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Targeted Alpha Therapy of mCRPC with ^{225}Actinium-PSMA-617: Swimmer-Plot analysis suggests efficacy regarding duration of tumor-control

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ABSTRACT

The aim of this evaluation is to identify first indicators regarding the efficacy of ^{225}Ac-PSMA-617 therapy in a retrospectively analyzed group of patients. **Methods:** Forty patients with metastatic castration-resistant prostate cancer were selected for treatment with 3 cycles of 100 kBq/kgBW ^{225}Ac-PSMA-617 in 2 months intervals. Prostate-specific antigen (PSA) and blood cell count were measured every 4 weeks. Prostate-specific membrane antigen (PSMA)-PET/CT or PSMA-SPECT/CT were used for baseline staging and imaging follow-up at month six. Follow-up included duration of PSA-response and radiological progression free survival at month six. Patient histories were reviewed for the duration of previous treatment lines and a Swimmer-Plot was used to intra-individually compare the duration of tumor control by PSMA-therapy vs. prior treatment modalities. **Results:** 31 of 40 patients were treated per protocol. 5 patients discontinued due to non-response, 4 patients due to xerostomia. In patients surviving at least eight weeks, a PSA decline >50% was observed in 24/38 (63%) and any PSA response in 33/38 (87%) of patients. Median duration of tumor-control under ^{225}Ac-PSMA-617 last-line therapy was 9.0 months; 5 patients presented with enduring responses of > 2 years. As all patients had very advanced disease this compares favorably with the tumor-control rates associated with earlier phase disease; the most common preceding 1st, 2nd, 3rd and 4th line therapies were abiraterone (median duration 10.0 months), docetaxel (6.5 months), enzalutamide (6.5 months) and cabazitaxel (6.0 months). **Conclusion:** Positive response of surrogate parameters demonstrates remarkable anti-tumor activity of ^{225}Actinium-PSMA-617. Swimmer-plot analysis indicates promising duration of tumor-control, especially taking into account the unfavorable prognostic profile of the selected advanced-stage patients. Xerostomia was the main reason to discontinue therapy or to refuse additional administrations and was in the same dimension as non-response; this indicates that further modifications of the treatment regimen with regard to side effects might be necessary to further enhance the therapeutic range.

Key words: PSMA, Ac-225, 225Ac, targeting therapy, prostate cancer

INTRODUCTION

PSMA-617 is a small molecule targeting PSMA. Due to its conjugation to “DOTA” it can be labeled with several radio-metals for imaging or radio-ligand therapy (RLT) of prostate cancer (*1*).

Several centers worldwide now offer PSMA-RLT with the beta-emitter ^{177}Lu as a salvage therapy or in early phase clinical trials for patients with metastatic castration-resistant prostate cancer (mCRPC). These centers confirmatively reported promising anti-tumor activity with regard to PSA serum levels or radiological response (*2-9*); however, a considerable number of patients were found to be short or non-responders. Dose escalation was limited by chronic hematological toxicity (*10*).

Due to theoretical advantages in the physics and radiation-biology of alpha vs. beta particle emitters and promising pre-clinical literature data, although most of them done with ^{213}Bi-labeled PSMA-ligands (*11-15*), we introduced PSMA-targeting alpha-therapy (TAT) for salvage therapy of end-stage mCRPC patients in our hospital. Based on dosimetry estimates (*16,17*) and preliminary clinical experience with individual patients (*17-19*), ^{225}Ac was considered the first-choice radionuclide for clinical application and we defined a ^{225}Ac treatment activity level which became the basis of our first standard operating procedure (SOP) (*19*).

Here we report our clinical findings for the first forty patients that were treated with the intention to receive this dosing regimen. As PSMA-TAT was always offered last-line, i.e. after exhausting other options, the duration of tumor control achieved with the approved standard drugs could serve as an intra-individual reference regarding the respective tumor aggressiveness. The “swimmer-plot”, with bars showing the length of response duration to the various therapies, presents a graphical way of showing the chronology of each patient’s treatment history in one glance, respectively.

MATERIALS AND METHODS

Patients

^{225}Ac-PSMA-RLT was performed under the conditions of the updated declaration of Helsinki, § 37 (Unproven interventions in clinical practice) and in accordance to the German Pharmaceuticals Law §13(2b) as a salvage therapy for patients with mCRPC, which had to be resistant against or ineligible for approved options and presented with progressive disease. This report describes 40 consecutive patients. All had a PSMA-positive tumor phenotype in ^{68}Ga-PSMA-11 PET/CT or ^{99m}Tc-MIP-1427 scans (planar whole-body, torso per SPECT/CT). Due to its short tissue penetration range there is a theoretical advantage of ^{225}Ac-PSMA-617 regarding hematological toxicity in patients with diffuse type bone-marrow infiltration; However, some cases of sever xerostomia have been reported following ^{225}Ac-PSMA-617 (*17,19*). Neither xerostomia nor hematological toxicity was a relevant issue in the literature about ^{177}Lu-PSMA-617, but was only demonstrated for the less advanced patients reported by these groups (*4-7*). Consecutively, we tailored patients to receive either ^{177}Lu-PSMA or ^{225}Ac-PSMA according to Fig. 1. Patients were informed about the experimental nature of this therapy and gave written informed consent. Our ethical committee approved the retrospective evaluation as an observational study.

