TECHNISCHE UNIVERSITÄT MÜNCHEN

TUM School of Medicine and Health

Activity, therapeutic efficacy and adverse events of ^{225}Actinium-PSMA-617 in advanced metastatic castration-resistant prostate cancer after failure of ^{177}Lutetium-PSMA-I&T

Ali Beheshti

Vollständiger Abdruck der von der TUM School of Medicine and Health der Technischen Universität München zur Erlangung eines Doktors der Medizin genehmigten Dissertation.

Vorsitz: Prof. Dr. Kathrin Schumann

Prüfende der Dissertation:

1. apl. Prof. Dr. Matthias Eiber
2. Prof. Dr. Maximilian Reichert

Die Dissertation wurde am 19.02.2024 bei der Technischen Universität München eingereicht und durch die TUM School of Medicine and Health am 07.08.2024 angenommen.

Medizinische Fakultät der Technischen Universität München

Nuklearmedizinische Klinik und Poliklinik des Universitätsklinikums
Rechts der Isar der
Technischen Universität München
Direktor: Prof. Dr. med. W. Weber

Activity, therapeutic efficacy and adverse events of ^{225}Actinium-PSMA-617 in advanced metastatic castration-resistant prostate cancer after failure of ^{177}Lutetium-PSMA-I&T

Author: Ali Beheshti, born September 8th, 1995 (Tehran, Iran)
Supervisor: apl. Prof. Dr. med. Matthias Eiber

Table of Contents

List of tables

List of figures

List of abbreviations:

ADT	Androgen deprivation therapy
Bq	Becquerel
BR	Biochemical recurrence
CR	Complete remission
CRPC	Castration-resistant prostate cancer
CT	Computed Tomography
CTx	Chemotherapy
DGU	Deutsche Gesellschaft für Urologie (German Association of Urology)
DRE	Digital rectal examination
mCRPC	metastatic castration resistant prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
MR	mixed response
MRI	Magnetic resonance imaging
NA	not available
OS	overall survival
PD	progressive disease
PET	Positron-Emission Tomography
PFS	Progression-free survival
PR	partial response
PCa	Prostate cancer
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
RCT	Randomized controlled trial
RPE	Radical prostatectomy
RLT	Radioligand therapy
RT	radiation therapy
SD	stable disease
TAT	Targeted alpha therapy
TR	treatment response

1. INTRODUCTION:

1.1 Background

Prostate cancer (PCa) is the second cancerous disease in men and the fifth leading cause of cancer-related mortalities in the whole population. According to the Global Cancer Observatory (GLOBOCAN) about 1,277,000 cases were diagnosed with prostate cancer and approximately 359,000 men (3,8% mortality rate worldwide) died of this disease in 2018. [2] Prostate cancer incidence and mortality varies internationally, and it is highly correlated with increasing age, the worldwide average being at 66 years. [3] [4] Known risk factors include age, habitat and family history and can include inherited genetic factors and ethnicity. African American males were found to be significantly more affected than reference groups with Caucasian males.[5, 6] Between 30% and 70% of patients over the age of 60 years, who died of other reasons, are diagnosed with prostate cancer post-mortem through autopsies.[7, 8] However, due to the establishment of the screening programs, mainly by prostate specific antigen (PSA), prostate malignancies are usually detected at early stage of the disease, when the cancer is locally confined to the prostate gland. This led to better management of the disease and improvement of the overall survival. According to the National Cancer Institute in Bethesda, the 5-year survival rate in the United States was around 98%. The Eurocare project (EUROCARE-5) showed the overall 5-year survival rate from 2003 to 2007 at around 83%, with an increasing survival rate over the years the study was conducted. [3, 9] Primary diagnostics include PSA testing, digital rectal examination, sonography and transrectal biopsy. Radical prostatectomy (RPE), percutaneous radiotherapy and interstitial brachytherapy are the standard treatment approaches for organ-confined prostate cancer. Recurrent PCa occurs in about 30% of patients with localized prostate cancer after RPE. Despite long-term complete remission of patients after salvage radiotherapy, around 50% of the patients experience disease progression [10]. Challenges remain in the treatment of advanced or metastatic disease, with 5-year overall survival rates of about 30%. [11, 12] Nevertheless, the recent developments of novel therapeutic aspects including radionuclide therapy in the setting of theranostics seem to be promising treatment approaches in PCa patients with advanced metastatic diseases.

1.2. Screening and primary clinical assessment

The progress of the cancer may run asymptomatic, as there are no definite symptoms at the early stages. In advanced stages patients can experience urinary retention, dysuria, incontinence, impotence, hematuria, renal insufficiency by urinary tract obstructions and pain or discomfort in the pelvic region.[6] In a meta-analysis conducted by Ilic et al of five randomized controlled trials (RCTS) including 341,342 patients, the efficacy of PSA-screening was assessed. [13, 14] The authors reported that only one of the RCTs done by the European randomized study of screening for Prostate cancer (ERSPC) demonstrated a reduction in PCa-specific mortality. [13, 14] However, it is generally consented and is recommended to inform patients about the possibility of screening and to educate them about the advantages and disadvantages of such measures [15]. In addition, digital-rectal examination belongs to the first clinical evaluations. The combination of digital-rectal examination (DRE) and PSA-screening offers higher specificity, sensitivity, and positive predictive value. In other words, if PSA and DRE are normal, the chance of not detecting a prostate malignity is about 10%. [16] In case of suspicious DRE or suspicious PSA values >4 ng/ml, a transrectal punch biopsy should be performed in men aged 50-75 years with a biological life expectancy >10 years.[17] The German Society of Urology (DGU) lists transrectal ultrasound as one of the precise diagnostic methods. Nevertheless, its test quality parameters are very similar to those of rectal palpation. As of today, contrast-enhanced ultrasound, ultrasound elastography, or computer-assisted ultrasound are also used for primary diagnostic of PCa. However, their clinical impact in patient's management has to be further investigated.[18]

1.3. Clinical stages of prostate cancer

Like other malignant tumors, the clinical staging of prostate cancer is done through the tumor node metastasis (TNM) classification. According to the guidelines of the International Union against Cancer (UICC) prostate cancer is classified as demonstrated in Table 1:

Table 1: **Clinical TNM classification of PCa [19]**

T – Primary tumor (stage based on digital rectal examination [DRE] only)		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Clinically inapparent tumor that is not palpable	
	T1a	Tumor incidental histological finding in 5% or less of tissue resected
	T1b	Tumor incidental histological finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA-values)
T2	Tumor that is palpable and confined within prostate	
	T2a	Tumor involves one half of one lobe or less
	T2b	Tumor involves more than half of one lobe, but not both lobes
	T3c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N – Regional (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M – Distant Metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Metastasis no larger than 2mm can be designated pNmi.*
[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Further classification to help deduce the malignity of the adenocarcinoma is the histopathological grading system Gleason score (GS). The score consists of two grades, the first defining the most dominant histological pattern of the PCa tissue and the latter describing the second-most frequent. The sum of the two grades combines to give the Gleason score, which can then be used to further evaluate malignity, especially regarding risk assessments.[7] It is also worth mentioning that in some cases of prostate cancer, such as in adenocarcinomas post radiation therapy, squamous cell, small cell, neuroendocrine, urothelial or PCa metastases Gleason grading is not used.[20]

1.4. Risk stratification and staging workup

Histopathological subtypes play a crucial role in firstly asserting a diagnosis and secondly planning the accurate treatment and prediction of the prognosis of the disease.[21] In a study performed by Kendal et al, the histopathological subtypes of around 455,000 cases of PCa were reviewed. Adenocarcinoma were the prominent subtype with more than 99% followed by ductal carcinomas (0.141%), mucinous adenocarcinomas (0.103%), small cell carcinomas (0.056%), and lastly neuroendocrine subtype.[22] Neuroendocrine prostate cancer (NEPC) is described as a rapid progressive subtype with low androgen receptor expression. The etiology of NEPC is subject of current research but some studies have suggested that it develops because of androgen-deprivation therapy. In about 10-17% of CRPC patients treatment induced NEPC occurs through transdifferentiation process from adenocarcinomas. The Gleason score, tumor volume, gene profiles, clinical and pathological staging and surgical margins are other prognostic factors.[23] Various imaging modalities such as skeletal scintigraphy, CT, MRI, PET/CT have been introduced for staging of PCa. In locally advanced prostate cancers, magnetic resonance imaging (MRI) is mentioned as an option for primary local staging (T-staging) in the guidelines of the European Association of Urology (EAU).[24] In order to differentiate prostate cancer from other benign diseases with high prevalence in the elderly population, a multiparametric examination protocol (mMRI) is applied, which allows tissue characterization in addition to morphological changes.[25] The specificity of this examination is high, but with only moderate sensitivity.[26] In intermediate and high-risk PCa patients computed tomography and skeletal scintigraphy are the common diagnostic imaging modalities for the N- and M-staging of the disease. [18] PET/CT using prostate membrane specific antigen specific (PSMA) radioligands (e.g., ^{68}Ga-PSMA-11) showed promising results in primary staging of high-risk PCa patients.[27] The National Comprehensive Cancer Network (NCCN) suggests following risk stratification and staging workup in patients with prostate cancer, as shown in *Table 2*:

