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PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with Lu-177 labeled PSMA-617

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Running Title: ^{177}Lu-PSMA-617 targeted therapy of mCRPC

ABSTRACT

Prostate-specific membrane antigen (PSMA) is an excellent target for radionuclide therapy of metastasized castration-resistant prostate cancer (mCRPC). Besides high affinity and long tumor retention, the DOTA-conjugated ligand PSMA-617 has low kidney uptake making it an excellent choice for therapeutic application.

We retrospectively report our experience with ^{177}Lu-PSMA-617 targeted radionuclide therapy in a case series of mCRPC patients resistant to other treatments.

Methods: Patients with PSMA-positive tumor phenotypes were selected by molecular imaging. 30 patients received 1-3 cycles of ^{177}Lu-PSMA-617. During therapy pharmacokinetics and radiation-dosimetry were evaluated. Blood cell count was checked every two weeks after the first and every four weeks after succeeding cycles. Prostate specific antigen (PSA) was determined every four weeks. Radiological restaging was performed after three cycles.

Results: 21/30 patients had a PSA response; in 13/30 the PSA decreased >50%. After 3 cycles 8/11 patients achieved a sustained PSA response (>50%) for over 24 weeks which also correlated with radiological response (decreased lesion number and size). Normally, acute hematotoxicity was mild. Diffuse bone marrow involvement was a risk factor for higher grade myelosuppression but could be identified by PSMA-imaging in advance. Xerostomia, nausea and fatigue occurred sporadically (<10%). Clearance of non-tumor-bound tracer is predominantly renal and widely completed by 48h. Safety dosimetry reveals kidney doses of approx. 0.75 Gy/GBq, red-marrow 0.03 Gy/GBq, salivary glands 1.4 Gy/GBq; irrespective of tumor burden and consistent on subsequent cycles. Mean tumor absorbed dose ranged 6-22 Gy/GBq during cycle-1.

Conclusion: ^{177}Lu-PSMA-617 is a promising new option for therapy of mCRPC and deserves more attention in larger prospective trials.

Keywords: PSMA, Lu-177, castration-resistant prostate cancer, radionuclide therapy, pharmacokinetics and dosimetry

INTRODUCTION

Despite recent approval of some novel drugs, metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease and additional treatment options are still needed.

PSMA is a promising target for directing new therapies. It is found in the majority of prostate cancers (*1*) and its overexpression correlates with traditional adverse prognostic factors (*2*). Binding of a ligand leads to internalization via clathrin-coated pits (*3*) and prolonged retention in the cell. PSMA-antibody-auristatin conjugates have been considered one option (*4*) but they face the inherent resistance of mCRPC against most (excepting taxanes) conventional chemotherapies. In contrast, prostate cancer is usually radiosensitive. Radiotherapy is a standard treatment for localized prostate cancer, for palliative management of mCRPC and even radiopharmaceuticals targeting the surrounding bone matrix instead of the tumor itself can improve survival (*5*). Therefore it seems more promising that a radioactive PSMA-ligand which is directly internalized into tumor cells will be effective in delivering high doses for systemic endo-radiotherapy. A phase-2 study using the radiolabelled antibody ^{177}Lu-J591 already demonstrated moderate anti-tumor effects (*6*), but the slow diffusion of antibodies into solid lesions and hematotoxicity caused by a long circulation time in blood are limitations (*7,8*). Due to faster kinetics, the PSMA targeted small molecule MIP-1095, when labelled with ^{131}I demonstrated superior outcomes to the antibody approach with PSA responses in 17/28 patients (*9*). Unfortunately, the co-emission of high energy photons from ^{131}I requires elaborate radiation protection. Unlike ^{131}I, ^{177}Lu is a more pure Beta particle emitter and preferable for clinical routine. The DOTA-conjugated PSMA-617 can be labelled with ^{177}Lu-Lu^{3+} and was further refined in tumor-targeting with low nanomolar affinity in the range of Ki = 0.37 nM (NAALADase assay) and K_i = 2.34 nM (equilibrium dissociation constant on

LNCaP) and highly efficient internalization with approx. 75% of the total cell associated activity internalized after 3 h of incubation on LNCaP (*10,11,12*).

Here we report our first clinical experience with ^{177}Lu-PSMA-617 in patients with advanced mCRPC resistant or with contraindications to other conventional therapies and PSMA-positive tumor phenotypes as demonstrated by molecular imaging using structurally related diagnostic analogues (Figure-1). All used PSMA-ligands share the Glu-Urea-motif for binding to the proteolytic domain and a lipophilic chelate or linker region to interact with the hydrophobic accessory pocket proposed by Bařinka et al. (*13*).

