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Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq

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Running title: Dose Escalation Experience ^{177}Lu-PSMA-617

ABSTRACT

Current treatment protocols for ^{177}Lu-PSMA-617 therapies were cautiously derived from dosimetry data, but their practical appropriateness have not yet been proven clinically. We retrospectively report our clinical observations using four different treatment activities. **Methods:** Forty patients with advanced prostate cancer and positive uptake in PSMA-imaging were treated in fractions of 4 GBq / 80 nmol, 6 GBq / 120 nmol, 7.4 GBq / 150 nmol or 9.3 GBq / 150 nmol ^{177}Lu-activity / precursor-amount (n=10, respectively) every 2 months. Safety lab was checked every 2 weeks, PSA-response every 4 weeks; other effects were assessed per anamnesis. **Results:** Initial PSA response presented no correlation to treatment activity. However, 2/10, 4/10, 4/10 and 7/10 patients with doses of 4, 6, 7.4 and 9.3 GBq were in partial remission 8 weeks after completing all 3 cycles; This would be in line with, but due to low patient numbers not proving, a positive dose-response-relationship. Acute hematological toxicity was also irrespective of treatment activity and no more than one grade-3/4 toxicity was observed in each group. Nevertheless, in contrast to the other groups the mean platelet count in the 9.3 GBq group chronically decreased over time. **Conclusions:** If patients with diffuse red marrow infiltration and extensive chemotherapeutical pretreatments are excluded, treatment activities up to three injections of 9.3 GBq ^{177}Lu-PSMA-617 every two months are well tolerable. Further dose escalation should be conducted with care as the MTD seems to be close.

Key words: PSMA-617, mCRPC, ^{177}Lu, Lutetium-177; PSMA-RLT

INTRODUCTION

Around 85-90% of prostate cancer relapses occurring after curative intended primary therapy present with a prostate specific membrane antigen (PSMA)-positive tumor phenotype (*1*). It has also been reported that invasive growth, metastasis and hormone independency are associated with an overexpression of PSMA histologically (*2-4*). Therefore the majority of patients with metastasized, castration resistant prostate cancer (mCRPC) might be suitable for PSMA-targeting radioligand therapy (PSMA-RLT). The Glu-urea based ligand PSMA-617 was pre-clinically optimized for low kidney uptake and improved ligand induced cellular internalization. Coupling with DOTA enables labeling with several diagnostic and therapeutic radionuclides (*5*). Different centers (*6-8*) reported favorable dosimetry for ^{177}Lu-PSMA-617, which in regard to kidney (approx. 0.6 Gy/GBq) and red marrow dose (approx. 0.03 Gy/GBq) outperforms the dosimetry of a ^{177}Lu-labeled PSMA-antibody (*9*), an ^{131}I-labeled small molecule PSMA-ligand (*10*) and the RLT reference compound ^{177}Lu-DOTA-TATE (*11*). Based on the available dosimetry data, the ^{177}Lu-PSMA-617 activities used for the first PSMA-RLTs have been chosen cautiously. However, even these very first reports demonstrated promising anti-tumor activity (*8, 12*). Nevertheless, tolerance limits for normal organs reported in the literature are based on external beam radiotherapy and have only been extrapolated to RLT using radiobiological models, which themselves have manifold limitations as reviewed recently (*13*). Thus, dosimetry in nuclear medicine can only approximate a guidance level for dosing RLT but the optimal treatment regime has still to be refined clinically.

In this retrospective analysis we report our clinical experience with fractions of 4 GBq, 6 GBq, 7.4 GBq or 9.3 GBq ^{177}Lu-PSMA-617 repeated every 2 months.

MATERIALS AND METHODS

Patients

^{177}Lu-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. Patient selection is outlined in Fig. 1. For patients stratified to ^{177}Lu-PSMA-617, each dose level was administered to 10 consecutive patients. If toxicities were comparable to the placebo group of the ALSYMPCA-trial (*14*), individual dose escalations for non-responders were considered ethically justified, resulting in a short learning-phase using heterogeneous dosing regimens between respective dose escalation groups. Data of these heterogeneous interim patients were not suitable for this kind of systematical evaluation, nevertheless some have been made public available within other publications (*8,15*). The chronology how this dose escalation was embedded into clinical practice is summarized in Fig. 2. Patient characteristics were summarized in (Table 1). All patients were informed about the experimental character of this therapy and signed written informed consent. The clinical data are reported retrospectively with approval of the ethical committee (Permit S-321).

