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Clinical-Prostate cancer

Clinical outcomes and molecular profiling of advanced metastatic castration-resistant prostate cancer patients treated with ^{225}Ac-PSMA-617 targeted alpha-radiation therapy

Maarten J. van der Doelen, M.D.[a,b,*], Niven Mehra, M.D., Ph.D.[a], Inge M. van Oort, M.D., Ph.D.[b], Monika G. Looijen-Salamon, M.D.[c], Marcel J.R. Janssen, M.D., Ph.D.[d], José A.E. Custers, Ph.D.[e], Peter H.J. Slootbeek, B.Sc.[a], Leonie I. Kroeze, Ph.D.[c], Frank Bruchertseifer, Ph.D.[f], Alfred Morgenstern, Ph.D.[f], Uwe Haberkorn, M.D.,Ph.D.[g], Clemens Kratochwil, M.D.[g], James Nagarajah, M.D.,Ph.D.[d,h], Winald R. Gerritsen, M.D.,Ph.D.[a]

[a] *Radboud University Medical Center, Department of Medical Oncology, Nijmegen, The Netherlands*
[b] *Radboud University Medical Center, Department of Urology, Nijmegen, The Netherlands*
[c] *Radboud University Medical Center, Department of Pathology, Nijmegen, The Netherlands*
[d] *Radboud University Medical Center, Department of Radiology and Nuclear Medicine, Nijmegen, The Netherlands*
[e] *Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Medical Psychology, Nijmegen, The Netherlands*
[f] *European Commission, Joint Research Centre, Nuclear Safety and Security, Karlsruhe, Germany*
[g] *University Hospital Heidelberg, Department of Nuclear Medicine, Germany*
[h] *Technical University Munich, Klinikum rechts der Isar, Department of Nuclear Medicine, Munich, Germany*

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Abstract

Introduction: Targeted alpha-radiation therapy (TAT) with ^{225}Ac-labeled prostate-specific membrane antigen (PSMA) ligands is a promising novel treatment option for metastatic castration-resistant prostate cancer (mCRPC) patients. However, limited data are available on efficacy, quality of life (QoL), and pretherapeutic biomarkers. The aim of this study was to evaluate the efficacy of ^{225}Ac-PSMA TAT and impact on QoL in advanced mCRPC, and to explore predictive biomarkers on pretherapeutic metastatic tissue biopsies.

Methods: Observational cohort study including consecutive patients treated with ^{225}Ac-PSMA TAT between February 2016 and July 2018. Primary endpoint was overall survival (OS). Furthermore, prostate-specific antigen (PSA) changes, radiological response, safety, QoL, and xerostomia were evaluated. Biopsies were analyzed with immunohistochemistry and next-generation sequencing.

Results: Thirteen patients were included. Median OS was 8.5 months for the total cohort and 12.6 months for PSMA radioligand therapy-naïve patients. PSA declines of ≥90% and ≥50% were observed in 46% and 69% of patients, respectively. Six patients were radiologically evaluable; 50% showed partial response. All patients showed >90% total tumor volume reduction on PET imaging. Patients experienced clinically relevant decrease of pain and QoL improvement in physical and role functioning domains. Xerostomia persisted during follow-up. Patients with high baseline immunohistochemical PSMA expression or DNA damage repair alterations tended to have longer OS.

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*Corresponding author. Tel.: +31 24 361 0353; fax: +31 24 361 5025.
E-mail address: Maarten.vanderDoelen@radboudumc.nl (M.J. van der Doelen).

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Conclusions: TAT with ^{225}Ac-PSMA resulted in remarkable survival and biochemical responses in advanced mCRPC patients. Patients experienced clinically relevant QoL improvement, although xerostomia was found to be nontransient. Baseline immunohistochemical PSMA expression and DNA damage repair status are potential predictive biomarkers of response to ^{225}Ac-PSMA TAT.

Keywords: Actinium-225; Castration-resistant prostate cancer; Next-generation sequencing; Prostate-specific membrane antigen; Quality of life; Radioligand therapy

1. Introduction

Prostate cancer is the most commonly diagnosed cancer in men, and development of metastatic castration-resistant prostate cancer (mCRPC) is associated with a poor prognosis. Despite registration of life-prolonging chemotherapeutic agents and androgen-receptor targeting therapies (ARTs), there is an ongoing need for additional effective therapeutic strategies with different mechanisms of action.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein showing significant overexpression in high grade and advanced stage prostate cancer, which makes it an attractive target for diagnostic and therapeutic approaches [1−3]. Several retrospective cohort studies have described the potential of beta particle emitting ^{177}Lu-PSMA-617 (^{177}Lu-PSMA) radioligand therapy (RLT) in mCRPC [4]. A recent prospective phase 2 study investigated ^{177}Lu-PSMA RLT in mCRPC patients after prior chemotherapy and ARTs and reported ≥50% PSA declines in 57% of the patients and median overall survival (OS) of 13.5 months [5].