Radiopharmaceuticals and Treatment Regimen

The PSMA-617 precursors were obtained from ABX (Radeberg, Germany) and labeled with ^{225}Ac as described previously (*17*). Nowadays, preparation of the imaging tracers for PSMA-PET/CT or PSMA-SPECT/CT can be considered clinical routine. The treatment regimen was 100 kBq/kgBW ^{225}Ac-PSMA-617 administered every two months via a 30 s free-hand injection through a low-protein-binding sterile filter (Filtropur S0.2, Sarstedt Nuembrecht, Germany). The patients were isolated as in-patients for 48 h, covering urinary clearance of non-tumor-bound radioactivity.

The SOP of PSMA-TAT, including prescribed vs. allowed vs. obligatory discontinued co-medication, is summarized in the Supplemental Table 1.

Follow-up and Response Assessment

PSA, blood-cell-count, liver and kidney lab-tests were routinely checked every 4 weeks during the first 24 weeks and every 8 weeks in the long term follow up. Other side effects were assessed by anamnesis. Imaging was routinely done baseline and 6 months after the first cycle, or earlier in case of clinical indication. Other imaging and long term imaging follow-up was only

done if indicated by the responsible uro-/oncologist. Interpretation of surrogate response markers was done in accordance to “Prostate Cancer Clinical Trials Working Group” (PCWG)-recommendations, including best-PSA-response, PSA-response at defined time-points, “Time to PSA-progression (TTP)”, radiological response at month six, and clinical duration of tumor control (20-22).

Definition of “Duration of Tumor-Control”

Evaluated medical records contained robust information about the chronology of prior treatments. However, reasons for discontinuation of prior treatments could not always be discerned. To address this problem we defined “Duration of Tumor-Control” as the time interval from the first administration of a particular drug to the initiation of the next treatment line.

As PSMA-TAT was offered as last-line therapy, the end-point “switch to next treatment line” was not applicable here. TTP was not considered an equivalent surrogate for evaluation of PSMA-RLT response. The methodical challenge is illustrated in Fig. 2: A patient starting with a serum PSA of 3000 ng/ml had a PSA-Nadir of <0.1 ng/ml but already relapsed 4 month later. However, he was followed during a treatment free interval of 2 years with slowly rising PSA until his PSA finally exceeded 100 ng/ml and he was considered for a second course of PSMA-TAT, which is currently ongoing. In this case the TTP would dramatically underestimate the obvious benefit of PSMA-TAT. Thus, for patients with an initial response to PSMA-TAT we defined “Duration of Tumor-Control” as either “PSA-relapse to baseline” or occurrence of new clinical tumor related symptoms (considering the criterion that was met first).

Swimmer-Plot Analysis

Swimmer-plot analysis, as an early option to obtain a longitudinal response parameter, is encouraged by the PCWG3-recommendations (22). In addition to the absolute durations of PSA-response and clinical benefits, we also analyzed the relative contribution of ^{225}Ac-PSMA-617 to the entire disease course from reaching the castration resistant stage to the final switch to palliative care. The rationale is evident from the patient example in Fig. 2. The persistent response at >27 months implies a dramatic therapeutic benefit for this patient. However, in comparison to 38 months tumor control with docetaxel the relative benefit of this treatment line appears less impressive and might be attributed to an indolent tumor behavior. In contrast, patient no. 2 presented with only a 3 months response to abiraterone, 4 months to docetaxel, 6 months to cabazitaxel and 3 months to enzalutamide. Taking into account the documented tumor aggressiveness, the 14 months response to ^{225}Ac-PSMA-617, an average outcome for other patients, is remarkable. Thus, to eliminate a random bias by selecting patients with

different tumor differentiation, Swimmer lanes were normalized to the duration of previous treatment lines.

RESULTS

Clinical Findings

From 50 patients scheduled to our department for PSMA-RLT, 45 were considered PSMA-positive; 10% were rejected after baseline imaging. However, a clear cut-off on what should be considered an adequate uptake on PSMA-imaging has not been elaborated, yet. Thus, the current patient selection and tailoring process is still an individual approach based on visual imaging interpretation and clinical considerations.

The characteristics of the included patients are summarized in the first column of Table 1. Median duration of previous androgen deprivation therapy was 24 months; median time from initial diagnosis to first cycle of PSMA-TAT was 49 months.

The delay from the first outpatient consultation to the first administered treatment averaged 4 weeks (range 0-8 weeks). During this time 5 patients died. In contrast, only 2/40 patients died within the first 8 weeks after the first RLT cycle. This may suggest and additional indicator of treatment efficacy.

Treatment per protocol was applied to 31/40 patients. 11 of them had further treatment cycles indicated as consolidation therapy or as a second treatment series after relapse. Nine patients discontinued treatment earlier; 5 due to non-response or soon PSA-relapse; 4 patients discontinued due to intolerable xerostomia or loss of taste, despite promising initial PSA-response. Consolidation therapy was offered, but due to the lack of life-threatening situations not strongly recommended to 15 of the other per protocol patients, which were presenting with partial remissions and PSMA-positive residual lesions in PSMA-imaging at week-24. However, these patients were reluctant to additional elective treatment cycles because they reported severe xerostomia and wanted to preserve some remaining salivary gland function. No other clinical side-effects led to discontinuing therapy. The amplitude of hematological changes was small (Fig. 3).

Exactly 50% of patients showed up to the follow-up exam 1 year after first treatment; i.e. median overall survival (mOS) is >12 months, even if worst case was assumed for all patients lost to follow-up.

Surrogate Markers of Response

Restaging 6 months after first treatment revealed a median radiological PFS of 6 months. The response in PSMA-imaging was closely related to serum PSA levels and 19 patients showed tumor regression. The second modality regularly confirmed PSMA imaging and serum PSA findings, but often with an additional delay of 3-6 months (Fig. 4).

