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# First clinical results for PSMA targeted alpha therapy using $^{225}$Ac-PSMA-I&T in advanced mCRPC patients

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Running title: $^{225}$Ac-PSMA-I&T TAT for mCRPC

**ABSTRACT:**

**Background:** Treatment of advanced metastatic castration resistant prostate cancer (mCRPC) after failure of approved therapy options remains challenging. Prostate-specific membrane antigen (PSMA) targeting β- and α-emitters have been introduced with promising response rates. Here, we present the first clinical data for PSMA targeted α-therapy (TAT) using $^{225}$Ac-PSMA-I&T.

**Methods:** 14 patients receiving $^{225}$Ac-PSMA-I&T have been included in this retrospective analysis. 11/14 had prior second line antiandrogen treatment with abiraterone and/or enzalutamide, prior chemotherapy and prior $^{177}$Lu-PSMA treatment, respectively. Patients were treated at bi-monthly intervals until progression or intolerable side effects. Prostate-specific antigen (PSA) was measured for response assessment. Hematological and non-hematological side effects were recorded according to CTCAE v5.0 criteria.

**Results:** 34 cycles of $^{225}$Ac-PSMA-I&T were applied (median dose 7.8 MBq, range 6.0 – 8.5) with 1 cycle in 3/14, 2 cycles in 7/14, 4 cycles in 3/14 and 5 cycles in 1 patient. No acute toxicity was observed during hospitalization. Baseline PSA was 112 ng/ml (range 20.5 - 818). Best PSA response after TAT with a PSA decline ≥ 50% was observed in 7/14 and any PSA decline in 11/14 patients. 3 patients had no PSA decline at any time. A subgroup analysis of 11 patients with prior $^{177}$Lu-177-PSMA treatment showed any PSA decline in 8/11 and a PSA decline ≥ 50% in 5/11 patients. After TAT, grade 3 anemia was observed in 3/14 patients with 2 of them presenting with grade 2 anemia already at baseline. Grade 3 leukopenia was observed in 1 patient. 8/14 patients with pre-existing xerostomia after $^{177}$Lu-177 PSMA showed no worsening after

TAT. Newly diagnosed grade 1/2 xerostomia after TAT was observed in 5 patients. One patient reported no xerostomia at all.

**Conclusion:** Our first clinical data for TAT using $^{225}$Ac-PSMA-I&T showed promising antitumor effect in advanced mCRPC. These results are highly comparable to data on $^{225}$Ac-PSMA-617 TAT.

Key words: metastatic castration-resistant prostate cancer; radioligand therapy; targeted alpha therapy; $^{225}$Ac and $^{177}$Lu; PSMA

## INTRODUCTION

Progression of Prostate Cancer (PC) after salvage therapy and androgen deprivation therapy (ADT) marks the transition to metastatic castration resistant prostate cancer (mCRPC), which describes the incurable and lethal form of advanced PC where treatment remains highly challenging (*1*). Approved therapy options for mCRPC include second generation antiandrogen therapy, taxane based chemotherapy and radium-223 (*2*). Novel therapy options including immunotherapy with checkpoint inhibitors, poly ADP-ribose polymerase inhibitors and prostate-specific membrane antigen (PSMA) targeting radionuclides have been introduced in the recent years (*2*).

PSMA overexpression in PC represents the ideal target for theranostic approaches using radiolabeled ligands for imaging and therapy (*3*). Radioligand Therapy (RLT) using $^{177}$Lu-PSMA ligands is offered in many centers worldwide and results of the first Phase III trial comparing $^{177}$Lu-PSMA-617 RLT and best supportive care versus best supportive care alone are expected in 2021 (VISION, NCT 03511664). Nonetheless, a considerable number of mCRPC patients do not show sufficient response to RLT using the β-emitter $^{177}$Lu. In the largest retrospective cohort with overall 145 patients, 40% did not show any response at all (*4*). The efficacy of $^{177}$Lu-PSMA RLT was confirmed in the phase-2 LuPSMA trial with any PSA decline in almost all patients (29/30, 97%) (*5*). However, the primary endpoint defined as best PSA decline of 50% or more was not met in 43% of patients.

Targeted alpha therapy (TAT) using $^{225}$Ac-PSMA-617 has been introduced with substantial therapeutic efficacy and has the potential to overcome resistance to β-emitter therapy (*6, 7*). However, clinical experience for TAT is still limited. Clinical data

on 40 patients treated with 8 MBq (100 kBq/kgBW) every two months have shown highly promising results with PSA decline ≥ 50% in 63% and any PSA response in 87% of patients (*8*). Several approaches have been proposed to improve tolerability and determine optimal treatment regimen for $^{225}$Ac-PSMA-617 TAT with (de)-escalating dose reduction or increase in dependence of PSA response (*9*). Such a protocol was also applied in 17 chemotherapy-naïve mCRPC patients and overall PSA decline ≥ 50% was observed in 15 (88%) patients while maintaining low toxicity (*10*).

