

# Activity and Adverse Events of Actinium-225-PSMA-617 in Advanced Metastatic Castration-resistant Prostate Cancer After Failure of Lutetium-177-PSMA

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## 1. Introduction

Treatment of metastatic castration-resistant prostate cancer (mCRPC) remains a major challenge. One of the most recent treatment options are the beta-emitting agents Lu-177-labeled prostate-specific membrane antigen (PSMA)-617 and Lu-177-PSMA-I&T. Although still experimental, they have shown promising effects and a favorable toxicity profile in patients with mCRPC [1,2]. The German S3 guideline already recommends Lu-177-PSMA after exhaustion of all approved treatments [3]. Depending on patient selection criteria, Lu-177-PSMA achieves a biochemical response with a prostate-specific antigen (PSA) decline of  $\geq 50\%$  in 38–64% of patients and a median overall survival of about 1 yr [1,4,5]. While these are respectable results for advanced mCRPC, they also indicate the need for further improvement of PSMA-targeted therapies.

Owing to higher linear energy transfer and different microdosimetry in tumor tissue targeted alpha therapy (TAT) has the potential to induce cell damage even at radioresistance of beta emitters (such as Lu-177) [6,7]. By inducing efficiently more DNA double-strand breaks, TAT has been more effective than targeted therapy with beta emitters in preclinical studies [8,9]. Therefore, Ac-225 PSMA radioligand therapy (RLT) could be an effective option for mCRPC resistant to the beta-emitting Lu-177-PSMA. Initial promising results using Ac-225-PSMA-617 in mCRPC have been reported [7,10,11]. However, given the limited availability of Ac-225 [12], clinical experience (eg, adverse events and oncological outcomes) is still sparse, and patients included in initial reports were at different stages of their disease.

The aim of this retrospective analysis was to investigate the efficacy and adverse events of the alpha-emitting Ac-225-PSMA-617 RLT in late mCRPC after failure of Lu-177-PSMA RLT.

## 2. Patients and methods

### 2.1. Inclusion criteria

Ac-225-PSMA-617 was offered to patients with mCRPC as salvage therapy after failure of abiraterone/enzalutamide, taxane-based chemotherapy, and Lu-177-PSMA (including either failure during primary treatment or failure to rechallenge after a therapy break). One patient was not eligible for chemotherapy. Treatment with Ac-225-

PSMA-617 was discussed individually and recommended by an interdisciplinary tumor board. Patients fulfilling the following criteria were eligible: castration-resistant metastatic adenocarcinoma of the prostate, treatment with previous novel androgen-receptor targeted therapy (abiraterone and/or enzalutamide), previous taxane-based chemotherapy or ineligibility, previous treatment with Lu-177-PSMA, life expectancy of  $>6$  mo, Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , PSMA expression of all tumor lesions in PSMA-ligand positron-emission tomography (PET) at least higher than liver within 4 wk prior to treatment, creatinine  $<1.5$  mg/dL, hemoglobin  $>8$  g/dL, leucocytes  $>2.5 \times 10^9$ /L, platelets  $>80 \times 10^9$ /L, glutamic oxaloacetic transaminase/glutamic pyruvic transaminase  $<2.5$  upper limits of normal (ULN), bilirubin  $<2$  ULN and if liver metastases are present  $<5$  ULN, and no obstruction on baseline renal scintigraphy. Exclusion criteria were untreated renal obstruction, active secondary malignancy, and acute or chronic glomerulonephritis. All patients provided informed consent under a compassionate use clinical treatment program. The retrospective analysis was approved by the local institutional review board (115/18S).

### 2.2. Treatment regime

Radiolabeling of PSMA-617 with Ac-225 is described in the Supplementary material. Patients were treated every 8 wk. After each application, a restaging PSMA-ligand PET was performed in week 6, followed by interdisciplinary discussion (Supplementary Fig. 1). Treatment was continued in absence of radiographic or clinical progression and a lack of severe toxicity. Androgen-deprivation therapy was continued.

