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^{177}Lu-PSMA for Extended Treatment of Metastatic Castration-Resistant Prostate Cancer

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ABSTRACT

To evaluate feasibility, additional benefit and toxicity of treatment extension of prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) in patients with metastatic castration-resistant prostate cancer (mCRPC).

Methods: From 208 patients treated with ^{177}Lu-PSMA every 6-8 weeks, 26 patients who had not progressed and not experienced ≥grade 3 toxicity after 6 cycles continued to receive ^{177}Lu-PSMA until disease progression or complete remission or removal from treatment for toxicity or patient preference. Response rates, the additional benefit of treatment extension, and toxicity were assessed.

Results: During treatment extension (up to 13 cycles), 50% of patients achieved an additional PSA decline (-52%±34%, range -1% to -100%), with 8% of patients receiving congruent PSA-based and imaging-based complete response. Median PFS was 450 days. Acute toxicity, including myelosuppression, was mild (≤ grade 2). Xerostomia and chronic kidney disease became more common with repetitive dosing.

Conclusion: Extension of ^{177}Lu-PSMA treatment is feasible and effective in mCRPC.

Key words: Prostate-specific membrane antigen (PSMA); Lu-PSMA; duration; treatment extension; therapy

INTRODUCTION

Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) has been shown to induce high prostate-specific antigen response rates, and to prolong imaging-based progression-free survival and overall survival when added to standard care in patients with advanced metastatic castration-resistant prostate cancer (mCRPC) (*1, 2*). The standard RLT regimen consists of intravenous infusions of ^{177}Lu-PSMA for four cycles, with two additional cycles (up to six cycles in total) administered in patients having evidence of response (*1, 3*). This standard four-cycle regimen was chose empirically, based on limited experience and in absence of individual dosimetry (*4, 5*).

In a post hoc analysis of the Mainsail study, the total number of delivered docetaxel cycles is an independent factor for overall survival. Patients who received more than 10 cycles of docetaxel had a higher median overall survival (*6*). In other therapies for mCRPC such as second-line hormonal therapy, reasons for any treatment discontinuation pertain to either disease progression or to unacceptable adverse events (*7*). Moreover, the safety and efficacy of extended treatment with ^{177}Lu-DOTATATE in other entities has recently been reported (*8*).

To our knowledge, there are limited data evaluating if extended treatment beyond 6 cycles is feasible and can enhance PSA response rates. Here, we retrospectively analyzed feasibility, additional benefit and toxicity of extended treatment in all patients who had undergone extended ^{177}Lu-PSMA therapy at our institution.

MATERIALS AND METHODS (see supplemental data for full version)

Study Population

26 patients with advanced mCRPC referred for a ^{177}Lu-PSMA RLT between November 2016 and May 2021 were included in this retrospective analysis (Table 1). Prior to start of ^{177}Lu-PSMA RLT, all patients had demonstrated progression following standard systemic therapies (*2*). ^{177}Lu-PSMA-617 was administered in compliance with the Declaration of Helsinki, §37 and the German Medicinal Products Act, AMG §13.2b. The institutional review board at Hannover Medical School approved this retrospective study (No. 9182_BO_S_2020). All patients provided written informed consent for the retrospective data analysis.

^{177}Lu-PSMA RLT, Assessment of Treatment Response and Toxicity

Patients received 6.0-7.4 GBq of a ^{177}Lu-PSMA-ligand every 6-8 weeks (*2, 9*). Patients proceeded to the next cycle if not showing PSA progression about 2 weeks before the next administration, and continued to receive ^{177}Lu-PSMA until disease progression or death or complete remission or removal from treatment for toxicity or deterioration in performance status or patient preference. From 208 mCRPC patients, 26 patients continued to receive ^{177}Lu-PSMA beyond 6 cycles. These patients received either ^{177}Lu-PSMA-617 (*n*=8) (*2, 9*) or ^{177}Lu-PSMA I&T (*n*=7) (*10*) or both ligands (*n*=11). PSA levels and additional laboratory parameters (including full blood count, liver function parameters, and serum creatinine levels) were re-evaluated every 2 weeks. Treatment response was defined as PSA response rate according to *Prostate Cancer Clinical Trials Working Group 2* criteria (*11*), in conjunction with PSMA-targeted PET/CT. Toxicity was

assessed according to the *Common Terminology Criteria for Adverse Events* (CTCAE) (version 5.0).