Table 2: **Risk stratification and staging workup of PCa (NCCN)** ***[28]***

Risk Group	Clinical/pathological features	Imaging	Molecular testing	Genetic testing
Very low	All the following: • T1c • Gleason score ≤6 • PSA <10ng/mL • <3 prostate biopsy fragments positive, ≤50% cancer in each fragment • PSA density <0.15ng/mL/g	Not indicated	Not indicated	To be considered with strong family history
Low	All the following: • T1-T2a • Gleason score ≤6 • PSA <10ng/m	Not indicated	If life expectancy is ≥ 10 yrs.	To be considered with strong family history
Intermediate-favorable	Any of the following: • T2b-c • Gleason score 7 • PSA 10-20ng/mL AND: <50% positive biopsy fragments	• Bone: not recommended for staging • Pelvic/abdominal: recommended if >10% probability of pelvic lymph node involvement	If life expectancy is ≥ 10 yrs.	To be considered with strong family history
Intermediate-unfavorable	Any of the following: • T3a • Gleason score 7 (3+4 or 4+3) • PSA 10-20ng/mL	• Bone: recommended if T2 and PSA >10ng/mL • Pelvic/abdominal: recommended if >10% probability of pelvic lymph node involvement	Not routinely recommended	To be considered with strong family history
High	Any of the following: • T3a • Gleason score 8 or 9 • PSA >20ng/mL	• Bone: recommended • Pelvic/abdominal: recommended if >10% probability of pelvic lymph node involvement	Not routinely recommended	To be considered
Very high	Any of the following: • T3b-T4 • >4 biopsy fragments with Gleason score 8-10	Bone: recommended Pelvic/abdominal: recommended if >10% probability of pelvic lymph node involvement	Not routinely recommended	To be considered
Regional	Any T, N1, M0	Already performed	Homologous recombination gene mutations MSI/ dMMR*	To be considered
Metastatic	Any T, any N, M1	Already performed	Homologous recombination gene mutations MSI/ dMMR*	To be considered

**MSI: microsatellite instability. dMMR: deficient mismatch repair*

Primary treatment approaches for organ-confined prostate cancer are radical prostatectomy, percutaneous radiotherapy, and interstitial brachytherapy. Adjuvant therapeutic procedures include ADT and radiotherapy.[29]

Second and further therapy line concepts come into play if curative therapy is no longer possible in case of clinically advanced diseases with distant metastases at primary diagnosis. As disease progression is often slow, the palliative phase in PCa can last many years. [30] Treatments include ADT (e.g., abiraterone, enzalutamide), chemotherapy (e.g., docetaxel, cabazitaxel), radiotherapy, radionuclide therapy (e.g. ^{223}Ra-Dichlorid, ^{117}Lu-PSMA-labeled agents, ^{225}Ac-PSMA-617), and immunotherapy or combination treatment of the aforementioned approaches. [30, 31]

At present, theranostics, an individual approach in diagnostics and therapy utilizing the application of radiolabeled targeted molecules, is gaining importance in management and treatment cancer. It is being used more frequently as salvage and in rare cases as primary therapy. [32]

1.5. Recurrent prostate cancer and different phases

Recurrent PCa is seen in about 30% of patients with localized prostate cancer after radical prostatectomy. Initially biochemical recurrence (BR), in form of elevated blood serum PSA level, is observed. [10] Relapse or biochemical recurrences after primary therapy is defined as an increase in PSA-level > 0.2 ng/mL after radical prostatectomy (RPE) or > 2 ng/mL following radiation therapy (RT).[33]

The probability of BR is related to a few different factors such as tumor burden post RPE, histopathological subtype of the primary, and the risk category of the disease. The European association of Urology (EAU) has defined risk groups for BR of both local and locally advanced prostate cancers. Table 3 gives an overview of the EAU outline of the risk groups:

Table 3: **EAU risk group for biochemical recurrence of localized and locally advanced PCa [12]**

Definition			
Low risk	Intermediate risk	High risk	
PSA <10 ng/mL	PSA 10-20 ng/mL	PSA >20 ng/mL	Any PSA
and GS < 7	or GS 7	or GS > 7	Any GS
and cT1-2a	or cT2b	or cT2c	cT3-4 or cN+
Localized			Locally advanced

PSA = prostate-specific antigen, GS = Gleason score

A large number of patients achieve long-term complete remission after BR through salvage radiation therapies. However, about 50% of patients experience disease progression. [10] Difficulties arise in the therapy of advanced or metastatic diseases as the 5-year overall survival reaches only 30%. [11, 34] Nonetheless, recent development of novel therapeutic agents offers more treatment possibilities for patients.

ADT using androgen receptor (AR) pathway blockers are common procedures for advanced metastatic diseases in hormone-sensitive prostate cancer (HSPC) patients. In such patients luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or surgical castration in form of mono or combination therapy have been recommended by the American Urological Association/ American Society for Radiation Oncology/ Society of Urologic Oncology. [11] Although these therapeutic options mostly lead to long-term remissions, almost all patients develop hormone ablation resistance over time, a state called castration-resistant prostate cancer (CRPC).[35] Progression from hormone therapy response to castration-resistance represents the shift to the lethal course of this disease.[36] At this stage second-generation antiandrogens such as abiraterone and enzalutamide or chemotherapeutical agents like docetaxel and cabazitaxel can be considered. [37, 38] Some investigations showed that the combination of radiotherapy and ADT can result in prolonged progression-free survival (PFS) and overall survival (OS) in recurrent PCa patients.[10] A meta-analysis performed in 2019 showed that the combination of docetaxel, abiraterone, enzalutamide or apalutamide in combination with ADT yields significant benefits in OS in comparison to solo ADT therapy in metastatic HSPC (mHSPC) patients. The different combinations of the beforementioned pharmaceuticals did not show any significant differences in OS.[39] Especially enzalutamide with ADT was found to improve the clinical outcome in mHSPC patients with bone and/or lymph node metastases. Unfortunately, it did not show superior efficacy in visceral metastases patterns.[40] Despite these measures, progressive metastatic diseases are expected in CRPC patients, which is then termed metastatic CRPC (mCRPC). Novo treatment approaches like immunotherapy, radionuclide treatment by using bone-seeking or PSMA-based agents have been investigated as later lines of therapy in the concept of personalized salvage treatment. To date, PSMA has been proved as a promising target in PCa diagnostics and therapies. PSMA-targeted treatments are rapidly evolving and recent studies have shown that these can be a tolerable and effective approaches with antitumor activity in mCRPC patients.[31]

1.6. PSMA characteristics suitable for targeting prostate cancer

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein (other biochemical descriptions include folate hydrolase I, glutamate carboxypeptidase II, N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALDase I), or N-acetyl-L-aspatyl-L-glutamate (NAAG) peptidase), which can be found on prostate tissues cells. As a transmembrane protein, PSMA is a zinc-containing enzyme with three domains on its polypeptide chain. On the extracellular domains the molecule has a ligand binding site, which is catalytical and enables ligand absorption into the cancer cell through endocytosis.[41] PSMA is overexpressed in the majority of PCa types and has been found to correlate with tumor progression, recurrence of disease and metastases. [32]

Mainly two pathways have been used for targeting PSMA for clinical indications. One method utilizes the protein structure to characterize monoclonal antibodies as targeting vectors. [42] The second method relies on PSMA's enzymatic activity and utilizes radiolabeled enzyme inhibitors as target-seeking substrates. [43] In development of diagnostic and therapeutic radioactive tracers the latter method is used preferably. This pathway makes use of radiolabeled small molecules to target the enzyme activity of PSMA. Rapid blood clearance, higher target-to-nontarget ratio and better detectability on molecular imaging modalities are all upsides of this method compared to the monoclonal antibodies. Furthermore, this pathway enables more effective transportation into cells due to the radiolabeled small molecules, hence resulting in higher tumor uptake and retention. [44]

Amongst different PSMA enzymatic pathways, the most frequently used one for development of diagnostic and therapeutic radiopharmaceuticals is the NAALDase pathway. Modified forms of NAALDase inhibitors are used for imaging and therapy as PSMA targeting substances. These NAALdase inhibitors are subdivided into three categories: (a) phosphorous-based subtrates, (b) thiol, indole-thiol, hydroxamate and sulfonamide compounds, and (c) urea-based derivatives. Due to its metabolic stability and selectivity, urea based PSMA ligands have advanced in clinical fields. [45, 46] Urea based PSMA radioligands, such as $^{123/124/131}$I-MIP-1072/-1095, [47, 48], ^{99m}Tc-MIP-1404/-1405[49], ^{68}Ga-PSMA-11 [50], ^{18}F-DCFBC [51], ^{18}F-DCFPyl [52], ^{18}F-PSMA-1007 [53], ^{177}Lu-PSMA-617 [54], and ^{177}Lu-PSMA-I&T [55] have gained importance in the diagnosis and treatment of prostate cancer. Among these, ^{68}Ga-PSMA-11 has proved itself as one of the most dominating radiotracers in the field of PCa imaging with

positron emission tomography (PET). [50, 56, 57] In recent years Iodine-131, Lutetium-177, Yttrium-90 and Rhenium-188 have also been employed as radiolabeled PSMA radioligands in RLT of PCa. [58-60] Within these beta-decaying radioisotopes used in RLT, Lutetium-177 has been found to be more feasible for the clinical routine application because of its less complicated synthesis and reduced toxicity in comparison to Iodine-131. Differences in toxicity can be related to the lower proportion of gamma radiation of Lutetium-177. [61] Hence, recent studies have highlighted their focus on ^{177}Lu-PSMA radioligands. Following this, targeted RLT with alpha(α)-decaying radioisotopes such as Actinium-225 and Bismuth-213 are currently under investigation in preclinical and clinical settings [32], such as our study with ^{225}Ac-PSMA-617 as salvage therapy in patients with mCRPC. [1]

1.7. PSMA-based radioligand therapy in mCRPC

Prostate-specific membrane antigen is a protein structure, which acts as a peptidase with both N-acetylated α-linked acidic peptidase and folate hydrolase activity. The expression of prostate-specific membrane antigen (PSMA) has been suggested as a potential biomarker of disease severity in prostate cancer [62]. It is expressed at low levels in normal prostate epithelial cells and is upregulated several-fold in high-grade, metastatic and androgen-insensitive prostate cancer.[62] Interestingly, PSMA was found to be involved in tumor angiogenesis in mouse models as well. [63, 64] It is virtually absent in non-prostate tissues but is expressed in the process of neovascularisation in many solid tumors.[65]

PSMA is overexpressed in 90% of prostate cancer metastases, while it is low expressed in normal prostate, small intestine, salivary and lacrimal glands, and kidneys. [66]. These characteristics make it a specific favorable target for therapeutic and diagnostic measures and emphasizes on the importance of this molecule in theranostics approach. [67] Various radioligands have been specifically developed in nuclear medicine for targeting PSMA, that can be used for both molecular PET imaging as well as PSMA radioligand therapy (PRLT). In PRLT of prostate cancer, the PSMA-ligand is labelled with a radioactive substance with either alpha or beta decay, that enables a tumor-specific therapy of malignant lesions with PSMA-overexpression. Initial clinical experiences in PSMA-targeted therapy using beta-radiation emitters like ^{131}I-MIP-1095, ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T were described, of them

^{177}Lu -based radioligands showed feasible with more favorable characteristics for clinical use [48, 55, 68] [36].