Beta emitters like ^{177}Lu show therapeutic efficacy in large tumor masses due to long radiation range and the ability to induce a cross-fire effect [6,7]. Targeted alpha-radiation therapy (TAT) with ^{225}Ac may be more effective in patients with disseminated metastatic disease, due to the shorter radiation range coupled with high-linear-energy transfer that induces targeted tumor cell killing by causing higher number of double-strand DNA breaks compared to ^{177}Lu, while minimizing damage to surrounding tissues such as red bone marrow [7−9]. In addition, ^{225}Ac-PSMA-617 (^{225}Ac-PSMA) TAT is able to overcome refractory disease after ^{177}Lu-PSMA RLT [10−12].

Limited data are available on the effect on quality of life (QoL) and side effects of ^{225}Ac-PSMA TAT. Additionally, pretherapeutic biomarkers are needed to guide clinicians to select the most susceptible patients for ^{225}Ac-PSMA TAT to improve outcome. The aim of this observational cohort study was to evaluate the efficacy, impact on QoL, and safety of ^{225}Ac-PSMA TAT in advanced mCRPC patients. Furthermore, we explored predictive biomarkers on pretherapeutic tissue biopsies.

2. Patients and methods

2.1. Study design and patient population

This was an observational cohort study including consecutive patients with advanced mCRPC who were referred to receive ^{225}Ac-PSMA TAT at the nuclear medicine department of the Heidelberg University Hospital, Germany. We performed retrospective analyses of a prospectively maintained database. Screening and eligibility assessment, as well as patient follow-up were performed at the Radboudumc, Nijmegen, The Netherlands. Patients were eligible if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and PSMA expression of metastatic lesions above the physiologic background liver uptake at ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11) PET/CT. Laboratory requirements were baseline hemoglobin level >8.0 g/dl, white blood cell count $>2.0 \times 10^9$/l, platelet count $>75 \times 10^9$/l, and creatinine clearance <2 mg/dl. Permitted therapies during ^{225}Ac-PSMA TAT were luteinizing hormone-releasing hormone analogues, low-dose steroids, bone protective therapies (bisphosphonates or RANK-ligand inhibitors), and analgesics. Concomitant systemic antiprostate cancer therapies, including abiraterone and enzalutamide, were not allowed during TAT.

2.2. Application of ^{225}Ac-PSMA TAT

PSMA-617 was labeled with ^{225}Ac as published previously [10,11]. The radioligand was produced in-house using the PSMA-617 precursor from ABX (Radeberg, Germany) and ^{225}Ac was provided from the European Commission's Joint Research Centre (Karlsruhe, Germany). ^{225}Ac-PSMA was injected intravenously every 8 weeks up to 4 cycles, with an initial activity of 8 MBq, thereafter reduced to 6 MBq per subsequent cycle. Patients were hospitalized for 48 hours with external cooling of the salivary glands and received dexamethasone to reduce radiation inflammation. Therapy was discontinued at evidence of disease progression, deterioration of clinical condition, treatment-related adverse events or patient refusal to continue.

2.3. Outcome measures

Primary endpoint was OS, defined as the time interval from first ^{225}Ac-PSMA TAT cycle to the date of death or last follow-up. Secondary endpoints were clinical, biochemical, and radiological efficacy, safety, and patient-reported outcomes. Clinical disease progression was defined as the moment of no longer clinically benefiting according to Prostate Cancer Working Group 3 (PCWG3) criteria, start of a new systemic treatment or best supportive

care, or death [13]. PSA response was defined as ≥50% decrease from baseline, according to PCWG3 criteria [13]. In addition, ≥90% confirmed PSA decline was included. Changes in alkaline phosphatase (ALP) levels were calculated as percentage change from baseline. Radiological evaluation by ^{68}Ga-PSMA-11 PET with contrast-enhanced high-dose CT from skull base to mid-thigh was performed 8 weeks after end of therapy and during follow-up based on clinical indications. Scans were evaluated according to RECIST 1.1 and PERCIST by 2 nuclear medicine physicians [14,15]. In addition, whole body tumor volume was measured using the semiautomatic 3D ROI Visualisation, Evaluation and Image Registration software (ROVER, ABX, Radeberg, Germany). We used a maximum standardized uptake value of 15 as threshold to automatically select PSMA positive lesions and removed of areas with physiologic uptake manually. Treatment-emergent adverse events were scored using the Common Terminology Criteria for Adverse Events, version 5.0. Skeletal-related events (SREs) were defined according to PCWG3 criteria [13].

Patients were asked to complete the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaires Core-30 (QLQ-C30) and Bone Metastases-22 (BM-22) [16,17] and the Xerostomia Inventory [18] at baseline, at end of therapy and during follow-up at 12 and 18 months.

