et al.* compared ^{177}Lu-PSMA-617 (6.0-7.4 GBq, every 8 weeks for up to 4 cycles) with docetaxel in patients with mCRPC and reported a median PFS of 4.0 months (95% CI: 1.8-6.2 months) (*3*). Besides, Sartor et al. revealed a median OS of 15.3 months (*1*). Quite a few studies confirmed that prior chemotherapy and visceral metastasis were correlated with worse

time-to-event outcomes after PRLT (*22-24*). In our study, all patients received chemotherapy prior to PRLT, and 30.0% of patients were diagnosed with visceral metastasis, which may partly contribute to relatively shorter PSA-PFS and OS durations. In addition, some patients did not complete their established treatment plans due to COVID-19, which may be another important reason. Of course, these speculations need to be further confirmed in subsequent studies.

We analyzed the possible predictors of treatment response and prognosis. We found that whole-body PSMA SUVmean was an independent predictor of the best PSA response, and this has also been confirmed by some previous studies (*14,25,26*). At present, most clinical trials on PRLT use PSMA PET/CT to screen participants, and the SUVmax of the tumor is the most common evaluation parameter. However, whole-body PSMA SUVmean may be more suitable than SUVmax to assess the heterogeneity of PSMA expression in mCRPC patients. In addition, previous dosimetry study demonstrated that whole-body PSMA SUVmean was associated with the average absorbed radiation dose and therapeutic response (*27*). Hence, we suggest that whole-body PSMA SUVmean may be a better biomarker for guiding enrollment screening in future studies. Higher baseline ALP and larger PSMA-VOL were correlated with worse PSA-PFS, which is consistent with other studies (*14,28*). Higher ALP and larger PSMA-VOL indicate 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, which is also in agreement 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 aPERCIST criteria and RECIP criteria. We observed that baseline TLP and PSMA-VOL had a moderate correlation with baseline PSA, respectively. In addition, we depicted 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 better value, even better than with the Response Evaluation Criteria in Solid Tumors criteria and the adapted PCWG 3 Criteria (*33-35*). In our study, some parameters derived from PSMA PET, such as whole-body PSMA SUVmean and PSMA-VOL,

were also significantly correlated with therapeutic response evaluation and PSA-PFS. Hence, we believe that PSMA PET should be used not only as a basis 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 has some limitations. The most notable issue is the limited number of study participants and treatment cycles, especially 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 utilization of ^{177}Lu by improving the internal pharmacokinetics of the therapeutic drug, whereas the resulting systemic toxicity should be closely monitored.

CONCLUSION

This study demonstrates that ^{177}Lu-EB-PSMA may be an alternative radiopharmaceutical in the therapy of mCRPC. Low dose (approximately 2.0 GBq) of ^{177}Lu-EB-PSMA for up to 3 cycles may reach a comparable PSA response rate and hematological toxicity with 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 partly attributed to fewer cycles of ^{177}Lu-EB-PSMA RLT, further studies with increased number of patients and more cycles of treatment are warranted.

Declarations

Conflicts of interest: None of the authors have any conflicts of interest or relevant financial activities to disclose.

Ethics approval: The study was approved by the Institutional Review Board of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (no. JS-2105) and registered at ClinicalTrials.gov (NCT04996602).

KEY POINTS

QUESTION: Is radioligand therapy based on low dose of ^{177}Lu-EB-PSMA safe and efficacious?

PERTINENT FINDINGS: This study found that 2.0 GBq (55 mCi) doses of ^{177}Lu-EB-PSMA for up to 3 cycles can achieve 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.