### 2.3. Antitumor outcome

We report the maximum PSA decline, PSA progression-free survival (PSA-PFS), clinical progression-free survival (cPFS), and overall survival (OS); cPFS was defined as the time from treatment initiation to clinical progression (worsening of disease-related symptoms or new cancer-related complications), progressive disease on PSMA-ligand PET, or death, whichever occurred first. A swimmer plot was generated to visualize individual treatment outcomes. Patients were treated between October 2017 and November 2019.

### 2.4. Adverse events and assessment of health status and quality of life

Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and treatment-emergent adverse events were reported. Patients were asked to complete the European Organisation for Research and Treatment of Cancer quality of life (EORTC-QLQ30) questionnaire before each treatment and 4–8 wk after each treatment [13].

### 2.5. Statistical analyses

PSA-PFS, cPFS, and OS were calculated using the Kaplan-Meier method. Details are presented in the Supplementary material.

## 3. Results

### 3.1. Patients and treatment with Ac-225-PSMA-617

Twenty-six patients (Table 1 and Supplementary Table 1) were treated with a median activity of 9 MBq (interquartile range [IQR] 8–10; Supplementary Table 1). Overall, 61 cycles were given with a median of two cycles per patient (IQR 1.3–3.0). The median time on treatment was 3.7 mo (95% confidence interval [CI] 2.4–5.1).

Patients have been exposed to a median of six prior mCRPC lines (range from three to eight) including a median of four cycles of Lu-177-PSMA (IQR 2–6). Lymph node, bone, and visceral metastases were present in 24 (92%), 26 (100%), and 11 (42%) patients, respectively. Of 26 patients, six (23%) had lung metastases, five (19%) had liver metastases, two (8%) had brain metastases, and three (12%) had peritoneal metastases.

### 3.2. Adverse events

Irreversible grade 1/2 xerostomia was observed in all patients. Xerostomia started after the first cycle and deteriorated with additional cycles. Other grade 1/2 adverse events are summarized in Table 2. No grade 3/4 non-hematological adverse events were observed.

Grade 3 hematological adverse events were as follows: anemia in eight (31%, 95% CI 16–50%), leucopenia in seven (27%, 95% CI 13–46%), thrombocytopenia in three (12%, 95% CI 3–29%), grade 4 anemia in one (4%, 95% CI 0–20%), leucopenia in zero (0%, 95% CI 0–15%), and thrombocytopenia in two (8%, 95% CI 1–25%) of 26 patients. Transfusion of erythrocytes was needed in 11/26 (42%, 95% CI 26–61%) patients during treatment. One patient continued granulocyte-colony stimulating factor injections for long-term pre-existing granulocytopenia. Changes of hemoglobin, platelets, leucocytes, and creatinine during treatment for individual patients are presented in Supplementary Figure 2. Median time to nadir was 3.3 (IQR 1.9–5.4), 1.7 (IQR 0.8–3.4), and 2.6 (IQR 1.5–4.1) mo for hemoglobin, leucocytes, and platelets, respectively.

**Table 1 – Baseline patient characteristics**

No. of patients	26
Age (yr), median (IQR)	72.5 (63–75.75)
Primary metastatic prostate cancer, <i>n</i>	10
PSA (ng/mL), median (IQR)	331 (142–682)
LDH (U/L), median (IQR)	360 (296–657)
AP (U/L), median (IQR), <i>n</i> = 25	200 (143–517)
Hb (g/dL), median (IQR)	10 (8.7–10.9)
ECOG, median (IQR)	1 (0–1)
Gleason score, median (IQR), <i>n</i> = 26	8 (7–9)
Prior systemic treatments, <i>n</i> (%)	
Docetaxel	25 (96)
Docetaxel rechallenge	3 (12)
Cabazitaxel	14 (54)
Abiraterone	23 (88)
Enzalutamide	22 (85)
Abiraterone and enzalutamide	19 (73)
Radium-223	6 (23)
Other systemic treatment for CRPC	5 (19)
Lutetium-177-PSMA	26 (100)
Prior lines of systemic treatment, <i>n</i>	
3	2
4	6
5	5
6	6
7	2
8	5
Site of metastasis, <i>n</i> (%)	
Lymph node, overall	23 (88)
Lymph node only	0 (0)
Bone, overall	26 (100)
Bone only	2 (8)
Visceral, overall	11 (42)
Liver	5 (19)
Lung	6 (23)
Other	5 (19)
Visceral only	0 (0)