1.8. ^{177}Lu-PSMA-labeled-radioligand therapy

In a retrospective analysis, Kratochwil et al [69] reported about the use of ^{177}Lu-PSMA-617 in 30 mCRPC patients. The patients received an initial dosis of 3.7-4.0 giga-Becquerel (GBq) and were monitored for 48 hours. Therapy cycle was repeated after eight weeks, and the dose was increased to 6.0 GBq. Sixteen patients (16/30, 53%) were chemotherapy-naïve, and 11 patients received three cycles of ^{177}Lu-PSMA-617. The results demonstrated PSA-reduction >50% in 13 patients (43%), and 8 of 11 patients (73%) who had undergone three therapeutic cycles showed a consistent PSA-reduction >50% for over 24 weeks. RLT was tolerated well. However, because of physiologic expression of PSMA in the salivary glands, high ^{177}Lu-PSMA accumulation during RLT may disturb normal cells. Xerostomia can be considered as an important side effect of this treatment regime and can drastically influence patient compliance and quality of life.[1] Nevertheless, under beta-decay-ligand therapy, xerostomia proved to be temporarily and reversible. Non-hematological side effects such as fatigue, nausea and intermittent xerostomia were reported in less than 10% of patients in the latter study. [69] High-grade hematological toxicities such as anemia grade III or thrombocytopenia grade III were seen in only 2 (6%) of patients of the aforementioned trial. [69]

Another study documented up to two cycles ^{177}Lu-PSMA-617 in 24 patients with mCRPC, of which 14 (58%) were chemotherapy-naïve. [70] All patients (100%) had bone metastases and three (13%) showed visceral hepatic metastatic spread. A total of 46 cycles were completed, 22 patients underwent two cycles, and a mean dose of 6.0 GBq was applied. After the first cycle 10 of 24 patients (41%) reached PSA-reduction >50%, and 13 of 22 (60%) did so after the second cycle. Post-therapy PSMA-imaging (PET/CT-scan) depicted partial remission in 16 of 20 patients (80%) and tumor progress in 4 of 20 (20%) (Figure 1). Side effects included anemia grade III in two patients (8%) and non-hematological toxicities, like fatigue (17%), nausea (13%) and temporary xerostomia (8%).[70]

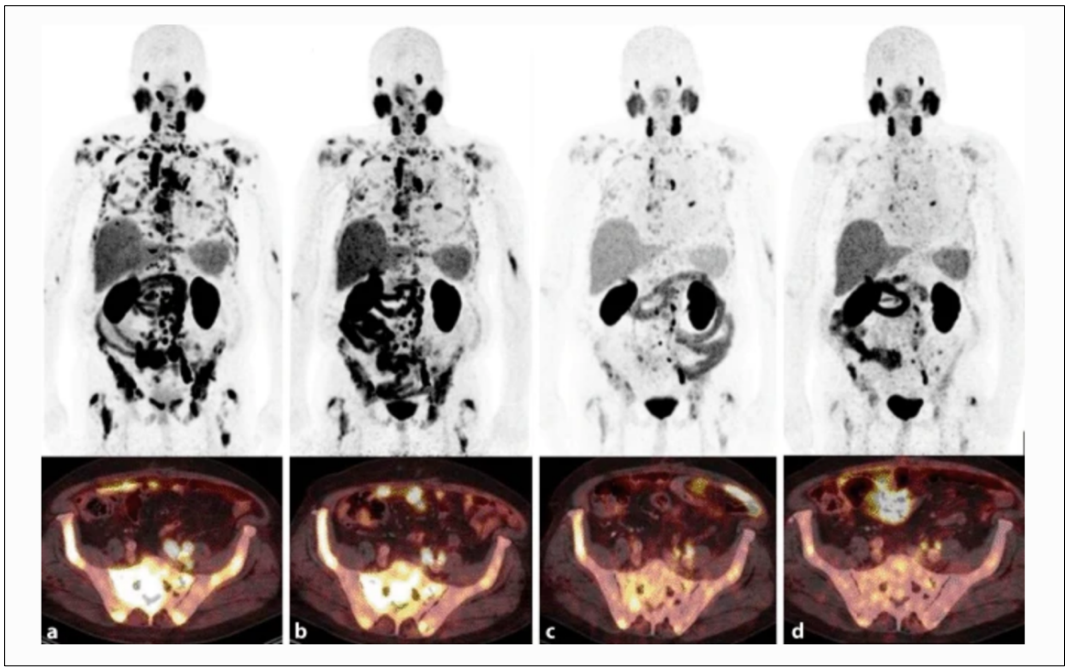
The common side effects reported in other clinical trials using ^{177}Lu-PSMA-617 therapy in mCRPC patients include:

- Grade 1 side effects such as xerostomia, mild nausea, fatigue, and appetite loss. [55, 68-77]
- Grade 3-4 hematological toxicities in 12% of patients was reported in a multicenter study by Rahbar et al., which included 145 patients with 248 cycles of radionuclide therapy.[78] Anemia, leukopenia and thrombocytopenia were recorded in 10%, 3%, and 4% of patients, respectively. A limiting factor for long term assessment was the short follow up time with a median of 16 weeks (range 2-30 weeks). This made it challenging to determine side effects of toxicity such as bleeding or febrile neutropenia. Opposed to this, another retrospective cohort (n=59), with a median follow up 24 weeks, demonstrated a higher incidence of grade 3-4 anemia. [79] In this series of patients, grade 3-4 anemia, thrombocytopenia, and leukocytopenia were recorded in 18%, 3% and 3% of the cases, respectively.

Despite varying patient collectives and therapy protocols, following regimes were found to be common between them [36]:

1. PSMA-ligand PET scan prior to treatment to determine ligand binding with PSMA-expression of target cells.
2. Patients were treated at nuclear medicine departments, receiving inpatient treatment for two to four days in a radioactive exclusion zone.
3. Six-to-eight-week intervals between therapy cycles.
4. Given adequate therapy response, four to six cycles were completed.

Figure 1: **Antitumor effect of ^{177}Lu-PSMA-I&T-RLT in a 76-year-old mCRPC patient**



a: baseline ^{68}Ga-PSMA-PET/CT-scan. **B-d:** therapy response after 1st, 2nd, and 4th cycles.

The figure visualizes an example of the antitumor effect of ^{177}Lu-PSMA-I&T RLT in a 76-year-old mCRPC patient with bone and lymphatic metastases. [36] Prior to radionuclide therapy the patient had undergone chemotherapy (Docetaxel, Cabazitaxel), ^{223}Ra-Dichlorid-RLT and hormone therapy (Abiraterone, Enzalutamide). The patient received four cycles ^{177}Lu-PSMA-I&T and showed PSA-decrease from 228ng/mL to 45ng/mL after the fourth cycle. [36]

Recent studies show that radionuclide therapy has demonstrated its efficacy in the clinical management of mCRPC patients. The PSMA-targeting radiopharmaceutical ^{177}Lu-PSMA has established its role as a forerunner in this field and does provide an effective alternative for patients with progressive mCRPC.[48, 55, 68]

In July 2023 the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) published following procedure guideline for the use of ^{177}Lu-labeled PSMA-targeted radioligand therapy [80]:

1. PSMA-positive patients with metastatic castration-resistant prostate cancer (mCRPC) who have experienced progression despite treatment with at least one advanced androgen-targeting drug (such as enzalutamide or abiraterone) and at least one

taxane therapy (and are either unsuitable for or decline a second taxane therapy) are strongly recommended to consider ^{117}Lu-PSMA-617. [81]

2. Patients diagnosed with PSMA-positive mCRPC who have experienced progression despite treatment with at least one advanced androgen-axis inhibitor such as enzalutamide or abiraterone, as well as docetaxel, but could still be considered eligible to receive cabazitaxel. This strong recommendation was supported by substantial evidence from the 11-center phase-2b RCT TheraP. This study showed that ^{177}Lu-PSMA-617 had higher response rates (measured biochemically and through imaging), longer progression-free survival while maintaining an equal median overall survival, an increased count of long-term responders at the 12-month mark, better patient-reported outcomes across multiple aspects, and a reduction in the number of severe (grade 3/4) side effects compared to cabazitaxel. [82]
3. PSMA-positive mCRPC patients who progressed under at least one novel androgen axis drug but are still taxane-naïve.
4. Presently, diverse clinical scenarios are under assessment in ongoing phase 2/3 randomized controlled trials. In instances where participation in a randomized controlled trial is not possible, and other treatment alternatives have been used up or are not suitable, it is considered reasonable and ethical (in line with Article 37 of the Helsinki Declaration) to consider providing ^{177}Lu-PSMA-RLT on an individualized patient basis or within a compassionate care framework. However, adherence to national regulations governing such treatments is crucial.