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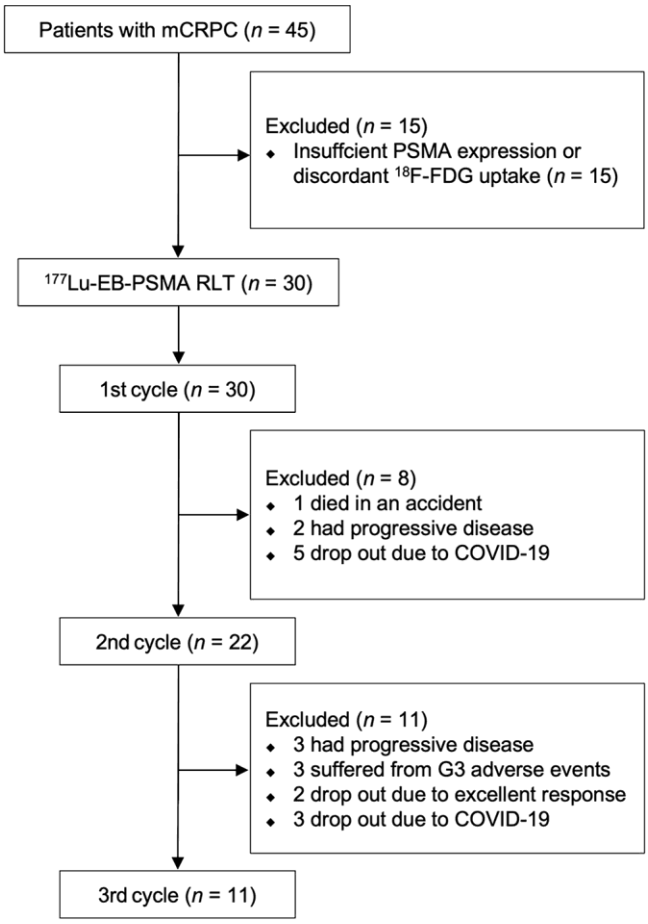


FIGURE 1. Flowchart of the patient enrollment process and follow-up.

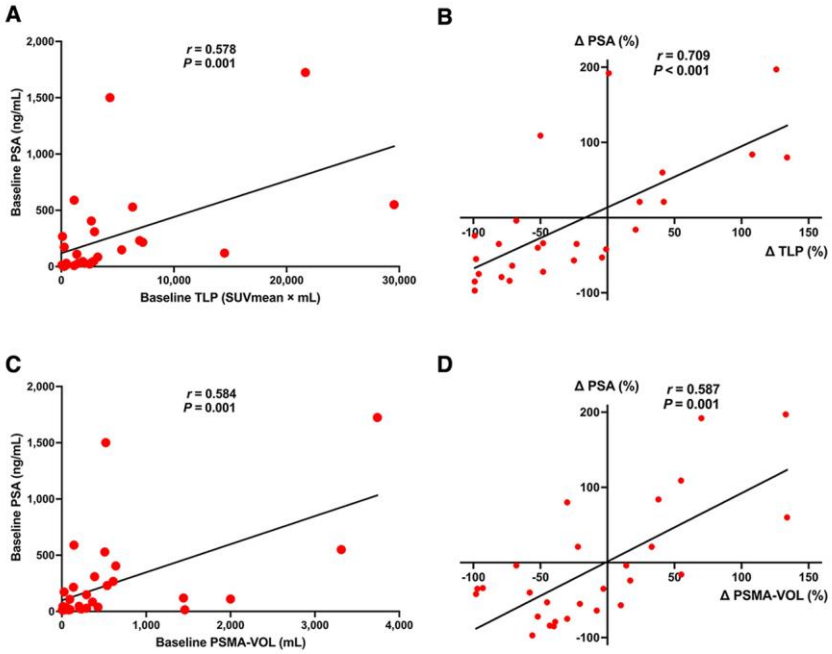


FIGURE 2. Correlations of baseline total lesion volume (TLP) with baseline prostate specific antigen (PSA) (**A**), ΔTLP and ΔPSA in patients during the matched cycle of PRLT (**B**); baseline PSMA-positive tumor volume (PSMA-VOL) and baseline PSA (**C**), ΔPSMA-VOL and ΔPSA in patients during the matched cycle of PRLT (**D**).

