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German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients

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Abstract

^{177}Lutetium labeled PSMA-617 is a promising new therapeutic agent for radioligand therapy (RLT) of patients with metastatic castration resistant prostate cancer (mCRPC). Initiated by the German Society of Nuclear Medicine a retrospective multicenter data analysis was started in 2015 to evaluate efficacy and safety of ^{177}Lu-PSMA-617 in a large cohort of patients.

Methods:

145 patients (median age 73 years, range 43-88) with mCRPC were treated with ^{177}Lu-PSMA-617 in 12 therapy centres between February 2014 and July 2015 with one to four therapy cycles and an activity range of 2 to 8 GBq per cycle. Toxicity was categorized by the common toxicity criteria for adverse events (CTCAE 4.0) based on serial blood tests and the attending physician's report. Primary endpoint for efficacy was biochemical response as defined by a PSA decline ≥ 50% from baseline to at least two weeks after start of RLT.

Results:

A total of 248 therapy cycles were performed in 145 patients. Data for biochemical response were available in 99 patients and data for physician-reported/lab-based toxicity in 145/121 patients. The median follow-up was 16 weeks (range 2-30 weeks). Nineteen patients died during the observation period. Grade 3 to 4 hematotoxicity occurred in 18 patients: 10%, 4% and 3% of the patients experienced anemia, thrombocytopenia and leukopenia, respectively. Xerostomia occurred in 8%. Overall biochemical response rate was 45% following all therapy cycles, while 40% of patients already responded after a single cycle. Elevated alkaline phosphatase and presence of visceral metastases were negative predictors and the total number of therapy cycles positive predictors of biochemical response.

Conclusion:

The present retrospective multicenter study of ^{177}Lu-PSMA-617 RLT demonstrates favorable safety and high efficacy exceeding those of other third line systemic therapies in mCRPC patients. Future Phase II/III studies are warranted to elucidate the survival benefit of this new therapy in patients with mCRPC.

Introduction

According to the American Cancer Society, prostate cancer is the most common cancer and second most frequent cause of cancer related death in Men in the United States *(1)*. The five year survival rate of locally advanced prostate cancer is nearly 100%, however the rate is significantly lower in case of metastatic disease (31%)*(2)*. Therefore, developing new strategies for diagnosis, imaging and treatment of metastatic prostate cancer is of major importance.

Prostate specific membrane antigen (PSMA) is overexpressed in prostate cancer and even more so with increasing de-differentiation or castration resistant disease *(3)*. Radiolabeled ligands targeting PSMA have recently been subject of numerous studies showing high sensitivity and contrast in detecting recurrent prostate cancer and its metastases with remarkable detection rates *(4-7)*. Recent studies have also shown high sensitivity of PSMA targeted imaging in determining local extent of disease prior radical prostatectomy *(8-10)*. The high PSMA expression in prostate cancer metastases makes it also a promising approach to develop new tracers for targeted radionuclide therapies.

Benesova et al. introduced a high-affinity PSMA ligand (PSMA-617) that can be labeled with ^{68}Ga or ^{177}Lu and demonstrates superior tumor to background uptake *(11)*. Since 2015, several studies reported promising results for response rates and a favorable safety profile after RLT with ^{177}Lu-PSMA-617 in patients with metastatic castration resistant prostate cancer (mCRPC)*(12-16)*. In a single center study of 28 patients a slight improvement of survival compared to a matched group of best supportive care patients (historical population) was demonstrated *(16)*. However, each group only presented insight into a small patient cohort with insufficient power for the evaluation of a new therapy.

To overcome this limitation, a retrospective multicentre study was initiated by the German Society of Nuclear Medicine in July 2015. Twelve therapy centers retrospectively collected and pooled

data on safety and efficacy of ^{177}Lu-PSMA-617 RLT. This retrospective multicentre study aims at analyzing the optimal dose and number of therapy cycles and predictors of response in more detail.