Withal, due to the nature of PSMA radioligand therapy, it is imperative to always bear the toxicity and adverse events in mind. Absolute contraindications cannot be defined as ^{117}Lu-PSMA-labeled RLT itself is indicated in a malign disease with life-threating consequences. The decision to treat patients experiencing severe myelosuppression should be made cautiously, and there should be proper infrastructure in place to manage any potential complications adequately. Nevertheless, the current guidelines proposed some contraindications for ^{117}Lu-PSMA-labeled RLT such as low life expectancy (< 3 months), an ECOG status scale score ≥ 3, acute urinary tract obstructions, severe preexisting comorbidities (unmanageable psychiatric conditions, cardiovascular conditions, acute infections, myelosuppression) or progressive organ dysfunction with the risk of organ failure. [80]

1.9. ^{225}Ac-PSMA alpha radioligand therapy

Initial efforts were made to treat prostate cancer with monoclonal antibody ^{213}Bismuth-J591 as early as about 22 years ago.[83] However, ^{177}Lu-PSMA showed advantageous properties such as a favorable dosimetry, good tolerability, and therapeutic efficacy. While it remains a frequently used PSMA-radioligand therapeutic agent in the setting of theranostics, about 30% of patients yet remain as non-responders. In addition, its application is limited in cases with diffuse bone marrow metastases as a risk factor predisposing clinically significant hematological toxicity. [73, 78] Therefore, targeted therapies using alpha-radiation have been investigated in the clinical trials as a therapeutic option for radioresistant patients to beta-emitters and to reduce hematological toxicities in cases with diffuse bone marrow infiltration. Nonetheless, adverse events such as permanent xerostomia were reported in high-energetic alpha-decay radionuclide treatment with ligands such as Actinium-225 (^{225}Ac). [84]

To date, PRLT experience with alpha-emitters has mainly been made with PSMA-617 labelled Actinium-225 (^{225}Ac-PSMA, half-life 9.9 days) or Bismuth-213 (^{213}Bi-PSMA, half-life 46 min). Physical properties, safety, and tolerability as well as therapeutic efficacy of these alpha-particle-emitting isotopes have been examined for approaching targeted alpha therapy (TAT) in the recent years. Compared to beta-particle-emitting radionuclides, alpha-particle-emitting isotope have higher energy, lower emission range and higher linear energy transfer (LET) (Table 4). [85] These properties induce an increased number of DNA double strand breaks, which may improve the therapeutic efficacy without affecting adjacent healthy cells. [86, 87] Table 4 summarizes physical characteristics of therapeutic radionuclides.

Table 4: **General characteristics of therapeutic radionuclides. [85]**

Decay	Particles (#)*	$E_{(min)}$-$E_{(max)}$	Range	LET
α^{++}-particle	He nuclei (1)	5 to 9 MeV	40 to 100 µm	~80 keV/ µm
β^{-}-particle	Energetic electrons (1)	50 to 2300 keV	0.05 to 12 mm	~0.2 keV/µm
EC/IC	Nonenergetic electrons (5 to 30)	eV to keV	2 to 500 nm	~4 to 26 keV/µm

** Number of particles emitted per decaying atom. eV = electron volt. MeV = mega electron volt. keV = kilo electron volt. E = energy. LET = linear energy transfer.*

Preclinical studies have found targeted alpha therapy by radioligands like ^{225}Ac-PSMA or ^{213}Bi-anti-CD38 to be more effective than beta-particle emitter ^{177}Lu-PSMA.[88, 89]

Initial first-in-human experience with ^{225}Ac-PSMA-617 radioligand took place in 2016 in Heidelberg, Germany. Kratochwil et al [84] disclosed the use of ^{225}Ac-PSMA-617 to treat two mCRPC patients. They received ^{225}Ac-PSMA-617 RLT with a mean activity dose of 100 KBq per kilogram bodyweight, over the course of 8 weeks. Biochemical response and hematologic toxicity were reevaluated at least every 4 weeks. Both patients had received up to fifth line androgen deprivation therapies (ADT) and chemotherapies prior to RLT, one of them having been treated with ^{177}Lu-PSMA-617 as well. The authors reported a complete remission in both patients after three cycles of ^{225}Ac-PSMA-617 RLT based on clinical and biochemical (i.e., PSA decline to below measurable level) as well as imaging (^{68}Ga-PSMA PET/CT scans) findings. No clinically relevant hematological toxicities were noted, but both cases suffered from permanent xerostomia. One patient reported a moderate dryness of mouth while the other revealed severe xerostomia treated with synthetic saliva substitution. [84]

Another pilot study was conducted with ^{225}Ac-PSMA-617 therapy in South Africa with a cohort of 17 chemotherapy-naïve mCRCP patients [90].The initial activity of RLT was at 8 MBq and therapy was deescalated in case of good response to 7 MBq, 6 MBq or 4 MBq. A mean activity of 7.4 ± 1.5 MBq were administered. A total of three cycles were applied to 14 patients and therapy was discontinued in 3 patients after two cycles due to complete remission. A significant baseline PSA-decline ($\geq$ 90%) was observed in 82% (14/17) of the mCRPC patients. Overall, 88% (15/17) of the patients showed a $\geq$50% reduction in PSMA-expression on ^{68}Ga-PSMA-11 PET/CT. In 1 patient without significant response to the first two cycles, the administered activity was increased to 13 MBq in the third cycle. Therapy failure was reported in only one patient. [90] According to the authors no acute toxicity was observed in any patient throughout treatment. The whole 100% (17/17) patient's population experienced either grade 1 or 2 xerostomia, grade 3 was not observed. No hematological side effects were reported in this cohort. Furthermore, the authors found a better trend to response to ^{225}Ac-PSMA-617 in chemotherapy-naive patients comparing to patients who were completed the treatment. This pattern raises the issue that ^{225}Ac-PSMA-617 RLT might be indicated at earlier phases of advanced and aggressive disease rather than later phases when all treatment approaches are outperformed.

Similar results were reported in another study in 40 mCRPC patients, who each received three cycles of 100 KBq/kg/bw ^{225}Ac-PSMA-617 at 8-weeks intervals. In 38 patients who survived at least eight weeks, 63% (24/38) had a PSA decline of more than 50%, and 87% (33/38) had any PSA response at all. Tumor control was achieved in median time of 9 months. A swimmer-plot analysis highlighted the encouraging duration of tumor control, with respect to the advanced disease profile of the selected patients. [32, 84]

^{213}Bi-PSMA-617 is another alpha-emitter therapeutic radioligand that has also been investigated in mCRPC patients. Sathekge and his colleagues reported the first mCRPC case treated with ^{213}Bi-PSMA-617. [91] The patient received two cycles of RLT with ^{213}Bi-PSMA-617 with a cumulative activity of 592 MBq. After 11 months, follow-up ^{68}Ga-PSMA-11 PET/CT demonstrated significant morphological and molecular imaging response. A marked PSA-baseline decline of 81.9% was also noted in this case. [91]

Despite favorable physical characteristics and promising reported therapeutic efficacy of ^{225}Ac-PSMA-617, there are only incoherent clinical data (mainly due to its scarce availability) with small patients' cohorts available for drawing a statement about its impact in management of mCRPC patients [92]. This study is one of the first clinical investigations assessing the therapeutic performance of ^{225}Ac-PSMA-617 in mCRPC patients with advanced diseases.

2. Aim

The aim of this retrospective analysis was to evaluate the safety, tolerability, therapeutic efficacy, and adverse events of alpha emitting ^{225}Ac-PSMA-617 radioligand therapy in mCRPC patients with advanced metastatic diseases, who revealed progression after ^{177}Lu-PSMA-I&T RLT and have failed to response to all prior lines of antitumour therapy. To assess this aim, patients' treatment response, adverse therapy events and clinical outcome of the disease were investigated.

3. Material and methods

3.1. Patients

The data of 26 mCRPC patients who underwent ^{225}Ac-PSMA-617 RLT as salvage therapy between 10/2017 to 11/2019, with progressive disease after beta emitting ^{177}Lu-PSMA-I&T RLT and failure to response to ADT (i.e. Abiraterone or Enzalutamide) and chemotherapy (Taxane-based), were retrospectively analyzed. Clinical and imaging data of each case had been discussed in the uro-oncology interdisciplinary tumor board and decision making for this ^{225}Ac-PSMA-617 RLT was made based on a consensus of the board members. Inclusion and exclusion criteria are summarized in Table 6. The median age of the cohort (n=26) lied at 72.5 years (range 48-85) and the number of patients with primary metastatic PCa was 10 (38%). Overall, the median PSA level at therapy initiation was 348 ng/mL (range 48 ng/mL to 4073 ng/mL). The median Gleason score was 8 (range 5-10) and all patients had received prior lines of systemic treatment (range 3-8). Further patient characteristics are seen in Table 8. This study was performed in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable standards and was authorized by the local institutional review board with the approval number of 115/18S. All patients signed informed consent form and were comprehensively informed about the treatment and its possible adverse events.

3.2. ^{225}Ac-PSMA-617 synthesis

Actinium-225 is obtained via radiochemical extraction from Thorium-229. Through ion exchange and novel extraction chromatography in nitric acid mediums with different molarities, Actinium-225 is yielded. This process of separation and purification is robust and quick, making it possible to be done on-site. The efficiency and high-overall yield process only allow few amounts of Actinium-225 to be lost in the procedure, and the result is an alpha-emitter with high purity and adequate for targeted alpha therapy. [93] At Klinikum rechts der Isar, ^{225}Ac-PSMA-617 was synthesized on the day of the treatment under good manufacturing practice (GMP). Prior to injection, sterile filtration and thin layer chromatography were performed to measure the radiochemical purity. ^{225}Ac-PSMA-617 was administered in

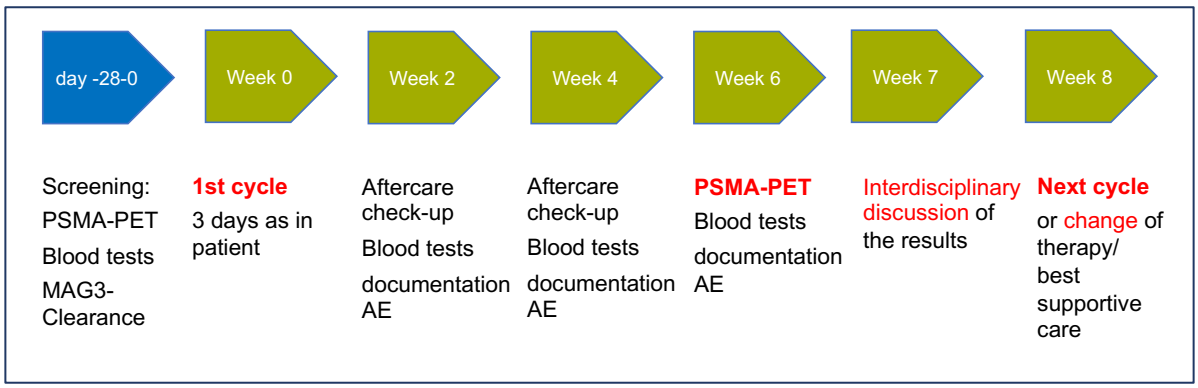
compliance with The German Medicinal Products Act, AMG §13 2b, and in accordance with the responsible regulatory body (Government of Upper Bavaria). [1]