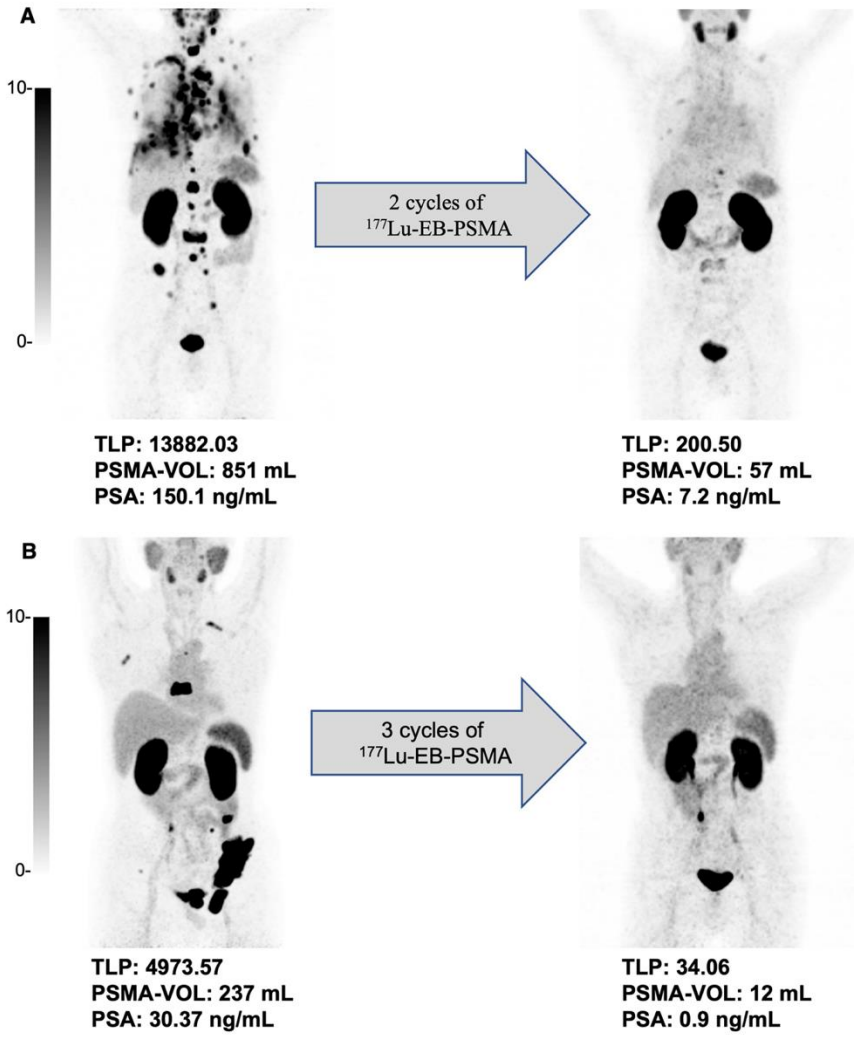


FIGURE 3. Representative molecular imaging and PSA responses in two patients before and 8 weeks after ^{177}Lu-EB-PSMA therapy. TLP = total lesion prostate-specific membrane antigen (PSMA); PSMA-VOL = PSMA-positive tumor volume; PSA = prostate-specific antigen.

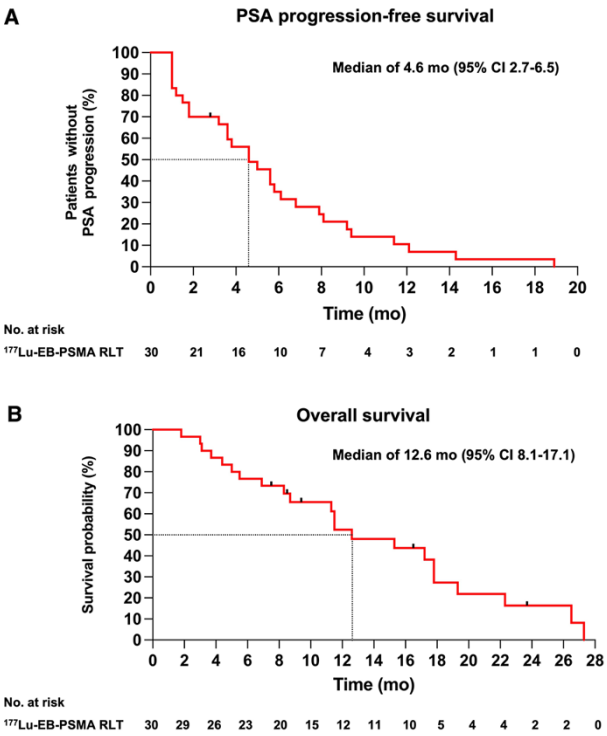


FIGURE 4. Kaplan–Meier curves of prostate-specific antigen progression-free survival (PSA-PFS, **A**) and overall survival (OS, **B**).