Any PSA-response was observed in 33/38 patients that survived at least 8 weeks after the first treatment and in 24 of them (63%) PSA decreased by >50%. mTTP was 7.0 months. Best PSA-response and PSA-response at defined time-points are presented in Fig. 5.

Swimmer-Plot Analysis

The median duration of any 1st, 2nd, 3rd and 4th line therapy, irrespective of the particular treatment modality (i.e. each treatment line presents a mixture of abiraterone, docetaxel, enazalutamide, etc.), was 8.0, 7.0, 6.0 and 4.0 months.

The median duration to abiraterone, docetaxel, enzalutamide, cabazitaxel and ^{223}Ra, irrespective of treatment line (i.e. irrespective weather the respective drug was administered as 1st, 2nd, 3rd or 4th line treatment), was 10.0, 6.5, 6.5, 6.0 and 4.0 months, respectively.

The most common 1st line therapy was abiraterone with a median duration of 12.0 months in this setting; administered as a ≥2nd line therapy the median duration of response dropped to 7.0 months. The second most common 1st line therapy was docetaxel with a median duration of 8.0 months, which was also the most common 2nd line treatment strategy; however, median duration dropped to 6.5 months, if administered ≥2nd line. Enzalutamide was the most common 3rd line therapy with a median duration of 6.0 months; 7.0 months when given earlier, 5.5 months when given later.

In contrast, median duration of tumor control under ^{225}Ac-PSMA-617, always applied as the last-line therapy, was 9.0 months.

The absolute values of tumor control in months are graphically summarized in Fig. 6A. The “swim lanes” of ^{225}Ac-PSMA-617 normalized relative to the duration of preceding treatment lines are provided as Fig. 6B.

DISCUSSION

Here we report our clinical findings for forty patients receiving ^{225}Ac-PSMA-617 as a salvage therapy. Dosimetry estimates and an empirical dose finding, i.e. adverse events were used to define the maximum tolerable treatment activity, have already been published previously (*17*). This evaluation is dedicated to identify first indicators to project the clinical efficacy of PSMA-TAT.

In contrast to “medical research” (Declaration of Helsinki paragraph 1-36), the paragraph 37 “unproven intervention in clinical practice” and our national regulatory adaption thereof does not allow systematical patient selection criteria, randomized controls, or follow-up exams exceeding the clinical demand making the obligatory retrospective, interpretation of derived findings difficult. Nevertheless, it is explicitly requested that new information must be recorded and, where findings are considered appropriate to affect clinical decision making, made publicly available.

“ALSMYPCA” (*23*), the only recent formal clinical trial accepting patients either after or ineligible to receive docetaxel, recruited 43% patients which were declared unfit for chemotherapy by their supporting oncologist. The fact that 70% of our patients had prior chemotherapy (despite approval of secondary hormone manipulation already in the pre-docetaxel setting) is underlining our attempt to keep patients as often and long as possible on approved treatment lines before offering an unproven intervention as a salvage option.

Surrogate Markers of Response

To assess anti-tumor activity of new drugs in early phase clinical trials the PCWG2-criteria (*21*) recommended PSA response, preferable reported in waterfall graphs, as one of the most established surrogate parameters. At week-8 and at week-16 we observed a decline of PSA >50% in 24/38 (63%) patients. This exceeds the biochemical response rates of ^{177}Lu-PSMA-617, which were reported in a range of 30-59% (Table 2). In addition, a complete response with regard to PSA and PSMA-PET/CT was achieved in 5/38 (13%) ^{225}Ac-PSMA-617 patients; In contrast, under ^{177}Lu-PSMA-RLT complete remissions are anecdotic (~1%) even in less advanced patients (*9,10*). However, PSA presents only a surrogate for response and an improved PSA-response is not necessarily predictive, that ^{225}Ac-PSMA patients will have longer PFS and OS than ^{177}Lu-PSMA patients. In Phase-2 studies the drugs Cabozantinib and Tasquinimod presented significant anti-tumor activity by biomarker and imaging response (*24,25*), but failed to demonstrate improvement of mOS in succeeding Phase-3 trials (*26,27*).

However, the PSA-response rates for Cabozantinib and Tasquinimod, have been remarkable lower in comparison to both, ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617.

Comparison to Historical Controls

Another way to cope with the lack of randomized controls would be comparison to historical controls. However, prognostic baseline findings have significant impact on PFS and OS. For example, abiraterone demonstrated a PFS / OS of 16.5 / 35.3 months in the pre-docetaxel setting but only 5.6 / 15.8 months in the post-docetaxel setting (*28,29*). The situation is similar for enzalutamide: OS was 32.4 months in the pre-docetaxel but only 18.4 months in the post-docetaxel setting (*30,31*). In contrast, the absolute improvement of OS for the newly approved drugs was in the dimension of 3.4 months (34.7 vs. 30.3 abiraterone vs. placebo), 2.2 months (32.4 vs. 30.2 enzalutamide vs. placebo), 2.4 months (15.1 vs. 12.7 cabazitaxel vs. mitoxantrone) and 3.6 months (14.9 vs. 11.3 Ra-223 vs. placebo) (*23, 28-31*). Thus, different inclusion criteria had a higher impact for the observed OS than the treatment related absolute benefit itself had. It is difficult to compare PSMA-RLT to these recent phase-3 trials because the stringent inclusion criteria of formal clinical trials translate into artificial patient collectives (e.g. either 0% or 100% previous docetaxel), not ideally reflecting clinical reality (*23, 28-31*). As the recently approved drugs have been developed simultaneously, there are no large historical controls, which had already access to various secondary hormone manipulations.