Statistical Analysis

Continuous variables are expressed as mean±standard deviation (SD) and range. Waterfall plots were used to visualize PSA response. Survival curves were created using the Kaplan-Meier method. Statistical significance was established for *P* values of ≤0.05. Statistical analysis was performed using GraphPad Prism (version 9.0 for Windows; Graphpad Software).

RESULTS

26 (12.5%) of 208 patients (see Supplemental Figure 1 for reasons for treatment discontinuation) continued to receive Lu-PSMA after 6 cycles. Patients received up to 13 cycles of Lu-PSMA (9±2, range 7 to 13). Patients were treated until disease progression (*n*=18) or complete remission (*n*=2) or removal from treatment for toxicity (*n*=1) or patient preference (*n*=2 in near CR, *n*=1 after stroke, *n*=1 after radiation of cerebral metastases). Treatment was ongoing in one patient at the time of analysis.

Extended Treatment may Deepen the Response to Lu-PSMA, but only in a Subset of Patients

Efficacy of 6 cycles. Following 6 cycles of Lu-PSMA (Figure 1A), PSA at C7D1 had declined in all patients (-86%±24%, range -4% to -100%), and 23 (88%) of 26 patients had demonstrated a PSA response. The best PSA decline until C7D1 was

-88%±22%, range -11% to -100%), and 24 (92%) of 26 patients demonstrated a PSA response. PSA declined more than 90% in 19 (73%) of patients (Figure 1B).

Efficacy of additional cycles. During treatment extension (Figure 1C), 50% of patients achieved an additional PSA decline (-52%±34%, range -1% to -100%). Two patients who had already achieved biochemical CR (one during the first 6 cycles, one during treatment extension), but still had PSMA-positive disease, achieved also imaging-based CR during treatment extension (Figure 2). However, the PSA nadir was reached within the first 6 cycles in 11 (42%) of 26 patients.

Median PFS was 450 days (276 to 1742 days; time from first RLT cycle to progression, Figure 3). With treatment extension, 42% of patients had stable disease for at least 6 additional months after end of standard regimen (in patients with CR: 1126 and 931 days).

Extended Treatment was Generally well Tolerated

After 6 cycles and during extended treatment, toxicities did not exceed grade 2. Acute toxicity, including myelosuppression, was mild. Chronic kidney disease and xerostomia (Table 2) became more common with repetitive dosing, and aggravated over time, although these side effects did not exceed grade 2. Dose reductions were made for 2 patients, exclusively because of hematotoxicity. One patient discontinued RLT because of aggravating grade 2 nephrotoxicity.

DISCUSSION

Extended PSMA RLT is feasible, and may contribute to deeper responses. Both additional PSA responses and a further PSA decline could be induced in patients undergoing extended treatment. Nevertheless, only 12.5 % of all patients proceeded to treatment extension, and an even smaller number of all patients will actually benefit from such an approach. For the majority of patients, the standard 4+2 cycles regimen may therefore be the maximum amount of treatment (*1, 4*). Of note, pursuing such a more aggressive treatment regimen, we nevertheless demonstrated that even consistent PSA-based and imaging based complete remission may be induced in patients having shown a partial response after 6 cycles. In the VISION trial, imaging-based progression-free survival was 8.7 months (*1*). PFS in our extended treatment cohort was 15 months. Although these cohorts cannot be directly compared, these findings support the potential of maintaining treatment success in selected patients through additional RLT cycles. However, even patients with CR ultimately relapsed, underling that even the best PSA response may not be durable, although remarkable PFS of up to 1742 days could be achieved.