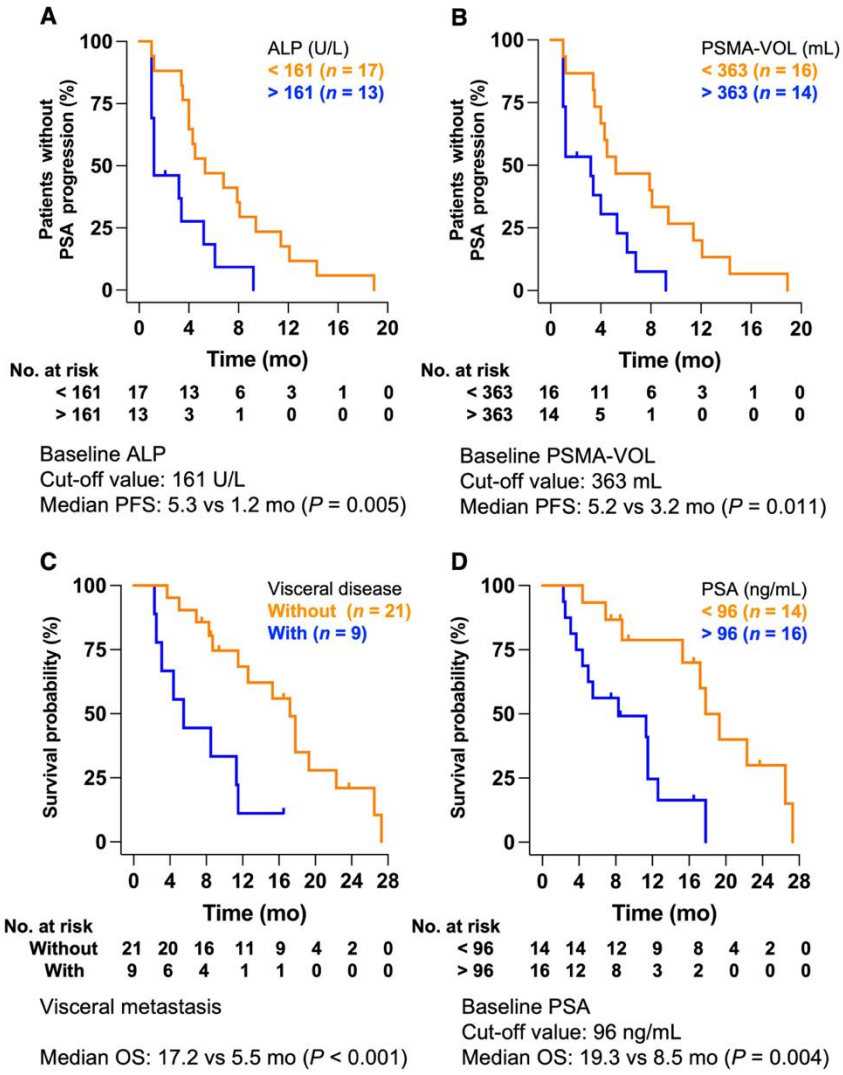
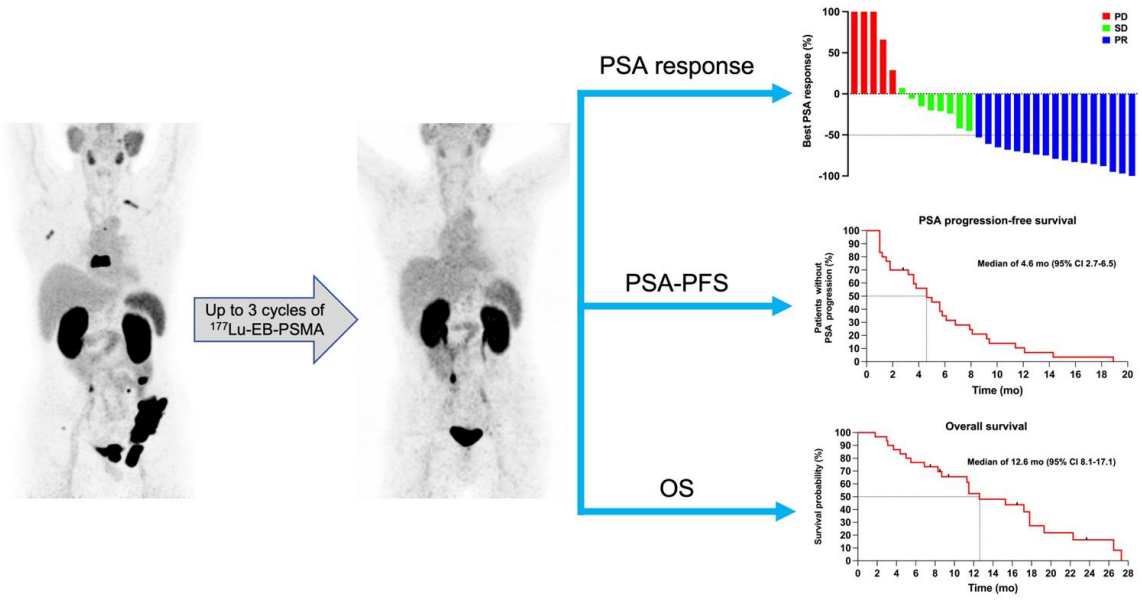