3.3. ^{225}Ac-PSMA-617 administration

3.3.1. Patient preparation for pre and post treatment

The administration of ^{225}Ac-PSMA-617 RLT was done under a compassionate use for clinical indication. All 26 cases were treated as in-patients. Patients would present on the day of the treatment with recent laboratory findings (e.g., either brought in with the patients themselves or done at our in-hospital laboratory) and in good health (respectively) for treatment. A known, common side effect is xerostomia. To potentially decrease this adverse event, salivary glands were cooled by icepacks 30 minutes prior and up to 2 hours post injection of ^{225}Ac-PSMA-617. To reduce the risk of the side effects of xerostomia, patients were advised to rinse and thoroughly clean the oral mucosa, gums, and teeth with Glandomed® solution on the day of the treatment and continue to do so for about 10 days thereafter, every 5 to 8 hours. The manufacturer states that the regular use of this mouthwash can prevent plaque and infections of the oral cavity or mucosa. Artificial salivary solutions were suggested to patients to keep the mouth moist, and patients were encouraged to use food items that stimulate salivary production, such as chewing gums. One to two weeks post treatment, lymphatic drainage of the salivary glands was started as well. Figure 2 visualizes our studies treatment schedule and regime. [1]

Figure 2: **Treatment schedule for one cycle of Ac-225-PSMA-617 radioligand therapy**



3.4. ^{225}Ac-PSMA-617 RLT activity

^{225}Ac-PSMA-617 was administered to the patients through intravenous application through a cannula (gauge range 18-20). The median administered activity of ^{225}Ac-PSMA-617 was 8 MBq (range 4 – 13 MBq). Collectively, 59 cycles were applied at a median of 2 cycles per patient (range 1 – 6). Average time on therapy was 3.6 months (95%CI 2.2 – 4.8). Table 9 demonstrates an overview of the number of cycles with their respecting activities, as described before.

3.5. Treatment assessment

Patients received treatment in 8-week intervals. 6 weeks after treatment a restaging ^{68}Ga-PSMA-11 PET/CT scan was done, and each case was discussed by an interdisciplinary team. Decline of PSA was set as parameter to assess treatment response. To assess the biochemical response, we collected data on any PSA decline, PSA decline ≥30% and <50%, minimum PSA decline ≥50% from baseline, and maximum PSA decline. Moreover, morphological, and molecular effects as well as lesion expressions were analysed by PSMA-PET/CT and PSMA-PET/MRI scans. According to the consensus statements on PSMA PET/CT response assessment criteria in PCa [94], disease progression was defined as a 30% increase of tumor burden, in line with other studies and modified PET response criteria in solid tumors (PERCIST) [95-97]. Complete response (CR) was stated as the disappearance of any lesion with tracer uptake. Partial response (PR) was defined as the reduction of uptake and tumor PET volume by > 30%. Furthermore, the panel describe stable disease (SD) as change of uptake and tumor PET volume ± ≤ 30% without evidence of new lesions. Progressive disease (PD) was put down as appearance of > 2 new lesions or increase of uptake or tumor PET volume ≥ 30% [94]. RLT and ADT were continued in case of absence of radiographic or clinical progression and a lack of severe adverse events was observed.

3.6. Outcome assessment

For evaluation of the patient's outcome, progression free survivals (PFS), PSA-PFS, clinical PFS (cPFS), time to PSA decline ≥50% and overall survival (OS) were determined.

cPFS was defined as the point of time at which treatment was started until clinical progression (exacerbation of disease-related symptoms or new cancer-related complications), progression of disease in imaging (PSMA-ligand PET) or death, whichever ensued first.

3.7. Adverse events and assessment of health status and quality of life

Toxicity, hematological and non-hematological, was assesses based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and adverse events emerging from therapy were reported. Table 5 gives an overview of the CTCAE v.5.0 criterions. Any clinical symptoms were recorded approximately after three days as well as three- and six-weeks post radioligand therapy. Prior to treatment and 4-8 weeks after (at restaging after each individual cycle), patients were asked to fill out the EORTC-QLQ 30 questionnaire (Supplement 1) [98] The questionnaire is based on self-assessment and covers various areas affected by treatment, including mental health. Based on the patients' ratings, changes in life quality and possible clinical adverse events were quantified. This questionnaire has been used before in PCa patients and experience was given for the assessment. To put a picture on this questionnaire, questions included were as follows:

- Did you experience any pain in the past week?
- Did you feel any weakness in the past week?
- Did you feel nauseous in the past week?
- Does your present health status affect your personal/family life?

To quantify these questions, a four-point scale was used from "not at all" to "very much". Following these questions, patients were asked to evaluate their state of health and life quality during the past week on a seven-point scale, the lowest being "very poor" and the highest "excellent".

Table 5: **Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [99]**

Disorder	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia (Hemoglobin in g/dL)	14.0 – 10.0	10.0 – 8.0	< 8.0	life threatening	Death
Leucopenia (Leukocytes per uL)	4000.0 – 3000.0	3000.0 – 2000.0	2000.0 – 1000.0	<1000.0	-
Thrombocytopenia (Platelets per nL)	150.0 – 75.0	75.0 – 50.0	50.0 – 25.0	<25.0	-
Renal (increase in creatinine from baseline level in mg/dL)	>1.5x	>1.5 – 3.0x	>3.0x – 6.0x	>6.0x	-
Xerostomia	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms: oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva	-	-
Weight loss (body weight decrease in kg from baseline)	5 to <10%	10 to <20%	>20%	-	-
Fatigue	Relieved by rest	Not relieved by rest, limiting instrumental ADL	Not relieved by rest, limiting self care ADL	-	-
Loss of appetite	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition	significant weight loss or malnutrition	Life threatening	-

*__Grade 1__: Mild, asymptomatic. __Grade 2__: Moderate, intervention might be indicated.
__Grade 3__: Severe, not life threatening. __Grade 4__: Life threatening, urgent intervention. __Grade 5__: Death. __ADL__: activities of daily living

3.8. Statistical analyses

To assess commonness and frequency of collected data, descriptive statistics was used. Data included patient characteristics, laboratory blood test results and significant changes in data, if any. Kaplan Meier method was used to perform time to event analyses for cPFS, PSA-PFS and OS with a 95% confidence interval (95% CI). Comparison of the results from the EORTC-QLQ 30 questionnaire were performed with unpaired T-Tests with Welch's correction. Software used for analyses included MedCalc 19.0.3 (MedCalc Software, Belgium) and GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA).

4. Results

4.1. Patients

Overall, 26 mCRPC patients received treatment with the alpha emitter ^{225}Ac-PSMA-617. Prior to ^{225}Ac-PSMA-617 RLT patients had been exposed to an average of 6 preceding mCRPC treatment lines (range 3 – 8). Metastases of lymph nodes, bones and visceral organs were present in 24 (92%), 26 (100%) and 11 (42%) patients, respectively. Table 6 provides an overview of the inclusion and exclusion criteria for ^{225}Ac-PSMA-617 RLT.

The median age was at 72.5 years (n = 26, range 48 – 85) and median baseline PSA lied at 348 ng/ml (range 48 – 4073 ng/ml). Median Gleason score was at 8 (n =26, range 5 – 10) and median ECOG was found to be 1 (n =26, range 0 – 2). In 10 of 26 (38%) patients' metastatic cancers were diagnosed at primary staging. Patient serology revealed average lactate-dehydrogenase (LDH) and alkaline phosphatase (ALP) at 360 U/l (n = 26, range 198 – 5700) and 200 U/l (n = 25, range 48 – 1064), respectively. The median of hemoglobin level was at 10 g/dl (n = 26, range 7.8 – 12.6). Previous systemic treatments included Docetaxel (25/26, 96%), Docetaxel re-challenge (3/26, 8%), Cabazitaxel (14/26, 54%), Abiraterone (23/26, 88%), Enzalutamide (22/26, 85%), Radium-223 (6/26, 23%) and other systemic treatments for CRPC (5/26, 19%). Table 7 shows the patient characteristics mentioned.