Materials and Methods

Patient population

Between February 2014 and end of July 2015 a total of 145 patients (median age 73 years, range: 43-88) with mCRPC were treated with 248 cycles of ^{177}Lu-PSMA-617 in 12 nuclear medicine centers throughout Germany. All patients meeting the inclusion criteria within the study timeline were included. There were no random or systematic exclusions. Numbers of patients previously included in smaller cohort studies are given in *Supplemental Table 1*. Inclusion criteria for this retrospective analysis were: (a) progressive castration resistant prostate cancer, (b) PSMA-expression of the majority of lesions as determined by PSMA-targeted imaging and (c) at least one cycle of ^{177}Lu-PSMA-617 RLT. In addition patients experienced progression under (a) next generation androgen deprivation therapy (e.g. Abiraterone, Enzalutamide) or (b) first or second line chemotherapy (e.g. Docetaxel, Cabazitaxel) or were not eligible for chemotherapy. All patients eligible for ^{223}Ra, received this treatment before undergoing ^{177}Lu-PSMA-617 RLT. The decision for ^{177}Lu-PSMA-617 RLT was made by the local interdisciplinary tumor board at each therapy center.

RLT with ^{177}Lu-PSMA-617 was based on a compassionate use. Patients gave their written consent after being informed about possible side effects and risks of this new therapeutic agent. The production and administration of ^{177}Lu-PSMA-617 was performed in accordance to the German Medical Products Act AMG §13 2b. Anonymized data were collected by the Department of Nuclear Medicine of the Ludwig-Maximilians-University Munich (LMU) and the local ethics

committee approved this retrospective analysis. Requirement to obtain informed consent for entry into the study was waived.

Preparation and administration of ^{177}Lu-PSMA-617

PSMA-617 was obtained from ABX GmbH (Radeberg, Germany). Detailed radiosynthesis procedures have been described in detail before *(12, 14-16)*. Quality control parameters were monitored by experienced radiochemists and double checked by attending physician as follows: a) radiochemical purity, b) radiochemical identity, c) pH value, d) ethanol content, e) endotoxin content and f) proof of sterility.

^{177}Lu-PSMA-617 was administered by slow intravenous injection (1 – 30 minutes) followed by a Ringer or Saline solution. Cooling of salivary glands (performed in 11 of 12 therapy centers) using cool pack started 30 minutes prior to injection and was applied until 4 hours after injection. Further therapy cycles were performed 8 to 12 weeks apart.

Whole body scintigraphy and additional SPECT/CT were performed at least one time 24-48 hours after injection in order to confirm uptake and retention of ^{177}Lu-PSMA-617 in tumor tissue. Patients were released from the ward as per local regulatory guidelines (less than 3.5 µSv/h measured at a distance of 2 m).

Safety

Blood levels for hemoglobin, white blood cells, platelets, creatinine, alkaline phosphatase and liver parameters were obtained at each participating therapy center shortly before RLT and every 2 to 4 weeks thereafter. Based on blood levels, toxicity was categorized using the Common Toxicity Criteria for Adverse Events (CTCAE, Version 4.03). In addition, investigators reported

all (also if unlikely associated with RLT) adverse events (AE) and serious AE (SAE) during and after RLT with ^{177}Lu-PSMA-617.

Efficacy and response

The prostate specific antigen (PSA) was determined by the participating center shortly before each RLT and at 2 to 4 week interval thereafter. The primary endpoint was biochemical response determined by change of PSA values. According to Prostate Cancer Work Group 3 Criteria (PCWG3) a PSA decline ≥ 50% and more was considered as a response *(17)*.

Statistics

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for analysis. Data are presented as medians and ranges or as frequencies. Univariate and multivariate logistic regression was applied to obtain predictors of biochemical response. Results of logistic regression are presented as odds ratios (OR) and corresponding 95% confidence intervals (CI). P-values ≤ 0.05 were considered significant. Parameters with a P-value <0.05 in the univariate analysis were included in the multivariate analysis.

Results

Patient characteristics are given in table 1. A total of 248 therapy cycles were performed in 145 patients (median age: 73 years, range: 43-88) until July 31th 2015. An average dose of 5.9 GBq ^{177}Lu-PSMA-617 was administered (range: 2 – 8 GBq, Table 2). 54% of the patients (N=79) had previously received at least one line of chemotherapy, 64% (N=93) and 52% (N=76) received

Abiraterone and Enzalutamide, 17% (N=24) had received ^{223}Ra prior to ^{177}Lu-PSMA-617 RLT. Other previous therapies are listed in table 1.