2.4. Exploratory biomarker analyses

Patients underwent CT-guided metastatic tissue biopsies before and after ^{225}Ac-PSMA TAT for immunohistochemistry (IHC) and next-generation sequencing (NGS), to explore predictive biomarkers. Patients underwent a ^{68}Ga-PSMA-11 PET/CT prior to bone biopsy to improve the success rate [19]. Archival prostate specimens were utilized when baseline metastatic biopsies were unavailable or not evaluable. IHC assessment by 2 independent urological pathologists included revision of prostate cancer diagnosis and staining for neuroendocrine markers (CD56 antigen, chromogranin, and synaptophysin), PSMA, the androgen receptor and Ki-67 expression. Membranous PSMA expression heterogeneity was assessed semiquantitatively by H-scores (scale 0−300), defined as the product of the percentage of immunopositive tumor cells (0%−100%) and the staining intensity (0 = negative; 1+ = weak; 2+ = moderate; 3+ = intense). Other IHC results were expressed as the percentage of immunopositive tumor cells (0%−100%). Specimens that showed different staining intensities were scored for the most prevalent intensity. Tumor samples were sequenced by nonprofit institutes (Center for Personalized Cancer Treatment; CPCT), by fee-for-service providers (FoundationOne), and by a custom in-house NGS panel [20]. The pathogenicity of alterations was assessed according to the guidelines for the interpretation of sequence variants.

2.5. Statistical methods

Descriptive statistical methods were used to characterize the cohort and to analyze changes in QoL. Survival curves were estimated using Kaplan-Meier statistics. QoL data are presented as median scale scores plus interquartile ranges. Clinically relevant QoL changes were defined as small (5−10 points), moderate (10−20 points), or large (>20 points), according to Osoba et al. [21]. Alterations in the Xerostomia Inventory scores were tested using the Wilcoxon signed-rank test for paired data. Two-sided *P*-values <0.05 were considered statistically significant.

2.6. Ethics

This study was approved by the medical ethics review committee and it was performed in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. ^{225}Ac-PSMA TAT was applied in accordance to the German pharmaceuticals law as salvage therapy for mCRPC patients, presenting progressive disease after

Table 1
Baseline patient demographics and clinical characteristics

Characteristic	Total cohort (*N* = 13)
Age, years, median (IQR)	71 (64−77)
Time CRPC to ^{225}Ac-PSMA-617 TAT, months, median (IQR)	35 (17−64)
Gleason score ≥8, *n* (%)	6 (46.2)
Extent of disease on ^{68}Ga-PSMA-11 PET/CT	
Bone metastases, *n* (%)	13 (100.0)
Bone metastases only, *n* (%)	3 (23.1)
Locoregional lymph node metastases, *n* (%)	10 (76.9)
Visceral metastases, *n* (%)	8 (61.5)
Prior systemic therapies	
Number of different systemic therapies, median (range)	4 (1−5)
Docetaxel, *n* (%)	13 (100.0)
Cabazitaxel, *n* (%)	8 (61.5)
Abiraterone, n (%)	11 (84.6)
Enzalutamide, *n* (%)	10 (76.9)
^{223}Ra-dichloride, n (%)	4 (30.8)
^{177}Lu-PSMA-617 RLT, *n* (%)	2 (15.4)
Opioid use, *n* (%)	7 (63.6)
ECOG performance status	
ECOG 0, *n* (%)	3 (23.1)
ECOG 1-2, *n* (%)	10 (76.9)
Hemoglobin level, g/dl, median (IQR)	10.1 (9.0−11.2)
Platelet count, x10^9/l, median (IQR)	314 (177−405)
Prostate-specific antigen level, ng/ml, median (IQR)	878 (203−1611)
Alkaline phosphatase level, U/l, median (IQR)	356 (155−671)
Lactate dehydrogenase level, U/l, median (IQR)	294 (239−858)
Prostate-specific antigen doubling time, months, median (IQR)	1.9 (1.1−2.2)

CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PSMA = prostate-specific membrane antigen; RLT = radioligand therapy; TAT = targeted alpha-radiation therapy.

approved therapies. Patients were informed about the experimental nature of ^{225}Ac-PSMA TAT and gave written informed consent. Biomarker assessment was performed following informed consent to the urology biobank (CWOM 9803-0060) and the NGS protocol by FoundationOne and the CPCT-02 biopsy protocol (NCT01855477).

3. Results

3.1. Baseline patient characteristics

Between February 2016 and July 2018, 13 consecutive mCRPC patients received ^{225}Ac-PSMA TAT. Median age was 71 years (Table 1). All patients received prior taxane-based chemotherapy and 11 (85%) patients previously received ARTs. Two (15%) patients had progressed on previous ^{177}Lu-PSMA RLT. Patients received a median of 4 prior systemic therapies (range 1–5) (Supplementary Table 1). All patients had bone metastases, 11 (85%) patients had lymph node metastases and visceral metastases were present in 8 (62%) patients. Median PSA and ALP at baseline were 878 μg/l and 356 U/l, respectively.

3.2. Overall survival

Eleven (85%) patients had deceased at time of analysis. For the total cohort, median OS was 8.5 months (Fig. 1A). Median OS was 12.6 months for PSMA RLT-naïve patients vs. 1.3 months in patients who underwent prior ^{177}Lu-PSMA RLT (Fig. 1B). Two (15%) patients were alive, 29 and 34 months since first ^{225}Ac-PSMA TAT injection; one of them is having an ongoing response to PSMA RLT.

