



Radioligand therapy using [¹⁷⁷Lu]Lu-PSMA-617 in mCRPC: a pre-VISION single-center analysis

Robert Seifert¹ · Katharina Kessel¹ · Katrin Schlack² · Matthias Weckesser¹ · Martin Bögemann² · Kambiz Rahbar¹

Received: 21 September 2019 / Accepted: 21 January 2020 / Published online: 16 February 2020
© The Author(s) 2020

Abstract

Background Radioligand therapy with [¹⁷⁷Lu]Lu-PSMA-617 is efficacious for the treatment of patients with metastasized castration-resistant prostate cancer (mCRPC). Various studies have evaluated the efficacy and safety of [¹⁷⁷Lu]Lu-PSMA-617 using a dose of 6.0 GBq and an 8-week therapy interval. However, the first prospective phase III trial (VISION) plans to use an elevated cumulative dose by applying 7.5 GBq in a 6-week interval. The aim of the present study was to compare safety and efficacy of the two aforementioned [¹⁷⁷Lu]Lu-PSMA-617 therapy regimes (7.5 GBq every 6 weeks vs. 6.0 GBq every 8 weeks).

Methods A total number of 78 consecutive patients with mCRPC and a history of first-line chemotherapy were included in this retrospective analysis. The outcome of patients treated with 6.0 GBq [¹⁷⁷Lu]Lu-PSMA-617 per cycle ($n = 37$) were compared with those treated with 7.5 GBq ($n = 41$) per cycle. The median therapy intervals were 8.4 weeks (6.0 GBq group) vs. 6.5 (7.5 GBq group). PSA response, PSA progression-free survival (PSA-PFS), overall survival, and adverse events were evaluated and compared between both groups. Chi-squared test, Kaplan Meier estimates, Cox regression, and log-rank test were used. The highest decline from pretherapeutic PSA levels was measured as percentage (best PSA response) and compared between groups by Wilcoxon test.

Results There was no significant difference comparing the rate of > 50% PSA decline or best PSA response between the 6.0 GBq and 7.5 GBq group (35% vs. 54%, $p = 0.065$; and -40.2% vs. -57.8% , $p = 0.329$). The median estimated survival and PSA-PFS did not significantly differ between the 6.0 GBq and 7.5 GBq groups as well (11.3 vs. 12.7 months, $p = 0.384$; and 9.5 vs. 12.3 months, $p = 0.258$). There was no significant difference regarding the change of kidney, liver, and blood cell parameters under therapy between the treatment groups.

Conclusion Higher cumulated doses of [¹⁷⁷Lu]Lu-PSMA-617 were well tolerated and caused no significantly increased rate of adverse reactions. Moreover, 7.5 GBq of [¹⁷⁷Lu]Lu-PSMA-617 every 6 weeks causes slightly higher, though not statistically significant, response rates and seems therefore to be the preferable treatment regime. However, future studies are needed to elucidate the dose-related efficacy of [¹⁷⁷Lu]Lu-PSMA-617 as a way to personalized medicine.

Keywords ¹⁷⁷Lu-PSMA-617 · mCRPC · Radioligand therapy · VISION Trial

Introduction

Radioligand therapy regimes targeting the prostate-specific membrane antigen (PSMA) by [¹⁷⁷Lu]Lu-PSMA-617 have

become a promising option for patients with metastasized castration-resistant prostate cancer (mCRPC) and have been extensively evaluated by multiple retrospective studies [1–6]. A prospective phase II trial at the Peter McCullum Center, Australia, was giving additional evidence to the efficacy and favorable toxicity profile of [¹⁷⁷Lu]Lu-PSMA-617 [7]. Furthermore, the prospective phase III registrational trial (VISION) is currently running to evaluate the efficacy and safety in these patients and aims to bring this promising therapeutic to approval [8].