Up to now all clinical data on PSMA TAT is available only for $^{225}$Ac-PSMA-617. However, the development and clinical implementation of new compounds is the hallmark of nuclear medicine theranostics (*3*). PSMA-I&T was introduced in 2014 as a theranostic PSMA-targeting small molecule (*11, 12*). First clinical results for $^{177}$Lu-PSMA-I&T were highly comparable to $^{177}$Lu-PSMA-617 data (*13*). Considering the remarkable efficacy of TAT, the implementation and evaluation of $^{225}$Ac labeled PSMA-I&T expands the clinical armamentarium for the treatment of mCRPC. Here we report our first clinical experience in patients receiving $^{225}$Ac PSMA-I&T at a single center.

## MATERIALS AND METHODS

### Patients

This is a retrospective analysis of mCRPC patients that were consecutively treated with $^{225}$Ac PSMA-I&T between September 2018 and December 2019 at our institution. TAT was performed in accordance with the German Medical Products Act

(AMG) §13.2b and the updated declaration of Helsinki, § 37 (Unproven Interventions in Clinical Practice). $^{18}$F-PSMA-1007 PET was performed in all patients to test for sufficient PSMA expression prior to TAT. Included patients were either not eligible for or rejected other approved therapy options. Indication for TAT was decided in an interdisciplinary tumor board. All patients were informed about the experimental nature of this unapproved therapy as well as possible risks and side effects. All patients gave written informed consent. This retrospective evaluation was approved by the local institutional review board.

**Radiopharmaceuticals and Treatment Regimen**

PSMA-I&T was obtained from Scintomics/att GmbH (Fürstenfeldbruck, Germany). $^{225}$Ac was obtained from ITM Medical Isotopes GmbH (Garching, Germany). Radiolabeling of $^{225}$Ac-PSMA-I&T was performed by adding a mixture of 0.1 mL PSMA-I&T (200 µg) and 0.9 mL 0.1 M Sodium Ascorbate solution into a conical vial containing 10 MBq $^{225}$Ac in 100 µl 0.1 M HCl (ITM Medical Isotopes GmbH, Garching, Germany). The vial was heated to 90°C for 30 minutes. After cooling the reaction mixture was diluted with 8.9 mL formulation buffer (0.25 M Sodium Ascorbate). Quality control was performed by instant thin-layer chromatography with 0.05 M citric acid (pH 5) as the solvent. After development, the chromatography strip was stored for at least 1 h until radiochemical equilibrium was obtained between $^{225}$Ac ($T_{½}$ = 9.9 d) and its daughter nuclide $^{221}$Fr ($T_{½}$ = 4.8 min). The radiochemical purity was determined by measuring the activity using a TLC-scanner miniGITA (Elysia-Raytest GmbH, Straubenhardt, Germany). Free $^{225}$Ac migrates with the front while labeled product stays on the bottom.

The mean radiochemical purity of the radiolabeled peptide was 98.2 ± 0.8%. The final pH of the formulation was 7.2 and sterility was ensured via sterile filtration. 100 kBq/kgBW of $^{225}$Ac-PSMA-I&T was administered as free-hand injection over 30 seconds. The dose was adapted by Kratochwil et al. as a trade off between therapy efficacy and side effects (*14*). According to their data on $^{225}$Ac-PSMA-617 a therapy activity of 100 kBq per kilogram bodyweight (kBq/kgBW) represents the maximum-tolerable dose and activities of 150 and 200 kBq/kgBW are dose limiting for the development of xerostomia and xerophtalmia, respectively. As a standard operating procedure, patients received cool packs 30 min before und up to 4 hours after injection of $^{225}$Ac-PSMA-I&T to cool salivary glands to reduce perfusion. Furthermore decortin 50 mg p.o. was administered every day and zofran 4 mg p.o. on the day of therapy. Additionally, 2 l 0.9% NaCl i.v. were infused at the day of therapy. Therapy was performed during an inpatient stay of at least 48 h in accordance with German radiation protection regulations.