3.3. Efficacy

Patients received a median of 3 ^{225}Ac-PSMA TAT cycles. Nine (69%) patients achieved ≥50% PSA decrease and 6 (46%) patients showed ≥90% PSA decline (Fig. 2A and Supplementary Fig. 1). The median best PSA decline following the first cycle was 68% and median best PSA decline at any time during therapy was 88% from baseline. Median time from TAT initiation to PSA nadir was 3.9 months. All patients achieved ALP decline in response to therapy, with a median best ALP decline of 48% (Fig. 2B). Eight (62%) patients showed ≥30% ALP decline, and 6 (46%) patients had ≥50% ALP decline.

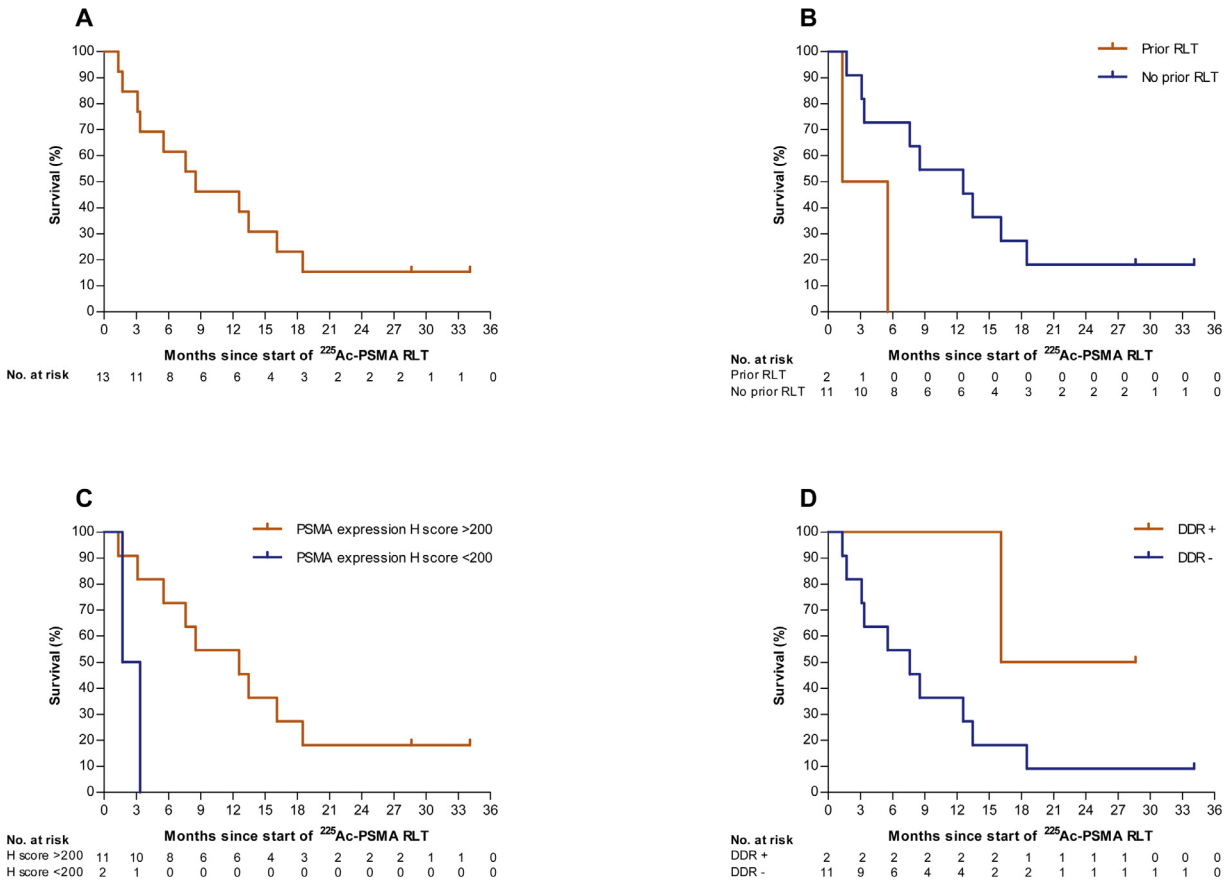

Fig. 1. Kaplan-Meier estimates of overall survival in patients with metastatic castration-resistant prostate cancer treated with ^{225}Ac-PSMA-617 targeted alpha-radiation therapy. (A) Survival estimate for the total cohort. (B) Survival stratified by prior ^{177}Lu-PSMA-617 radioligand therapy. (C) Survival stratified by immunohistochemical prostate-specific membrane antigen expression. (D) Survival stratified by DNA damage response mutation status.

DDR = DNA damage repair; PSMA = prostate-specific membrane antigen; RLT = radioligand therapy.