Radiopharmaceuticals

The GMP grade precursor for PSMA-617 was obtained from ABX advanced biochemical compounds (Radeberg, Germany) and labeled with ^{177}Lu, which was either obtained from iTG (Garching, Germany) or Perkin Elmer (Waltham, Massachusetts, USA), as described previously (*8*). The molar activity was 1 GBq ^{177}Lu per 20 nmol of precursor with a maximum ammount of 150 nmol injected substance amount. Quality control of the drug was performed by RP-HPLC and ITLC pre-therapeutically and always revealed labeling yields of >99%.

Treatment protocol

According to the German Radiation Protection Ordinance, patients were treated as in-patients for 48 h and discharged as the gamma emission from the patient was <3.5 µSv/h in 2 m distance. On therapy day lab-tests and anamnesis were performed. The

therapy-solution was injected free-hand over 30-60 s via a low-protein-binding sterile filter (Filtropur S 0.2, Sarstedt, Nuembrecht, Germany). Starting 30 min before application, patients received concomitant i.v.-hydration (2000 ml). The ITT was a three-cycle PSMA-therapy, with cycles administered every two month. Radiological restaging was planned 2 months after the 3rd cycle or preponed in case of clinical and biochemical progression.

Follow-up

Lab tests were performed every 2 weeks for 8 weeks following each cycle. Blood-cell-count was checked every 2 weeks; serum Kreatinin, blood-urea-nitrogen, alkaline phosphatase, liver enzymes and PSA were checked every 4 weeks. Hematological toxicity was translated into a grading scale according to the “common toxicity criteria for clinical trials, version 4.03” (*16*). Clinical side effects were assessed amnestic at each treatment cycle.

RESULTS

Clinical findings

The administration of each treatment cycle was tolerated well by all patients. No serious non-hematological side effects were observed and only one grade-4 hematological toxicity was observed (in the 9.3 GBq-group). Especially after the first cycle, patients with symptomatic bone metastases reported, irrespective of dose-group, a short increase of pain (flair up) in the known metastases in the first 1-4 days after treatment, followed by a decrease of pain-symptoms below baseline.

Hematological toxicity

8 weeks of follow-up are available for all patients of each group. Their mean count of platelets and WBC versus time is presented in (Fig. 3). In the 4, 7.4 and 9.3 GBq-group platelets imply a nadir at week-4 but this trend was very moderate and the typical pattern was not demonstrated with 6 GBq. WBC typically dropped during the first two weeks, later they were undulant over serial time-points. For the patients who completed 3 cycles inclusive its respective follow-up, the course of platelets and WBC are presented over the complete follow-up period of 24 weeks, i.e. 6 months (Fig. 3). In the 9.3 GBq-group, chronically decreasing of platelets during follow up was observed but in the majority of patients the absolute numbers were still in the normal range.

After the first cycle, one grade-3 thrombocytopenia (38 /nl) and two grade-2 leukopenias ($WBC_{baseline}$ 2.46 /nl to WBC_{week-8} 2.3 /nl and $WBC_{baseline}$ 3.63 /nl to WBC_{week-8} 2.7 /nl) were observed in the 4 GBq-group. In the 6 GBq-group, only one grade-1 thrombocytopenia and no pathological leukopenia was observed. In the 7.4 GBq-group, one patient had grade-2 leukopenia ($WBC_{baseline}$ 3.3 /nl to WBC_{week-8} 2.8 /nl). One patient had grade-3 leukopenia ($WBC_{baseline}$ 4.35 /nl to WBC_{week-6} 1.9 /nl, recovery to WBC_{week-8} 2.54 /nl), accompanied with a grade-1 thrombocytopenia. In the 9.3 GBq-group, only blood cell count worsening by one toxicity grade and no grade-3/4 result was observed after the first therapeutic injection.