**Toxicity and response assessment**

Vital signs, complete blood count (CBC) and blood chemistry were documented at the day of therapy and during hospitalization. Laboratory analysis included among other parameters CBC, metabolic panel including sodium, potassium, calcium, liver enzymes (alanine aminotransferase and aspartate aminotransferase), albumin, bilirubin, alkaline phosphatase (ALP), lactate dehydrogenase, creatinine, estimated glomerular filtration rate, prostate-specific antigen (PSA). During follow-up blood parameters were checked every 4 to 8 weeks. Follow-up further included clinical investigation, renal

scintigraphy in 8-week intervals and PSMA-PET/CT every two to three months (shorter intervals during consolidation therapy and longer intervals after completion of TAT). Additional imaging and follow-up was performed if clinically indicated by the treating urologist / oncologist. All therapy related adverse events (AEs) were documented at baseline and during follow-up according to common terminology criteria for adverse events v5.0 (CTCAE v5.0). Xerostomia was assessed using standardized questions regarding chewing and swallowing difficulties, food and beverage intake and xerostomia related symptoms.

Biochemical response was evaluated using PSA changes at defined time points and best PSA response. Furthermore, best ALP and LDH response after TAT was documented.

**Statistical Analysis**

Patient and treatment data as well as response characteristics are presented as descriptive statistics in absolute and relative frequencies. PSA and ALP change after TAT is presented using waterfall plots showing individual changes sorted by the extent. Due to the small sample size no statistical analysis has been performed to test for differences between baseline and post-treatment values during follow-up.

## RESULTS

### Patients

18 consecutive patients received TAT using $^{225}$Ac-PSMA-I&T. 4 patients were excluded from this analysis due to lack of access to medical records from outside of our institution. Detailed patient characteristics including baseline PSA values, pattern of metastatic disease and prior therapies are provided in Table 1. 11 patients received prior $^{177}$Lu-PSMA RLT (median 2 cycles, 43 cycles in total). Early progression / therapy failure after median 2 cycles was observed in 4 patients. Remaining 7 patients showed initial response and later progression after a median of 4 $^{177}$Lu-PSMA RLT cycles with a PSA decline ≥ 50% in 6 and a PSA decline of 37% in 1 patient as best PSA response.

A total of 34 cycles $^{225}$Ac-PSMA-I&T cycles were applied (median dose 7.8 MBq, range: 6.0 – 8.5). 3 patients received 1 cycle (median dose: 7.0 MBq), 7 patients 2 cycles (median cumulative dose: 16.0 MBq), 3 patients 4 cycles (median cumulative dose: 27.6 MBq) and 1 patient 5 cycles (cumulative dose: 39 MBq). 3 patients (17%) refused further treatment due to xerostomia after one therapy cycle. Median follow-up time after $^{225}$Ac-PSMA-I&T TAT was 23.6 weeks (range 8 to 77 weeks).

### Surrogate markers for response

Figure 1 shows waterfall plots of PSA, ALP and LDH response after PSMA TAT. Response assessment at 8 week after one cycle of $^{225}$Ac-PSMA-I&T showed any PSA decline in 8/14 (57%) and PSA decline ≥ 50% in 3 (21%) patients, respectively. Evaluation of best PSA response after 1 (3/14 patients), 2 (7/14 patients), 4 (3/14

patients) or 5 (1 patient) cycles showed any PSA decline in 11/14 (79%) and PSA decline ≥ 50% in 7/14 (50%). Best ALP response assessment revealed any decline in 10/14 patients (71%) and a decline ≥ 50% in 5 patients (36%). Best LDH response was any decline in 11/14 (79%) and a decline ≥ 50% in 1 patient (7%). In a subgroup of 11 patients (79%) with prior $^{177}$Lu-PSMA RLT, any PSA decline was observed in 8/11 (73%) and a PSA decline ≥ 50% in 5/11 (45%) patients.

**Toxicity**

After administration of $^{225}$Ac-PSMA-I&T and during hospitalization no therapy related grade 1-4 tachycardia, hypertension or fever was observed. Self-limiting slight increase of body temperature from normal values at baseline to subfebrile values was noted in two patients. Heart rate and blood pressure remained unchanged during hospitalization (Supplemental Table 1).

Therapy related AEs during follow-up are provided in table 2. Grade 3 anemia was overall observed in 3 patients (21%) with 2 patients (14%) having grade 3 anemia already at baseline with transfusion dependence and a history of docetaxel chemotherapy or 2 cycles of $^{177}$Lu-PSMA RLT, respectively. The remaining patient (7%) had mild anemia before TAT with a history of docetaxel chemotherapy and 10 cycles of $^{177}$Lu-PSMA RLT. One patient (7%) with a history of chemotherapy and 4 cycles of $^{177}$Lu-PSMA RLT presented with grade 2 leukopenia before TAT, which worsened to grade 3. Therefore, TAT was suspended after one cycle of $^{225}$Ac-PSMA-I&T and changed to best supportive care (patient 11, figure 2).