MATERIALS AND METHODS

Patients

^{177}Lu-PSMA-617 was offered as surrogate therapy in accordance with the updated Declaration of Helsinki, paragraph-37 “Unproven Interventions in Clinical Practice” and in accordance with German regulations for “compassionate use” which includes priority of all approved treatments (without contraindications) and confirmation of the indication by both a nuclear medicine physician and an external expert in urology or oncology. In brief: All 30 patients were refractory to LHRH-analogs and anti-androgens (Table 1). 23 patients had prior treatment with abiraterone or enzalutamide, 11 of them had received both. 14 patients were refractory to docetaxel, 4 had subsequently also been treated with cabazitaxel and 4 with estramustine. 6 patients were pretreated with Ra-223. In contrast to a formal clinical trial, no systematic patient selection was performed, except all patients had to present with a PSMA-positive tumor phenotype based on PSMA-imaging. All patients were informed about the experimental nature of this therapy and gave written

informed consent. The institutional review board approved this retrospective study.

Imaging based patient stratification

PSMA-imaging was performed <4 weeks prior to the first treatment cycle. Two different kinds of PSMA-imaging were used prior to treatment.

Patients with a public health care provider (only reimbursement for scintigraphy) received planar scans and dual bed position SPECT/CT (GE Infinity) covering thorax/abdomen/pelvis 3h after i.v. injection of 500-700 MBq ^{99m}Tc-MIP1427 (50 nmol ligand). The precursor was produced in house as previously described (*14*) and labeled according to the protocol described with minor modifications; in short the deprotected precursor was radiolabeled with the tricarbonyl method using the CRS Isolink kit (PSI, Switzerland). The intensity of tumor uptake was scored visually.

Patients with a commercial health care provider and reimbursement for positron emission tomography/ computed tomography (PET/CT) received PSMA-PET/CT. This was either done in our department on a Biograph 6 PET/CT (Siemens, Erlangen) 1h post injection of 150 MBq +/-20% (2 nmol ligand) ^{68}Ga-PSMA-11 (*15*) or in outside PET centers before the patients were scheduled to receive therapy in our department. PSMA-PET scans were quantified by measuring SUVmax values for the hottest bone, soft tissue and lymph node metastasis (as prospectively defined index lesions), respectively.

^{177}Lu-Labeling of PSMA-617

The precursor PSMA-617 was synthesized as described previously (*10*) or was obtained from ABX advanced biochemical compounds (Radeberg, Germany) and dissolved with DMSO to obtain a 10 mM solution. 2 µl (20 nmol) of this solution was used per 1 GBq of [^{177}Lu]$LuCl_3$ (Perkin Elmer, NEZ307D; 0.04M HCl) mixed with 1.25 µl 20% ascorbic acid and 100µl 0.4M sodium acetate buffer (pH 5; adjusted with acetic acid) and injected directly into the [^{177}Lu]$LuCl_3$ delivery vial. After heating to 95°C for 10 minutes quality check per RP-HPLC and ITLC was performed and the final product was diluted in 2 ml 0.9% NaCl.

Pharmacokinetics and Dosimetry

Thorough descriptions of the methods used for evaluation of pharmacokinetics and dosimetry are provided online (Supplemental Methods).

Treatment regime and follow-up

According to German radiation protection laws the patients were treated as in-patients on the nuclear medicine ward until 48h post injection. Clinical exam was done prior and 1 day after therapy. Patients received i.v. hydration (2000 ml 0.9% NaCl, flow 333ml/h) starting 30 min prior to therapy. The therapy solution was administered with a slow (30-60 s) freehand injection through a 0.20 µm sterile filter with low protein binding (Filtropur S 0.2, Sarstedt, Nuembrecht, Germany). Our initial treatment regime was based on 3.7-4.0 GBq per cycle repeated every 2 months which was derived from data with I-131-MIP1095 (*9*). Once first ligand specific dosimetry data became available for Lu-177-PSMA617 the dose was increased to 6 GBq per cycle. An overview of the administered activities is provided in (Table 1). After the first cycle blood

cell count was done every 2 weeks, during the succeeding cycles at least every 4 weeks. Serum creatinine, blood-urea-nitrogen, liver enzymes and PSA were checked every 4 weeks. Baseline and follow-up values of lab tests were classified into toxicity gradings using the Common Terminology Criteria for Adverse Events 3.0 (*16*). After 3 cycles imaging-based restaging was performed with either ^{68}Ga-PSMA11-PET/CT or ^{99m}Tc-MIP1427-SPECT/CT as available baseline.