During the 24 week regimen we additionally observed one grade-1 thrombocytopenia ($platelets_{week-8}$ 85 /nl, recovery to $platelets_{week-12}$ 218 /nl) and one grade-2 leukopenia ($WBC_{week-10}$ 2.57 /µl, recovery to $WBC_{week-24}$ 4.38 /µl) in the 6 GBq-

group. For the 7.4 GBq-group, only one grade-1 leukopenia after the second cycle ($WBC_{week\text{-}10}$ 3.0 /µl) was observed. In the 9.3 GBq-group, one grade-4 thrombocytopenia ($platelets_{week\text{-}20}$ 21 /nl) was observed. Also one grade-1 and two grade-2 leukopenias were observed in the 9.3 GBq-group. The patient with grade-4 thrombocytopenia and concurrent grade-2 leukopenia received a dose reduction to 6 GBq for the third cycle to reduce hematological side effects.

In sum, - and similar to the mean cell count - the small number of patients that developed worsening of cell blood count by more than one grade was present in all dose regimes. All affected patients were sharing a superscan character in the intra-therapeutic ^{177}Lu emission scans, indicating red marrow infiltration and progression in comparison to the pre-therapeutic PSMA-imaging, and were also sharing history of chemotherapy.

Response

The PSA response 8 weeks after the first treatment cycle, as presented graphically in waterfall-graphs (Fig. 4), demonstrated no major differences between the four dosing groups. Any PSA decline was observed in 90 %, 70 %, 70 % and 80 %. A PSA decline of >50 % was observed in 40 %, 30 % 50 %, 30 % of the 4 GBq, 6 GBq, 7.4 GBq and 9.3 GBq patients, respectively.

Due to biochemical progression or delayed recovery of blood-cell-count only 21/40 patients completed the treatment as planned. From the ITT population 2/10 patients (4 GBq-group), 5/10 patients (6 GBq-group), 5/10 patients (7.4 GBq-group) and 9/10 patients (9.3 GBq-group) accomplished the three cycles of RLT per protocol. Objective radiologic response at week-24 was demonstrated for 2/10 (4 GBq), 4/10 (6 GBq), 4/10 (6 GBq) and 7/10 (9.3 GBq) patients and, except one patient who experienced a 61% PSA-progression but radiological “stable disease”, the imaging based restaging correlated well with the PSA-response, respectively. The PSA follow-up of the “per protocol”-patients is summarized in Fig. 4.

DISCUSSION

Here we retrospectively report our clinical experience with various treatment activities of ^{177}Lu-PSMA-617 during salvage therapy of forty patients suffering from metastasized, castration resistant prostate cancer (mCRPC).

First clinical application of PSMA-RLT has been done in 2011-2012 using a ^{131}I-labeled PSMA-ligand. The treatment activity was chosen after ^{124}I PET-based dosimetry taking into account a 1 Gy red-marrow tolerance and hematological toxicities were mild (*10*). During repeated treatments grade-3/4 hematological toxicities remained rare (*16*). Any PSA response was demonstrated in 84% (21/25) of the patients (*10*), a PSA decline >50% after the first treatment cycle was achieved in 70.6% of 34 patients (*17*). PSMA-RLT based on ^{177}Lu has practical advantages and ligand PSMA-617 even presents with refined pharmacokinetics and radiation dosimetry (*5,8*). Thus, theoretically ^{177}Lu-PSMA-617 should improve the therapeutic range of PSMA-RLT. Nevertheless, until now the reported PSA response rates are commonly remarkable lower; the actually largest multicenter investigation of ^{177}Lu-PSMA-617 reported only a 40% biochemical response rate after the first treatment cycle (*17*). Therefore a critical discussion about the currently used treatment protocols seems warranted.