Initial studies like the German Multicenter Study predominantly employed a target dose of 6.0 GBq (range 2–8 GBq) of lutetium every 8 weeks to evaluate the safety and efficacy of

This article is part of the Topical Collection on Oncology - Genitourinary

✉ Kambiz Rahbar
rahbar@uni-muenster.de

¹ Department of Nuclear Medicine, University Hospital Münster, Albert-Schweitzer-Campus 1, D-48149 Münster, Germany

² Department of Urology, University Hospital Münster, Münster, Germany

^{177}Lu -PSMA-617 [1]. Yet, in recent studies, the actual applied dose per cycle varies from 6.0 to 7.5 GBq, and some groups have shortened the therapy interval to 6 weeks [7]. The dose escalation toward 7.5 GBq was pursued analogously to the NETTER trial, which recommended the use of 200 mCi (~7.5 GBq) for the treatment of neuroendocrine cancer [9]. Yet, to date, no systematic evaluation of the efficacy of 6.0 GBq every 8 weeks vs. 7.5 GBq every 6 weeks has been reported. Therefore, it is hard to assess the dose-specific efficacy of [^{177}Lu]Lu-PSMA-617.

The study protocol of the VISION trial requests the administration of 7.5 GBq every 6 weeks. As outlined above, it is currently unclear which efficacy and safety profile is to expect from the VISION trial protocol: Will it result in a higher rate of adverse reactions or in an improved efficacy compared with initial studies, which used 6.0 GBq every 8 weeks? Moreover, the VISION trial requires previous treatment by at least one taxane chemotherapeutic, which is known to influence the response to [^{177}Lu]Lu-PSMA-617 therapy [10]. The combination of mixed target doses per cycle (6.0 or 7.5 GBq), mixed therapy interval (6 or 8 weeks), and mixed patient collectives (naïve to or pre-treated with taxanes) in current literature is challenging for the clinical decision making.

We hypothesize that higher cumulated doses (7.5 GBq [^{177}Lu]Lu-PSMA-617 every 6 weeks) have no systematic effect on response or survival compared with 6.0 GBq every 8 weeks and that the efficacy of newer therapy regimens should therefore be comparable with the initial [^{177}Lu]Lu-PSMA-617 studies. Therefore, the aim of the present study was to compare two patient collectives that were both previously treated with taxane chemotherapy and received 6.0 GBq (8-week interval) or 7.5 GBq (6-week interval) of [^{177}Lu]Lu-PSMA-617. To our best knowledge, this study is thereby applying an adapted version of the VISION trial protocol for the first time in a large patient collective, which is of importance to estimate the anticipated efficacy (1) and to investigate, if the efficacy is dose dependent and safe (2).

Methods

Inclusion criteria and patient stratification

Patients with prostate cancer were referred to [^{177}Lu]Lu-PSMA-617 therapy after critical evaluation in an interdisciplinary tumor board on a case by case bases. Patients were eligible for therapy, if the established inclusion criteria were met: presence of mCRPC; hemoglobin > 8 g/dL; leukocytes > $2.0 \times 10^9/\text{L}$; platelets > 75,000/ μL ; creatinine < 2.0 mg/dL; aspartate transaminase (AST) and alanine transaminase (ALT) < 5 times of upper limit of normal, history of at least one line of chemotherapy (taxane) as well as history of at least

one line of new generation anti androgenic therapy (abiraterone or enzalutamide, if tolerated) [11].

Patients referred to our department for [^{177}Lu]Lu-PSMA-617 from December 2014 to December 2018 were considered for this study. Patients were treated with either 6.0 GBq every 8 weeks or 7.5 GBq every 6 weeks. The choice of treatment regime was independent from performance status or tumor volume and solely attributed to changed therapy protocols at our department caused by the announcement of the VISION trial protocol.