RESULTS

Pharmakokinetics

The initial volume of distribution 1h p.i. was 22 (+/- 12) liters, which approximates extracellular body water (EBW) (*17*). Comparison of full-blood samples and serum revealed that there is neither a relevant passive diffusion of PSMA-617 into cellular blood components nor absorption at their surface. Blood clearance could be fitted bi-exponential with half-lives of 4 h and 95 h (Supplemental Fig. 1a); interpretable as fast clearance from EBW and a slow clearance averaged from organs with specific uptake (including tumor tissue) assuming equilibrium between blood and the particular compartment, respectively. Approximately 50% of the injected activity is eliminated by urine during the first 48h, then the cumulative clearance curve reaches a plateau (Supplemental Fig. 1b). The intestine presented maximum contrast in the 20h p.i. image followed by a normal colon passage speed. Approximately 1-5% of the injected dose is eliminated by fecal excretion.

After 48 h the direct gamma emission was <2 µSv/h at 2 m distance for all patients. Due to the observation that urine clearance of non-tumor bound PSMA-617 is almost completed 48h p.i. and clearance from the intestine can be stimulated with moderate laxatives administered 24h after ^{177}Lu-PSMA-617,

all patients could be discharged after 48h in accordance with our currently valid radiation protection regulations (*18*).

Dosimetry

The dosimetry analyses of 4 patients during their first and second treatment cycle revealed a mean (+/- standard-deviation) kidney dose of 0.75(+/-0.19) Gy/GBq ^{177}Lu-PSMA-617. Red marrow (RM) dose was 0.03(+/-0.01) Gy/GBq, parotid 1.28(+/-0.40) Gy/GBq and submandibular gland 1.48(+/-0.37) Gy/GBq. There was no relevant difference in dosimetry for the patients with low or high tumor-load. In addition, there was no relevant difference in the kidney and red marrow dose between the first and second treatment cycle. Distinct values and additional (not dose limiting) organs are presented in (Table-2). The red marrow dose consists from approx. 45% “self-dose”, i.e. beta radiation during perfusion and passive diffusion into the interstitial space, and 55% “spill-in” radiation (5% from the delineable source organs, 50% from the “remainder body” including tumor lesions).

Treatment efficacy

8 weeks after the first treatment cycle 21/30 patients demonstrated a decrease in PSA, in 18 patients the decrease was >25%, in 13 patients even >50%. However, 8 patients demonstrated a rising PSA and 1 patient remained stable (Fig. 2A). After 24 weeks, i.e. nearly 6 month after initial therapy, 9/11 patients receiving 3 treatment cycles presented with a sustained decrease in PSA in comparison to the baseline value, the decrease was >25% for all of these 9 patients and >50% in 8 pt (Fig. 2B). Follow up between the week-8 and week-24 PSA response (Fig. 2C) revealed that in 8/11 patients the PSA levels

further decreased from cycle-1 to cycle-3. One patient who already presented with PSA progression after the 1st cycle continued therapy due to favorable symptomatic response and had further PSA progression after the 3rd cycle. Two patients initially responded to cycle-1 but had PSA relapse by cycle-3; however, in one of them the PSA was still <50% in comparison to baseline. In these patients imaging findings also demonstrated partial remission in comparison to baseline staging.

Imaging based restaging revealed a positive response in 10 of the 11 patients; surprisingly, a positive imaging response was even found in 1 of the 2 patients with rising PSA. 6 patients were re-staged with PSMA-PET/CT and all presented with a decrease of >50% (average of index lesions) in SUVmax (Fig. 3A). Three patients were assessed with ^{99m}Tc-PSMA-SPECT/CT and presented with visual response (Fig. 3B). In patients with soft tissue or lymph node metastases (target lesions according to RECIST) response was additionally demonstrated with CT (Fig. 3C). Also the post-therapeutic emission scans based on the inherent imaging capabilities of ^{177}Lu (co-emission of gamma radiation) seem sufficient to monitor treatment response despite a minimal lower resolution and higher noise (Fig. 4). Due to the multitude of lesions we did not assess the exact lesion number; as long as the total number of delineable metastases decreased by visual estimation the situation was considered a radiological response. Thus, in similar to the use of bone scans in clinical trials (*19*), single new lesions were not considered “progressive disease”.

Clinically, the treatment was able to stabilize the patient’s well-being. None of the patients discontinued treatment due to worsening of their general clinical condition. The body weight remained fairly stable (mean body weight at baseline: 83kg, at week-24: 81 kg). None of the 24/30 patients without opioid analgesics at baseline had to start such a medication during follow-up. The dose of the 6/30 patients with opioid analgesics at baseline remained stable.

Treatment toxicity

Creatinine and urea as well as liver enzymes were not significantly changed during the complete follow up period, which was 12 weeks for the 19 patients receiving one treatment cycle and 24 weeks for the 11 patients receiving three treatment cycles. Thus, follow-up is sufficient to report acute and mid-term toxicities but not late effects.