Dosimetry studies for ^{177}Lu-PSMA-617 have been performed with variable methodology at different centers but all investigators confirmatively reported similar results (*6-8,18,19*). The vitally essential organs red-marrow (approx. 0.03 Gy/GBq) and kidneys (approx. 0.6 Gy/GBq) should be considered as dose limiting organs (*6-8,18,19*). Assuming a 1 Gy red-marrow tolerance dose, single cycle activities up to 30 GBq ^{177}Lu could be proposed (*7*). Taking into account the concept of biological effective dose during low dose-rate radionuclide therapy a kidney tolerance of 28-40 Gy was suggested for ^{177}Lu-radiopharmaceuticals (*20*); theoretically making cumulative treatment activities in the magnitude of 50 GBq ^{177}Lu-PSMA-617 reasonable. Confirmatively, no grade-3/4 renal toxicity were observed in 55 patients treated with 3x6GBq ^{177}Lu-PSMA-617 (*21*). However, high prevalence of bone metastases and priority of approved chemotherapeutical options before salvage therapy as well as an elderly patient collective introduced some doubt, whether literature values about tolerance doses of red-marrow and other organs are still valid for the addressed patient cohort. Thus, it was reasonable that ^{177}Lu-PSMA-617 RLT was initially introduced with cautious treatment

regimens. Recent publications predominantly focused on treatment activities of 6 GBq administered every 2 months (*22-28*) and results were confirmative to each other. All authors reported few cases of grade-3/4 toxicities, i.e. in the same dimension as the incidence of tumor-related adverse events observed in the placebo arm of the ALSYMPCA-trial (*14*) and despite moderate xerostomia there is no evidence of relevant treatment-related toxicity. However, the used treatment activities are remarkably lower than the projected maximum tolerable dose according to dosimetry estimates, exploiting only 0.2 Gy red-marrow dose (6 GBq x 0.03 Gy/GBq). Simultaneously, the PSA response rates are lower in comparison to the older ^{131}I-PSMA-RLT data exploiting the full 1 Gy red-marrow tolerance limit (*10,16*). Surprisingly, none of the authors (*22-28*) discussed the possibility that escalation of ^{177}Lu treatment activity to an estimated red-marrow absorbed dose between 0.2-1.0 Gy should still be well tolerable but offers the chance to further improve anti-tumor-activity because a positive dose/response-relationship is normally expected in radiotherapy. Therefore, after clinical introduction of ^{177}Lu-PSMA-617, for us it seemed ethical mandatory to increase treatment activity until either non-dramatically grade-1/2 toxicities appear or patients achieve enduring remissions.

With the limited numbers of reported patients it is statistically not reasonable, and also not in the scope of the actual report, to draw a final conclusion which dosing concept provides the optimal therapeutic range. It was already reported that PSA and objective radiological response to PSMA-RLT poorly correlate to the individual tumor absorbed dose (*29*). For individual patients rather the respective radio-sensitivity of the particular tumor as well as other clinical factors (*30*) seems relevant to determine response probability. It is possible that even high dose ^{177}Lu-PSMA-617 cannot achieve identical response rates than observed with ^{131}I-MIP1095 because this older ligand was used in the pre-abiraterone/pre-enzalutamide era and current patients have more previous therapies than these historical controls. Thus, efficacy analysis cannot be based on case series of serially treated patients but needs group comparison after random assignment. For such a purpose a prospective phase-2 study would be needed.

Up to the highest 9.3 GBq treatment activity we did not observe increasing numbers of dose limiting grade-3/4 toxicities. However, in contrast to a formal clinical trial, salvage therapy has to stay away from the edges. Thus we stopped dose

escalation as a clinical decision once we observed incomplete recovery of blood cell count to baseline; even before reaching critical absolute numbers. As there was no randomization (this would define “medical research” and is not possible during “unproven interventions in clinical practice”), simply by chance the 9.3 GBq group contained the most patients with previous chemotherapy, highest alkaline phosphatase and PSA, which by itself already might be a sufficient explanation for reduced red-marrow reserve. Thus, it is possible that the dose limiting effects, attributed to the 9.3 GBq activities, might present an accidental observation caused by patient selection and even higher activities might be possible for well selected patients. However, our aim was to establish a reasonable standard operating procedure appropriate for the real live patients currently scheduled to receive PSMA-RLT and without regular need for sophisticated pre-therapeutic dosimetry to identify statistical outliers in advance. The good tolerability observed in our patient series is well in line with the dosimetry based expectations. An estimated average red-marrow dose of 0.3 Gy per cycle (9.3GBq x 0.03Gy/GBq) is far below the accepted tolerance limit of 1 Gy acute red-marrow tolerance and with a ratio of three there are enough safety margins for patient-individual variability to warrant application of standard doses.