During the observation period (median 16 weeks, range 2-30 weeks) 19 patients (13%) died. Of these patients, ten patients received 1 RLT cycle, six received 2 and three patients received 3 cycles. The participating centers did not document a therapy related death.

Safety

Data for physician-reported/lab-based toxicity in 145/121 patients. 29 patients had lab follow-up for less than 6 weeks after the first cycle. Adverse events after ^{177}Lu-PSMA-617 are summarised in Table 3. Grade 3-4 hematologic adverse events occurred in 18 of 145 patients (12%): one patient experienced severe leukopenia, 11 (8%) patients anemia, 2 (2%) patients thrombocytopenia and four patients a combination of these conditions. Grade 3 to 4 hematotoxicity was higher in patients with prior ^{223}Ra (5 of 24, 21%). Grade 3 to 4 hematotoxicity was not significantly higher in patients with prior chemotherapy (10 of 79, 13%) as compared to chemotherapy-naive patients (8 of 66, 12%). Average administered dose in patients with grade 3 and 4 hematotoxicity was 5.6 GBq (Range 4 – 7.4 GBq, versus 5.9 GBq in the entire cohort). Data according baseline CTCAE status are added to supplemental materials *(Supplemental Table 2).* Despite 24 grade 3-4 adverse events, the median values in hemoglobin, red and white blood cells and platelets were not changed during the follow-up period (Figure 3). No nephrotoxicity grade 3 or 4 occurred. Mild to moderate xerostomia was reported for 11 (8%) patients by the participating centers. Administered dose in patients with xerostomia was 5.5 GBq (versus 5.9 GBq in the entire cohort). Mild to moderate nausea was reported in 9 (6%) patients.

Efficacy

Serial PSA levels for analyzing biochemical response were available in 99 patients (68%). 46 patients had PSA follow-up of less than 8 weeks after the first cycle or were not eligible for analysis and were not considered for PSA response. Over the entire follow-up period 45 of 99 (45%) patients demonstrated a PSA decline ≥ 50% and were considered biochemical responders. Any PSA decline occurred in 59 of 99 (60%) patients (Figure 1). After the first cycle a PSA decline ≥ 50% occurred in 40 of 99 (40%), any PSA decline in 65 of 99 (66%) patients (Figure 2A). After the second therapy cycle of ^{177}Lu-PSMA-617 RLT a PSA decline ≥ 50% occurred in 35 of 61 (57%) and any PSA decline in 44 of 61 (72%) patients (Figure 2B). Patients receiving a third or fourth cycle of therapy showed a PSA decline ≥ 50% in 13 of 20 (65%) and 3 of 3 (100%) patients, respectively.

To evaluate the probability of biochemical response for different subgroups, odds ratios were calculated (Table 4). The presence of visceral metastases (P<0.01) and alkaline phosphatase ≥ 220 U/L (P<0.01) were associated with a lower rate of biochemical response. Patients with a higher number of therapy cycles (≥3) had a higher rate of biochemical response (P=0.02). All other variables including the activity administered per cycle or cumulatively did not have a relevant effect on response rates (Table 3). In a multivariate analysis, alkaline phosphatase, number of therapy cycles and the presence of visceral metastases remained relevant factors ($p \leq 0.05$) associated with the rate of biochemical response. Response as determined by imaging was available in 47 patients *(Supplemental Figure 1).* Of these, 21 of 47 (45%) experienced partial response and 13 of 47 (28%) had stable disease by imaging follow-up.

Discussion

The present study analyzed data of a retrospective multicentre study for safety and efficacy after ^{177}Lu-PSMA-617 RLT in mCRPC patients from 12 different therapy centers. To our knowledge,

this is the largest cohort analyzed in a multicenter approach for ^{177}Lu-PSMA-617 RLT of prostate cancer. There was no therapy related death after 248 therapy cycles in 145 patients. Few patients experienced serious adverse events. Overall biochemical response rate by PSA decline ≥50% occurred in 45% and 58% of those patients showed a biochemical response already after a single cycle. In the present study any PSA decline occurred in 65% of patients after one cycle of RLT with ^{177}Lu-PSMA-617 and in 72% after the second cycle.