Among 15 patients with normal baseline hemoglobin 6 developed I° anemia, 9 patients had no red cell toxicity. In 10 patients with I° anemia before therapy only 3 patients had an decline to II°, 6 patients remained stable and one patient improved to the normal range, this patient simultaneously presented with striking radiological improvement of bone metastases. From 3 patients that already had II° anemia at baseline, one worsened to III° (after only one treatment cycle), one was stable, one improved to I°. In comparison to baseline, 18/27 patients had no worsening of anemia (66%), 9/27 worsened by one grade (33%); no patient had a decline of more than one grade. The only patient with III° anemia had diffuse pattern bone marrow involvement on pre-therapeutic imaging. 2 patients had already received substitution of erythrocytes <6 weeks before PSMA-therapy and were omitted from evaluation of anemia.

With regard to white blood cell (WBC) count (Fig. 5A) 22 patients never developed CTCAE-toxicity higher than baseline. Grade I leucopenia was observed in 6 patients mainly after the third cycle. Grade II was observed in 2 patients, both with diffuse pattern bone marrow involvement.

Platelet count (Fig. 5B) demonstrated high inter-individual variability. However, in 23 patients the absolute platelet count never dropped below the normal range. In 4 patients grade I thrombocytopenia was observed. One patient

developed grade II and one patient grade III thrombocytopenia. Both patients had previously presented with diffuse pattern bone marrow infiltration during imaging and were the same patients who developed the highest WBC toxicity. In one patient grade IV thrombocytopenia was already present at baseline. Despite the fact that the absolute platelet count stayed within the normal range (150-300/nl) for 23/30 patients, we observed a relative decline in the mean platelet count of -14% with nadir 4-6 weeks after the first therapy that recovered after 8 weeks. However, in the 11 patients receiving 3 cycles we found a chronic decrease of platelets (-20%) from baseline to week-24.

Most of the patients reported no relevant dysfunction of salivary glands. Substitution of saliva (spray/gel) was prescribed to 2/30 patients; both developed the xerostomia after the third cycle. After the first and second treatment cycle only temporal xerostomia without relevant loss in quality of life was occasionally reported. Mild fatigue over baseline was regularly reported but only two times it was attributed to affect activities of daily living. Nausea and loss of appetite during the first weeks after therapy were reported infrequently.

DISCUSSION

Here we report our clinical experience with ^{177}Lu-PSMA-617, which revealed anti-tumor activity in the majority of patients with mild to moderate toxicities.

In contrast to conventional pharmaceuticals, the toxicity and response probability of a radiopharmaceutical predominantly depends on the radiation absorbed dose to healthy and tumor tissue, respectively. There are well-defined radiation tolerance limits for normal organs. Therefore, empiric dose escalation studies can partially be omitted and dosing of radioactive drugs can be based on dosimetry. Our dosimetry data are well in line with two other

recent investigations (*20,21*). The highest normal organ dose was found for the salivary glands. Thus, the sporadic incidence of reversible xerostomia which was mainly observed after the third cycle is reasonable taking into account published radiation tolerance limits (*22*). However, if mild xerostomia is considered to be an annoying but harmless side effect, kidneys are the only essential dose limiting organs and their tolerance limits would permit about twice the cumulative dose, i.e. 36 GBq ^{177}Lu-PSMA-617 (*23*), which vice versa would still stay below the limits to provoke severe and irreversible xerostomia (*22*). Additionally, recent attempts to reduce kidney uptake of PSMA-ligands raise hope to further increase the therapeutic index (*24*). Selecting the ideal single fraction dose is more challenging because bone-marrow reserve can be reduced after previous chemotherapy and the published tolerance limits are not reliable (*25*). Also dosimetry can underestimate red-marrow dose because the beta-radiation arising from bone metastases cannot be sufficiently modeled. The 497 keV beta-energy of ^{177}Lu corresponds to a mean/max tissue range of only 0.5mm/2mm (i.e. 10-50 cell diameters) and it is plausible to neglect this dose contribution if only a limited number of solid bone metastases are present. However, it might be relevant in case of diffuse bone-marrow involvement. Therefore, we initially administered conservative 4 GBq fractions. Once it became clear, that only diffuse-type bone-marrow involvement, eventually in combination with previous chemotherapy, present a risk factor for higher hematotoxicity, we escalated to 6 GBq and patients with diffuse-pattern were subsequently stratified to receive PSMA-617 labeled with an alpha emitter. Targeted alpha radiation therapy was already demonstrated to reduce red-marrow toxicity in similar situations (*26*). However, the reliability of this tailored approach has still to be proven. Despite moderate acute hematotoxicity, we observed a chronic decline of platelets during 3 cycles, thus further dose escalations of ^{177}Lu-PSMA-617 should be conducted cautiously. Nevertheless, there is still some room to improve the treatment regime.