However, it should be noted that we are tailoring patients with diffuse red-marrow infiltration toward ^{225}Ac-PSMA-617 targeted alpha-therapy (Fig.-1) whenever this radionuclide is available. Therefore our patient collective might underrepresent this kind of challenging patients. Modeling red-marrow absorbed dose normally neglects the contribution of beta-particles that are emitted from bone metastases toward the surrounding healthy red-marrow. For ^{177}Lu the 1.5 mm maximum beta range in water corresponds up to approx. 30 cell layers and this routinely neglected factor might become relevant in very advanced patients. Thus, individual dose reductions should be considered for patients with diffuse-type red-marrow infiltration.

CONCLUSION

For patients without extensive red-marrow involvement, repeated application of 7.4-9.3 GBq ^{177}Lu-PSMA-617 per cycle is associated with moderate acute hematological toxicity and other non-hematological side-effects. Incomplete platelet recovery observed

in the 9.3 GBq group might imply that the potential for further dose escalations is limited. However, there is still a high demand for prospective controlled clinical trials to evaluate the fractionation regime that enables the longest duration of tumor control and survival.

FINANCIAL DISCLOSURE
Patent application for PSMA-617 for UH, KK. The other authors declare that they have no conflict of interest.

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FIGURE LEGENDS

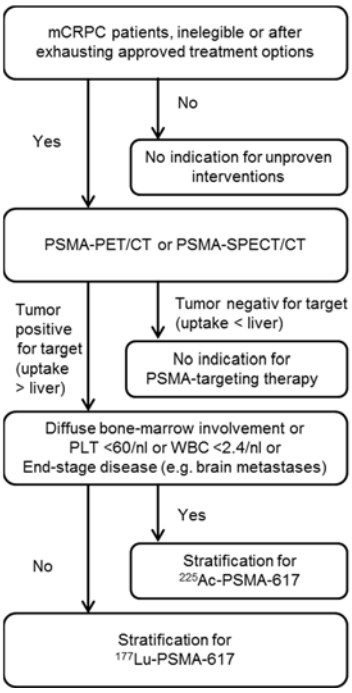


FIGURE 1: Clinical standard operating procedure how patients were selected to receive ^{177}Lu-PSMA-617 therapy. (Metastatic castration-resistant prostate cancer, mCRPC; prostate-specific membrane antigene, PSMA; platelets, PLT; white blood cells, WBC)