The following inclusion criteria were employed to clearly distinguish two groups with regard to given therapeutic activity. These inclusion criteria were needed to minimize the influence of varying radiochemical yield:

1. Mean activity per patient (of all cycles): ≥ 6.9 GBq (7.5 group) or < 6.9 GBq (6.0 group) (patients receiving 7.5 GBq were treated with a 6-week interval)
2. Range (=difference between smallest and largest doses) of all cycles of a patient: < 1.0 GBq
3. Maximum interval between cycles: 6 months (patients with a therapeutic pause between the administration of two [^{177}Lu]Lu-PSMA-617 cycles were not included)

A total number of 78 (37 patients, 6.0 GBq; 41 patients, 7.5 GBq group) patients met these criteria and were thus included in this retrospective analysis; a detailed patient characterization is given in Table 1.

[^{177}Lu]Lu-PSMA-617 therapy preparation and administration

The conjugation of lutetium (ITG Isotopes Technology, Garching, Germany) and PSMA-617 (ABX advanced biochemical compounds, Radeberg, Germany) was described previously [12]. Therapy was administered in a 6- to 8-week interval until tumor progression, severe adverse reactions, death, or an altered therapy strategy. A prophylactic cooling of the salivary glands was conducted with growing expertise in administration, as described elsewhere [3].

Therapy monitoring

Blood samples and their toxicity were evaluated at least at each cycle administration. Adverse reactions were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The following upper/lower limits of normal were used for the grading according to CTCAE: leukocytes $< 3.9 \times 10^9/\text{L}$; hemoglobin < 13.5 g/dL; platelets $< 166,000/\mu\text{L}$; creatinine 1.4 mg/dL; AST 50 U/L; ALT 50 U/L.

PSA progression-free survival (PFS) was defined by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3)

Table 1 Patient characteristics

Characteristics	7.5 GBq group (<i>n</i> = 41)		6 GBq group (<i>n</i> = 37)	
	Median (IQR)	% (<i>n</i>)	Median (IQR)	% (<i>n</i>)
Age (years)	68.7 (10.4)	–	72.7 (10.0)	–
Gleason score	8 (2)	–	9 (2)	–
PSA (ng/mL)	195.0 (479.3)	–	420.6 (1061.1)	–
ECOG				
0	–	32.4% (12)	–	25.7% (9)
1	–	56.8% (21)	–	54.3% (19)
2	–	10.8% (4)	–	17.1% (6)
3	–	0% (0)	–	2.9% (1)
Alkaline phosphatase (U/L)	129.5 (171.0)	–	185.0 (218.5)	–
Lactase dehydrogenase (U/L)	338.5 (210.5)	–	331.0 (228.0)	–
Hemoglobin (g/dL)	11.4 (1.9)	–	10.1 (2.5)	–
Site of metastases				
Bone	–	87.5% (35)	–	97.3% (36)
Lymph nodes	–	77.5% (31)	–	83.8% (31)
Liver	–	17.5% (7)	–	30.6 (11)
Lung	–	10.0% (4)	–	28.6 (10)
Brain	–	5.0% (2)	–	8.3% (3)
Previous therapy of mCRPC				
Docetaxel	–	100% (41)	–	100% (37)
Cabazitaxel	–	41.5% (17)	–	16.2% (6)
Abiaterone or enzalutamide	–	97.6% (40)	–	94.6% (35)
Abiaterone and enzalutamide	–	70.7% (29)	–	73.0% (27)
Abiaterone	–	90.2% (37)	–	78.7% (29)
Enzalutamide	–	78.0% (32)	–	89.2% (33)
Median number of cycles	4 (4)	–	3 (2)	–
Median Lu-PSMA activity per cycle (GBq)	7.4 (0.2)	–	6.1 (0.1)	–
Median Lu-PSMA activity range of all cycles (GBq)	0.3 (0.4)	–	0.4 (0.3)	–
Median cumulated Lu-PSMA activity of all cycles (GBq)	29.6 (28.8)	–	18.2 (12.6)	–
Median therapy interval (weeks)	6.5 (1.0)	–	8.4 (2.4)	–
Time from prostate cancer diagnosis to start of PSMA therapy (years)	7.2 (7.4)	–	6.9 (8.2)	–

IQR interquartile range

as a PSA incline of 25% from baseline (minimal 2 ng/mL absolute incline), which has to be confirmed by a second measurement (3 weeks later) [13]. Biochemical response was defined in accordance with PCWG3 as 50% PSA decline from baseline [13]. Additionally, the rate of 30% PSA decline from baseline was reported in accordance with previous publications [14].