FIGURE 5. Kaplan–Meier curves of prostate-specific antigen progression-free survival (PSA-PFS) and overall survival (OS) using log-rank comparison. Patients with higher baseline alkaline phosphatase (ALP) (**A**) and larger baseline PSMA-positive tumor volume (PSMA-VOL) (**B**) showed worse PSA-PFS. Patients with visceral metastasis (**C**) and higher baseline PSA (**D**) showed worse OS.



Graphical Abstract

PSMA-617 was synthesize in-house for research use. EB-PSMA was labeled following our previously published procedure *(1)*. This study was registered at clinicaltrials.gov (NCT04996602) and approved by the institutional review board of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College (no. JS-2105). We confirmed that our trial complied with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients signed written informed consent forms.

Patient Inclusion Criteria

The inclusion criteria for ^{177}Lu-EB-PSMA RLT were progressive mCRPC patients with rising serum PSA levels who were previously treated with at least 1 line of taxane-based chemotherapy (cabazitaxel or docetaxel) and at least 1 second-generation androgen deprivation therapy (abiraterone or enzalutamide). All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2. Patients were not eligible if they had clinically significantly impaired bone marrow, liver, or kidney function defined by a white blood cell count < 2.5×10^9/L, hemoglobin count < 9.0 g/dL, platelet count < 75×10^9/L, serum creatinine > 150 μmol/L, serum albumin < 25 g/L, and total bilirubin > 60 μmol/L.

Statistical Analysis

All patients who had received at least one cycle of PRLT were included in the outcome analyses. A two-sided exact binomial 95% confidence interval (CI) was calculated for the PSA response. Percentage changes in PSA value were recorded and represented as waterfall plots. The Kaplan–Meier method was used to analyze time-to-event outcomes, including PSA-PFS and OS, and to estimate medians (presented with 95% CIs). Logistic regression and Cox proportional hazards regression were used to identify prognostic factors for the best PSA response and time-to-event outcomes, respectively. Variables found to be significant in the univariate model (*P* value < 0.2) were included in multivariable analysis to identify independent predictors.

The correlation between changes in TLP (ΔTLP) and change in PSA (ΔPSA) was analyzed using Spearman’s rank correlation tests. Student's t test was used to evaluate the change in

HRQOL scores. Data analyses were performed using SPSS software (Version 26.0, IBM Corp., USA) and GraphPad Prism (Version 9.0, GraphPad Software, USA). A *P* value < 0.05 was considered statistically significant.

1. 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.

Supplemental Table 1 Clinical characteristics of the patients

Characteristic	Summary
Number of patients	30
Age in years, median (range)	68 (48-81)
GS, median (range)	8 (6-10)
PSA (ng/ml), median (range)	109.4 (11.5-1724.1)
TLP, median (range)	2300.5 (155.4-29543.3)
ECOG performance status	
0	6 (20.0%)
1	16 (53.3%)
2	8 (26.7%)
Prior treatments	
ADT	30 (100%)
Radiotherapy	12 (40.0%)
Chemotherapy	30 (100%)
Second-generation ADT	
Abiraterone only	16 (53.3%)
Enzalutamide only	1 (3.3%)
Both	13 (43.3%)
Extent of disease	
Bone metastasis	30 (100%)
Lymph node metastasis	17 (56.7%)
Visceral metastasis	9 (30.0%)
Liver metastasis	7 (23.3%)
Lung metastasis	3 (10.0%)
Brain metastasis	1 (3.3%)
Number of treatment cycles	
1	30 (100%)
2	22 (73.3%)
3	11 (36.7%)
Median	2