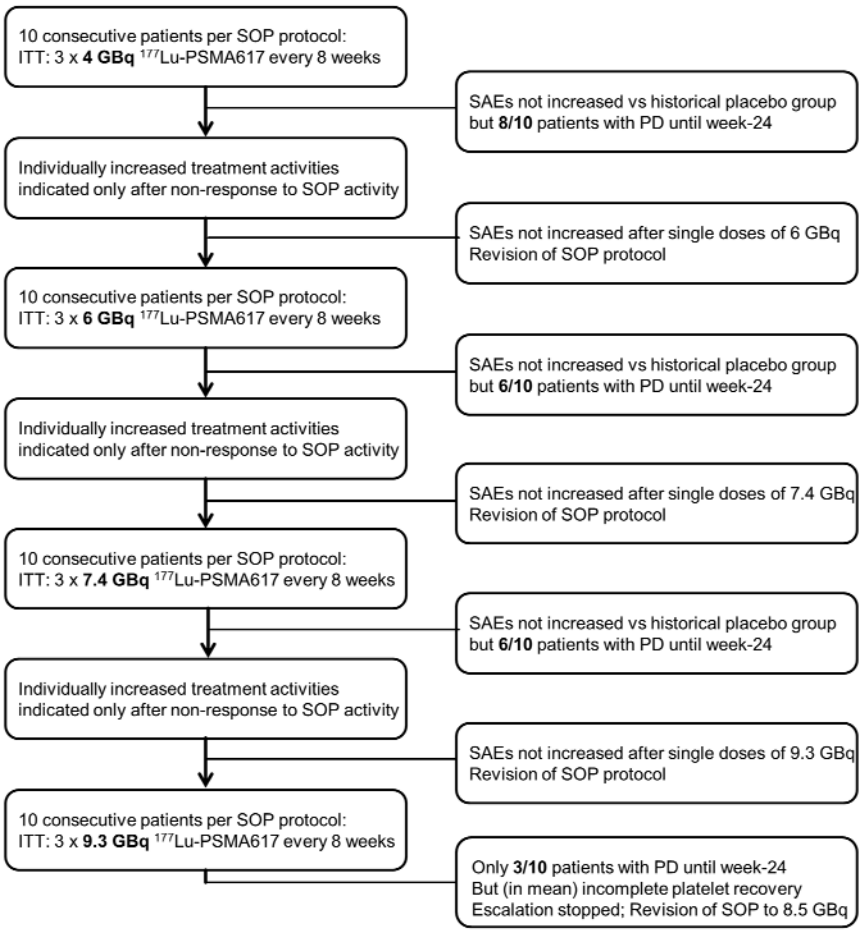


FIGURE 2: Chart-flow demonstrating how dose-escalation was embedded in clinical practice, resulting into chronological tailoring of patients into the respective dosing-groups. (Intention to treat, ITT; progression of disease, PD; standard operating procedure, SOP)

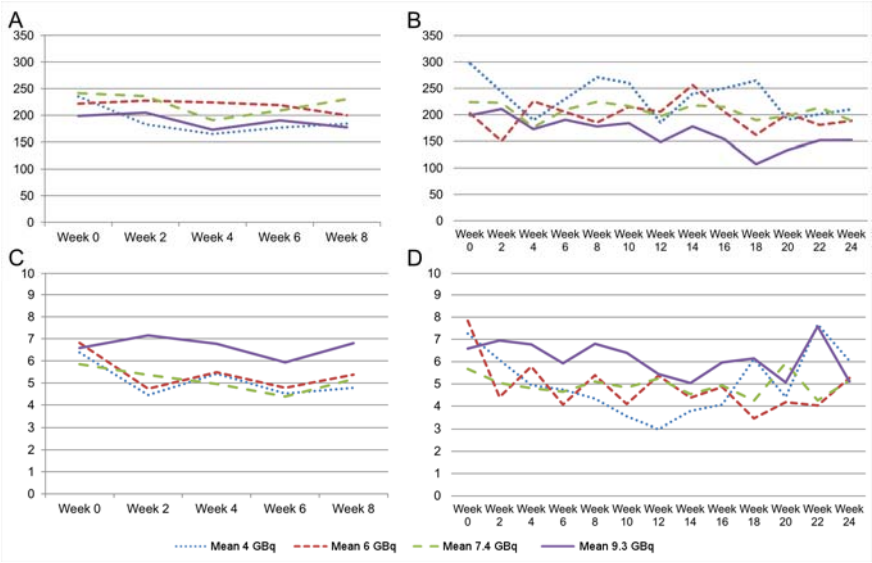


FIGURE 3: Hematological toxicity over 8 weeks (A and C) and for 24 weeks (B and D) during ^{177}Lu-PSMA-RLT. Subfigure A and B present platelet count (/nl), normal range 150-440 /nl. Subfigure C and D present WBC (/nl), normal range 4-10 /nl.