AP = alkaline phosphatase; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; IQR = interquartile range; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

**Table 2 – Hematological and nonhematological adverse events after Ac-225-PSMA-617 according to CTCAE v5.0<sup>a,b</sup>**

	Baseline parameters				Treatment-emergent adverse events			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
<b>Hematological toxicities</b>								
Anemia	11 (42) 25–61	12 (46) 29–65	1 (4) 0–20	0 (0) 0–15	2 (8) 1–25	4 (15) 6–34	8 (31) <sup>c</sup> 16–50	1 (4) <sup>d</sup> 0–20
Leucopenia	3 (12) 3–29	2 (8) 1–25	1 (4) 0–20	0 (0) 0–15	3 (12) 3–29	3 (12) 3–29	7 (27) <sup>e</sup> 13–46	0 (0) 0–15
Thrombopenia	6 (23) 11–42	1 (4) 0–20	0 (0) 0–15	0 (0) 0–15	7 (27) 13–46	2 (8) 1–25	3 (12) <sup>f</sup> 3–29	2 (8) <sup>g</sup> 1–25
<b>Nonhematological toxicities</b>								
Xerostomia	–	–	–	ND	23 (88) <sup>h</sup> 70–96	3 (12) <sup>i</sup> 3–29	–	ND
Renal disorders	5 (19) 8–38	2 (8) 1–25	0 (0) 0–15	0 (0) 0–15	5 (19) 8–38	–	–	–
Fatigue	NE	NE	NE	NE	12 (46) 29–65	–	–	–
Loss of appetite	NE	NE	NE	NE	8 (31) 16–50	–	–	–
Weight loss	NE	NE	NE	NE	3 (12) 3–29	–	–	–

CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; ND = not defined; NE = nonhematological toxicities at baseline have not been evaluated for all categories; PSMA = prostate-specific membrane antigen.

Data are shown as n (%), and 95% confidence intervals.

<sup>a</sup> CTCAE version 5.0 criteria for xerostomia: grade 1 is defined as symptomatic without significant dietary alterations, grade 2 as moderate symptoms and oral intake alterations, and grade 3 as inability to adequately aliment orally (eg, tube feeding indicated).

<sup>b</sup> Permanent grade 3/4 anemia, leucopenia, and thrombopenia occurred in 3/9 (33%, 95% CI 12–65), 3/7 (43%, 95% CI 16–75), and 2/5 (40%, 95% CI 12–77) patients, respectively.

<sup>c</sup> In two patients permanent, in one patient transient, and five patients received transfusions.

<sup>d</sup> Permanent.

<sup>e</sup> In three patients permanent and in four patients transient.

<sup>f</sup> In one patient transient, in one patient permanent, and in one patient not evaluable.

<sup>g</sup> In one patient permanent and one patient received multiple transfusions.

<sup>h</sup> Five of 26 (19%) patients requested halt of treatment.

<sup>i</sup> One of 26 (4%) patients requested halt of treatment.

Six of 26 (23%) patients requested treatment termination due to xerostomia. In two of 26 (8%) patients, treatment was discontinued to avoid worsening of pre-existing leucopenia ( $n=1$ ) or thrombocytopenia ( $n=1$ ). Loss of weight and appetite was experienced by eight (31%) and three (12%) patients, respectively.

### 3.3. Antitumor effect

Fig. 1 displays a swimmer plot for the individual treatment outcomes. Waterfall plots of maximum PSA decline are shown in Fig. 2. Any PSA decline and a PSA decline of  $\geq 50\%$  were observed in 23 (95% CI 70–97%) and 17 (95% CI 46–81%) of 26 patients, respectively.