The baseline characteristics provided in the actual reports about ^{177}Lu-PSMA-RLT (Table 1) were found closer to today's clinical practice and more appropriate to serve as comparators. Nevertheless, the reported cohorts present remarkable heterogeneity. An initial read of Table 1 demonstrates a factor three difference in PFS (4.5 vs 13.7 months) and OS (8 vs >28 months) between different centers (*4,6*). However, the prognostic factors have been identified to serve as tools for comparison of studies with different inclusion criteria: ECOG performance score, site of visceral metastasis and high baseline PSA have the highest effect on OS (32-34).

In comparison to Baum et al, who is reporting the longest PFS and OS of all groups (*6*), our patient cohort is remarkable more challenging with regard to all relevant prognostic parameters: time from diagnosis to first treatment cycle 7.5 vs 49 months, percentage of ECOG ≥2 patients 0 vs 20%, baseline PSA 43 vs 169 ng/ml, twice as much patients with visceral metastases, more than twice as much patients with previous chemo- and secondary hormone therapy (Table 1) in history. Regarding site of metastasis, baseline PSA, clinical performance score and previous therapies our cohort is rather comparable to the experiences from the Muenster- (*4*) or Munich- (*7*) groups. In addition, offering both ^{177}Lu-PSMA-RLT or ^{225}Ac-PSMA-TAT in our department and performing patient tailoring with diffuse type bone(marrow)

involvement as a main stratification criterion, our patient cohort presents a remarkable high percentage of 45% “superscan pattern” patients (Table 1); this subgroup was not highlighted by most other centers (*4-7*); however, in the ALSYMPCA-trial such an advanced tumor spread was only found in <10% of the patients (*23*). Despite reporting an even more challenging patient cohort our mTTP and OS for ^{225}Ac-TAT appears more preferable in comparison to the ^{177}Lu-PSMA experience (mTTP 7.0 vs. 4.5 and 5.5 months; mOS >12 vs. 8 months) (*4,7*). Nevertheless, a comparison of heterogeneous patient cohorts to historical controls will always be affected by several uncertainties and possible bias effects.

Swimmer-Plot Analysis

As several new drugs for mCRPC have been approved during recent years and it became apparent that the respective sequence of treatment modalities is important with regard to potential cross-resistance between drugs with a similar mechanism of action (*35,36*), the updated PCWG3-criteria (*22*) now recommend to report rather the number and sequence of lines of prior systemic treatments than using the nomenclature pre-docetaxel vs. post-docetaxel anymore. PCWG3-criteria also introduces the “no longer clinically benefiting” (NLCB)-concept, which leaves more room for more individualized provider-patient decisions, e.g. to continue therapy even in case of PSA-progression as long as clinical symptoms remain sufficiently controlled. The swimmer plot has been suggested a preferable option to visualize the sequence and duration of different treatment options (*22*). For a heterogeneous patient collective without matching controls, such as the group of patients evaluated in this report, this kind of analysis demonstrates some welcome advantages. Using the same patient as his intra-individual comparator attenuates the random effects normally introduced by the selection bias. Visual presentation also simplifies the interpretation if an observed effect is not only “statistically significant” but also if the effect is clinically relevant in comparison to the typical course of disease.

It is well in line with the literature and the theoretical background of cross-resistance and advancing tumor-dedifferentiation (*35,36*), that each of the approved drugs (abiraterone, enzalutamide, docetaxel, cabazitaxel) performed best when used in earlier treatment lines. It should be emphasized that therapy with ^{225}Ac-PSMA-617 resulted in longer duration of tumor control than most of the preceding treatment modalities (with 1st line abiraterone the only exception) even when given in the last-line setting. After reaching the castration-resistant stage in mean approx. 30% of the remaining time was sufficiently controlled with PSMA-TAT (Fig. 3). If ^{225}Ac-PSMA-617 could benefit from being given as an earlier treatment-line should be elaborated in additional studies.

One critical observation during this evaluation is the high number of patients who discontinued therapy despite promising PSA-response due to intolerable xerostomia. However, our treatment regimen was based on dosimetry and empirical dose escalation of the first treatment cycle with only a limited number of observations available for succeeding cycles (*17*). It was reported that salivary gland uptake is dependent on tumor load and the tumor-sink-effect may have a protective effect for the first injection (*37*). As we often observed remarkable PSA-response already after cycle-1 (Fig. 1), we consider it reasonable to de-escalate the treatment activity of the 2nd and 3rd administration for these patients. The masses of salivary glands are independent from body-weight and no other organs were found dose limiting; thus, we also presumed that the treatment activity could be simplified to a fixed dose. As a consequence, we adopted our SOP accordingly (Supplemental Table 1). Hopefully, treatment de-escalation will provide improved tolerability without losing to much anti-tumor activity. Furthermore blocking or displacement strategies should be developed to reduce the dose in critical organs as already performed in a preclinical study for the kidneys (*38*).

CONCLUSION

Clinical anti-tumor activity is highly supported by positive response of surrogate parameters such as radiological progression free survival and PSA. As far as different baseline patient characteristics allow a reliable interpretation, the clinical efficacy against tumor but also co-radiation to salivary glands of ^{225}Ac-PSMA-TAT seems further enhanced in comparison to ^{177}Lu-PSMA-RLT. Swimmer-plot analysis provides first longitudinal indicators that PSMA-TAT presents clinical efficacy with regard to duration of tumor control. Hopefully, minor modifications to the treatment regimen will further refine the therapeutic range of this novel treatment concept.