The main non-hematological side effect after $^{225}$Ac-PSMA-I&T was xerostomia. After TAT grade 1 and 2 xerostomia was observed in 8 (57%) and 5 (36%) patients, respectively. However, 6 (43%) and 2 (14%) patients with prior $^{177}$Lu-PSMA RLT already reported grade 1 and 2 xerostomia at baseline, respectively. No patient with pre-existing xerostomia reported worsening after TAT. Newly diagnosed xerostomia after TAT was observed in 5 patients (36%) with 1 patient (7%) with grade 1 and 4 patients (29%) with grade 2 xerostomia. 2 of these patients had prior $^{177}$Lu-PSMA RLT without any xerostomia symptoms. Only one patient described no xerostomia after TAT (patient 14 with a history of 2 cycles of $^{177}$Lu-PSMA RLT and one cycle of $^{225}$Ac-PSMA-I&T).

Other non-hematological AEs included grade 1/2 anorexia in 9 patients (all with grade 1 anorexia at baseline) and newly diagnosed grade 1/2 nausea in 5 patients (36%). Grade 1 and 2 fatigue at baseline was observed in 10 (71%) and 1 (7%) patients at baseline, respectively; after TAT grade 1 and 2 fatigue was observed in each 6 (43%) patients, respectively. Other AE parameters are given in Table 2. No grade 4 hematological, grade 3/4 renal or non-hematological AEs were observed during the follow-up period. Likewise, remaining laboratory parameters showed no relevant, therapy related changes. Detailed numbers before and 8 weeks after completion of the final $^{225}$Ac-PSMA-I&T cycle are provided in Table 3.

## DISCUSSION

PSMA-I&T was introduced as a PSMA targeting small molecule enabling imaging and therapy of prostate cancer using the same compound (*11*). Since then, RLT using

$^{177}$Lu labeled PSMA ligands gained increasing clinical value and results of the first randomized Phase 3 trial for $^{177}$Lu-PSMA-617 are expected in 2021. TAT using α-emitters such as $^{225}$Ac provides a higher biological effectiveness compared to the β-emitter $^{177}$Lu and can induce cell killing regardless of oxygenation, cell cycle position or fluency (*14, 15*). In the last years several groups presented remarkable clinical efficacy of PSMA TAT using $^{225}$Ac-PSMA-617 in different settings including chemotherapy-naïve, diffuse metastatic and $^{177}$Lu-PSMA RLT refractory patients (*8, 10, 14, 16, 17*). Here, we present our first clinical results using $^{225}$Ac-PSMA-I&T.

Our data confirms the anti-tumor effect of TAT in advanced mCRPC patients. In our subgroup of 11 patients (79%) with prior $^{177}$Lu-PSMA RLT, any PSA decline was observed in 8/11 (73%) and a PSA decline ≥ 50% in 5/11 (45%) patients. Preliminary data on $^{225}$Ac-PSMA-617 TAT in 18 mCRPC patients after failure of $^{177}$Lu-PSMA RLT was presented recently by the Technical University Munich (*17*). Any PSA decline was observed in 15 (83%) and PSA decline ≥ 50% in 5 (28%) patients, indicating comparable results for $^{225}$Ac labelled PSMA-617 and PSMA-I&T after failure of $^{177}$Lu-PSMA RLT (*17*). Recently, Khreish et al. presented data on the efficacy of PSMA TAT in 20 mCRPC patients after previous $^{177}$Lu-PSMA RLT (*16*). Their approach introduced “tandem RLT”, describing a combination of a reduced $^{225}$Ac-PSMA-617 dose (median 5.3 MBq) with $^{177}$Lu-PSMA-617 (median 6.9 GBq), a concept that was also presented by other groups (*18*). They observed any PSA decline and PSA decline ≥ 50% in 13 (65%) and 18 (90%) patients, respectively. Consolidation therapy after PSA response was performed using $^{177}$Lu-PSMA-617. A subgroup analysis of patients with initial response to $^{177}$Lu-PSMA treatment compared to patients with early failure showed a

tendency towards better response (best PSA response ≥ 50% in 83.3% vs. 50.0%) despite not reaching statistical significance. In summary, TAT represent a highly promising option for advanced mCRPC patients, even after exhaustion of $^{177}$Lu-PSMA RLT. Regardless of lower doses and consolidation therapy with $^{177}$Lu-PSMA RLT, the results of Khreish et al. are comparable to our data using fixed doses of 100 kBq/kgBW. This also indicates the clinical feasibility of de-escalation after response to PSMA-TAT as the main goal is to reduce TAT induced toxicity while maintaining high therapeutic efficacy of α-emitter therapy (*9, 16, 18*).