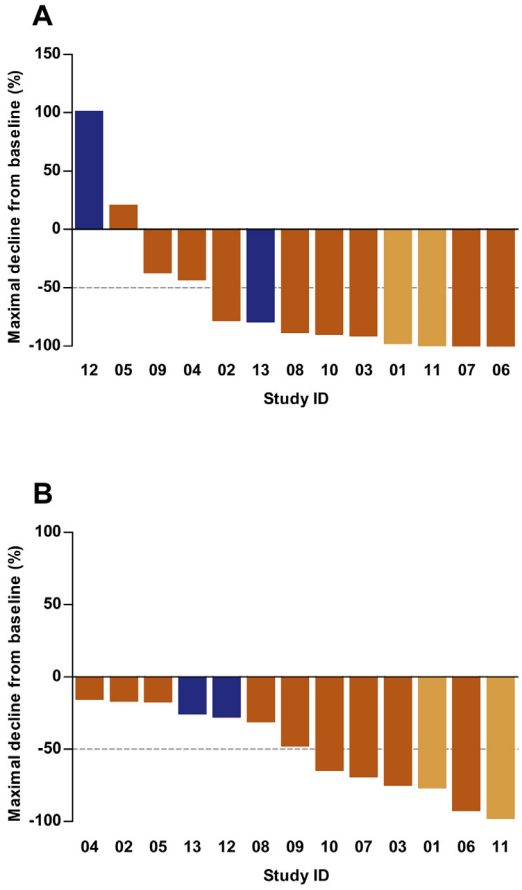

Fig. 2. Waterfall plots of maximal biochemical changes among patients treated with ^{225}Ac-PSMA-617 targeted alpha-radiation therapy. (A) Maximum prostate-specific antigen decline from baseline. (B) Maximum alkaline phosphatase decline from baseline. Blue bars indicate patients previously treated with ^{177}Lu-PSMA-617 radioligand therapy. Yellow bars indicate patients with pathogenic DNA damage repair alterations.

Follow-up imaging with CT scans was available in 9 patients. Due to absence of extraskeletal disease at baseline in 3 patients, 6 patients were evaluable according to RECIST. Partial response was observed in 3 (50%) patients, and 1 (17%) patient had stable disease (Supplementary Table 2). Follow-up ^{68}Ga-PSMA-11 PET/CT scans were available in 7 patients, of which 6 (86%) showed partial responses according to PERCIST. All 7 patients demonstrated >90% total tumor volume reduction as determined by the whole body tumor volume measurements. ^{68}Ga-PSMA-11 PET/CT overviews are presented in Fig. 3.

Twelve (92%) patients developed clinical disease progression. Median time to clinical disease progression was 5.5 months. Seven patients (54%) received subsequent systemic therapies, including 3 patients who received PSMA RLT retreatment. Two patients did not respond to retreatment, whereas 1 patient, treated with ^{225}Ac-PSMA plus ^{177}Lu-PSMA combinatory RLT, has ongoing response (Fig. 4).

3.4. Safety

Grade 3-4 toxicity was not observed. None of the patients discontinued treatment due to side effects. However, all patients reported grade 1-2 xerostomia symptoms, including complaints of swallowing, speech, and dysgeusia. During ^{225}Ac-PSMA TAT, 4 SREs occurred in 3 (23%) patients (Fig. 4). In 5 (38%) patients therapy was discontinued due to disease progression and 1 patient stopped after 2 cycles due to immobilization after 2 SREs while having good response to TAT.

3.5. Patient reported outcomes

EORTC QLQ-C30 and BM-22 questionnaires revealed clinically relevant decrease of pain complaints, corresponding with the observed reduced use of analgesics. Scores of physical and role functioning scales showed moderate improvement at end of therapy, and large improvement at 12 months follow-up (Supplementary Table 3). Furthermore, large improvement of fatigue and dyspnea was objectified. Overall, moderate improvement in global health status was measured, reflecting higher QoL after ^{225}Ac-PSMA TAT. A significant increase in the subjective feeling of dry mouth was determined with the Xerostomia Inventory ($P < 0.001$), which was nontransient at 18 months follow-up (Supplementary Table 4).

3.6. Explorative biomarker analyses

Tumor tissue obtained prior to TAT consisted of biopsies from the prostate ($n = 4$), lymph node metastases ($n = 6$), and bone metastases ($n = 3$) (Fig. 5). Patients with low baseline PSMA expression H-scores (<200; $n = 2$) had worse survival when compared to patients with H-scores ≥200 ($n = 11$) (median OS 1.8 vs. 12.6 months; Fig. 1C). One patient showed an H-score <200 due to lacking PSMA expression at 80% of prostate cancer cells. Furthermore, patients with low H-scores presented high (20%–30%) expression of proliferation marker Ki-67. Patients with therapy-induced features of neuroendocrine prostate cancer showed numerically shorter survival (median OS 7.6 vs. 12.6 months). In 2 patients pathogenic DNA damage repair (DDR) alterations were identified; both in the *BRCA1* gene. These patients showed longer survival (16.1 vs. 7.6 months; Fig. 1D). In 3 patients with progressive disease, post-TAT biopsies were obtained and analyzed. IHC was feasible in 2 samples. One specimen revealed reduced PSMA expression and increased expression of neuroendocrine and proliferative markers as potential explanation for progression, whereas unchanged PSMA expression was detected in the other patient.