GS = Gleason score; PSA = prostate-specific antigen; TLP = total lesion prostate-specific membrane antigen; ECOG = Eastern Cooperative Oncology Group; ADT = androgen deprivation therapy

Supplemental Table 2 Cumulative treatment-related toxicity and side effects of all grade

Adverse Events		Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	baseline	2 (6.7%)	1 (3.3%)	0	0
	1 cycle	7 (23.3%)	3 (10.0%)	0	0
	2 cycles	10 (33.3%)	5 (16.7%)	0	0
	3 cycles	11 (36.7%)	5 (16.7%)	0	0
Dry mouth	baseline	0	0	0	0
	1 cycle	5 (16.7%)	2 (6.7%)	0	0
	2 cycles	7 (23.3%)	3 (10.0%)	0	0
	3 cycles	8 (26.7%)	4 (13.3%)	0	0
Nausea	baseline	1 (3.3%)	0	0	0
	1 cycle	6 (20.0%)	1 (3.3%)	0	0
	2 cycles	9 (30.0%)	2 (6.7%)	0	0
	3 cycles	10 (33.3%)	2 (6.7%)	0	0
Temporary ostealgia	baseline	0	0	0	0
	1 cycle	6 (20.0%)	0	0	0
	2 cycles	8 (26.7%)	1 (3.3%)	0	0
	3 cycles	8 (26.7%)	1 (3.3%)	0	0
Diarrhea	baseline	0	0	0	0
	1 cycle	2 (6.7%)	0	0	0
	2 cycles	2 (6.7%)	0	0	0
	3 cycles	3 (10.0%)	0	0	0
Decreased appetite	baseline	0	0	0	0
	1 cycle	1 (3.3%)	0	0	0
	2 cycles	2 (6.7%)	0	0	0
	3 cycles	2 (6.7%)	0	0	0
Anemia	baseline	6 (20.0%)	1 (3.3%)	0	0
	1 cycle	5 (16.7%)	4 (13.3%)	0	0
	2 cycles	6 (20.0%)	5 (16.7%)	3 (10.0%)	0
	3 cycles	8 (26.7%)	7 (23.3%)	5 (16.7%)	0
	Long-term	8 (26.7%)	8 (26.7%)	5 (16.7%)	
Thrombocytopenia	baseline	0	0	0	0
	1 cycle	1 (3.3%)	2 (6.7%)	1 (3.3%)	0
	2 cycles	6 (20.0%)	3 (10.0%)	2 (6.7%)	0
	3 cycles	9 (30.0%)	6 (20.0%)	3 (10.0%)	0
	Long-term	9 (30.0%)	6 (20.0%)	4 (13.3%)	
Leukopenia	baseline	2 (6.7%)	0	0	0
	1 cycle	4 (13.3%)	1 (3.3%)	0	0
	2 cycles	7 (23.3%)	4 (13.3%)	1 (3.3%)	0
	3 cycles	10 (33.3%)	5 (16.7%)	3 (10.0%)	0
	Long-term	11 (36.7%)	5 (16.7%)	3 (10.0%)	
Hepatic insufficiency	baseline	0	0	0	0
	1 cycle	0	0	0	0
	2 cycles	0	0	0	0
	3 cycles	0	0	0	0
Renal insufficiency	baseline	0	0	0	0
	1 cycle	0	0	0	0
	2 cycles	0	0	0	0
	3 cycles	0	0	0	0
	Long-term	2 (6.7%)	1 (3.3%)	0	0

1 cycle: the time interval between 1st and 2nd administration of ^{177}Lu-EB-PSMA;

2 cycles: the time interval between 1st and 3rd administration of ^{177}Lu-EB-PSMA;