The main limitation of this report is that the patients were not systematically selected in a prospective manner with stringent inclusion criteria like in a typical clinical trial. Therefore, the results of this retrospective evaluation should only be considered explorative. Nevertheless, the findings are noteworthy in view of the high number of prior treatments seen by our patients prior to receiving ^{177}Lu-PSMA-617. The novel mCRPC-agents have been approved with hormone therapy (Cougar-302, PREVAIL) or hormone and docetaxel (Cougar-301, AFFIRM, TROPIC) being the only pre-treatments (*27*). In contrast, if the novel drugs are applied consecutively, the >50% PSA response rate is commonly less than 40% (*28*). Our cohort is very high risk with negative prognostic factors such as high Gleason score and visceral metastases (*29*) making the high response rate with the absence of severe toxicity all the more remarkable.

It has been reported that tubulin-targeting with taxanes inhibits androgen receptor (AR) nuclear translocation (*30*). As abiraterone or enzalutamide also interfere with AR-signaling, these drugs are somehow competitive in their mechanism of action and cross resistance may occur, making optimal sequencing of the new drugs challenging (*28,30*). In contrast, PSMA genes are suppressed by androgens; and androgen independency as well as androgen-deprivation therapy may even increase the expression of PSMA in mCRPC (*31,32*). Thus, PSMA-targeting is rather complementary to the currently approved drugs and can still be effective when targeting the AR-axis fails. This would explain the high rate of radiological and PSA responses despite excessive pretreatment.

On the other hand, the reported patients include some selection bias. Patients with diffuse bone-marrow involvement were excluded, once it became apparent that these patients have a higher probability to develop

hematotoxicity. Additionally, a PSMA-positive tumor phenotype based on PET or scintigraphy was a precondition to receive therapy. However, treatment stratification based on prognostic factors is a desired objective in modern oncology and it is beneficial that PSMA-positive tumors can be easily identified noninvasively with PSMA-imaging (*33*). In addition, a diagnostic study with PSMA-PET/CT found PSMA-positive tumor phenotypes in 88% of prostate cancer relapses, suggesting that the majority of mCRPC patients may be potential candidates for PSMA-targeted therapy (*34*).

CONCLUSION

^{177}Lu-PSMA-617 is a new treatment option for mCRPC that demonstrates substantial anti-tumor activity with few side-effects. ^{177}Lu-PSMA-617 therefore, deserves more attention in larger prospective trials.

DISCLOSURE

Pending Patent for PSMA-617: M. Benesova, M. Eder, K. Kopka, U. Haberkorn

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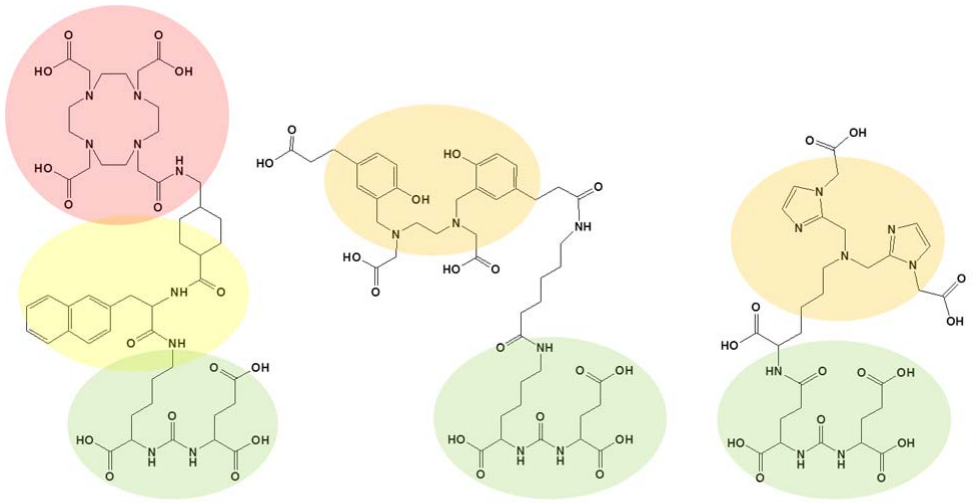

FIGURE 1: PSMA equals the enzyme glutamate carboxypeptidase II. Its proteolytic domain can be targeted with a Glu-Urea-motif (marked green). A hydrophobic pocket accessory to the proteolytic domain adversely interacts with highly polar chelates like DOTA (red) but favours more lipophilic chelates (marked orange) like CIM (MIP-1427) for labelling with ^{99m}Tc or HBED-CC (PSMA-11) for labelling with ^{68}Ga. In PSMA-617 an aromatic linker (marked yellow) exploits the lipophilic accessory pocket to keep the more universal DOTA-chelate remote to the Glu-Urea binding site.