Statistics and data analysis

MATLAB R2018b (The MathWorks, MA, USA), Excel (Microsoft, WA, USA), and SPSS Statistics 24 (IBM, NY, USA) were used for descriptive statistics and testing. The non-paired, non-parametric Mann-Whitney *U* test or the Chi-squared test was employed to compare the therapy

groups. Overall survival and PSA-PSF were investigated using Kaplan Meier and Cox regression estimates; log-rank test was used to test for statistical significance of estimated survival. *p* values < 0.05 were regarded as statistically noticeable.

Results

Patient characteristics

Depending on the employed therapy scheme, two patient groups were formed: the 6.0 GBq group with a median applied activity of 6.1 GBq and the 7.5 GBq group with a median activity of 7.4 GBq per cycle. The median range of

administered activity over all cycles was 0.4 GBq for the 6.0 GBq group or 0.3 GBq for the 7.5 GBq group, respectively. The cycle interval was shortened concomitantly with the increased therapy activity: the 6.0 GBq group was treated with a median interval of 8.4 weeks, whereas the 7.5 GBq group had a median interval of 6.5 weeks.

All patients were previously treated with docetaxel. Both abiraterone and enzalutamide were subsequently applied in 73% of patients (6.0 GBq group) or 71% of patients (7.5 GBq group). The 6.0 GBq group had a notably higher rate of liver (31 vs. 18%, $p = 0.280$) and lung (29 vs. 10%, $p = 0.072$) metastases. The median time from prostate cancer diagnosis to start of PSMA therapy was comparable (6.9 years for the 6.0 GBq group vs. 7.2 years, $p = 0.685$). Please see Table 1 for details.

PSA response

There was no significant difference between the 6.0 GBq and 7.5 GBq groups regarding the 50% PSA decline (35 vs. 54%, $p = 0.065$), 30% PSA decline (70 vs. 68%, $p = 1.000$), or the PSA-PFS (38 vs. 49 weeks, $p = 0.258$). Details are given in Table 2.

Overall survival

For all patients, the estimated overall survival was 47 weeks. The estimated overall survival did not differ between the 6.0 GBq and 7.5 GBq groups (45 vs. 51 weeks, $p = 0.384$ | HR 1.404, 95%CI 0.650–3.031, reference category = 6 GBq group; $p = 0.388$). Please see Fig. 1 for details.

Safety evaluation

Adverse reactions are presented in Tables 3 and 4. The changes in white blood cell, hemoglobin, platelet, and aspartate aminotransferase and alanine aminotransferase levels during therapy were not significantly different between the activity groups. Notably, 32% stated grade 1 or 2 xerostomia in the 6.0 GBq group, whereas no xerostomia was reported in the 7.5 GBq group. Consequent cooling of salivary glands was only introduced in our department after initial administrations of [^{177}Lu]Lu-PSMA-617, which were all covered by the 6.0 GBq group. Apart from xerostomia and eye dryness, a noticeable fraction of patients suffered from grade 3 or 4 anemia.

Discussion

The aim of the present study was the comparison of two different doses of [^{177}Lu]Lu-PSMA-617 regarding safety and efficacy for the therapy of end-stage mCRPC. Outcome and adverse reactions of patients receiving 6.0 GBq of [^{177}Lu]Lu-PSMA-617 every 8 weeks are retrospectively compared with

those of patients receiving 7.5 GBq [^{177}Lu]Lu-PSMA-617 every 6 weeks. This comparison is clinically needed, as initial studies that evaluated [^{177}Lu]Lu-PSMA-617 employed 6.0 GBq (8-week interval), whereas the currently enrolling prospective VISION trial protocol is demanding the usage of 7.5 Gbq (6-week interval) [1, 8]. To date, safety and efficacy of [^{177}Lu]Lu-PSMA-617 given as 7.5 GBq doses every 6 weeks has not been studied in large cohorts. In contrast, the Münster group adopted the VISION trial protocol in the past and could thus show here that higher cumulated doses of [^{177}Lu]Lu-PSMA-617 do not cause significant changes in the adverse reaction profile. Moreover, higher cumulated doses of [^{177}Lu]Lu-PSMA-617 caused a noticeable improved PSA response, PSA-PFS, and overall survival of mCRPC patients. However, efficacy and overall survival did not significantly differ between both treatment regimes.