REFERENCES

1. Benesová M, Schäfer M, Bauder-Wüst U, et al. Preclinical evaluation of a tailormade DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56:914–920.
2. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with Lu-177 labeled PSMA-617. *J Nucl Med.* 2016;57:1170-1176.
3. Fendler WP, Reinhardt S, Ilhan H, et al. Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. *Oncotarget.* 2017;8:3581-3590.
4. Bräuer A, Grubert LS, Roll W, et al. 177Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017;44:1663-1670.
5. Ahmadzadehfar H, Wegen S, Yordanova A, et al. Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using [177Lu]Lu-PSMA-617. *Eur J Nucl Med Mol Imaging*. 2017;44:1448-1454.
6. Baum RP, Kulkarni HR, Schuchardt C, et al. 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: Safety and efficacy. *J Nucl Med*. 2016;57:1006-1013.
7. Heck MM, Retz M, D'Alessandria C, et al. Systemic Radioligand Therapy with (177)Lu Labeled Prostate Specific Membrane Antigen Ligand for Imaging and Therapy in Patients with Metastatic Castration Resistant Prostate Cancer. *J Urol*. 2016;196:382-391.
8. Yadav MP, Ballal S, Tripathi M, et al. ^{177}Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging.* 2017;44:81-91.
9. Kulkarni HR, Singh A, Schuchardt C, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med*. 2016;57:97S-104S.
10. Rathke H, Giesel FL, Flechsig P, et al. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* August 10, 2017 [Epub ahead of print].
11. McDevitt MR, Barendswaard E, Ma D, et al. An alpha-particle emitting antibody ([213Bi]J591) for radioimmunotherapy of prostate cancer. *Cancer Res*. 2000;60:6095-6100.

12. Ballangrud AM, Yang WH, Charlton DE, et al. Response of LNCaP spheroids after treatment with an alpha-particle emitter (213Bi)-labeled anti-prostate-specific membrane antigen antibody (J591). *Cancer Res.* 2001;61:2008-2014.
13. Li Y, Tian Z, Rizvi SM, Bander NH, Allen BJ. In vitro and preclinical targeted alpha therapy of human prostate cancer with Bi-213 labeled J591 antibody against the prostate specific membrane antigen. *Prostate Cancer Prostatic Dis*. 2002;5:36-46.
14. Kiess AP, Minn I, Vaidyanathan G, et al. (2S)-2-(3-(1-Carboxy-5-(4-211At-Astatobenzamido)Pentyl)Ureido)-Pentanedioic acid for PSMA-targeted α-particle radiopharmaceutical therapy. *J Nucl Med.* 2016;57:1569-1575.
15. Nonnekens J, Chatalic KL, Molkenboer-Kuenen JD, et al. ^{213}Bi-Labeled prostate-specific membrane antigen-targeting agents induce DNA double-strand breaks in prostate cancer xenografts. *Cancer Biother Radiopharm*. 2017;32:67-73
16. Kratochwil C, Schmidt K, Afshar-Oromieh A, et al. Targeted alpha therapy of mCRPC: Dosimetry estimate of ^{213}Bismuth-PSMA-617. *Eur J Nucl Med Mol Imaging*. 2018;45:31-37.
17. Kratochwil C, Bruchertseifer F, Rathke H, et al. Targeted alpha therapy of mCRPC with ^{225}Actinium-PSMA-617: Dosimetry estimate and empirical dose finding. *J Nucl Med.* 2017;58:1624-1631.
18. Sathekge M, Knoesen O, Meckel M, Modiselle M, Vorster M, Marx S. ^{213}Bi-PSMA-617 targeted alpha-radionuclide therapy in metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2017;44:1099-1100.
19. Kratochwil C, Bruchertseifer F, Giesel FL, et al. ^{225}Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. *J Nucl Med.* 2016;57:1941-1944.
20. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 1999;17:3461-3467.
21. Scher HI, Halabi S, Tannock I, 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;26:1148-1159
22. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016;34:1402-1418.
23. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213-223.

24. Pili R, Häggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *J Clin Oncol*. 2011;29:4022-4028.
25. Smith MR, Sweeney CJ, Corn PG, et al. Cabozantinib in chemotherapy-pretreated metastatic castration-resistant prostate cancer: results of a phase II nonrandomized expansion study. *J Clin Oncol*. 2014;32:3391-3399.
26. Sternberg C, Armstrong A, Pili R, et al. Randomized, double-blind, placebo-controlled phase III study of tasquinimod in men with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2016;34:2636-2643.
27. Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol*. 2016;34:3005-3013.
28. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13:983-992.
29. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16:152-160.
30. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187-1197.
31. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424-433.
32. Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, Armstrong AJ. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. *Eur Urol.* 2014;65:3-6.
33. Halabi S, Lin CY, Kelly WK et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2014;32:671.
34. Chi KN, Kheoh TS, Ryan CJ et al: A prognostic model for predicting overall survival (OS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA) after docetaxel. *J Clin Oncol.* 2013;31 [Abstract 5013].