A total number of 61 cycles of ^{225}Ac-617-PSMA-RLT were applied. Twenty-six patients received a median of two cycles (interquartile range (IQR) 1.3-3.0) with a median activity of 9 MBq (IQR 8-10). Median treatment exposure was recorded at 3.7 months (95% confidence interval (CI) 2.4-5.1). [1]

Table 6: ^{225}Ac-PSMA-617 **RLT inclusion and exclusion criteria**

Inclusion criteria
Castration resistant metastatic adenocarcinoma of the prostate
Previous novel androgen-receptor targeted therapy (abiraterone and/or enzalutamide)
Previous taxane based chemotherapy or ineligibility
Previous treatment with ^{177}Lu-PSMA-I&T
Life expectancy of more than six months
ECOG performance score status ≤2
High PSMA-expression of tumor lesions in PSMA-ligand PET within 4 weeks prior to treatment
Creatinine < 1.5 mg/dl
Hemoglobin > 8 g/dl
Leucocytes > 2.5 x 10^9/l
Thrombocytes (platelets) > 80 x 10^9/l
GOT/GPT < 2.5x upper limits of normal (ULN), bilirubin < 2x ULN, if liver metastases are present < 5x ULN
Exclusion criteria
Untreated renal obstruction
Active secondary malignancy
Acute or chronic glomerulonephritis

Table 7: **Patient characteristics**

No.	GS	PSA[1]	aP & LDH	Primary therapy	Prior mCRPC treatments	Metastases
1	8	713.9	1064/348	RT	E, A, D, Lu	B, LN
2	7b	919.7	209/345	RT	D, C, A, C, E, C, Ra, Lu	B
3	5	1122.0	68/266	RRP, RT	D, A, Ra, C, E, Lu	B, LN, Lungs
4	9	49.2	78/198	RRP, RT	D, E, A, Lu	B, LN
5	9	313.6	134/297	RRP	A, E, Lu, D, Cis/Eto	B, LN
6	7b	1293.0	153/211	RRP, RT	D, A, Lu, C, E, Cis/Eto	B, LN, Liver, Lungs
7	8	136.0	172/554	None	D, Ra, E, C, A, Lu	B, LN
8*	10	4073.0	1059/8700	None	D, C, E, Lu	B, LN, Liver, Lungs, Brain
9	9	527.2	300/387	None	D, Ra, A, Lu	B, LN
10	8	480.0	517/464	RT	CureVac Study, A+CureVac, D, C, Lu, E, A	B, LN, Lungs
11	7	78.6	145/823	RT	A, D, Lu, E	B, LN, Peritoneal
12	7	470.1	564/381	RT	A, E, Lu	B, LN
13	8	498.1	316/372	None	D, D, A, E, Ra, E, Lu, A	B, LN
14	7	261.1	48/304	None	A, E, D, A, D, C, Lu	B, LN
15	8	268.9	909/213	RT	A, E, D, C, Lu, Cis/Eto	B, LN
16	8	48.4	198/691	None	E, D, A, E, Lu	B, LN, Liver, Lungs
17	10	2962.0	240/1226	None	A, E, D, C, Lu	B, LN, Liver, Brain
18	8	347.6	1009/925	None	CureVac Study, A, Ra, Lu, E, D, O, C	B, LN
19	7b	209.8	200/699	None	D, A, R, Lu, Atezolizumab + E, Lu, C	B, LN
20	9	57.7	183/408	None	E, D, A, Provenge, Lu, Ra	B, LN
21	8	141.0	-/311	None	A, E, D, Lu	B
22	9	587.0	634/1181	None	D, A, E, C, Lu, Cis/Eto	B, LN, Liver
23	7a	270.0	224/295	None	D, C, A, D, E, A, C, Lu	B, LN, Lungs
24	10	142.0	69/330	None	D/C, A, D/C, Carbo, Lu	B, LN, Peritoneal
25	8	114.0	143/290	RRP	A, Lu, D	B, LN
26	9	1698.0	83/285	None	I, E, A, Lu, D, C	B, LN, Peritoneal

Abbreviations: aP = Alkaline phophatase, LDH = Lactate-dehydrogenase.
E = Enzalutamide, A = Abiraterone, D = Docetaxel, Lu = ^{177}Lu-PSMA-I&T, RT = Radiotherapy, RRP = radical retropubic prostatectomy, C = Cabazitaxel, Ra = ^{223}Radium, Cis/Eto = Cisplatin/Etoposide, Carbo = Carboplatin; I = Immune therapy, O = Olaparib, CureVac = CureVac Study.
B = Bones, LN = Lymph nodes, Visceral = Liver, lungs, other. PSA[1] = baseline PSA.
*This patient received one additional cycle Ac-225-treatment at another institution.

Table 8: **Summary of baseline patient characteristics [1]**

Number of patients	**26**
Median age in years (interquartile range IQR)	72.5 (63-75.75)
Number of primary metastatic prostate cancers	10
Median PSA in ng/mL (IQR)	331 (142-682)
Median LDH in U/l (IQR)	360 (296-657)
Median aP in U/l (IQR), n = 25	200 (143-517)
Median Hb in g/dL (IQR)	10 (8.7-10.9)
Median ECOG score (IQR)	1 (0-1)
Median Gleason score (IQR)	8 (7-9)
Number of prior systemic treatments (%):	
Docetaxel	25 (96)
Docetaxel re-challenge	3 (12)
Cabazitaxel	14 (54)
Abiraterone	23 (88)
Enzalutamide	22 (85)
Radium-223	6 (23)
Other systemic treatments for CRPC	5 (19)
Lutetium-177-PSMA	26 (100)
Number of prior lines of systemic treatment:	
Three	2
Four	6
FIve	5
Six	6
Seven	2
Eight	5
Number of sites of metastases (%):	
Lymph node, overall	24 (88)
Lymph node, only	0 (0)
Bone, overall	26 (100)
Bone, only	2 (8)
Visceral, overall	11 (42)
Liver	5 (19)
Lung	6 (23)
Other	5 (19)
Visceral, only	0 (0)

Table 9: **^{225}Ac-PSMA-617 cycle and activity count**

Patient No.	No. of cycles	Activity [MBq] per cycle
1	3	8 – 10 – 6
2	3	8 – 10 – 6
3	3	8 – 10 – 12
4	3	8 – 12 – 12
5	2	8 – 10
6	1	8
7	1	10
8	1	10
9	2	8 – 6
10	2	8 – 8
11	1	10
12	1	10
13	2	13 – 13
14	3	8 – 7 – 9
15	6	13 – 12 – 8 – 6 – 12 – 8
16	2	11 – 4
17	1	6
18	1	10
19	4	10 – 6 – 6 – 9
20	5	8 – 6 – 8 – 6 – 10
21	2	8 – 6
22	2	8 – 5
23	3	12 – 10 – 8
24	2	9 – 12
25	2	10 – 13
26	1	13

4.2. Toxicity

The most reoccurring acute toxicity in all patients was nausea on treatment day or during the night after treatment, which was self-limiting. However, patients did receive antiemetics (such as 5-HT_3 receptor antagonists like Granisetron or Ondansentron) over the course of their inpatient management. Throughout the three days in which the patients were admitted in the hospital, the therapy was tolerated well. No other acute toxicities (for example haematological) were observed in this period. A rundown of all observed adverse events can be seen in Table 9. *Figure* 3 visualizes the course of laboratory findings after beginning of treatment and follow-up

4.3. Adverse events

Prior to radioligand therapy most patients showed aberrant blood levels, due to different reasons such as prior treatments or physiological factors like advanced biological age. Table 10 summarizes the baseline parameters.

Xerostomia grade 1-2 was observed in all patients after ^{225}Ac-PSMA-RLT. Xerostomia began after the first cycle and gradually aggravated with further cycles. Overall, any hematological adverse events were noticed in 100% (26/26) of patients. Grade 3 hematologic adverse events included anemia in 31% (8/26) of patients, leucopenia in 27% (7/26) and thrombocytopenia in 12% (3/26). Grade 4 anemia was observed in 4% (1/26), leucopenia in 0% (0/26) and thrombocytopenia in 8% (2/26) patients. In 42% (11/26) of patients, blood transfusions were required over the course of therapy. One patient received continuous G-CSF injections for preexisting long-term granulocytopenia. Changes during ^{225}Ac-PSMA-617 RLT are presented in Figures 3-6. In 23% (6/26) of patients, therapy was terminated over the course of treatment because of xerostomia. Treatment was also discontinued in 8% (2/26) to avoid deterioration of pre manifested leucopenia (n=1) and thrombocytopenia (n=1). To summarize the adverse events of ^{225}Ac-PSMA-617 RLT, Table 11 has been prepared to provide an overview of the adverse events mentioned and their respective numbers.

Table 10: **Hematological and non-hematological aberrations prior to ^{225}Ac-PSMA-617 RLT**

ADVERSE EVENTS	GRADE 1 NO. (%)	GRADE 2 NO. (%)	GRADE 3 NO. (%)	GRADE 4 NO. (%)
HEMATOLOGIC				
ANEMIA *95% CI* INTERVAL*	11 (42) *25-61*	12 (46) *29-65*	1 (4) *0-20*	0 (0) *0-15*
LEUCOPENIA *95% CI INTERVAL*	3 (12) *3-29*	2 (8) *1-25*	1 (4) *0-20*	0 (0) *0-15*
THROMBOPENIA *95% CI INTERVAL*	6 (23) *11-42*	1 (4) *0-20*	*0 (0)* *0-15*	0 (0) *0-15*
NON-HEMATOLOGIC				
XEROSTOMIA *95% CI INTERVAL*	-	-)	-	-
RENAL DISORDER *95% CI INTERVAL*	5 (19)	2 (8)	0 (0)	0 (0)
FATIGUE *95% CI INTERVAL*	-	-	-	-
LOSS OF APPETITE *95% CI INTERVAL*	-	-	-	-
WEIGHT LOSS *95% CI INTERVAL*	-	-	-	-

**CI = confidence interval*

Table 11: **Hematologic and non-hematologic adverse events after ^{225}Ac-PSMA-617 according to CTCAE v5.0 [1]**

ADVERSE EVENTS	GRADE 1 NO. (%)	GRADE 2 NO. (%)	GRADE 3 NO. (%)	GRADE 4 NO. (%)
HEMATOLOGIC				
ANEMIA	2 (8)	4 (15)	8 (31)	1 (4)
95% CI INTERVAL	*1-25*	*6-34*	*16-50*	*0-20*
LEUCOPENIA	3 (12)	3 (12)	7 (27)	0 (0)
95% CI INTERVAL	3-29	3-29	13-46	0-15
THROMBOPENIA	7 (27)	2 (8)	3 (12)	2 (8)
95% CI INTERVAL	13-46	1-25	3-29	1-25
NON-HEMATLOGIC				
XEROSTOMIA	23 (88)	3 (12)	-	-
95% CI INTERVAL	70-96	3-29		
RENAL DISORDER	5 (19)	-	-	-
95% CI INTERVAL	8-38			
FATIGUE	12 (46)	-	-	-
95% CI INTERVAL	29-65			
LOSS OF APPETITE	8 (31)	-	-	-
95% CI INTERVAL	16-50			
WEIGHT LOSS	3 (12)	-	-	-
95% CI INTERVAL	3-29			

**CI = confidence interval*

Hematological side effects included anemia, leucopenia, and thrombocytopenia. All patients experienced these adverse events to a different degree. Figures 3-6 outline and describe the details of hematological adverse events. These figures present the laboratory results over the time of treatment. The cohort showed no drastic tendency towards any clinically significant changes in blood values.