The VISION trial is the first prospective phase III trial investigating [^{177}Lu]Lu-PSMA-617 [8]. Patients suffering from mCRPC that were pretreated with a taxane and abiraterone or enzalutamide are eligible. For all enrolled patients, the VISION trial requests the administration of the hitherto not given next-generation antiandrogen substance (i.e., abiraterone or enzalutamide). Thereafter, patients are randomized to either receive 7.5 GBq [^{177}Lu]Lu-PSMA-617 every 6 weeks up to 6 cycles or not.

The determination of the optimal amount of activity for [^{177}Lu]Lu-PSMA-617 is not an easy task. Initial studies investigating the usage of [^{177}Lu]Lu-PSMA-617 were highly influenced by the dosimetry data of [^{131}I]MIP-1095, which employed a dose of 4.8 GBq [15]. Consequently, the first retrospective study evaluating the efficiency and toxicity of [^{177}Lu]Lu-PSMA-617 administered 4.0 GBq [16]. However, the administered doses were escalated after the first dosimetry studies were conducted [16, 17]. One of the first of these studies was done by Delker et al., who suggested the usage of 6.0 GBq for therapy [17]. This was corroborated later by Fendler et al. in a larger patient cohort [18]. The dose escalation toward 6.0 GBq seemed possible due to the different isotope characteristics of [^{177}Lu]lutetium compared with [^{131}I]iodine and became the reference standard in most departments.

It was shown that 6.0 GBq [^{177}Lu]Lu-PSMA-617 exhibits greater tumor to kidney ratios than 7.5 GBq [^{177}Lu]Lu-DOTATATE, which was extensively evaluated in the NETTER trial [9, 18]. Motivated by the promising dosimetry results, further dose escalations of [^{177}Lu]Lu-PSMA-617 seemed reasonable. Therefore, Rathke et al. analyzed the effect of escalated doses of [^{177}Lu]Lu-PSMA-617 (4.0, 6.0, 7.4, 9.3 GBq) on efficacy and toxicity. However, the authors predominantly discussed the benefit of dose escalation up to 9.4 GBq in the context of bone marrow toxicity and only included ten patients per dose group. Thus, a formal dose-escalating study to define a dose with an optimal efficacy-toxicity profile has not been done to this day. Additionally, transferability of the results of Rathke et al. to the

Table 2 PSA response evaluation

	7.5 GBq group (n = 41)		6 GBq group (n = 37)		p
	Median (IQR)	% (n)	Median (IQR)	% (n)	
Best PSA response (> 50% decline)	–	53.7% (22)	–	35.1% (13)	0.065
Best PSA response (> 30% decline)	–	68.3% (28)	–	70.3% (26)	1.000
Best PSA response	– 57.8 (74.5) %	–	– 40.2 (44.6) %	–	0.329
Initial PSA decline	– 37.0 (73.5) %	–	– 31.6 (45.4) %	–	0.414
(min 6–9 weeks after first therapy)					
PSA progression-free survival (weeks)	49.2 (40.7–57.7)*	–	38.0 (29.4–46.5) *	–	0.258

*Mean and 95% confidence interval; *IQR* interquartile range

clinical routine is impaired, as patients with end-stage mCRPC are rather evaluated for [²²⁵Ac]Ac-PSMA ligands and therefore not included in the analysis [19]. Moreover, only 40–50% of enrolled patients had received taxane chemotherapy, which is violating the VISION trial enrollment criteria. Finally, an 8-week therapy interval was used, which is in contrast to the VISION trial protocol; therefore, the study does not allow making conclusions of the anticipated efficacy or toxicity of higher cumulated doses. Interestingly, the authors reported PSA response (> 50% decline) rates of 30% and 50% for 6.0 and 7.5 GBq, respectively, which is in line with the results presented here.