Although the patients in our study were heavily pre-treated and received ^{177}Lu-PSMA-617 RLT as the last therapeutic option, these response rates are comparable and might be superior to response in mCRPC patients undergoing other systemic therapies approved for mCRPC. E.g. only 32% of patients undergoing enzalutamide after abiraterone therapy *(18)* demonstrated PSA decline of ≥50%. In another pooled multicenter cohort of patients with mCRPC and prior abiraterone and chemotherapy with docetaxel, enzalutamide therapy induced PSA decline ≥50% in only 18% of the patients *(19)*. Furthermore, Noonan et al reported a PSA decline ≥50% in only one of 30 (3%) patients treated with abiraterone after progression under enzalutamide *(20)*. A potential reason for this cross-resistance is the emergence of androgen receptor splice variants (AR-Vs) out of which AR-V7 seems to be the most important one *(18)*. ^{177}Lu-PSMA-617 targets PSMA and reveals its efficacy by beta radiation to the target cell and the surrounding environment. Based on its different mechanism of action, ^{177}Lu-PSMA-617 effectively reduced PSA in the majority of patients with advanced CRPC progressive under androgen deprivation therapy. ^{177}Lu-PSMA-617 RLT may thus represent a new treatment option in these patients.

Prior chemotherapy did not significantly influence response rates after ^{177}Lu-PSMA-617 RLT. Alkaline phosphatase < 220, the absence of visceral metastases and the number of therapy cycles were relevant independent predictors of biochemical response. Conversely patients with relevant risk factors (AP≥220 , visceral metastases) should be monitored closely to adjust therapy in case

of disease progression. Several patients underwent more than two cycles of ^{177}Lu-PSMA-617 underlining the potential of sustained disease control after multiple cycles of RLT.

In the current study grade 3-4 hematotoxic adverse events occurred in 12% of the patients: thrombocytopenia and anemia occurred in 4% and 10%, respectively (Table 4). The reported rate of adverse events is slightly lower or comparable to the rate in other mCRPC cohorts. Patients undergoing placebo or ^{223}Ra within the ALSYMPCA trial *(21)* demonstrated grade ≥3 anemia in 13 to 14% and grade ≥3 thrombocytopenia in 3% to 7%. The present study shows significantly lower hematotoxicity when compared to results of second line chemotherapy or radiolabeled antibody therapy: The TROPIC study *(22)* revealed a grade ≥ 3 leukopenia in 68% of patients receiving cabazitaxel and in 42% of patients receiving mitoxantrone vs. 3% in the our study. Application of ^{177}Lu labeled J591 monoclonal antibody was associated with grade 4 thrombocytopenia in 47% of patients, *(23)*. In the present study only 4% of the patients experienced a grade ≥ 3 thyrombocytopenia. Favorable safety of ^{177}Lu-PSMA-617 was previously reported in smaller patient cohorts *(13- 16)* and is now confirmed in this large multicenter dataset.

The adverse events may be due to the advanced disease, prior toxic therapies and in part related to the performed RLT. Mild to moderate xerostomia can be caused by high ^{177}Lu-PSMA-617 uptake and resulting radiation doses >40 Gy to the salivary glands *(24)*. Prior studies reported low rates of chronic xerostomia using beta-emitters like ^{177}Lu-PSMA-617*(13, 15, 16)*. However the overall toxicity profile was favorable. In the future, RLT with ^{177}Lu-PSMA-617 might become an option in patients with advanced mCRPC and multimodal prior therapies.

The major limitation of this study is its retrospective nature. Data were collected in 12 therapy centers which caused inhomogeneity of available data in term of follow-up timeline and

concomitant medication. Data might be biased by patient selection, loss of follow-up and undocumented adverse events. Therefore all inferential statistics are intended to be exploratory (hypotheses generating, as a limitation in all retrospective studies), not confirmatory, and are interpreted accordingly. Primary endpoint for efficacy was based on PSA level. In a retrospective multicenter study change in PSA is more objective and reliably than imaging follow-up, however its clinical value remains controversial *(25)*.