Non-hematological side effects included renal toxicity, fatigue, loss of appetite and weight loss. One patient showed grade 1 renal insufficiency and in two patients the serum creatinine levels were elevated during ^{225}Ac-PSMA-617 RLT, categorizing them as grade 2 renal side effects. Grade 3 or 4 non-hematological toxicities were not observed. Twelve patients (12/26) complained about fatigue, 8 of 26 reported loss of appetite and another 3 of 26 noticed

unintended weight loss over the course of time. Xerostomia, independent of its severity, was observed in all 26 patients. In 23/26 patients, grade 1 xerostomia was reported. Three patients revealed worse xerostomia categorizing them as grade 2. No grade 3 or 4 xerostomia was observed.

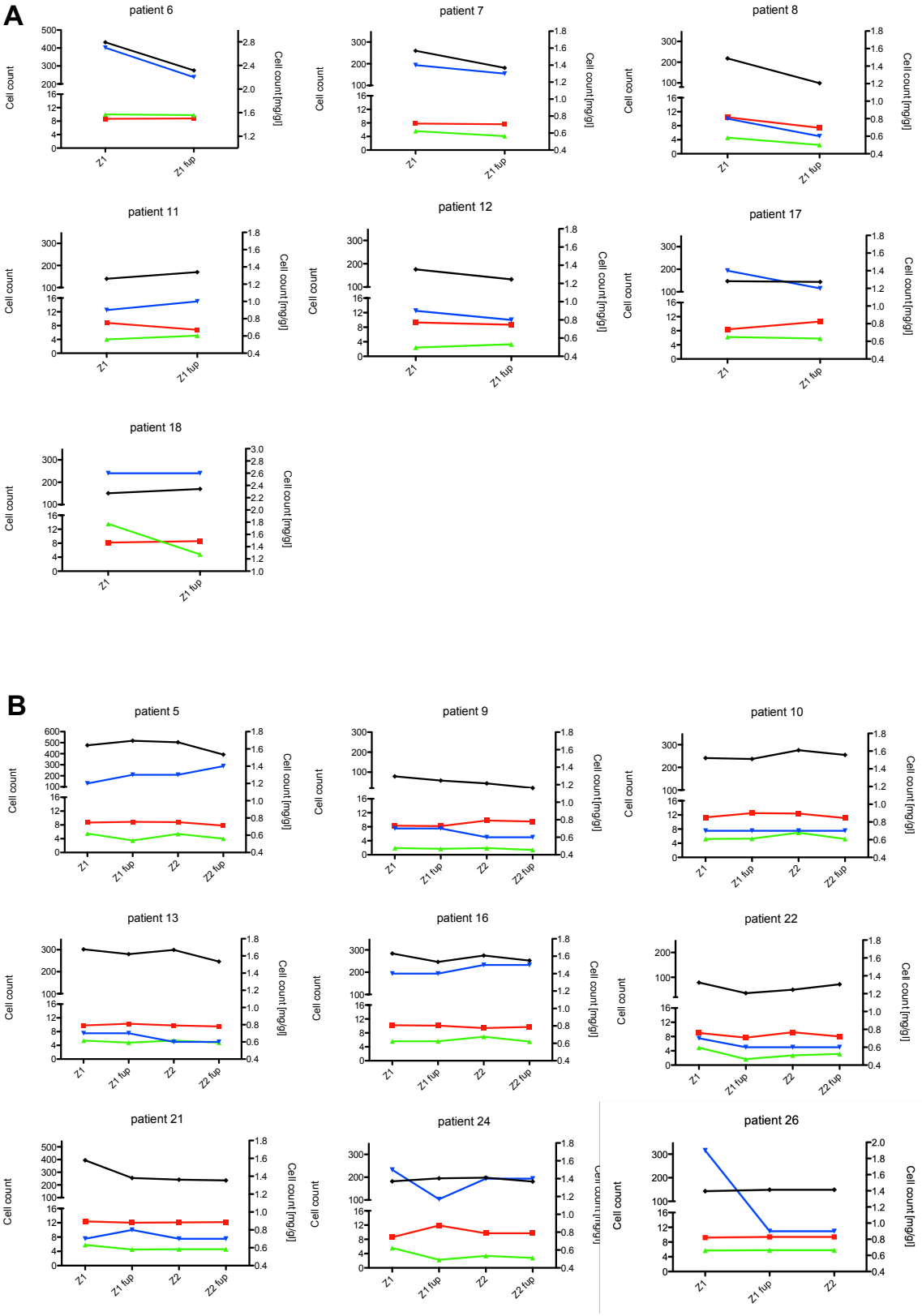
Figure 3 below visualizes the laboratory findings after initiation of ^{225}Ac-PSMA-617 RLT and their respective follow-up. In correspondence with our publication cluster A represents the first cycle, B second cycle, C third cycle and D to F respectively fourth till sixth cycle. Lines colored red are to indicate hemoglobin, green leucocytes, black thrombocytes, and blue lines represent creatinine values. As cycles progressed, the number of patients reduced. Some were unable to continue treatment because of toxicities, others had progression stops and another number of patients discontinued therapy due to adverse events. Because of this, as cycles progressed, the initial number of patients (n = 26) lessened. As mentioned before, cases of grade 3 and 4 anemia occurred over the course of the 46 weeks and 42% (11/26) patients received blood transfusions over the course of therapy. The average blood count stayed around 10 g/dL with a range between 8 and 12 g/dL hemoglobin (Hb).

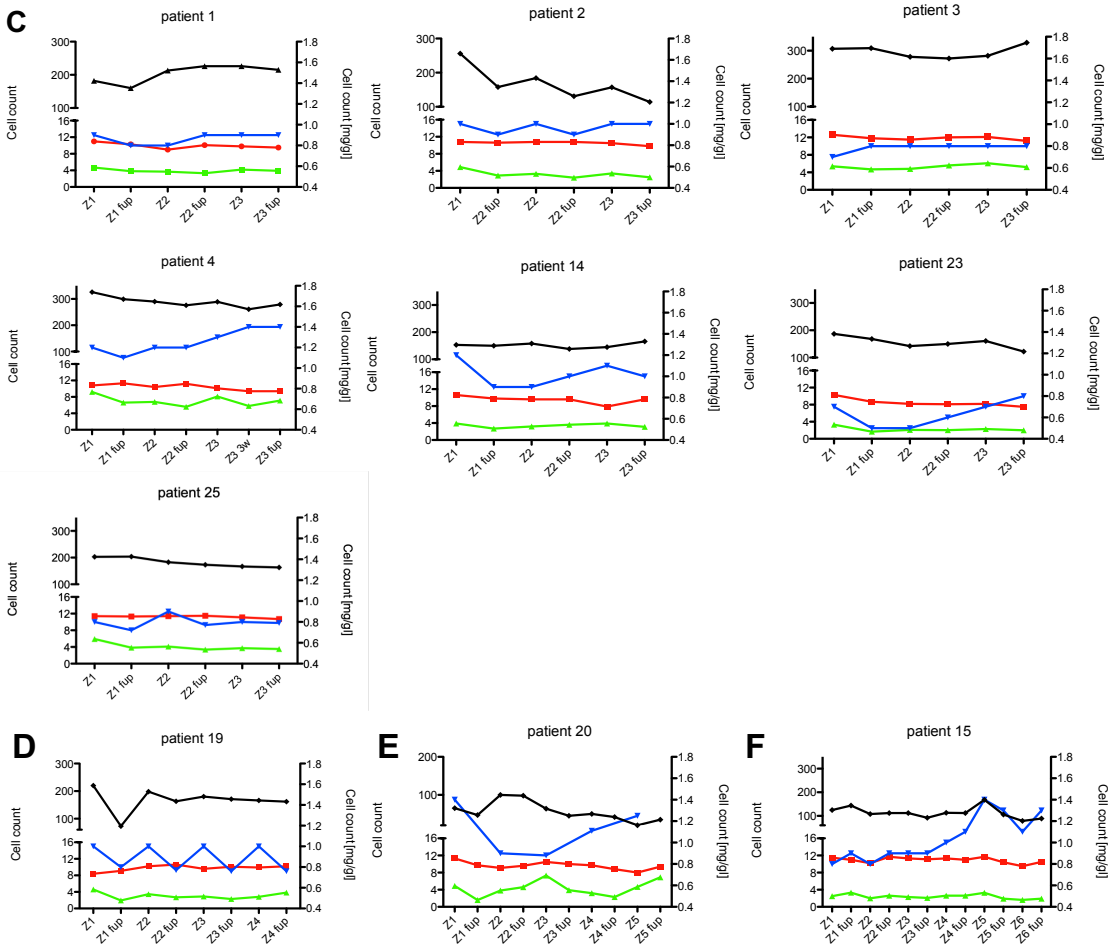
It is also noted that there was a trend towards leucopenia due to the nature (toxicity) of the treatment. Grade 1-3 leucopenia was recorded, 5 patients had a tendency towards grade 4 leucopenia. Follow-ups showed no significant change in leucocyte reductions.

During the time of the treatment and post-treatment patients experienced thrombopenia grade 1 to 4. One might be able to name an alternating trend in increase and decrease of platelet count as the mean numbers spike every other week, up- or downwards. However, these results cannot be seen as significant, as the standard deviations are too high to be representative. Grade 3 and 4 thrombocytopenia occurred in three patients. Two patients had to be cut off from therapy as platelet numbers were too low and received further treatment in this regard.

Furthermore only 5 patients were recorded to have grade 1 to 2 renal dysfunction (creatinine level increase over 1.1 mg/dL measured in blood serum). Renal function was measured by creatinine clearance and glomerular filtration rate. The rest of the cohort did not show any significant change in quantified renal function over the period of the therapy.