Despite encouraging anti-tumor activity, high doses of PSMA TAT result in a considerable number of patients demanding dose reduction or discontinuation of therapy (*14*). Xerostomia represents the main side effect of TAT. Khreish et al. reported grade 1 and 2 xerostomia in 8/20 (40%) and 5/20 (25%) patients, respectively. Unfortunately, pre-existing xerostomia after initial $^{177}$Lu-PSMA RLT is not mentioned in their study. Surprisingly, in our cohort no patient with pre-existing xerostomia after $^{177}$Lu-PSMA RLT (grade 1 in 6/14 and grade 2 in 2/14 patients) reported worsening after $^{225}$Ac-PSMA-I&T. However, 5 patients without prior xerostomia reported grade 1 and 2 xerostomia in 2 and 3 cases, respectively. Only one patient reported no xerostomia at all, however, this patient was only treated with 2 previous cyles of $^{177}$Lu-PSMA-617 and one cycle of $^{225}$Ac-PSMA-I&T. Three patients discontinued treatment due to side effects with xerostomia as the main complaint. Data on the value of sialendoscopy, saline irrigation and steroid injection after TAT describe significant improvement of symptoms (*19*). No such methods were applied in the current analysis, due to the difficult clinical implementation and patient acceptance of such invasive procedures. However,

straightforward salivary gland protection and mitigation of xerostomia represents a major challenge for PSMA TAT (*20*).

Further toxicities in our analysis include grade 3 anemia in 3/14 (21%) patients with 2 patients already presenting with grade 3 anemia at baseline. The remaining patient (patient 2) had grade 1 anemia at baseline with a history of docetaxel chemotherapy and 10 cycles of $^{177}$Lu-PSMA RLT, which might explain the cumulative hematotoxicity after $^{225}$Ac-PSMA-I&T. Furthermore, grade 3 leukopenia was observed in 1 patient (patient 11, figure 2). This patient had diffuse bone metastases with a history of docetaxel chemotherapy and 4 cycles of $^{177}$Lu-PSMA RLT. Despite the fact that deterioration of pre-existing hematological toxicities after TAT is not uncommon (*16*), the higher linear energy transfer (LET) and significantly shorter penetration range of $^{225}$Ac compared to $^{177}$Lu favors $^{225}$Ac-PSMA TAT over $^{177}$Lu-PSMA RLT in terms of hematological toxicity (*7, 21*). However, despite newly developed hematotoxicity was rare in our cohort (2 patients grade 1 thrombopenia and 3 grade 1 leukopenia), 4/14 patients with grade 1 anemia at baseline developed grade 2 anemia after $^{225}$Ac-PSMA-I&T and a further patient grade 3 anemia (patient 2). This is also reflected by significantly lower hemoglobin levels after treatment (table 3). This might be associated with our therapy protocol of fixed doses of 100 kBq/kgBW without therapy de-escalation and the fact that most patients were pretreated with chemotherapy and $^{177}$Lu-PSMA RLT.

Our study has several limitations. The retrospective design and inclusion of consecutively treated patients resulted in a mixed patient cohort. The sample size is small and median follow-up is relatively short with only 26.3 weeks. Nonetheless, as

TAT represents one of the most rapidly developing topics for radiopharmacy and nuclear medicine, we feel encouraged sharing our promising clinical results already at this early stage. The clinical implementation of $^{225}$Ac-PSMA-I&T TAT provides an interesting new option particularly in patients with advanced disease without further therapeutic options.

## CONCLUSION

$^{225}$Ac-PSMA-I&T TAT showed promising antitumor effects comparable to $^{225}$Ac-PSMA-617. Grade 3/4 hematological side effects are rare. Grade 1-2 xerostomia remains the main side effect of TAT. Nonetheless, overall moderate toxicity provides PSMA TAT as an additional therapy option in end-stage mCRPC patients.

## DISCLOSURE

All authors declare no conflict of interest related to this work.

## KEY POINTS

**Question:** What are the first clinical findings including therapy related adverse events and response after targeted α-therapy (TAT) using $^{225}$Ac-PSMA-I&T in patients with advanced metastatic castration resistant prostate cancer (mCRPC)?