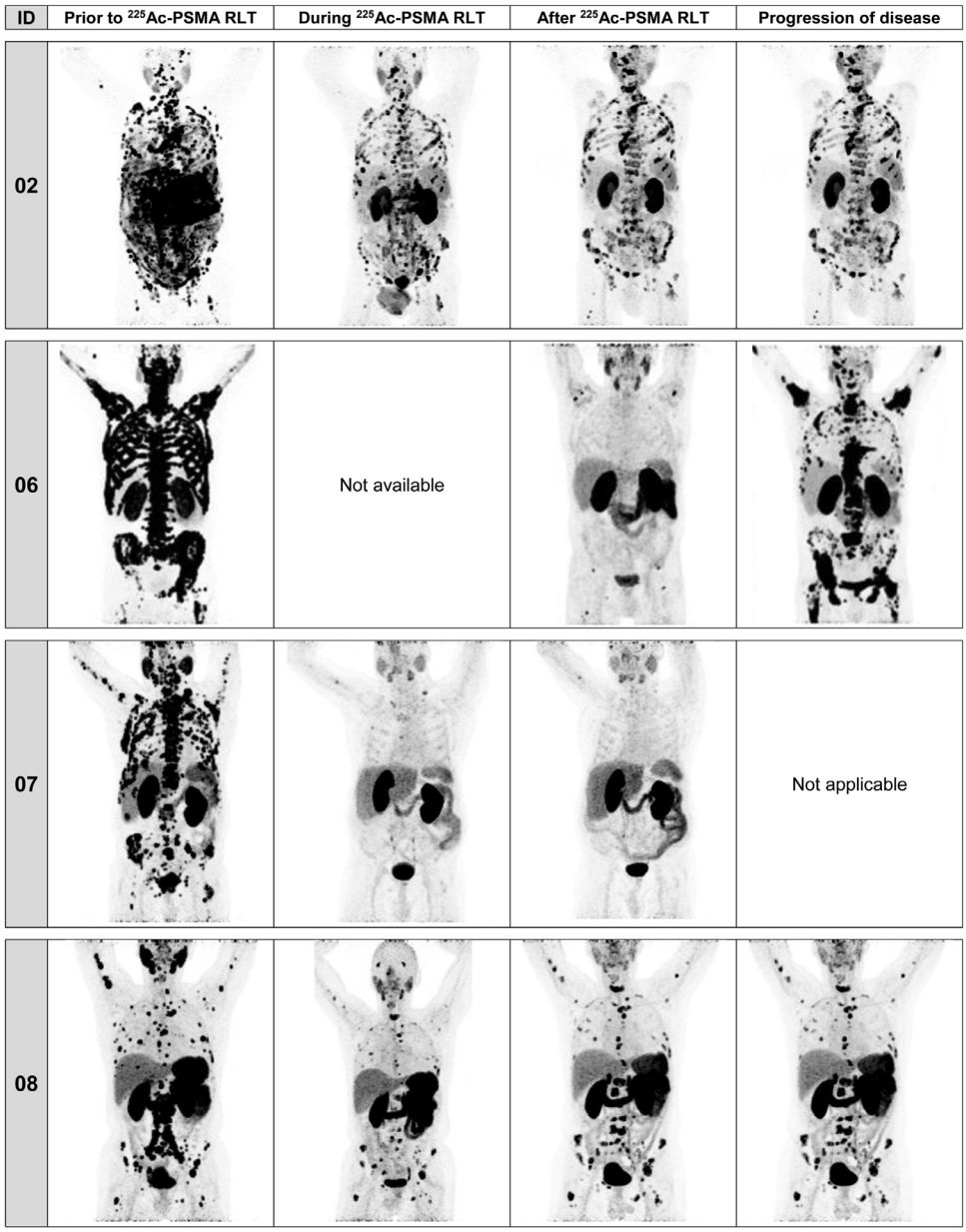

Fig. 3. ^{68}Ga-PSMA-11 PET/CT overviews of patients treated with ^{225}Ac-PSMA-617 targeted alpha-radiation therapy.

4. Discussion

In this cohort of heavily pretreated mCRPC patients, ^{225}Ac-PSMA TAT resulted in clinical, biochemical and radiological responses, and an improvement in functional QoL domains and general QoL score. Additionally, to our best knowledge, this is the first study that included pretherapeutic biomarker assessment in tumor biopsies of ^{225}Ac-PSMA TAT treated patients.

When compared to other studies evaluating end-stage mCRPC populations, the observed OS of 8.5 months in this cohort is exceptional [22]. Moreover, OS was 12.6 months for PSMA RLT-naïve patients. We observed ≥50% PSA responses in 69% of patients. When compared to the reported ≥50% PSA decline in 45% to 64% of the patients treated with ^{177}Lu-PSMA RLT, ^{225}Ac-PSMA TAT exceeds these rates [5,23,24]. Our data are well in line with previously reported response rates and OS in a cohort of 40 German mCRPC patients who underwent ^{225}Ac-PSMA TAT [8]. Remarkable better responses and longer OS have been reported in a cohort of South-African patients receiving ^{225}Ac-PSMA TAT [9]. However, the discrepancies are likely due to the recruitment of chemotherapy and ART-naive patients in the South-African study.