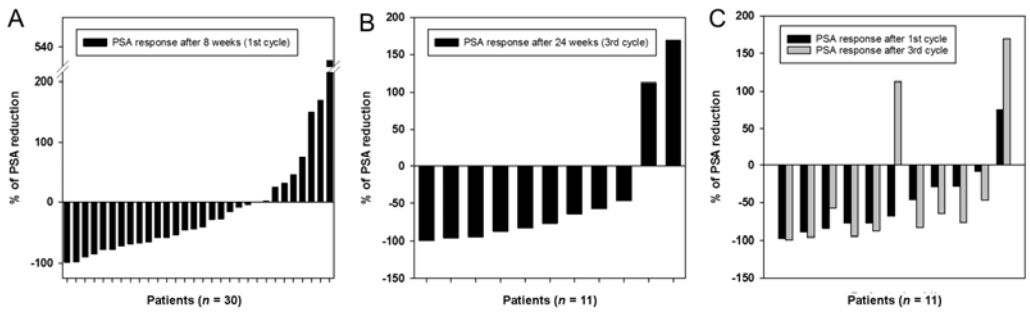

FIGURE 2: Waterfall-graph presenting PSA response after 1 cycle of ^{177}Lu-PSMA617 therapy (A). Waterfall-graph presenting PSA response after 3 cycles of therapy (B). Follow-up between PSA response after cycle-1 and cycle-3 (C).

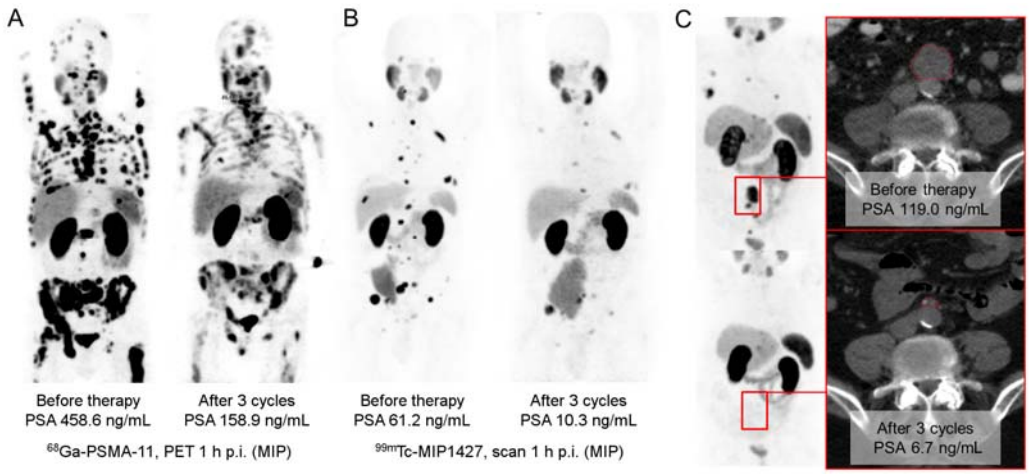

FIGURE 3: Imaging based response evaluation. ^{68}Ga-PSMA-11-PET (A) was evaluated semi-quantitatively. ^{99m}Tc-MIP1427-szintigraphiy (B) enables visual evaluation. If target lesions were available (C), CT was evaluated in accordance to RECIST chriteria. Abbr.: PET = positron emission tomography, MIP = maximum intensity projection, GM = geometric mean, CT = computed tomography.