35. Badrising S, van der Noort V, van Oort IM et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer.* 2014;120:968.
36. Noonan KL, North S, Bitting RL et al: Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol.* 2013;24:1802.
37. Gaertner FC, Halabi K, Ahmadzadehfar H, et al. Uptake of PSMA-ligands in normal tissues is dependent on tumor load in patients with prostate cancer. *Oncotarget*. 2017;8:55094-55103.
38. Kratochwil C, Giesel FL, Leotta K, et al. PMPA for nephroprotection in PSMA-targeted radionuclide therapy of prostate cancer. *J Nucl Med*. 2015;56:293-298.

FIGURE LEGENDS

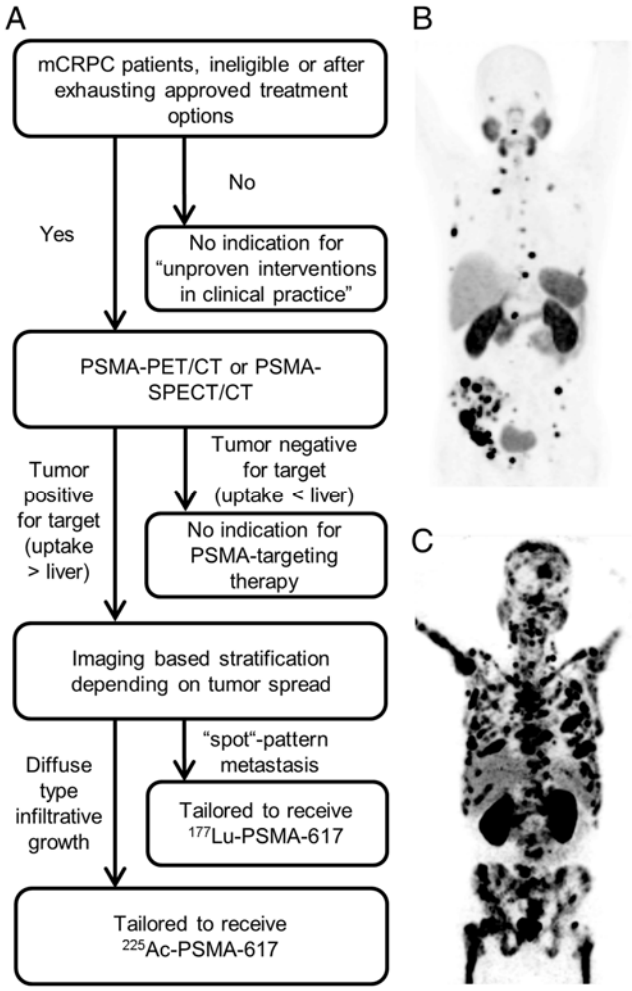

Figure 1: Patient selection criteria: Work-flow how patients were selected to receive PSMA-RLT as an unproven intervention in clinical practice (A). Patients with oligo-metastatic, "hot-spot"-pattern tumor spread (B) were preferably stratified to receive ^{177}Lu-PSMA-617, patients with "diffuse"-pattern bone marrow infiltration (C) were stratified for ^{225}Ac-PSMA-617.

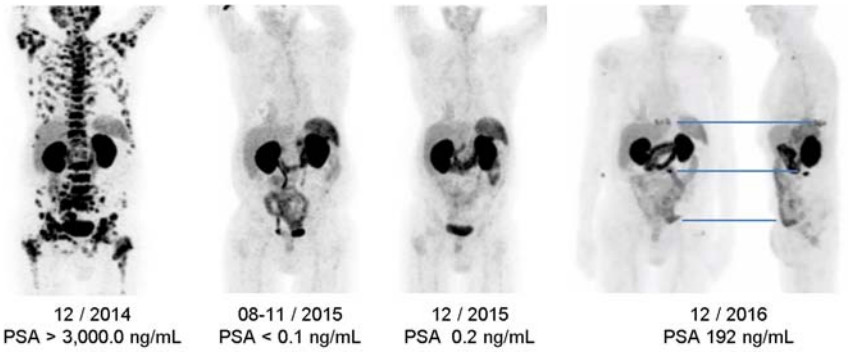

Figure 2: “Time to PSA-progression” versus “Duration of clinical benefit”: After a favorable initial PSA and imaging response to “complete remission”, patient no. 14 had a time to biochemical-progression of only 1 year (01/2015-12/2015). However, the duration of clinical benefit was more than 1 year longer; Due to asymptomatic disease and slow growth velocity the treatment free interval could be prolonged until 04/2017. Again responding to the 2nd series of ^{225}Ac-PSMA-617 the clinical benefit is currently still considered ongoing. (PET images in courtesy of Prof. Mottaghy, RWTH Aachen).