Toxicity was generally mild, as reported before for fewer cycles (*1-3*). However, xerostomia became more frequent as the number of treatment cycles increased. Likewise, kidney function declined and we had to discontinue RLT in one patient with a significant increase in creatinine levels. Nevertheless, we did not observe grade 3 or 4 toxicities. However, as some sequelae of high organ doses may develop with temporal delay, one cannot rule out that there are late toxicities which we did not became aware of during follow-up if patients continued care elsewhere. In addition, many patients prone to development of relevant toxicity likely already discontinued treatment before a

decision for extended treatment was made (*1*). Renal and salivary gland toxicity may become particularly relevant if patients will receive PSMA-targeted RLT earlier after diagnosis, e.g. at first biochemical recurrence.

Limitations of this study include its retrospective, single-center nature and limited patient number. Patients received two different compounds, i.e. ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA I&T. However, a recent study showed that both radiopharmaceuticals are similarly effective in patients with mCRPC, with very low rates of clinically relevant toxicities (*12*). The study concept comes along with an inherent selection bias towards patients with exceptional PSA response and mild toxicity. The selection bias along with the limited patient number prevented a reasonable analysis of predictors for actual benefit of extended treatment. Future work should therefore put effort in identifying those patients which will have deeper responses through extended treatment.

CONCLUSION

We demonstrated that extension of ^{177}Lu-PSMA treatment is feasible and effective in selected patients with mCRPC. However, only a small fraction of all treated patients may proceed to and benefit from extended treatment.

DISCLOSURE

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

KEY POINTS

QUESTION: Is extended treatment with prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT)) feasible and active in patients with metastatic castration-resistant prostate cancer?

PERTINENT FINDINGS: In a retrospective study in patients receiving up to 13 ^{177}Lu-PSMA cycles every 6 to 8 weeks until disease progression or complete remission or removal from treatment for toxicity or death or patient preference, 50% of patients achieved an additional PSA decline and/or complete response, but xerostomia and chronic kidney disease became more common with repetitive dosing.

IMPLICATIONS FOR PATIENT CARE: Extended treatment to deepen responses is feasible and active.