Of 26 patients, 18 (95% CI 49–84%) had died after a median follow-up of 7.0 mo (range 2.4–16). Until the last follow-up time in June 2020, eight of 26 patients were alive. The median time until the last follow-up in these patients was 6.4 mo. The median PSA-PFS, cPFS, and OS periods were 3.5 (95% CI 1.8–11.2), 4.1 (95% CI 3.0–14.8), and 7.7 (95% CI 4.5–12.1) mo, respectively (Fig. 3).

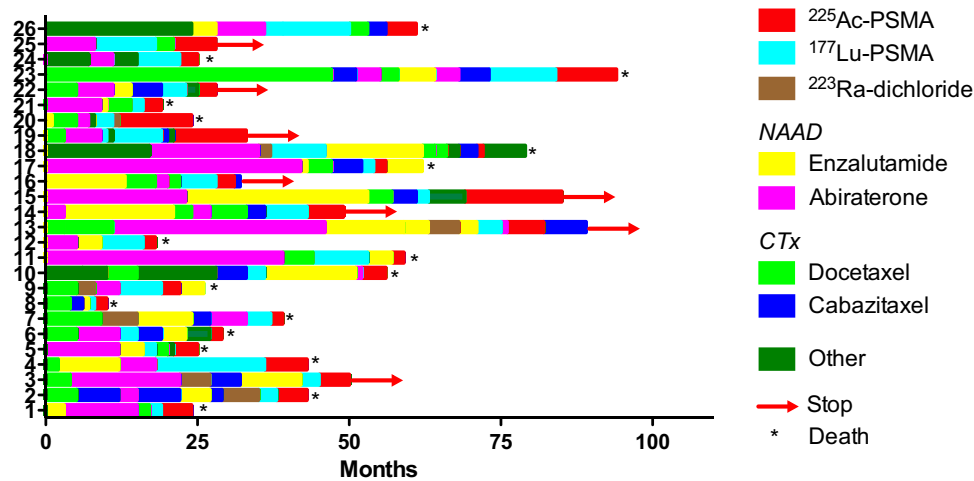
Liver metastases at initiation of treatment were a risk factor significantly associated with shorter PSA-PFS (1.9 vs 4.0 mo;  $p=0.02$ , hazard ratio [HR] 3.01, 95% CI 0.7–13.1), shorter cPFS (1.8 vs 5.2 mo;  $p=0.001$ , HR 4.38, 95% CI

0.8–24.7), and shorter OS (4.3 vs 10.4 mo;  $p=0.01$ , HR 9.35, 95% CI 1.5–56.9). The corresponding Kaplan-Meier curves are shown in Fig. 4.

Six of 26 patients with PSA progression on Lu-177-PSMA had a PSA response to Ac-225-PSMA-617 treatment (for details, see the Supplementary material and Fig. 2B). Two of 26 (8%) patients showed a PSA response after initial Lu-177-PSMA, but not after subsequent Ac-225-PSMA-617. Only one of 26 (4%) patients failed to show a PSA response after both Lu-177-PSMA and Ac-225-PSMA-617. Patient examples are presented in Supplementary Figures 4 and 5. Higher pretreatment ECOG performance status (2 vs 0/1) was an independent predictor of shorter OS on a multivariable analysis ( $p=0.02$ ; Supplementary Tables 4–7).