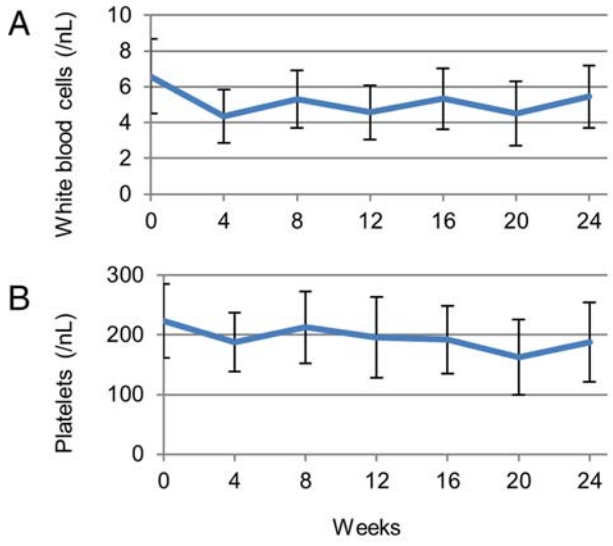

Figure 3: White blood cell (A) and platelet count (B) during 24 weeks

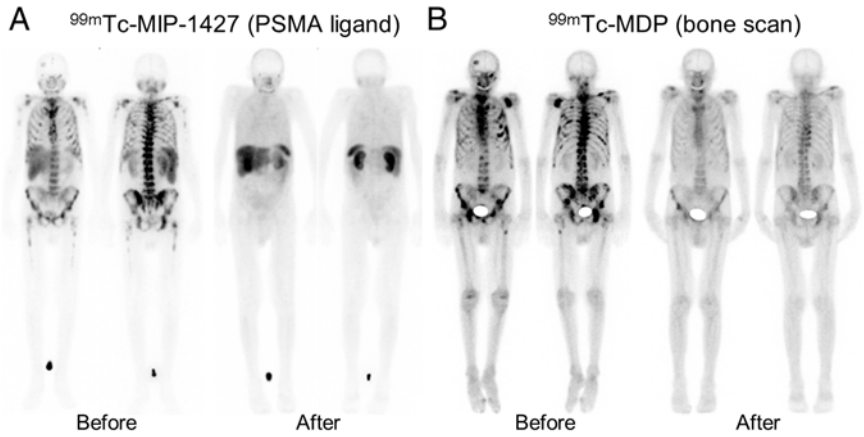

Figure 4: A patient with diffuse spine metastases at baseline presented with complete remission regarding serum PSA and PSMA-scan at month-6 (A). At month-9 bone-scan became confirmative presenting favorable response; however - most probably due to unspecific bone-reactions - some residual lesions did not diminish completely (B).

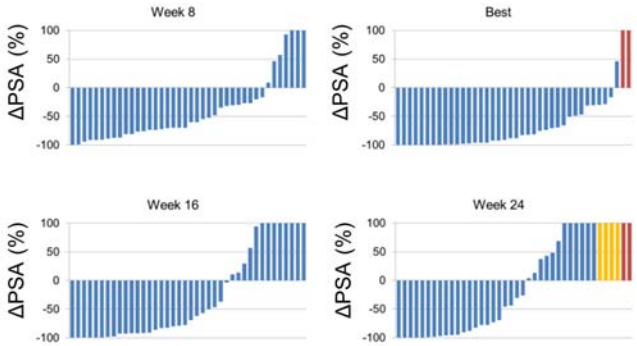

Figure 5: Waterfall graphs of PSA-response. Patients that died before week-8 (red) or discontinued due to xerostomia (yellow) were handled as progression.

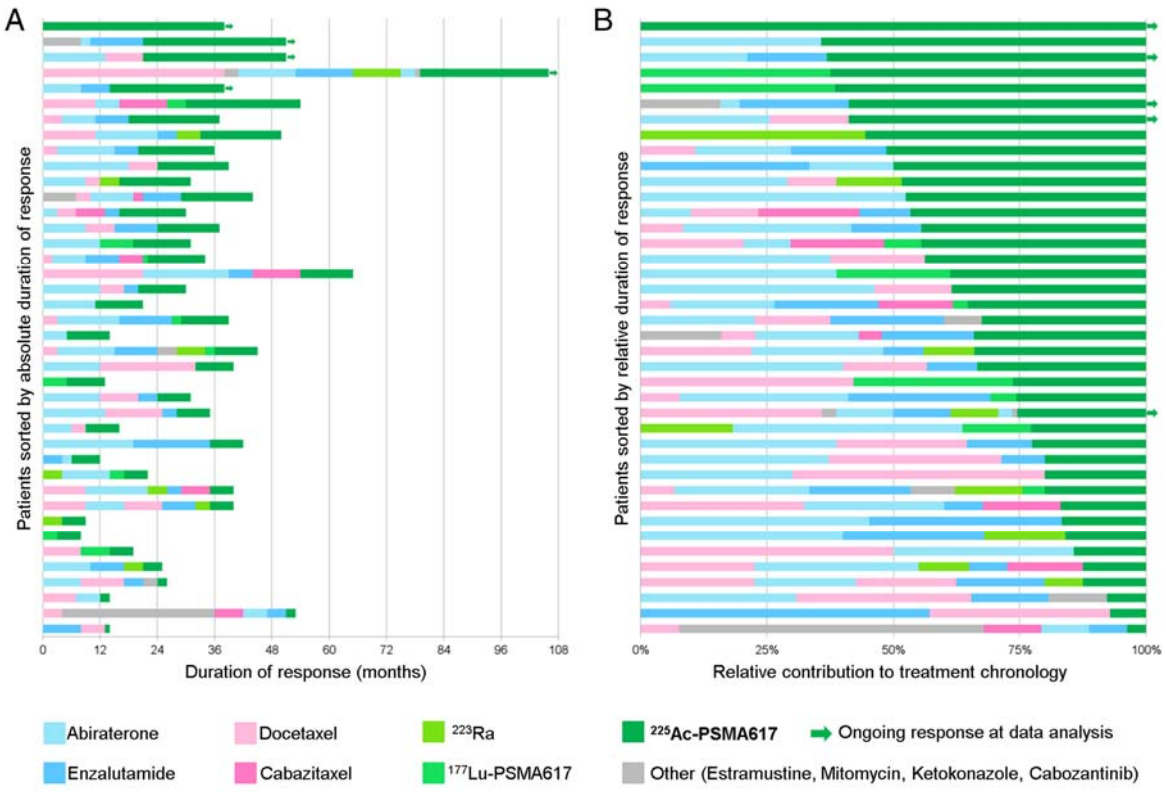

Figure 6: Swimmer-Plot: Duration of tumor control in months (A), and relative to the duration of previous treatment lines (B).