Hofman et al. investigated the usage of [¹⁷⁷Lu]Lu-PSMA-617 in a prospective study employing a mean activity of 7.5 GBq every 6 weeks [7]. However, the study protocol was designed for only 4 cycles, allowed the rechallenging of patients, and applied a dose that was dependent on the tumor burden and body weight. Therefore, direct transferability to a fixed 7.5 GBq scheme is not warranted. The preselection criteria (30% excluded) additionally impaired comparability with the VISION trial protocol. Finally, not all enrolled patients had received first-line taxane chemotherapy.

The treatment with [¹⁷⁷Lu]Lu-PSMA-617 seems to be less effective if chemotherapy, especially second-line chemotherapy, was applied previously [2, 10]. However, it still has to be

determined if this is caused by a meta-phenomenon or if the chemotherapy itself selects more aggressive tumor cells. Barber et al. has shown that first-line taxane chemotherapy is significantly decreasing the overall survival of mCRPC patients treated with [¹⁷⁷Lu]Lu-PSMA-617 [10]. Kessel et al. could demonstrate that second-line chemotherapy is a negative predictor in a highly pretreated patient collective [2]. Therefore, it seems necessary to only include patients pretreated with at least a first chemotherapy to estimate the efficacy of the VISION trial protocol.

Interestingly, the results of the present study indicate that higher cumulated doses (7.5 GBq, 6-week interval) did not lead to a significantly improved efficacy. On the contrary, the reported PSA response rates are similar to those of previously reported studies and only slightly better compared with the 6.0 GBq group. However, this is in line with a previous dose-escalating study by Rathke et al. (up to 9.3 GBq) which could not demonstrate a significant increase of response compared with 6.0 GBq [20]. This might partly be explained by immunological effects of radioligand therapies, which do not follow a linear dose-efficacy relationship. It might be possible that radioligand therapies cause an inflammatory reaction in the tumor (I) and lead to an antigen release (II), which taken together increases the T cell receptor variability and boost an immunogenic anti-tumor effect [21]. Future studies focusing on tumor inflammation caused by radioligand therapies seem warranted.

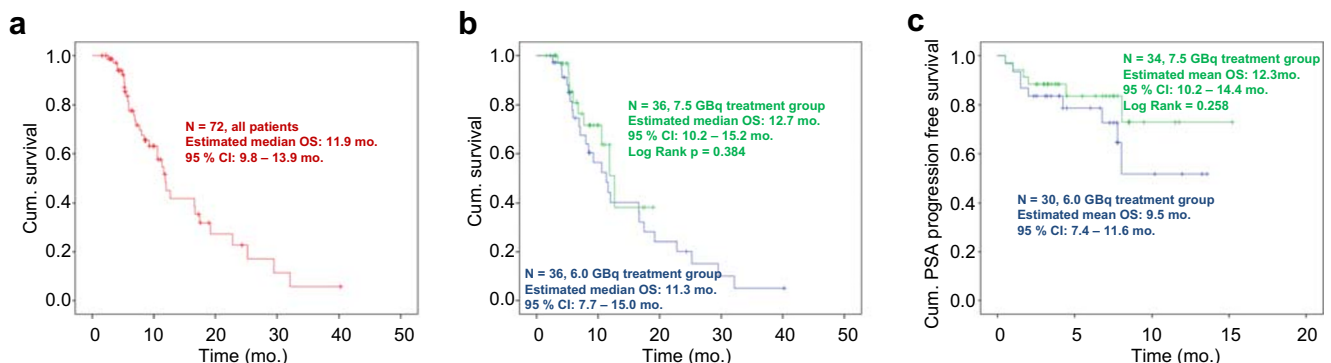


Fig. 1 Survival and progression-free survival. Panel **a** depicts the survival of all included patients. Additionally, the group-specific survival (**b**) and PSA progression-free survival (PSA-PFS, **c**) are shown