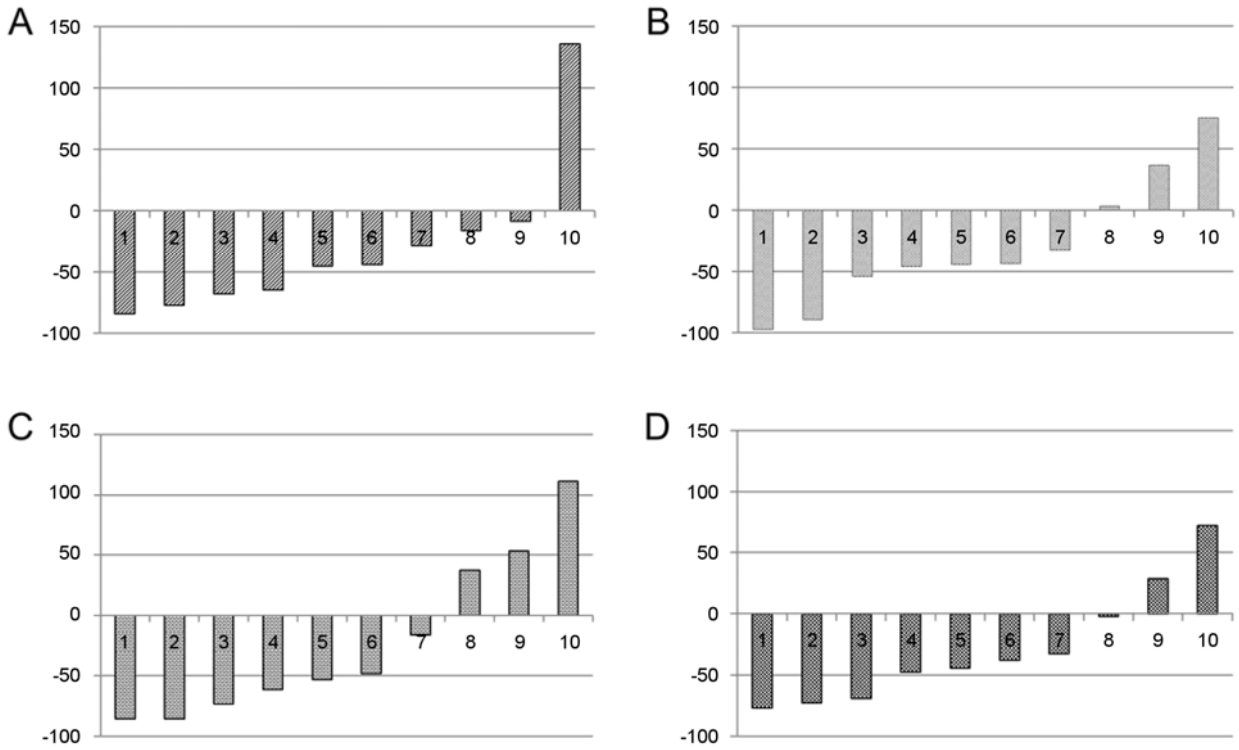
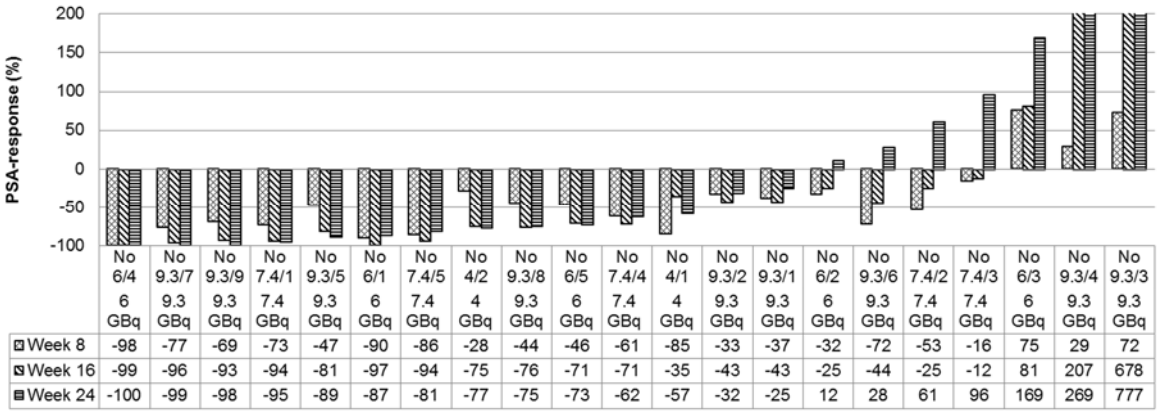


FIGURE 4: Waterfall-graphs of initial (week-8) PSA-response for the 4 GBq-group (A), the 6 GBq-group (B), the 7.4 GBq-group (C) and the 9.3 GBq-group (D).