**Pertinent Findings:** $^{225}$Ac-PSMA-I&T TAT was well tolerated in 18 patients without acute side effects. Best prostate-specific antigen (PSA) response in 14 patients after $^{225}$Ac-PSMA-I&T was any PSA decline in 11/14 (79%) patients and PSA decline ≥ 50% in 7/14 (50%). Best alkaline phosphatase (ALP) response was any decline in 10 (71%) and decline ≥ 50% in 5 patients (36%). Newly diagnosed, therapy related grade 2 anemia was observed in 4 patients (29%) and grade 3 in 1 patient (7%) and newly diagnosed grade 3 leukopenia in 1 patient (7%). Newly diagnosed grade 1 xerostomia was observed in 2 patients (14%) and grade 2 in 3 patients (21%). No further grade 3/4 hematological or non-hematological toxicities were observed.

**Implications for Patient Care:** TAT using $^{225}$Ac-PSMA-I&T is a novel therapy option for mCRPC with encouraging results in end stage patients.

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## FIGURES

**Figure 1:** Waterfall plots of PSA, LDH and ALP response after TAT using 225Ac-PSMA-I&T. (A) and (B) describe the PSA changes after 8 weeks and best PSA response after the first TAT cycle. (C) and (D) describe best LDH and ALP response after a median of 2 TAT cycles.