TABLES

Table 1: Patients characteristics in comparison to experience with ^{177}Lu-PSMA and ^{223}Ra

Identifier [Ref.]	This report	Münster (4)	Bonn (5)	Bad Berka (6)	TU Munich (7)	ALSYMPCA (27)
Therapy modality / drug	^{225}Ac-PSMA-617	^{117}Lu-PSMA-617	^{117}Lu-PSMA-617	^{177}Lu-PSMA-I&T	^{177}Lu-PSMA-I&T	^{223}Ra
Number patients (exp. arm)	40	59	52	56	22	614
Age [median]	70	72	71	72	71	71
Age [% 75 or older]	30					28
ECOG-0/1 [%]	80	54	75	100	100	87
ECOG-2 or greater [%]	20	46	25	0	0	13
PSA [median]	169	346	194	43.2	349	146
Alkaline Phosphatase [median]	181	188	122		148	211
AP >220 [%]	40.0	45.7				43
Hemoglobin [g/dL, median]	10.9	10.6		12.6		12.2
Hemoglobine 10 or less [%]	35.0			5.4		
Bone Metastasis [%]	97.5	93	100	76.8	95	
<20 lesions [%]	20		5.8 (< 6 lesions)			59.0
>20 lesions [%]	32.5		73.1			31.8
Superscan pattern [%]	45					8.8
Visceral Metastasis [%]	40				32	0
Lung [%]	22.5	15	11.5	12.5	14	0
Liver [%]	22.5	34	13.5	8.9	18	0
Brain [%]	5	-	3.8	1.8	-	0
Other [%]	7.5	7	-	8.9	-	0
Prior Docetaxel [%]	70	80	56	45	95	57
Prior Abiraterone [%]	85	80	44	38	86	-
Prior Enzalutamide [%]	60	92	27	20	63	-
Prior Cabazitaxel [%]	17.5	29	n.a.	-	27	-
Prior Ra-223 [%]	22.5	10	44	2	14	-
Other [%]	40	-	-	-	-	-
mOS	> 12	8	15	>28	n.r.	14.9
PFS / TPP	7.0	4.5	n.r.	13.7	5.5	3.6

ECOG = Eastern Cooperative Oncology Group Clinical Performance Score, mOS = median overall survival, PFS = progression free survival, TPP = time to PSA progression, n.r. = not reported

Table 2: Biochemical Response to first cycle PSMA-RLT

Identifier* (Ref)	Ligand	Activity	PSA decline >50%
This report	^{225}Ac-PSMA-617	100 kBq/kgBW	63% (24/38)
Kratochwil et al (2)	^{177}Lu-PSMA-617	4-6 GBq	43% (13/30)
Bräuer et al (4)	^{177}Lu-PSMA-617	6 GBq	53% (31/59)
Ahmadzadehfar et al (5)	^{177}Lu-PSMA-617	6 GBq	44% (23/52)
Baum et al (6)	^{177}Lu-PSMA I&T	3.6-8.7 GBq	59% (33/56)
Heck et al (7)	^{177}Lu-PSMA I&T	7.4 GBq	33% (6/19)
Rathke et al (10)	^{177}Lu-PSMA-617	6-9.3 GBq	30% (12/40)

* If groups double reported overlapping patient cohorts only the publication with the highest patient number was included.

Supplement Table 1: Standard operation procedures (SOP) used for PSMA-TAT

	Initial SOP, active during therapy of the reported patients	Modified SOP , to be used for future patients
Definition of “PSMA-positive”	Visual analysis: average tumor-uptake > liver uptake	Visual analysis: average tumor-uptake > liver uptake AND uptake of at least one lesions > salivary glands
Intended / maximum number of cycles	3 / up to 5 (physicians choice)	3 / up to 5 (physicians choice)
Treatment interval (rationale)	every 2 months (restricted by availability of ^{225}Ac)	every 2 months (restricted by availability of ^{225}Ac)
Treatment activity (rationale)	Cycle 1-3: 100 kBq/kg body-weight (dosimetry estimate and empirical data; Ref. *17,19*)	Cycle 1: fixed activity of 8 MBq; Cycle 2-3: consider dose reduction of 2 MBq, if decline of PSA is >60% in the preceding cycle (clinical experience with these first n=40 patients)
Co-Medication prescribed	Day 0: 2000ml i.v. hydration with electrolyte solution Day 1: HCT 12.5mg Day 1-2: 2000ml oral hydration Day 1-3: anticoagulation Day 1-5: dexamethasone 2mg	
Co-Medication allowed	GnRH-analogues or GnRH-antagonists Bisphosphonate (administered >3 days remote to PSMA-RLT) Analgesics All drugs related to benign co-morbidity	
Co-Medication discontinued	Cabazitaxel, Docetaxel, other i.v. chemotherapy: >3 weeks in advance of PSMA-TAT oral chemotherapy, abiraterone, enzalutamide: until day 0	
Follow-up markers	PSA, ALP	PSA, ALP, LDH, NSE or Chr.-A
Safety lab	blood-cell-count, liver enzymes, creatinine/BUN, electrolytes	

PSA prostate-specific antigen, ALP alkaline phosphatase, LDH lactate-dehydrogenases, NSE neuron-specific enolases, Chr.-A Chromogranine-A, BUN blood urea nitrogen, GnRH gonadotropin releasing hormone