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Figure legends

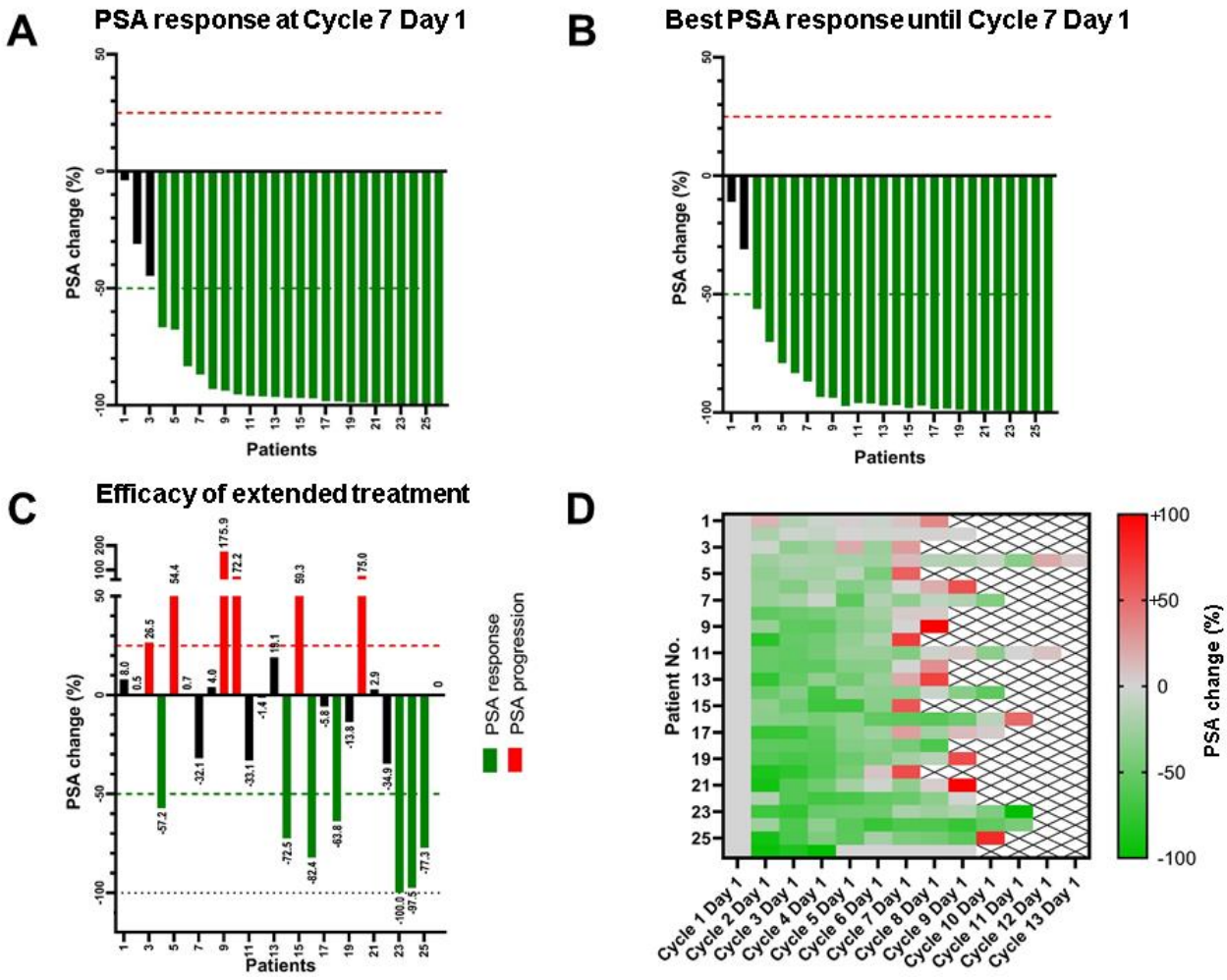

Figure 1 *Efficacy of PSMA-targeted RLT.* A Following 6 cycles of PSMA-targeted RLT, PSA had declined in all patients (-86%±24%, range -4% to -100%), and 88% of patients had demonstrated a PSA response. B Best PSA response within the first 6 cycles was -88%±21% (range, -11% to -100%), and 92% of patients demonstrated a PSA response. C During treatment extension, 13 patients achieved an additional PSA decline compared to nadir, whereas PSA increased in 12 patients. D Heat map showing % PSA reduction between individual cycles in patients receiving extended treatment. The majority of patients had progressed at Cycle 9 Day 1, or discontinued treatment.