Partial radiological responses were observed in 3 of 6 evaluable patients. Importantly, 3 (33%) patients were not RECIST evaluable due to lack of extraskeletal disease at baseline. Therefore, we included whole body PET-

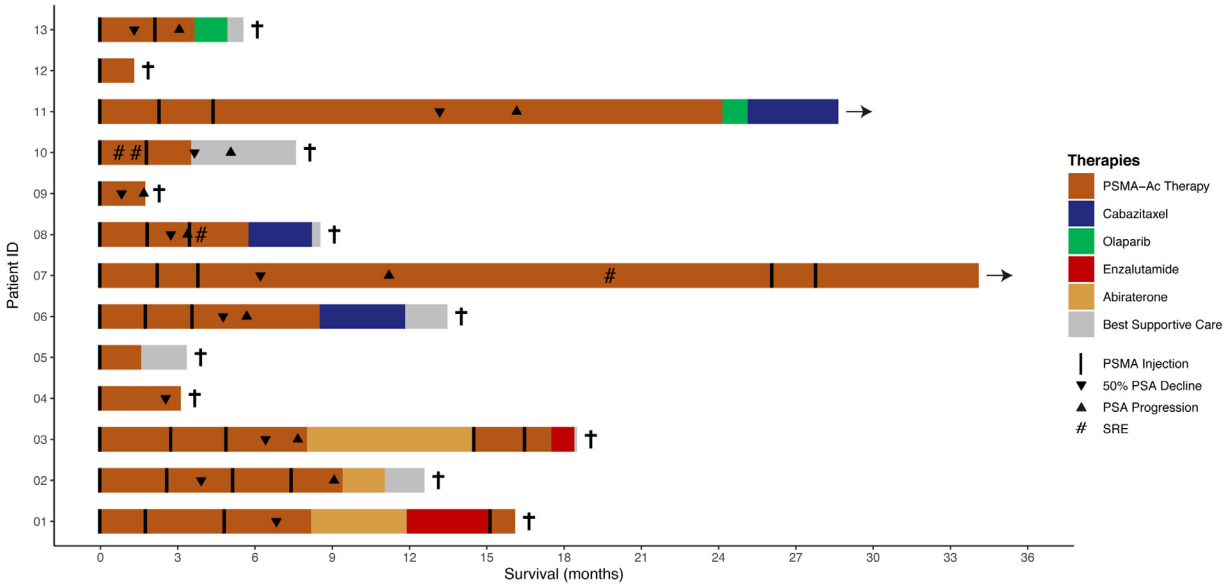

Fig. 4. Swimmer plot illustrating the duration of tumor control (in months), PSA response, the occurrence of skeletal-related events and the initiation of subsequent therapies after ^{225}Ac-PSMA-617 targeted alpha-radiation therapy.

Ac-225 = ^{225}Ac-PSMA-617 targeted alpha-radiation therapy; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SRE = skeletal-related event.

segmented tumor volume measurements, which showed >90% viable tumor volume decreases in all 7 evaluable patients. This method has been described previously and might be useful to analyze response of metastases to therapy [25].

Previous reports on ^{225}Ac-PSMA TAT were lacking standardized QoL elaboration [8,9]. In our evaluation, patients experienced clinically relevant decrease of pain complaints, reflected by the outcomes of the EORTC QLQ-C30, and BM-22 questionnaires. The observed QoL improvement is comparable to the outcomes of the phase 2 ^{177}Lu-PSMA RLT trial [5,24]. Although salivary glands were cooled during the application of ^{225}Ac-PSMA, xerostomia occurred in every patient. In theory, ^{177}Lu-PSMA RLT results in lower toxicity caused by lower absorbed dose delivered to the salivary glands. However, mild xerostomia was reported in up to 87% of patients treated with ^{177}Lu-PSMA [5]. Thus, salivary gland toxicity of ^{225}Ac-PSMA is slightly higher compared to patients treated with ^{177}Lu-PSMA. In case of high tumor load at start of therapy, xerostomia after the first ^{225}Ac-PSMA cycle was generally absent. In accordance with findings described in literature, xerostomia severity was found to be related to longer continuation of TAT and response to therapy [26,27]. Strategies such as drinking extra fluids, saliva substitutes, and citric acid candy relieved symptoms, but toxicity was irreversible. To date, the impact of interventions to prevent xerostomia, including external cooling, sialendoscopy with steroid injection, and the application of botulinum toxin, tends to be limited [28–30].

In this cohort, we identified pathogenic *BRCA1* mutations in 2 patients. These patients showed numerically longer survival when compared to patients without DDR aberrations. Indeed, tumors with germline or somatic DDR alterations reveal higher PSMA expression and therefore, DDR alterations might be valuable biomarkers of response to PSMA RLT [31]. Moreover, patients with defective DDR might be more vulnerable to TAT, due to inability to repair the excessive double-strand DNA breaks induced by alpha emitters [32]. Future research should include baseline metastatic biopsies for NGS to investigate whether patients with specific DDR mutations benefit more from PSMA RLT than patients without DDR. In addition, these studies should implement baseline PSMA expression analysis, since we observed less extensive responses to RLT in patients with reduced PSMA expression.