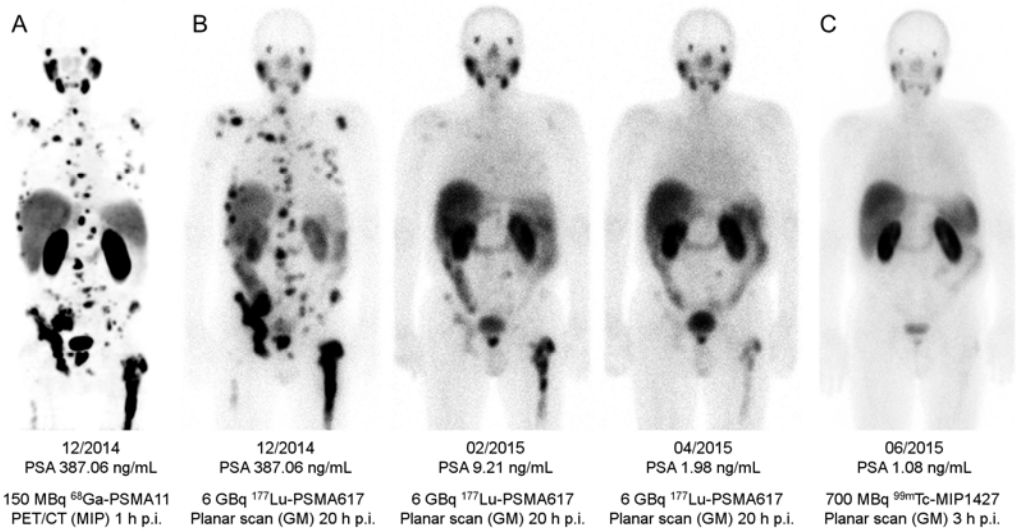

FIGURE 4: PSMA-PET/CT delivers highest resolution (A). The co-emission of gamma-rays enables imaging during therapy (B). ^{99m}Tc-PSMA-scintigraphy has minimally less noise than post therapy scans and can be used for imaging follow-up in an out-patient setting (C). Abbr.: MIP=maximum intensity projections, GM=geometric mean

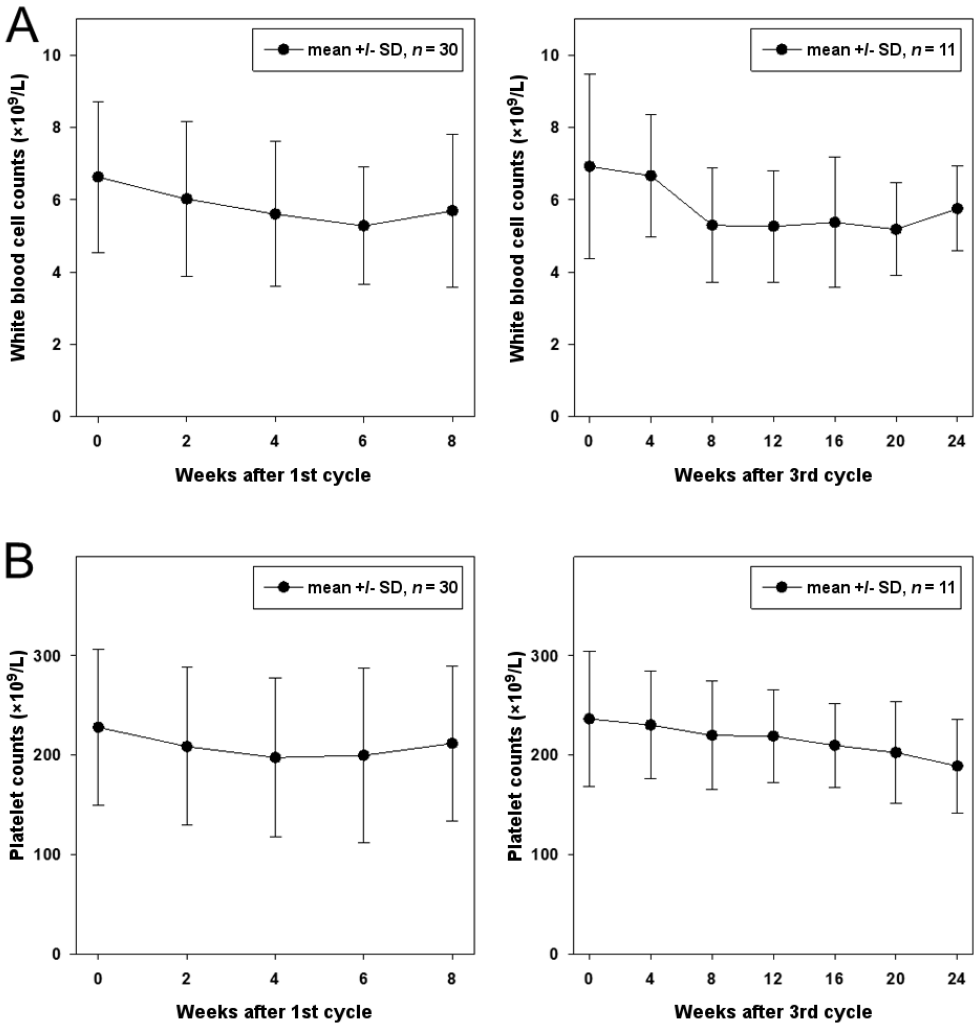

FIGURE 5: Course of white blood cell count (A) and platelets (B) during ^{177}Lu-PSMA617 therapy.