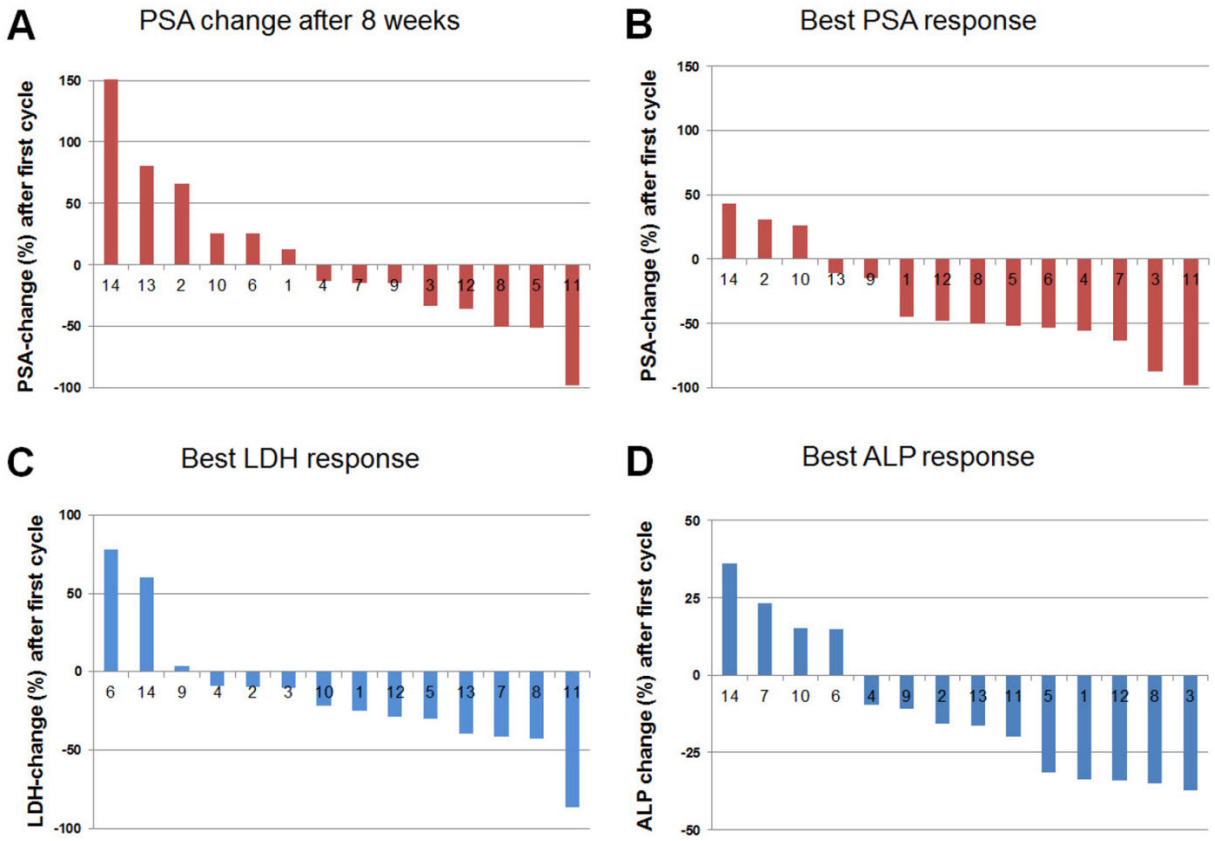

**Figure 2:** 79 year old mCRPC patient (patient 11) with lymphatic and bone metastases. The patient received 2 cycles of $^{177}$Lu-PSMA RLT (cumulative activity: 10.5 GBq) after failure of docetaxel and showed initial response. However, disease progression was observed in January 2019 after two additional $^{177}$Lu-PSMA RLT cycles (cumulative activity: 12 GBq) and the patient was admitted for $^{225}$Ac-PSMA-I&T TAT. PSA follow-up and PSMA PET showed impressive response after two cycles (cumulative activity 13.4 MBq). Unfortunately, the patient developed Grade 3 leukocytopenia and TAT could not be continued. Disease progression was observed in November 11/2019 after best supportive care (BSC).

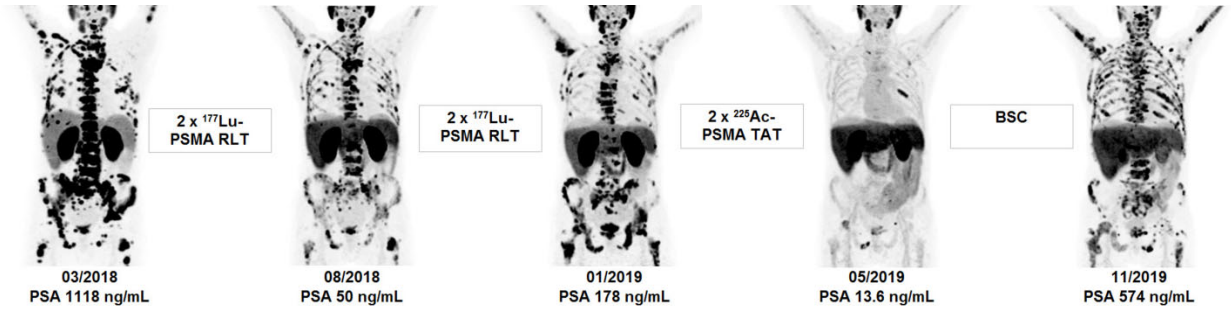

**Table 1: Patient Characteristics**

| Characteristic | Value |
|---|---|
| Number of Patients, n | 14 |
| Age, yr. | |
| Median (minimum - maximum) | 75 (64 - 80) |
| ≥ 75 yr. | 8 (57 %) |
| ECOG performance score, n (%) | |
| ≤1 | 11 (79 %) |
| 2 | 3 (21 %) |
| PSA at start of $^{225}$Ac-PSMA-I&T, ng/ml | |
| Median (minimum - maximum) | 112 (20.5 - 818) |
| Hemoglobin at start of $^{225}$Ac-PSMA-I&T, g/dL | |
| Median (minimum - maximum) | 10.3 (5.6 - 12.5) |
| Platelets at start of $^{225}$Ac-PSMA-I&T, G/L | |
| Median (minimum - maximum) | 246 (72 - 412) |
| ALP at start of $^{225}$Ac-PSMA-I&T, U/L (normal range 40 -130) | |
| Median (minimum - maximum) | 143 (67 - 695) |
| Site of metastases before $^{225}$Ac-PSMA-I&T | |
| Bone (any) | 13 (93 %) |
| Bone (superscan pattern) | 5 (36 %) |
| Lymph node | 10 (71 %) |
| Visceral metastasis | 3 (21 %) |
| Liver | 1 (7 %) |
| Lung | 3 (21%) |
| Other organs | 1 (7%) |
| Prior therapy before start of $^{225}$Ac-PSMA-I&T, n (%) | |
| Prostatectomy | 9 (64%) |
| Radiation Therapy | 12 (86 %) |
| Prostate and/or locoregional lymph nodes | 10 (71 %) |
| Distant (non regional lymph nodes, bone) | 6 (43%) |
| Androgen Deprivation Therapy | 14 (100 %) |
| Abiraterone OR enzalutamide | 11 (79 %) |
| Abiraterone AND enzalutamide | 4 (29 %) |
| Docetaxel | 11 (79 %) |
| Docetaxel AND cabazitaxel | 1 (7 %) |
| $^{177}$Lu-PSMA RLT | 11 (79 %) |
| $^{223}$Ra-Dichloride | 2 (14 %) |

ECOG = eastern cooperative oncology group; PSA = prostate specific antigen; ALP = alkaline phosphatase; RLT = radioligand therapy