Conclusion

The present multicenter study demonstrates favorable safety and efficacy of ^{177}Lu-PSMA-617 RLT in a large number of mCRPC patients. ^{177}Lu-PSMA-617 RLT might exceed the performance of other third line systemic therapies reported in the literature. Future prospective phase II/III trials are currently in preparation, to evaluate the potential of this new targeted radioligand therapy especially with regards to improve patient survival.

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Disclosure

Uwe Haberkorn is part of the PSMA-617 patent application. All other authors have nothing to disclose according to the subject and matter presented in this manuscript.

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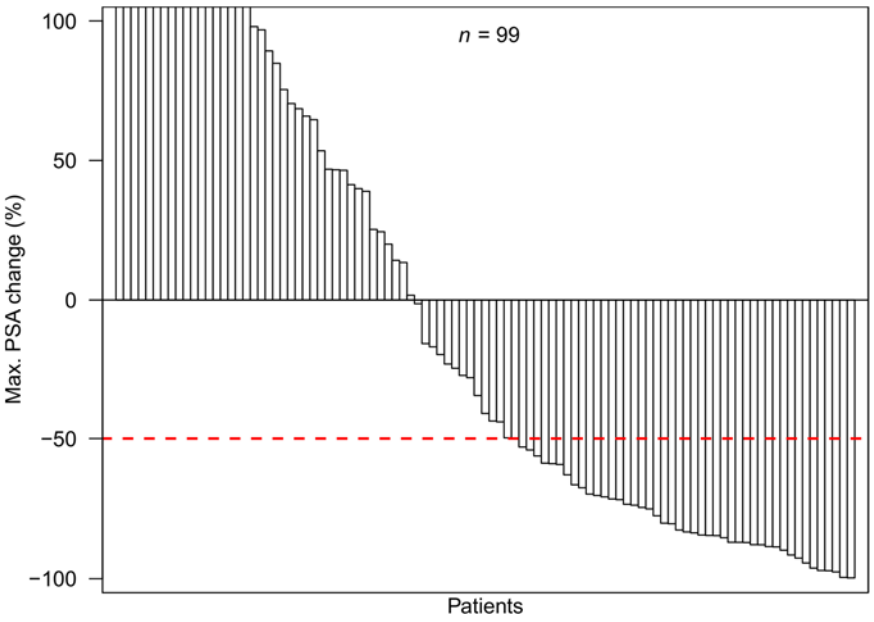


Figure 1. Waterfall plot of maximum PSA change (%) from baseline over total follow-up period. PSA increase of more than 100% was cropped due to simplification.

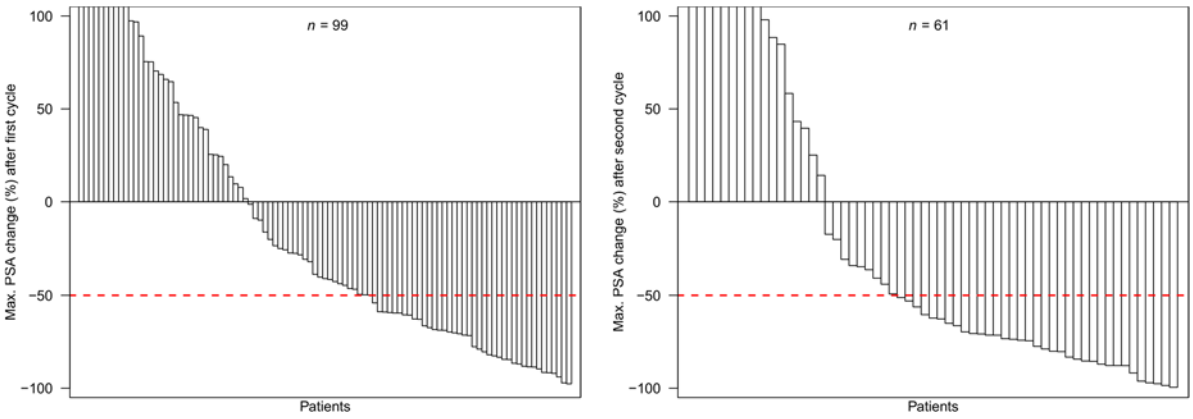


Figure 2. Waterfall plots of maximum PSA change (%) after the first cycle (A) and after the second cycle (B). PSA increase of more than 100% was cropped due to simplification.