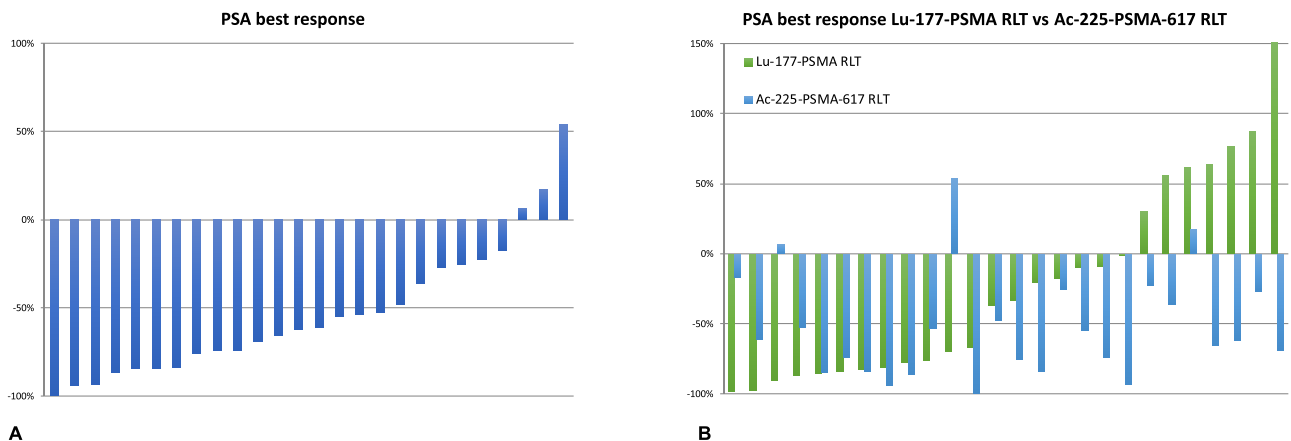
### 3.4. Assessment of health status and quality of life

The first and second cycles of Ac-225-PSMA-617 resulted in no measurable changes of the global health status/quality of life using the EORTC-QLQ30 questionnaire. Some evidence was present for higher scores for social functioning after the first cycle, lower score for pain after the first cycle, and appetite loss and insomnia after the first and second cycles. No further substantial changes were present (Supplementary Table 2).



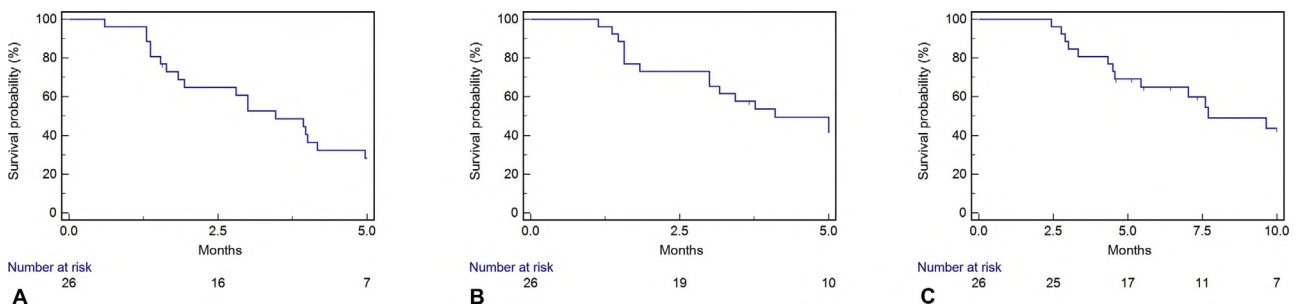
**Fig. 1 – Swimmer plot of mCRPC treatments.** The length of each bar symbolizes the duration for which a patient was on a specific treatment. Time on a specific treatment was calculated as the time between treatment initiation and initiation of a subsequent treatment. Details on treatments coded as “other” in dark green can be derived from Supplementary Table 1.

CTx = chemotherapy; mCRPC = metastatic castration-resistant prostate cancer; NAAD = novel androgen axis drug; PSMA = prostate-specific membrane antigen.