Table 3 Adverse reactions according to CTCAE v5.0

	7.5 GBq group (n = 41)		6 GBq group (n = 37)	
	Occurrence of grade 1 + 2 (%)	Occurrence of grade 3 + 4 (%)	Occurrence of grade 1 + 2 (%)	Occurrence of grade 3 + 4 (%)
Leukopenia	48.8	2.4	48.6	8.1
Anemia	26.8	24.4	35.1	21.6
Thrombocytopenia	34.1	2.4	40.5	8.1
Creatinine elevation	7.5	0.0	13.5	0.0
Aspartate aminotransferase elevation	20.0	7.5	37.8	0.0
Alanine aminotransferase elevation	10.0	0.0	13.5	0.0
Eye dryness	9.8	0.0	10.8	0.0
Xerostomia	0.0	0.0	32.4	0.0
Nausea	9.8	0.0	10.8	0.0
Diarrhea	17.1	0.0	18.9	0.0

IQR interquartile range

Response rates of the 7.5 GBq [¹⁷⁷Lu]Lu-PSMA-617 regime were noticeably higher compared with the 6.0 GBq regime, while the adverse reactions profile remained modest. Therefore, it seems reasonable to prefer the 7.5 GBq regime in most patients. However, especially in patients with limited hematopoietic reserve and extensive bone metastases, it might be advisable to reduce the employed therapeutic dose to 6.0 GBq.

A considerable fraction of patients suffered from grade 3 and 4 anemia. However, it must be noted that the hematologic reserve was limited in these end stage, heavily pretreated patient collective (> 87% suffered from bone metastases, median baseline hemoglobin was lowered to 11.4 and 10.1 g/dL for the 7.5 and 6.0 GBq group, respectively). Therefore, severe anemia seems to be rather attributed to the end-stage cancer rather than to a therapeutic side effect.

This study faces some limitations. It was designed as a retrospective analysis thereby facing biases of non-randomization. The patient collective referred to [¹⁷⁷Lu]Lu-PSMA-617 therapy might have changed over time due to a broad clinical acceptance of the therapy caused by its efficacy and

tolerability. This bias might have been aggravated, as patients treated with 6.0 GBq (8-week interval) were referred to therapy in the initial days of [¹⁷⁷Lu]Lu-PSMA-617 therapy, whereas patients treated with 7.5 GBq (6-week interval) are enrolled more recently. Therefore, prospective studies addressing this question are mandatory to optimize the application of the amount of activity and the respective frequency.

Conclusion

The toxicity profile of higher cumulated [¹⁷⁷Lu]Lu-PSMA-617 doses utilizing 7.5 GBq (6-week interval) is not significantly different compared with 6.0 GBq (8-week interval) in a taxane and abiraterone/enzalutamide pretreated mCRPC patient collective. The efficacy of [¹⁷⁷Lu]Lu-PSMA-617 therapy using higher cumulated activity is noticeably higher, although not statistically significant. Therefore, future studies evaluating the dose-specific efficacy of [¹⁷⁷Lu]Lu-PSMA-617 seem warranted.

Table 4 Adverse reactions—change of blood parameters under ¹⁷⁷Lu-PSMA-617 therapy

	7.5 GBq group (all cycles) Median (IQR)	6 GBq group (all cycles) Median (IQR)	<i>p</i>
WBC	− 35.9 (21.1) %	− 38.5 (18.0) %	0.555
HB	− 10.6 (12.7) %	− 11.1 (17.6) %	0.466
Platelets	− 34.5 (26.6) %	− 33.9 (18.9) %	0.635
Creatinine	+ 16.7 (30.9) %	+ 16.2 (30.3) %	0.815
Aspartate aminotransferase	+ 18.2 (76.0) %	+ 38.9 (81.1) %	0.153
Alanine aminotransferase	+ 16.7 (80) %	+ 38.2 (79.3) %	0.230

WBC, white blood cell levels; *HB*, hemoglobin levels; *IQR*, interquartile range

Funding Information Open Access funding provided by Projekt DEAL.