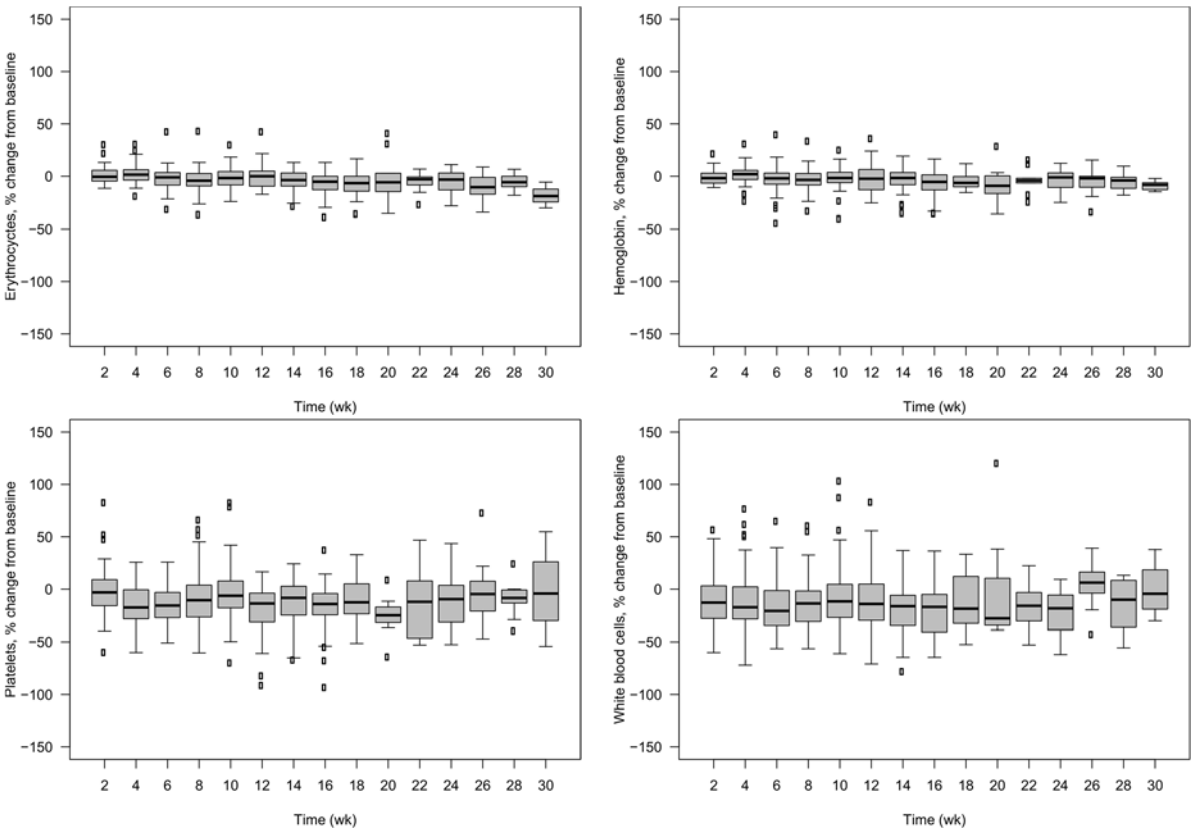


Figure 3. Box-plots of change (%) of erythrocyte count (A), hemoglobin (B), platelet count (C), and white blood cell count (D) from baseline up to 30 weeks after the first therapy cycle.

Tables

Table 1. Patient characteristics at baseline (n=145)

Characteristic		
Age (years)		
Median	73	
Range	43 - 88	
PSA (ng/ml)		
Median	214	
Range	0.35-5436	
AP (U/L)		
Median	120	
Range	38 - 1607	
Hb (g/dl)		
Median	11.3	
Range	6 – 16	
WBC (10^3/µl)		
Median	6.2	
Range	2.4 – 14.3	
Platelets (10^3/µl)		
Median	235	
Range	55 - 557	
Creatinine (mg/dl)		
Median	0.9	
Range	0.3 – 3.1	
Sites of metastases	**N**	**%**
Bone	126	87
Lymph node	112	77
Liver	30	20
Lung	20	14
Other	3	2
Previous therapy of mCRPC		
ADT	145	100
Chemotherapy	79	54
Abiraterone	93	64
Ezalutamide	76	52
^{223}Ra	24	17
EBRT to bone	51	35