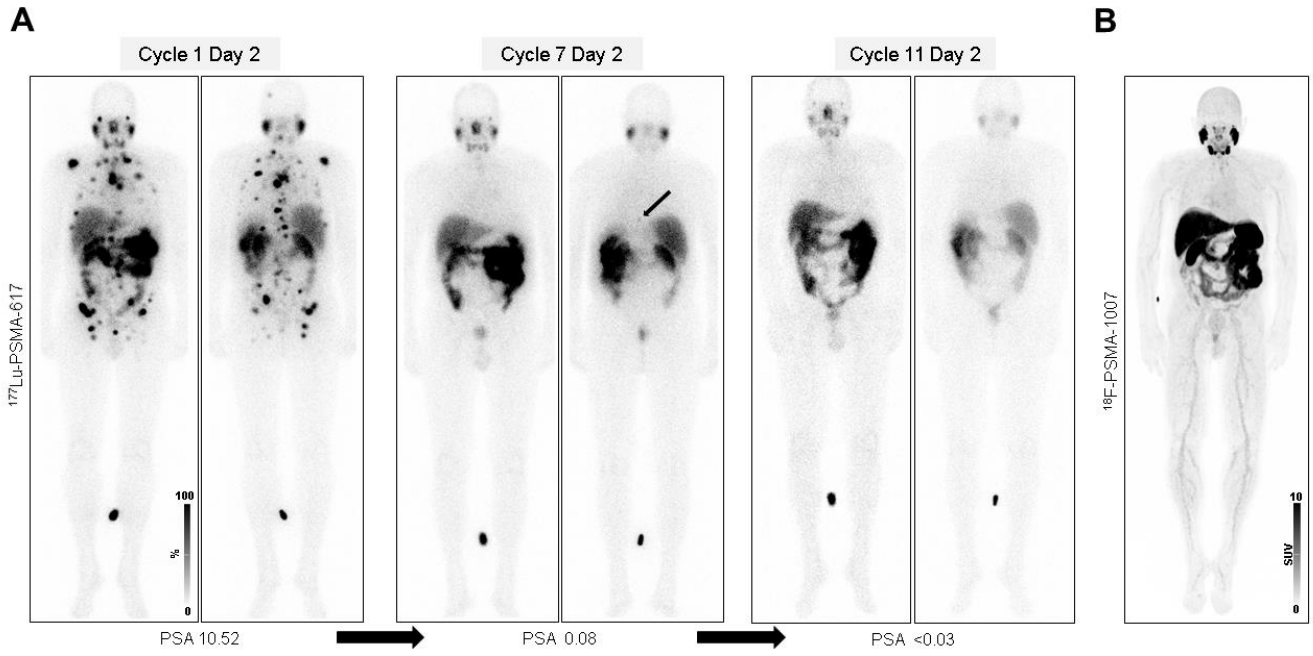

Figure 2 *Efficacy of extended ^{177}Lu-PSMA treatment in a 75-year-old man with mCRPC.* A Postherapeutic scintigraphic images at Cycle 1 Day 2 showing widespread osseous and lymph node metastases (*left panel*). Following 6 cycles, there was a PSA response, but PSA was still measurable and residual PSMA-expressing metastases could be noted (*middle panel, arrow*). At Cycle 11 Day 2, there was both PSA-based and imaging based complete remission (*right panel*), confirmed by targeted PET (B).

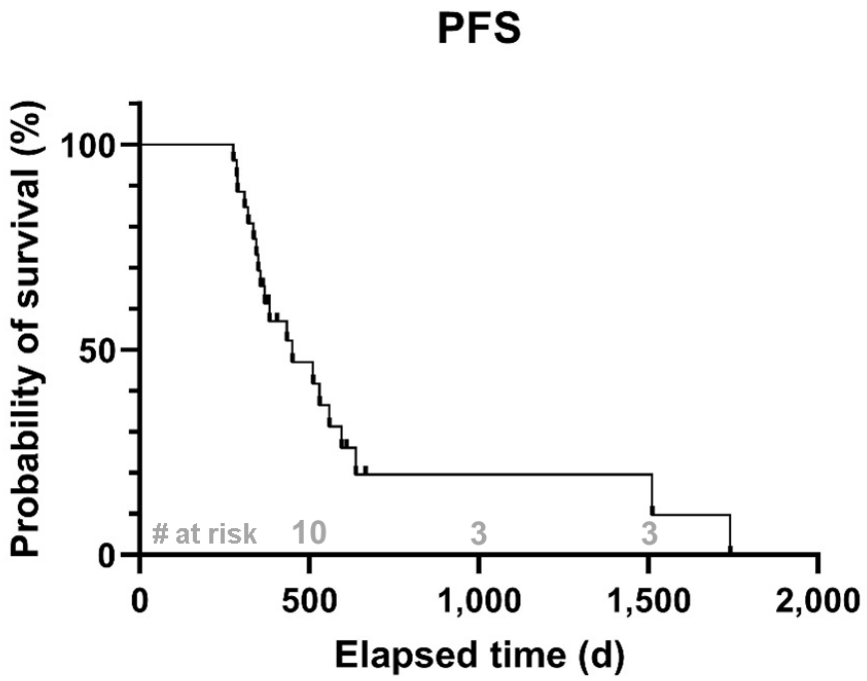

Figure 3 Median PFS was 450 days in patients receiving extended treatment.