Compliance with ethical standards

Conflict of interest The authors declare that they have no financial or non-financial competing interests according to the subject and matter of the presented article. The University of Muenster received consulting fees from ABX advanced biochemical compounds, Radeberg, Germany, for KR and M.B. Additionally, KR is a clinical consultant for ABX and has received consultant fees from Bayer and lectureship fees from Janssen Cilag, Amgen, AAA, and SIRTEX.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. This study was approved by the local ethics committee (No. 2016-585-f-S, Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Rahbar K, Ahmadzadehfahar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German multicenter study investigating ¹⁷⁷Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med*. 2017;58:85–90.
- Kessel K, Seifert R, Schäfers M, Weckesser M, Schlack K, Boegemann M, et al. Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving ¹⁷⁷Lu-PSMA-617. *Theranostics*. 2019;9:4841–8.
- Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. ¹⁷⁷Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017;44:1663–70.
- Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benesova M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;42:987–8.
- Rahbar K, Bögemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, et al. Delayed response after repeated ¹⁷⁷Lu-PSMA-617 radioligand therapy in patients with metastatic castration resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2018;45:243–6.
- Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, et al. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging*. Germany. 2018;45:12–9.
- Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Ping Thang S, Akhurst T, et al. [¹⁷⁷Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol*. Elsevier Ltd. 2018;19:825–33.
- Rahbar K, Bodei L, Morris MJ. Is the “VISION” of radioligand therapy for prostate cancer becoming reality? An overview of the phase III trial and the importance for the future of theranostics. *J Nucl Med*. 2019. <https://doi.org/10.2967/jnumed.119.234054>.
- Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of ¹⁷⁷Lu-DOTATATE for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–35.
- Barber TW, Singh A, Kulkarni HR, Niepsch K, Billah B, Baum RP. Clinical outcomes of ¹⁷⁷Lu-PSMA radioligand therapy in taxane chemotherapy pretreated and taxane chemotherapy naïve patients with metastatic castration resistant prostate cancer. *J Nucl Med*. 2019. <https://doi.org/10.2967/jnumed.118.216820>.
- Rahbar K, Afshar-Oromieh A, Jadvar H, Ahmadzadehfahar H. PSMA theranostics: current status and future directions. *Mol Imaging*. 2018;17:153601211877606.
- Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand therapy with ¹⁷⁷Lu-PSMA-617 as a novel therapeutic option in patients with metastatic castration resistant prostate cancer. *Clin Nucl Med*. 2016;41:522–8.
- Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26:1148–59.
- Ahmadzadehfahar H, Rahbar K, Kürpzig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with (¹⁷⁷Lu)-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res*. 2015;5:114.
- Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a ¹²⁴I/ ¹³¹I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *Eur J Nucl Med Mol Imaging*. 2014;41:1280–92.
- Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, et al. PSMA-Targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. *J Nucl Med*. 2016;57:1170–6.
- Delker A, Fendler WP, Kratochwil C, Brungraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for ¹⁷⁷Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2015;43:42–51.
- Fendler WP, Reinhardt S, Ilhan H, Delker A, Böning G, Gildehaus FJ, et al. Preliminary experience with dosimetry, response and patient reported outcome after ¹⁷⁷Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. *Oncotarget*. 2017;8:3581–90.
- Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, et al. Repeated ¹⁷⁷Lu-labeled PSMA-617 radioligand therapy using treatment activities of up to 9.3 GBq. *J Nucl Med*. 2018;59:459–65.
- Ferdinandus J, Eppard E, Gaertner FC, Kürpzig S, Fimmers R, Yordanova A, et al. Predictors of response to radioligand therapy of metastatic castrate-resistant prostate cancer with ¹⁷⁷Lu-PSMA-617. *J Nucl Med*. 2017;58:312–9.
- Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature*. 2015;520:373–7.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.