ADT: androgen deprivation therapy, WBC: white blood cells
Hb: hemoglobin, PSA: prostate specific antigen

Table 2. Administered ^{177}Lu-PSMA-617 activity (n = 248 RLT cycles)

administered activity (GBq)	Cycle 1	Cycle 2	Cycle 3	Cycle 4
≤ 3.5	9	3	0	1
> 3.5 – 4.5	32	14	2	0
> 4.5 – 5.5	16	12	9	0
> 5.5 – 6.5	71	37	14	2
> 6.5	17	8	1	0

Table 3. Adverse events after ^{177}Lu-PSMA-617 as determined by blood tests (n=121) or physician reports (n=145)

Organ system	Category	Evaluated for N	All grades	Grade 3-4
Blood and lymphatic disorders				
	Leukopenia	121	48 (40%)	4 (3%)
	Anemia	145	50 (34%)	15 (10%)
	Thrombocytopenia	121	38 (31%)	5 (4%)
Gastrointestinal disorders				
	AST elevation	121	27 (19%)	0 (0%)
	ALT elevation	121	11 (8%)	0 (0%)
	Xerostomia	145	11 (8%)	0 (0%)
	Nausea	145	9 (6%)	0 (0%)
	Dysgeusia	145	6 (4%)	0 (0%)
	Ascites	145	2 (1%)	0 (0%)
	Biliary obstruction	145	0 (0%)	1 (1%)
General disorders				
	Fatigue	145	19 (13%)	1 (1%)
	Pain	145	5 (3%)	0 (0%)
	Ileus	145	1 (1%)	0 (0%)
Urinary disorders				
	Renal failure	121	14 (12%)	0 (0%)
	Urinary tract infection	145	1 (1%)	0 (0%)
Cardiovascular disorders				
	Edema	145	2 (1%)	0 (0%)
	Lung embolism	145	0 (0%)	3 (2%)
Respiratory, thoracic and mediastinal disorders				
	Pleural effusion	145	1 (1%)	0 (0%)
	Dyspnea	145	1 (1%)	0 (0%)
Neurologic disorders				
	Vertigo	145	1 (1%)	0 (0%)
	Stroke	145	0 (0%)	2 (1%)
Musculoskeletal disorders				
	Bone facture	145	0 (0%)	3 (2%)

Table 4. Odds ratio for biochemical response in patient subgroups

Subgroup	no. of patients	no. of responders (%)	Odds ratio (95% CI)	*P*-value
Mean Activity per cycle				
≤5.5 GBq	40	20 (50)	1 (reference)	
>5.5 GBq	59	25 (42)	0.725 (0.328-1.647)	0.46
Previous chemotherapy				
Yes	55	21 (38)	1 (reference)	
No	44	24 (55)	1.94 (0.869-5.33)	0.11
Visceral metastases				
Yes	29	7 (24)	1 (reference)	
No	70	38 (54)	3.732 (1.412-9.864)	**<0.01**
Bone metastases				
No	13	6 (46)	1 (reference)	
Yes	86	39 (45)	0.968 (0.3-3.21)	0.96
Lymph node metastases				
No	77	34 (44)	1 (reference)	
Yes	22	11 (50)	0.791 (0.306-2.043)	0.63
Alkaline phosphatase*				
<220 U/L	72	39 (54)	1 (reference)	
≥220 U/L	25	5 (20)	0.21 (0.072-0.625)	**<0.01**
Cumulative activity after 2 cycles‡				
≤11.8 GBq	32	16 (50)	1 (reference)	
>11.8 GBq	29	19 (66)	1.9 (0.676-5.366)	0.22
Cumulative activity after 3 cycles				
≤17.4 GBq	8	6 (75)	1 (reference)	
>17.4 GBq	12	8 (67)	0.667 (0.09 - 4.928)	0.69
Number of cycles				
1	28	8 (29)	1 (reference)	
2	36	18 (50)	2.5 (0.87-7.13)	0.94
3 & 4	20	14 (70)	5.83 (1.65 - 20.559)	**0.02**