Table 1 Characteristics of study population (*n*=26).

Parameter	Total study population
Number (*n*)	26 (100%)
Age (years)	74.6 ± 6.5 (61.9 to 84.6)
Gleason grade (Median (range))	8 (7 to 9)
Laboratory values at C1D1	
PSA (ng/mL)	413 ± 719 (7 to 3341)
Hemoglobin (g/dL)	12.3 ± 1.0 (10.5 to 14.5)
Leukocyte count (10^3/µL)	7.0 ± 1.9 (3.4 to 10.2)
Platelets (10^3/µL)	247 ± 81 (131 to 480)
eGFR (ml/min/1.72m^2)	76 ± 17 (44 to 105)
AST (U/L)	29 ± 20 (13 to 97)
Alkaline phosphatase (U/L)	149 ± 120 (40 to 543)
LDH(U/L)	222 ±59 (61 to 332)
Laboratory values at C7D1	
PSA (ng/mL)	30 ± 48 (0 to 184)
Hemoglobin (g/dL)	11.0 ± 1.0 (8.7 to 12.8)
Leukocyte count (10^3/µL)	5.4 ± 1.1 (3.2 to 7.5)
Platelets (10^3/µL)	183 ± 52 (94 to 305)
eGFR (ml/min/1.72m^2)	72 ± 17 (45 to 96)
AST (U/L)	26 ± 9 (16 to 51)
Alkaline phosphatase (U/L)	91 ± 55 (41 to 314)
LDH(U/L)	214 ±51 (150 to 338)
Site of disease (no. of patients)	
Prostate (bed)	9 (35%)
Bone	21 (81%)
Lymph nodes	20 (77%)
Liver	2 (8%)
Other	2 (8%)
Previous therapies (no. of patients)	
Androgen-deprivation therapy	26 (100%)
Abiraterone acetate	16 (62%)
Enzalutamide	17 (65%)
Chemotherapy	19 (73%)
Docetaxel (1st line)	19 (73%)
Cabazitaxel (2nd line)	8 (31%)
External radiation therapy	17 (65%)

AST - Aspartate transaminase; eGFR - estimated glomerular filtration rate; LDH -lactate dehydrogenase; PSA - prostate-specific antigen; SD - standard deviation

Table 2 Toxicity (new events) following 6 cycles of ^{177}Lu-PSMA RLT and additional events during extended treatment

	Cycles 1 to 6	*Extended treatment*
Parameter	*Grade ≤ 2*	*Grade ≤ 2*
Anaemia	13 (50%)	5 (19%)
Leukopenia	0 (0%)	2 (8%)
Thrombocytopenia	5 (19%)	4 (15%)
Renal toxicity (CKD)	5 (19%)	3 (12%)
Hepatotoxicity	1 (4%)	1 (4%)
Dry mouth	12 (46%)	4 (15%)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	0 (0%)	2 (8%)
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617	0 (0%)	1 (4%)
Adverse event that led to death	0 (0%)	0 (0%)

CKD – chronic kidney disease; Lu – lutetium; PSMA – prostate-specific membrane antigen. No ≥ 3 grade toxicities were observed.

MATERIALS AND METHODS (Full version)