**Table 2: Therapy related hematological and renal adverse events after $^{225}$Ac-PSMA-I&T according to CTCAE v5.0**

| | prior to TAT | | | | after TAT | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr. 1 n (%) | Gr. 2 n (%) | Gr. 3 n (%) | Gr. 4 n (%) | Gr. 1 n (%) | Gr. 2 n (%) | Gr. 3 n (%) | Gr. 4 n (%) |
| **Hematological** | | | | | | | | |
| Anemia | 8 (57) | 4 (29) | 2 (14) | - | 3 (21) | 8 (57) | 3 (21) | - |
| Thrombopenia | 3 (21) | 1 (7) | - | - | 3 (21) | 3 (21) | - | - |
| Leukopenia | 2 (14) | 1 (7) | - | - | 4 (28) | - | 1 (7) | - |
| **Urinary** | | | | | | | | |
| Renal | 1 (7) | - | - | - | 1 (7) | 1 (7) | - | - |
| **Gastrointestinal** | | | | | | | | |
| Xerostomia | 6 (43) | 2 (14) | - | n.d. | 8 (57) | 5 (36) | - | n.d. |
| Dysgeusia | - | - | - | - | 5 (36) | 1 (7) | - | - |
| Anorexia | 9 (64) | - | - | - | 7 (50) | 2 (14) | - | - |
| Nausea | - | - | - | - | 4 (29) | 1 (7) | - | - |
| **General** | | | | | | | | |
| Fatigue | 10 (71) | 1 (7) | - | - | 6 (43) | 6 (43) | - | - |
| Weight loss | n.a. | n.a. | n.a. | n.a. | 4 (29) | - | - | - |

TAT = targeted alpha therapy; n = number of patients; Gr. = grade; CTCAE = common terminology criteria for adverse events; n.d. = not defined; n.a. = not applicable

**Table 3: Laboratory parameters at baseline and after $^{225}$Ac-PSMA TAT**

| | **prior to $^{225}$Ac-PSMA-I&T TAT mean (±SD)** | **after $^{225}$Ac-PSMA-I&T TAT mean (±SD)** |
|---|---|---|
| Hemoglobin (g/dl) | 10.11 ± 1.94 | 9.15 ± 1.52 |
| Platelets (G/l) | 225.29 ± 99.11 | 190.00 ± 104.28 |
| Leukocytes (G/l) | 5.59 ± 1.92 | 4.89 ± 1.78 |
| Sodium (mmol/l) | 138.00 ± 2.66 | 137.69 ± 4.31 |
| Potassium (mmol/l) | 4.39 ± 0.65 | 4.15 ± 0.32 |
| Calcium (mmol/l) | 2.20 ± 0.08 | 2.27 ± 0.09 |
| Creatinine (mg/dl) | 0.96 ± 0.18 | 0.95 ± 0.37 |
| eGFR (ml/min) | 82.57 ± 17.42 | 79.57 ± 18.72 |
| BUN (mg/dl) | 41.36 ± 14.68 | 35.69 ± 10.85 |
| ALT (U/l) | 16.77 ± 6.92 | 20.14 ± 11.35 |
| AST (U/l) | 41.36 ± 31.56 | 49.69 ± 33.96 |
| Albumin (g/dl) | 4.05 ± 0.45 | 3.80 ± 0.66 |
| Bilirubin (mg/dl) | 0.35 ± 0.20 | 0.49 ± 0.35 |
| ALP (U/l) | 237.21 ± 188.85 | 409.64 ± 312.49 |
| LDH (U/l) | 505.14 ± 416.90 | 618.62 ± 551.64 |

TAT = targeted alpha therapy; n= number of patients; SD = standard deviation; eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase

**SUPPLEMENTAL MATERIAL:**

**Supplemental Table 1: Therapy related changes of vital signs after application of $^{225}$Ac-PSMA-I&T TAT in all patients during hospitalization**

| | prior to $^{225}$Ac-PSMA-I&T TAT | after first $^{225}$Ac-PSMA-I&T TAT |
|---|---|---|
| **RR systolic (mmHg)** | | |
| Mean | 149 | 157 |
| Median | 140 | 160 |
| Min | 125 | 115 |
| Max | 195 | 185 |
| **Heart rate (beats per min)** | | |
| Mean | 84 | 84 |
| Median | 82 | 82 |
| Min | 72 | 68 |
| Max | 96 | 105 |
| **Body Temperature (°C)** | | |
| Mean | 37.0 | 37.2 |
| Median | 36.9 | 37.1 |
| Min | 36.2 | 36.8 |
| Max | 38.1 | 38.5 |

TAT = targeted alpha therapy; RR: blood pressure; Min: minimum; Max: maximum