	No 6/4 6 GBq	No 9.3/7 9.3 GBq	No 9.3/9 9.3 GBq	No 7.4/1 7.4 GBq	No 9.3/5 9.3 GBq	No 6/1 6 GBq	No 7.4/5 7.4 GBq	No 4/2 4 GBq	No 9.3/8 9.3 GBq	No 6/5 6 GBq	No 7.4/4 7.4 GBq	No 4/1 4 GBq	No 9.3/2 9.3 GBq	No 9.3/1 9.3 GBq	No 6/2 6 GBq	No 9.3/6 9.3 GBq	No 7.4/2 7.4 GBq	No 7.4/3 7.4 GBq	No 6/3 6 GBq	No 9.3/4 9.3 GBq	No 9.3/3 9.3 GBq
Week 8	-98	-77	-69	-73	-47	-90	-86	-28	-44	-46	-61	-85	-33	-37	-32	-72	-53	-16	75	29	72
Week 16	-99	-96	-93	-94	-81	-97	-94	-75	-76	-71	-71	-35	-43	-43	-25	-44	-25	-12	81	207	678
Week 24	-100	-99	-98	-95	-89	-87	-81	-77	-75	-73	-62	-57	-32	-25	12	28	61	96	169	269	777

FIGURE 5: Longitudinal PSA follow-up during three cycles of ^{177}Lu-PSMA-617. PSA-changes are presented in percent (%) comparing $PSA_{week\text{-}x}$ to $PSA_{baseline}$.

TABLES

Table 1: Patients baseline characteristics

Characteristics	**4 GBq** n=10	**6 GBq** n=10	**7.4 GBq** n=10	**9.3 GBq** n=10
Age (y)				
Median	75.5	70.5	70.5	73.5
Range	57-85	66-79	58-85	67-78
Gleason Score				
Median	8	8	9	8
Gl 7	4	2	0	4
Gl 8	2	3	3	1
Gl 9	3	3	6	3
Gl unknown	1	2	1	1
initial PSA (ng/ml)				
Median	83	61	107	92
Range	2.4-2801	1.2-387	12.9-1176	48.5-626.2
WBC (/nl)				
Mean	6.4	6.8	5.8	6.5
SD	3.2	3.4	2.3	2.3
Platelets (/nl)				
Mean	235.3	221.8	241.4	204.7
SD	83.2	70.6	81.0	47.6
Alkaline phosphatase (U/l)				
Mean	138.8	131.7	252.5	202.1
SD	77.1	60.1	217.5	345.4
Hemoglobin (g/dl)				
Mean	11.8	11.9	11.0	11.4
SD	2.4	1.5	2.1	1.7
Localisation of metastases				
LN	5	5	8	9

Bone	9	9	9	7
Liver	0	1	1	1
Lung	2	3	1	2
Brain	1	0	0	0
Other	3	2	3	0
Local recurrence	0	1	1	0
previous Therapy				
RPx (n=)	9	8	5	4
LRTx (n=)	5	6	6	3
CRPC (n=)	10	10	10	10
Abiraterone (n=)	4	6	8	8
Enzalutamid (n=)	3	2	7	10
Bisphosphonates (n=)	2	0	1	3
Denosumab (n=)	2	1	2	4
Ra-223 (n=)	1	3	0	3
Taxane (n=)	4	4	5	8
Total Dose (GBq)	10.1 ± 4.8	13.3 ± 5.1	18.5 ± 3.9	25.4 ± 4.3

Table legend. SD = standard deviation. LN = Lymphnode. RPx = radical prostatectomy. LRTx = local radiation therapy. CRPC = castration resistant prostate cancer. CTx = chemotherapy.