^{177}Lu-PSMA RLT, Assessment of Treatment Response and Toxicity

Patients received 6.0-7.4 GBq of a ^{177}Lu-PSMA-ligand every 6-8 weeks, as described previously (*2, 9*). Patients proceeded to the next cycle if not showing PSA progression about 2 weeks before the next administration, and continued to receive ^{177}Lu-PSMA until disease progression or death or complete remission or removal from treatment for toxicity or deterioration in performance status or patient preference. From 208 mCRPC patients treated at Hannover Medical School at the time of this analysis, 26 patients continued to receive ^{177}Lu-PSMA beyond 6 cycles based on the aforementioned criteria. These patients received either ^{177}Lu-PSMA-617 (*n* = 8) (*2, 9*) or ^{177}Lu-PSMA I&T (*n* = 7) (*10*) or both ligands (*n* = 11), depending on availability of the precursor at the time of treatment. PSA levels and additional laboratory parameters (including full blood count, liver function parameters, and serum creatinine levels) were re-evaluated every 2 weeks. Treatment response was defined as PSA response rate according to *Prostate Cancer Clinical Trials Working Group 2* (PCWG2) criteria defined as a 50% or more PSA decline from baseline with confirmation 3–4 weeks apart (*11*). In addition, a PSMA-targeted PET/CT scan was performed for evaluation of treatment response following every second cycle. In particular, unequivocal complete remission (CR) required undetectable PSA and no evidence of residual PSMA-positive disease on PET/CT. Progressive disease (PD) was defined as a PSA increase of 25 % or more. Toxicity was assessed according to the *Common Terminology Criteria for Adverse Events* (CTCAE) (version 5.0).

Statistical Analysis

Categorical variables are presented with absolute and relative frequencies. Continuous variables are expressed as mean±standard deviation (SD) and range. Waterfall plots were used to visualize PSA response. Survival curves were created using the Kaplan-Meier method. Due to limited sample size, only descriptive analyses were performed. Statistical significance was established for *P* values of ≤0.05. Statistical analysis was performed using GraphPad Prism (version 9.0 for Windows; Graphpad Software).

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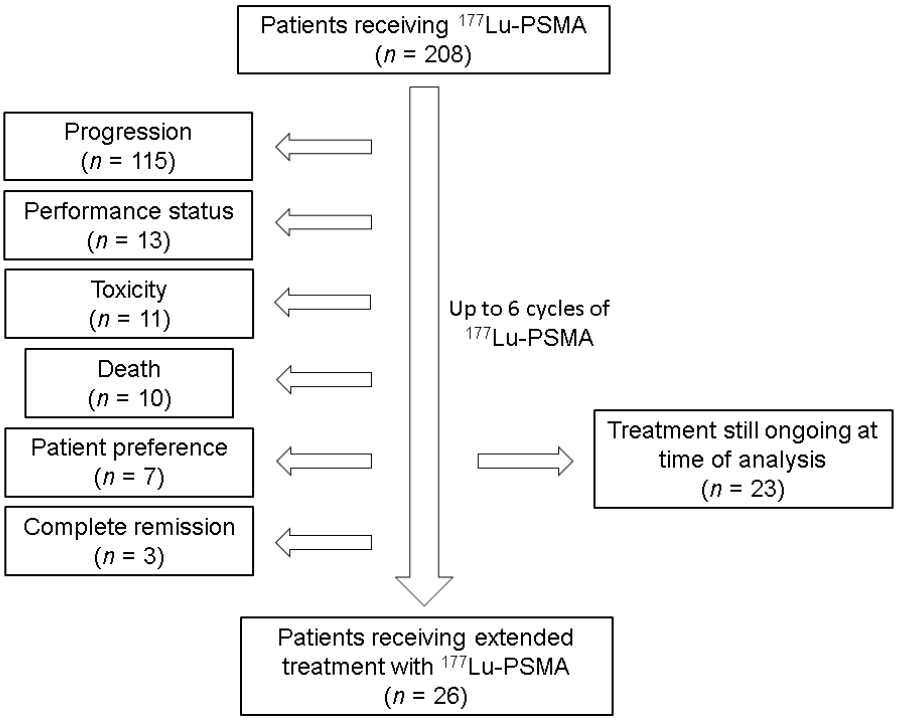
Supplemental Figures



Supplemental Figure 1 *Reasons for treatment discontinuation in patients treated with ^{177}Lu-PSMA at Hannover Medical School.* From 208 patients commencing RLT with ^{177}Lu-PSMA, 26 patients received extended treatment with more than 6 cycles at the time of analysis. The main reasons for treatment discontinuation following a maximum of 6 cycles of RLT were either progression (*n* = 115), deterioration in performance status (*n* = 13) or relevant toxicity (≥ grade 3, *n* = 11).