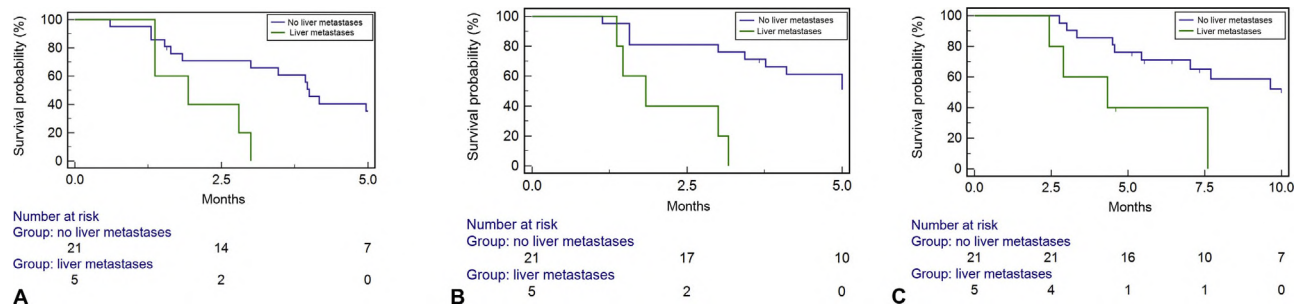
**Fig. 2 – PSA waterfall plot of maximum PSA decline after Ac-225-PSMA-617 and comparison with prior maximum PSA decline after Lu-177-PSMA.** (A) Any PSA decline was observed in 23/26 (95% CI 70–97) patients and a PSA decline of  $\geq 30\%$ ,  $\geq 50\%$ , and  $\geq 90\%$  was achieved in 19 (95% CI 54–87), 17 (95% CI 46–81), and three (95% CI 3–29) of 26 patients, respectively. (B) PSA waterfall plot illustrating respective maximum PSA decline after Lu-177-PSMA and Ac-225-PSMA-617 treatment. Six of 26 (95% CI 11–42) patients with biochemical progression after Lu-177-PSMA showed a PSA response after Ac-225-PSMA-617. Two of 26 (95% CI 1–25) patients showed a PSA response after initial Lu-177-PSMA, but not after subsequent Ac-225-PSMA-617. Only one of 26 (95% CI 0–20) patients failed to show a PSA response after both Lu-177-PSMA and Ac-225-PSMA-617.

CI = confidence interval; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RLT = radioligand therapy.



**Fig. 3 – PSA-PFS, cPFS, and overall survival after initiation of Ac-225-PSMA-617 RLT.** (A) Median PSA-PFS was 3.5 mo (95% CI 1.8–11.2). (B) Median cPFS was 4.1 mo (95% CI 3–14.8). (C) Median overall survival was 7.7 mo (95% CI 4.5–12.1).

CI = confidence interval; cPFS = clinical progression-free survival; PFS = progression-free survival; PSA = prostate-specific antigen.



**Fig. 4 – PSA-PFS, cPFS, and overall survival after initiation of Ac-225-PSMA-617 RLT in patients without (blue line) versus with (green line) liver metastases at the initiation of treatment: (A) longer median PSA-PFS (4.0 vs 1.9 mo;  $p = 0.02$ ; HR 3.01, 95% CI 0.7–13.1), (B) longer median cPFS (5.2 vs 1.8 mo;  $p = 0.001$ ; HR 4.38, 95% CI 0.8–24.7), and (C) longer median OS (10.4 vs 4.3 mo;  $p = 0.01$ ; HR 9.35, 95% CI 1.5–56.9). CI=confidence interval; cPFS=clinical progression-free survival; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen; PSMA=prostate-specific membrane antigen; RLT=radioligand therapy.**

#### 4. Discussion

In the present study, we analyzed the antitumor activity and adverse events of Ac-225-PSMA-617 in late-stage mCRPC after failure of Lu-177-PSMA. In this heavily pretreated population (a median of six prior mCRPC lines), Ac-225-PSMA-617 led to a maximum PSA decline of  $\geq 50\%$  in 65% of patients. The frequency of a PSA response and the duration of the response as measured by PSA-PFS, cPFS, and OS were, however, lower than in previous reports for Ac-225-PSMA-617 in less advanced and pretreated mCRPC [10,14–16]. Furthermore, grade 3/4 hematological toxicities and permanent xerostomia were more frequent than previously reported [15].

Supplementary Table 3 puts our results in the context of previous studies that used Ac-225-PSMA-617 in less advanced and/or more heterogeneous patient populations. The number of patients experiencing any PSA decline was relatively similar to that in these studies (88% vs 83–94%) [10,14,15]. However, a maximum PSA decline of  $\geq 90\%$  was achieved in only 12% of our patients but in 40–82% of patients in the previous studies. In addition, one study in chemo-naïve patients observed complete tumor response on PSMA PET imaging in 65% of patients, whereas no complete remissions occurred in our study [14].