Tables

Table-1: Patient characteristics

No	Age	GS	OP	RTx	CRPC	Abirat	Enza	Ra-223	CTx	Cycles [GBq]	Visceral Metastases
1	68	7	1	B	1	0	0	0	D	6 / 6 / 6	Lung
2	71	4	0	L/B	1	1	1	0	D/ C	4 / 4 /4	Liver
3	75	9	1	B	1	0	0	0	0	4 / 4 / 6	0
4	61	8	1	L/B	1	1	0	0	D/ Sorafenib	6 / 6 / 6	Liver
5	67	9	0	L/B	1	0	0	0	0	6 / 6 / 6	0
6	78	8	1	L/B	1	0	0	0	0	6 / 6 / 6	0
7	71	9	0	0	1	0	1	0	D/ C/ EMP/ HU	4 / PD	Liver
8	78	7b	1	B	1	1	1	1	D/ EMP	6	0
9	68	9	1	0	1	0	0	0	D	6 / 6/ 6	Brain
10	74	9	1	0	1	1	1	0	0	4/ 6/ 6	Liver
11	66	9	1	L	1	1	0	0	0	6 / 6 / 6	0
12	78	8	1	0	1	0	0	0	0	6 / 6	0
13	79	7b	1	0	1	0	0	1	0	3 / Tox	Lung, Adrenal
14	73	9	1	B	1	1	1	0	0	4 / 6/ 6	Liver, Adrenal
15	71	7	0	L	1	1	0	0	0	4/ 6	Liver
16	68	na	0	0	1	1	0	1	D/ EMP	6	0
17	73	na	1	L/B	1	1	0	1	0	4 / 4	0
18	78	8	1	L	1	1	0	1	0	4/ 6/ 6	0
19	73	na	1	L/B	1	1	0	0	D	4 / Tox	Lung
20	68	7	1	B	1	1	1	0	D	6	0
21	85	7a	1	B	1	1	1	0	D	6/ 6/	0
22	71	7	0	L	1	1	0	0	0	4 / PD	Rectum
23	66	9	1	L/B	1	1	1	0	0	6/ 6	0
24	75	8	1	B	1	1	1	0	D	6	0
25	80	7	1	B	1	1	1	0	D/ C	6	Liver, Lung
26	64	9	0	B	1	1	0	1	0	6	0
27	61	9	1	L/B	1	1	1	0	D/ C	6	Liver
28	69	8	1	L/B	1	1	0	0	0	6/ 6/	Lung
29	73	9	0	L	1	1	1	0	D	6/ 6	0
30	75	na	1	L	1	0	1	0	0	6/ Tox	0

Abbr.: 0 = patient did not receive that therapy, 1 = patient had history of that treatment, GS = gleason score, OP = prostatectomy, RTx = radiation therapy to prostate bed (=L) or bone (=B), CRPC = hormone therapy with both an LHRH-Analogue/Antagonist and an anti-androgen, Abirat = Abiraterone, Enza = Enzalutamide, CTx = chemotherapy with docetaxel (=D), cabazitacel (=C), estramustin monophosphate (=EMP) or hydroxyurea (=HU). Cycles = therapy with ^{177}Lu-PSMA-617 with the given activities [GBq] in bi-monthly fractions. Fractionated therapy had to be discontinued due to toxicity (=Tox) or progressive disease (=PD)

Table-2: Dosimetry

Patient-Cycle	P1-C1	P1-C2	P2-C1	P2-C2	P3-C1	P3-C2	P4-C1	P4-C2
Tumor load	low		Intermediate-low		intermediate-high		high	
	[Gy/GBq]		[Gy/GBq]		[Gy/GBq]		[Gy/GBq]	
Kidney	0,55	0,56	1,14	0,82	0,81	0,76	0,62	0,76
Red Marrow	0,02	0,02	0,02	0,02	0,03	0,03	0,05	0,03
Parotid Gl.	2,2	1,16	1,03	0,82	1,26	1,3	1,27	1,17
Submandibular Gl.	1,3	1,69	1,26	0,97	1,37	1,31	1,82	2,13
Liver	0,09	0,1	0,07	0,06	0,09	0,1	0,16	0,13
Spleen	0,19	0,15	0,26	0,14	0,11	0,13	0,28	0,27
Bladder Wall	0,03	0,16	0,16	0,17	0,29	0,23	0,41	0,36
Metastases (mean)	6,1		22,8		15,3		14	
	[mSv/GBq]		[mSv/GBq]		[mSv/GBq]		[mSv/GBq]	
Effective dose equivalent	81,8	77	114	82,5	96,3	91,2	126	111
Effective dose	48,2	46,5	37,2	43,9	58,3	54,3	83,4	65