Our study has several limitations that should be considered. Due to the observational nature of this study and the small sample size, statistical analysis of data was restricted and causal inferences cannot be made. QoL analysis was not possible in all patients due to the limited number of long-term respondents. We were not able to obtain pretherapeutic metastatic biopsies in all patients and reviewed archival prostate specimens in case metastatic biopsies we not evaluable or unavailable. Although there does not appear to be substantial tumor heterogeneity in key prostate cancer driver genes between different cancer sites within an individual with mCRPC, we cannot exclude the possibility of heterogeneity between sites [33]. Obtaining post-TAT biopsies turned out to be difficult, due to high proportion of radiographic responses. The exploratory data in this study should be considered hypothesis-generating and would benefit from prospective trials. However, since such trials are currently lacking, these small cohort studies are important to show real life data on this promising treatment.

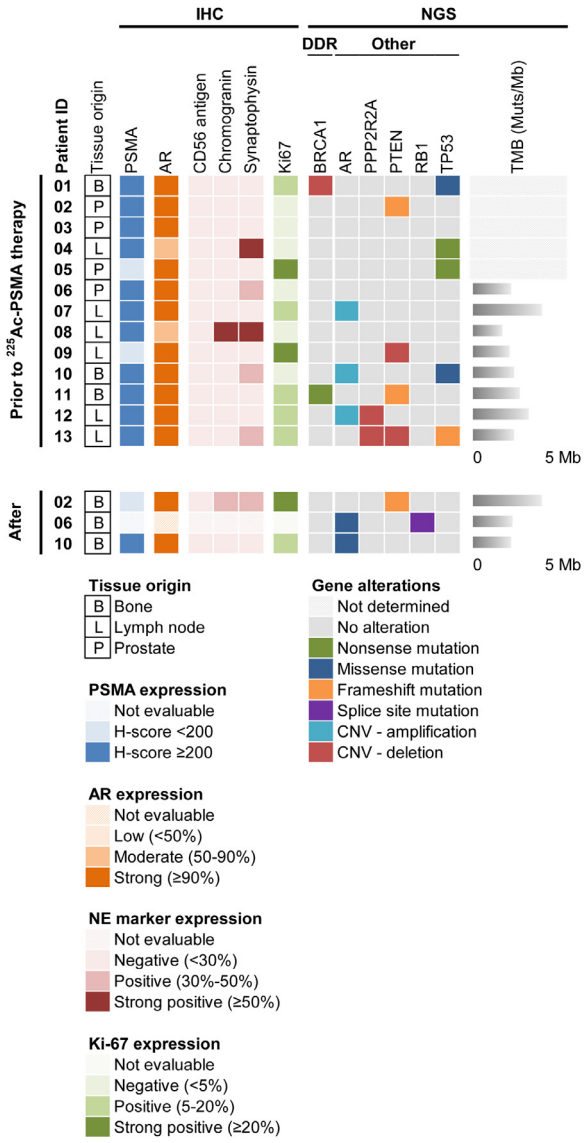

Fig. 5. Immunohistochemical analyses and genomic profiling of patients with metastatic castration-resistant prostate cancer prior and after treatment with ^{225}Ac-PSMA-617 targeted alpha-radiation therapy.

AR = androgen receptor; DDR = DNA damage repair; IHC = immunohistochemistry; NE = neuroendocrine; NGS = next-generation sequencing; PSMA = prostate-specific membrane antigen; TMB = tumor mutational burden (mutations per megabase).

5. Conclusions

In this observational cohort of heavily pretreated mCRPC patients, ^{225}Ac-PSMA TAT resulted in clinical, biochemical, and radiological responses. Patients experienced clinically relevant decrease of pain and QoL improvement in physical and role functioning domains. All patients reported xerostomia symptoms, which were non-transient at follow-up. Baseline immunohistochemical PSMA expression and DDR status are potential predictive biomarkers of response to ^{225}Ac-PSMA TAT and warrant further evaluation in prospective clinical trials.

Conflict of interest

Clemens Kratochwil and Uwe Haberkorn are patent holders of PSMA-617. Alfred Morgenstern, Frank Bruchertseifer, Clemens Kratochwil, and Uwe Haberkorn are holders of patent application on treatment of PSMA expressing cancers with ^{225}Ac. The other authors declare no conflict of interest.

Ethics approval

This study was approved by the medical ethics review committee and it was performed in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. ^{225}Ac-PSMA TAT was applied in accordance to the German Pharmaceuticals Law as salvage therapy for mCRPC patients, presenting progressive disease after approved therapies. Patients were informed about the experimental nature of ^{225}Ac-PSMA TAT and gave written informed consent.

Author contributions

Maarten J. van der Doelen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Van der Doelen, Mehra, Kratochwil, Gerritsen.

Acquisition of data: Van der Doelen, Mehra, Slootbeek, Nagarajah.

Analysis and interpretation of data: Van der Doelen, Looijen-Salamon, Custers, Slootbeek, Kroeze, Nagarajah.

Drafting of the manuscript: Van der Doelen, Mehra, Gerritsen.

Critical revision of the manuscript for important intellectual content: Mehra, Van Oort, Janssen, Morgenstern, Haberkorn, Kratochwil, Nagarajah, Gerritsen.

Statistical analysis: Van der Doelen, Custers.

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Supervision: Mehra, Van Oort, Kratochwil, Gerritsen.

Other: None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.12.002.

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