Notably, differences in response may be attributed not only to disease stage, but also to the pattern of tumor distribution. Sathekge et al [15] have shown that PFS was significantly longer in patients with lymph node metastases only than in those with bone involvement. Similar data were published for Lu-177-PSMA with longer OS in stage IVa versus IVb [17].

Clear differences are also present for the duration of response: in our cohort, the median cPFS was 4.1 mo compared with 15.2 (estimated) and 7 mo in previous reports on less advanced mCRPC [10,15]. However, caution is warranted as, in our analysis, PSMA-PET performed after every cycle was part of response assessment. This can

induce substantial bias as PSMA-PET very likely depicts new metastases earlier than conventional imaging [18]. The median OS of our cohort was 7.7 mo as compared with 12–18 mo in previous publications for less advanced mCRPC patients with fewer lines of previous therapies [10,15]. Nevertheless, the 7.7 mo OS after a median of six previous lines compares favorably with, for example, novel therapy agents (abiraterone, enzalutamide, and cabazitaxel) as a fourth-line treatment with a reported median OS of 5 mo [19]. Overall, the comparison of our results with literature data indicates that Ac-225-PSMA-617 has encouraging activity as a seventh-line therapy after Lu-177-PSMA failure, but that the frequency and duration of responses are lower than reported previously in less heavily pretreated patients.

Known prognostic factors for other therapies of mCRPC [1,20] also appear to apply to treatment with Ac-225-PSMA-617 in our patient population. Specifically, the presence of liver metastases was a negative prognostic factor for cPFS, PSA-PFS, and OS, as reported for Lu-177-PSMA and several other therapies [1,20]. In addition, multivariate analysis demonstrated higher pretreatment ECOG performance status as an independent predictor of shorter OS. Almost 20% of the patients in our study had liver metastases, possibly attributing to the surprisingly short OS. Future patient selection might take this into consideration, for example, excluding patients with a high metastatic liver burden and/or reduced performance status.

In our cohort, permanent grade 1/2 xerostomia has been experienced by all patients, which affected their quality of life significantly. Of the patients, 23% requested to stop treatment for this reason. Kratochwil et al [10] report of 10% of patients discontinuing treatment due to intolerable xerostomia. Sathekge et al [15] report grade 1/2 xerostomia in 85–100% patients; however, none of them discontinued treatment [14]. Yadav et al [16] report xerostomia grade I/II in only 29%. The increased frequency and severity of xerostomia in our patient population is probably the result of the cumulative toxicity of previous chemotherapy [21], Lu-177-PSMA RLT [22–24], and Ac-225-PSMA-617 RLT,



although none of our patients suffered from xerostomia before Ac-225-PSMA-617 therapy. Permanent xerostomia after prior Lu-177-PSMA did not occur in our patient cohort, although this can happen after Lu-177-PSMA as described; however, it is nearly always transient [1]. A quantitative comparison of irradiation from Lu-177-PSMA and Ac-225-PSMA-617 is currently not possible due to the limitation of alpha-emitter dosimetry. To date, the mechanisms for the high uptake of PSMA ligands in the salivary gland and the higher toxicity of Ac-225-PSMA-617 than subsequent Lu-177-PSMA are not understood fully. Our patients were asked to apply local mouth gel, use ice collars and ice cream, and stimulate saliva excretion via manual therapy. Some patients reported temporary improvement, but the fundamental loss of salivary gland function could not be prevented.

Of note, assessment of xerostomia might not be represented fully by the EORTC-QLQ30 questionnaire, and grading by CTCAE is limited as minor subjective changes, despite potentially impacting quality of life, are not represented adequately. Yet, almost one-third of patients had appetite loss after the first and second cycles potentially related to xerostomia, which was not observed using the questionnaire most likely because this questionnaire is not sensitive toward cancer-related toxicities. Furthermore, the definite etiology of weight loss and loss of appetite reported in our analysis is unclear but very likely related to xerostomia. Additional factors could be small bowel irradiation as well as tumor progression.