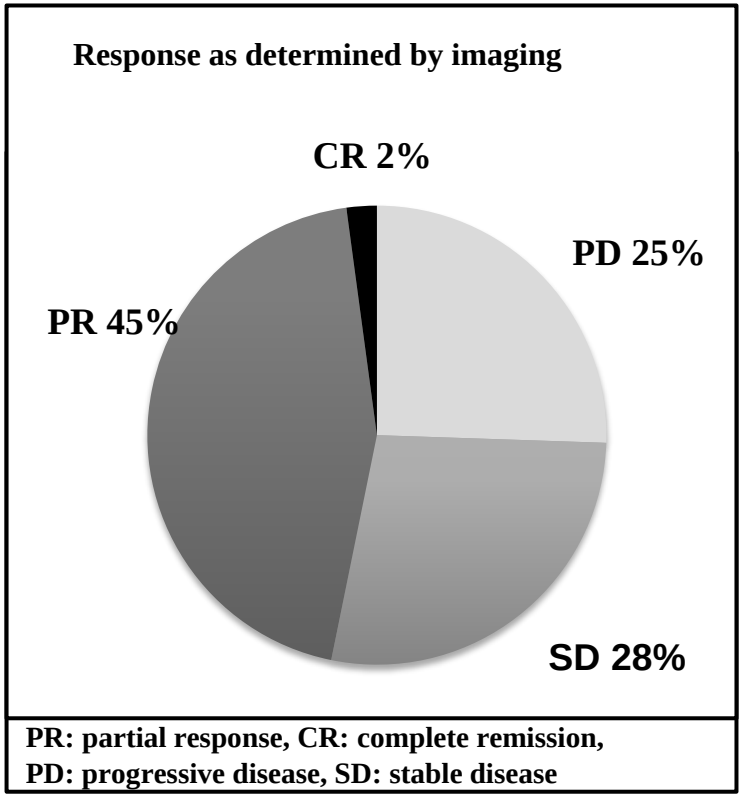
CI=confidence interval

*two patients had no baseline AP. ‡only patients with PSA follow-up after two cycles were included.

Supplemental Figure 1

Secondary endpoint was investigator assessed radiographic response in four categories: complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Because of different imaging modalities and different PET/CT scanners standard uptake value (SUV) was not analyzed.

Follow-up imaging data were available in 47 patients (45 patients with PSMA-PET/CT, one patient with ^{99}Tc-PSMA-scintigraphy and one patient with magnetic resonance imaging). CR, PR, SD and PD were reported in 1 (2%), 21 (45), 13 (28%) and 12 (25%).



Supplemental Table 1.

Department	Number of Patients enrolled	Number of Patients previously reported	Reference
Aachen	1		
Freiburg	1		
Rostock	1		
Berlin	3		
Kiel	3		
Marburg	4		
Munich	6	6	Delker et al. 2015 & Fendler et al. 2016
Cologne	8	8	Rahbar et al. 2016, Hohberg et al. 2016
Badberka	17		
Münster	22	22	Rahbar et al. 2016
Bonn	31	31	Ahmadzadefar et al. 2016 & Rahbar et al. 2016
Heidelberg	48	28	Kratochwil et al. 2016

Supplemental Table 2. Basline CTCAE status

Baseline (n=142)	N CTCAE 0 (%)	N CTCAE 1 (%)	N CTCAE 2 (%)	N CTCAE 3 (%)	N CTCAE 4 (%)	NA
Creatinine	109 (77)	31 (22)	2 (1)	0 (0)	0 (0)	0 (0)
AST	91 (65)	45 (32)	1 (0)	3 (2)	0 (0)	2 (1)
ALT	127 (91)	11 (8)	1 (0)	0 (0)	0 (0)	3 (1)
WBC	125 (88)	12 (9)	5 (3)	0 (0)	0 (0)	0 (0)
Hemoglobin	52 (36)	55 (39)	31 (22)	6 (4)	0 (0)	0 (0)
Platelets	125 (88)	14 (10)	2 (1)	0 (0)	1 (1)	0 (0)

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German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients

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