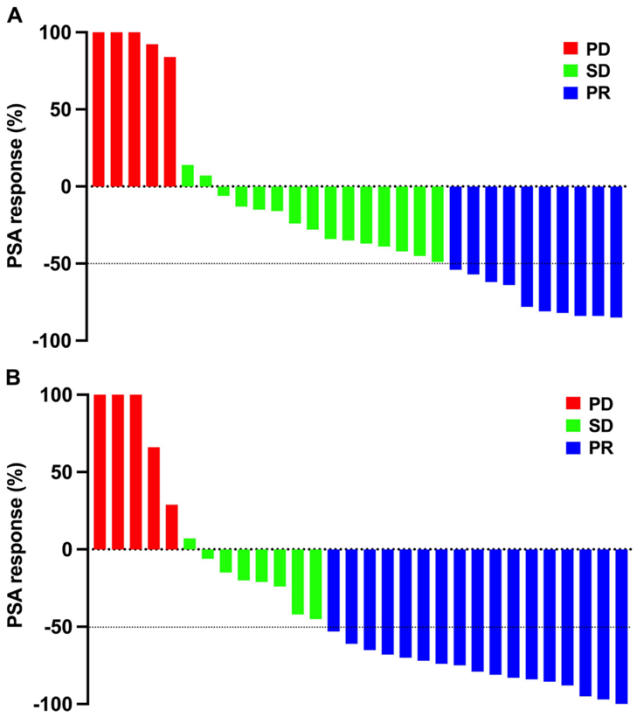
3 cycles: the time interval between 1st administration of ^{177}Lu-EB-PSMA and 10 weeks after the 3rd cycle of PRLT;

Long-term: the time interval between 1st administration of ^{177}Lu-EB-PSMA and (1) death from any cause, or (2) start of another treatment modality, or (3) the latest study visit.

Supplemental Table 3 Pre- and post-therapy HRQOL scores measured with EORTC QLQ-C30 and mean difference in scores from baseline

Scale	Baseline	Post-Cycle 1		Post-Cycle 2		Post-Cycle 3	
	30	29		21		11	
	Mean (SD)	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value
Functioning scales							
Physical	56.5 (20.9)	57.1 (20.1)	0.923	69.6 (12.4)	0.003	73.3 (14.3)	0.002
Role	62.7 (32.0)	77.5 (18.6)	0.082	65.9 (26.8)	0.907	69.1 (22.5)	0.601
Emotional	79.9 (22.1)	86.8 (21.3)	0.232	78.3 (15.4)	0.393	75.7 (21.3)	0.343
Cognitive	90.2 (11.9)	81.4 (14.3)	0.024	85.3 (15.1)	0.125	90.6 (12.5)	0.775
Social	72.5 (23.5)	83.3 (22.0)	0.102	69.0 (24.2)	0.625	71.3 (22.5)	0.918
Global QOL	48.0 (16.5)	51.0 (20.7)	0.429	59.9 (22.4)	0.013	69.0 (28.4)	0.006
Symptom scales							
Fatigue	33.3 (21.5)	45.7 (21.1)	0.008	39.6 (16.2)	0.132	21.5 (18.2)	0.671
Nausea and vomiting	5.8 (8.2)	10.8 (12.0)	0.087	8.3 (12.2)	0.432	11.9 (23.0)	0.068
Pain	32.4 (18.1)	33.3 (20.4)	0.848	14.6 (17.1)	0.002	8.9 (12.4)	0.000
Dyspnea	15.7 (16.1)	15.7 (20.0)	0.999	14.6 (14.7)	0.999	10.0 (12.3)	0.165
Insomnia	29.4 (28.6)	33.3 (28.9)	0.608	27.1 (30.4)	0.999	22.2 (16.2)	0.751
Appetite loss	7.8 (14.6)	23.5 (22.9)	0.016	12.5 (24.0)	0.544	2.2 (8.6)	0.082
Constipation	19.6 (26.5)	21.6 (28.7)	0.751	22.9 (29.1)	0.457	17.8 (30.5)	0.856
Diarrhea	3.9 (11.1)	15.7 (23.9)	0.029	8.3 (14.9)	0.333	6.7 (18.7)	0.719
Financial impact	31.4 (34.3)	27.4 (24.3)	0.496	25.0 (22.8)	0.270	17.8 (21.3)	0.089

QOL= quality of life



Supplemental Figure 1. Waterfall plots of PSA response after the first ^{177}Lu-EB-PSMA cycle (**A**) and best PSA response to all courses of ^{177}Lu-EB-PSMA therapy (**B**) in the entire cohort.