Grade 3/4 anemia, thrombocytopenia, and leucopenia occurred in 35% (nine/26), 19% (five/26), and 27% (seven/26) of our patients, respectively. In patients treated with Lu-177-PSMA-RLT, the frequencies of grade 3/4 anemia, thrombocytopenia, and leucopenia were only 9–10%, 2–13%, and 3–32%, respectively [1,2,4,5]. However, our patients have been treated at a substantial later stage. The frequency of adverse hematological events is similar to that of investigational agents [25] or, for example, carboplatin/etoposide [26] applied in advanced mCRPC. We observed grade 1/2 impairment of kidney function in 19% patients similar to that reported [15], but without clinical relevance.

Of note, our treatment concept was based on a previous empiric dose finding that proposed 8 MBq Ac-225-PSMA-617 for a standard patient as a reasonable tradeoff between toxicity and efficacy [7]. Given suboptimal antitumor effects at the beginning of our study, we subsequently tended to higher activities that were also influenced by individual tumor burden, hematological parameters, and PSA kinetics. For subsequent cycles, effects of xerostomia on quality of life, and the number of Ac-225-PSMA-617 treatments and its antitumor effect were considered.

The antitumor activity and toxicity of Ac-225-PSMA-617 can potentially be improved by using optimized doses or dose schedules. Since several responding patients showed a rise of PSA 6 wk after each Ac-225-PSMA-617 injection (Supplementary Fig. 5), shorter intervals between treatment cycles with less activity per cycle may be preferable. However, the effect of such dose schedules on salivary and hematopoietic function needs to be studied. In order to reduce salivary gland toxicity, it has been proposed to de-

escalate activities in well-responding patients [27]. However, reducing the activity of subsequent treatments was feasible only in 34% of our patients. A recent study showed promising tumor activity and limited xerostomia for a combination of Ac-225- and Lu-177-PSMA [28], but has to be evaluated in future studies especially focusing on side effects. Recent reports on the combination of Ac-225- and Lu-177-PSMA describe its salivary gland toxicity without detailing on treatment discontinuation [29–31].

The main limitations of this study are its retrospective design and small sample size. Particularly, the sample size of the collected EORTC-QLQ30 questionnaire allows for limited conclusions only. However, our patient population is more homogeneous than reported in previous studies, providing first stringent data on the use of Ac-225-PSMA-617 after Lu-177-PSMA failure in a heavily pretreated cohort.

## 5. Conclusions

Ac-225-PSMA-617 has activity in late mCRPC after Lu-177-PSMA failure, but the duration of tumor responses was shorter than observed previously in earlier disease states. Xerostomia caused by Ac-225-PSMA-617 can substantially impact the quality of life. Patients with liver metastases showed poor outcomes, and the benefits and risks of Ac-225-PSMA-617 in this patient population should be weighed carefully. Prospective trials systematically investigating the role of Ac-225-PSMA-617 in different prostate cancer disease states are needed.

**Author contributions:** Benedikt Feurecker had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Feurecker, Tauber, Knorr, Eiber.

*Acquisition of data:* Feurecker, Tauber, Beheshti, Gafita, Knorr, Pickhard, Kratochwil, Eiber.

*Analysis and interpretation of data:* Feurecker, Tauber, Beheshti, Eiber.

*Drafting of the manuscript:* Feurecker, Tauber, Eiber.

*Critical revision of the manuscript for important intellectual content:* Heck, Weber, Morgenstern, Retz, DAlessandria, Gschwend.

*Statistical analysis:* Heck, Feurecker, Eiber.

*Obtaining funding:* Eiber.

*Administrative, technical, or material support:* Seidl, Morgenstern, Bruchertseifer, DAlessandria, Weber, Gschwend.

*Supervision:* Weber, Eiber, Gschwend, Retz.

*Other:* None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eururo.2020.11.013>.

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