Figure 3 **Course of laboratory findings after beginning of treatment and follow-up (fup).[1]**



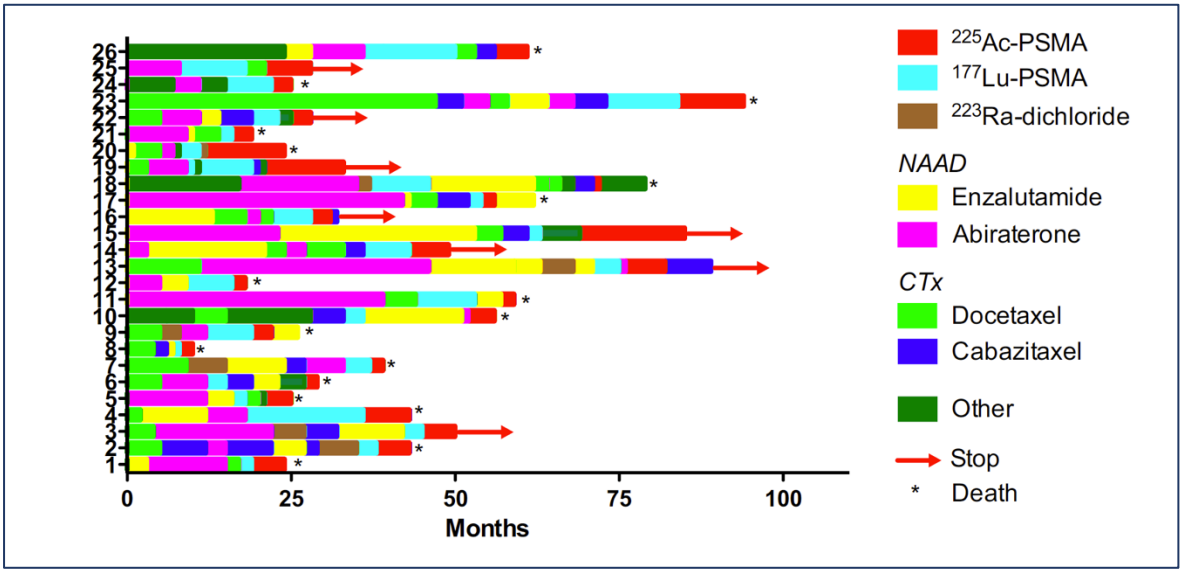


4.4. Treatment response

Biochemical monitoring of the treatment response was performed by collecting post ^{225}Ac-PSMA-617 RLT PSA values. The *lowest* serum PSA level was deemed as the minimum or least elevated PSA value compared to the baseline value. Mean PSA baseline was measured at 746.2 ng/mL, ranging from 49 ng/mL to 4073 ng/mL.

Visualized representations of the treatment response were achieved through waterfall and swimmer plots as well as Kaplan-Meier curves, as follow.

Figure 4 **Swimmer plot of mCRPC treatments [1]**



*****Every bar symbolizes the duration of time in which a patient underwent a specific therapy.

CTx = chemotherapy; mCRPC = metastatic castration-resistant prostate cancer; NAAD = novel androgen axis drug; PSMA = prostate-specific membrane antigen.

The above seen swimmer plot summarizes the course of the mCRCP treatments of each patient. Time on each treatment was calculated as the time between treatment initiation and inception of a subsequent treatment. [1]

Figure 5 **PSA waterfall plot of maximum PSA decline after ^{225}Ac-PSMA-617 RLT [1]**

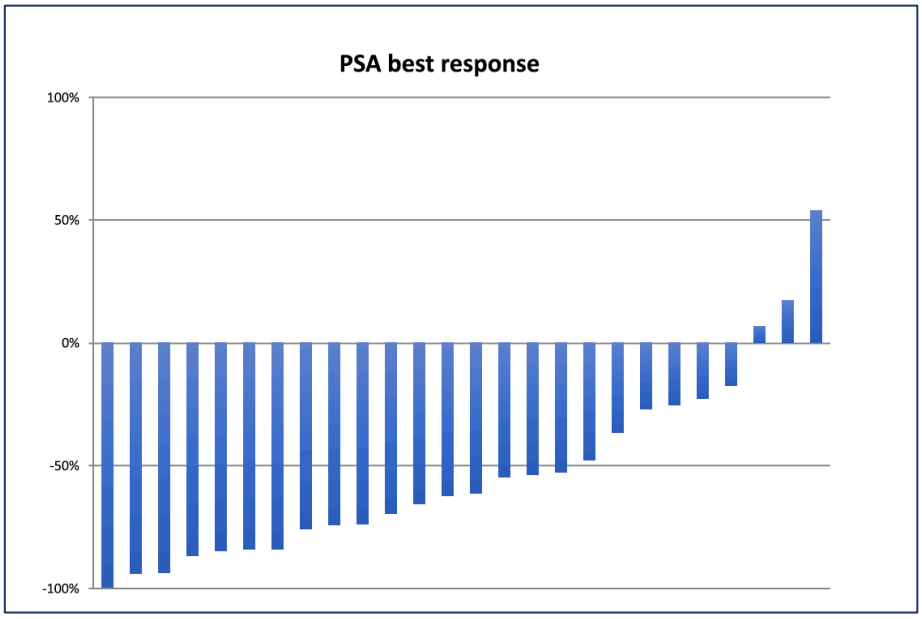
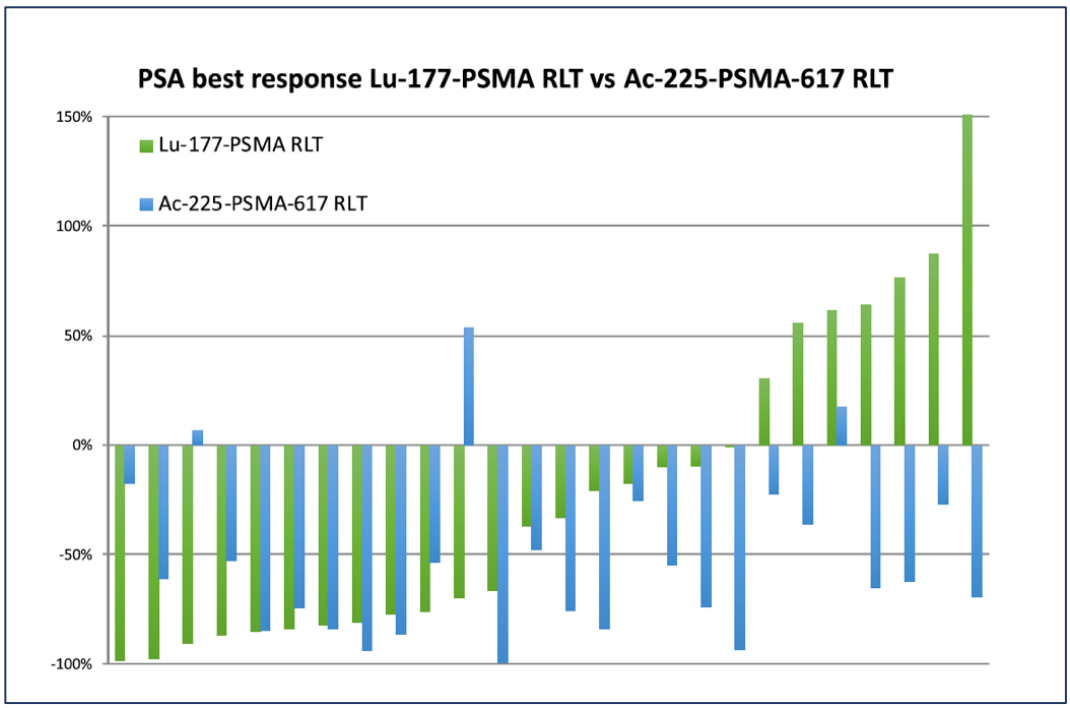


Figure 6 **PSA waterfall plot comparing maximum PSA decline after ^{177}Lu-PSMA and ^{225}Ac-PSMA RLT[1]**

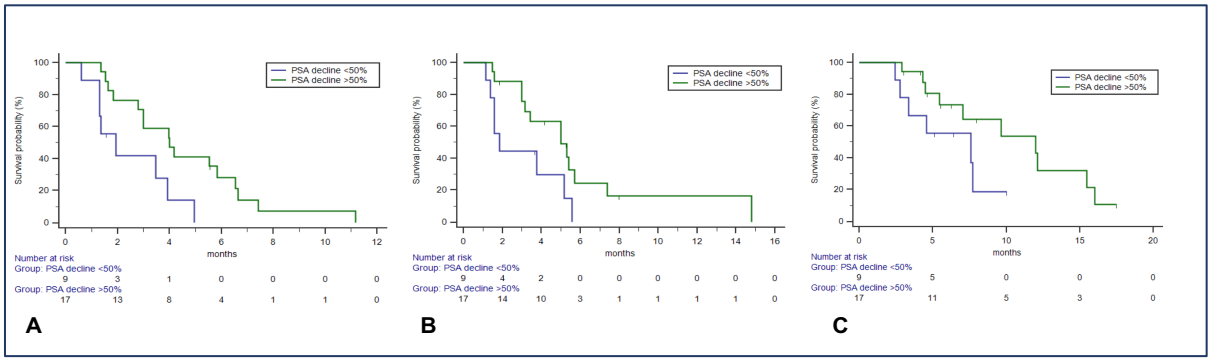


Any PSA decline was observed in 23/26 (95% CI 70–97) patients and a PSA decline of _30%, 50%, and 90% was achieved in 19 (73%) (95% CI 54–87), 17 (65%) (95% CI 46–81), and 3 (12%) (95% CI 3–29) patients, respectively. Out of all 26 patients with progression after ^{177}Lu-PSMA six (23%) demonstrated PSA decline after ^{225}Ac-PSMA-617 RLT. Two (8%) of 26 patients did show a PSA response after initial ^{177}Lu-PSMA RLT however remained unresponsive to further therapy with ^{225}Ac-PSMA-617. Unfortunately, one patient of the whole cohort (95% CI 0–20) did not show any response to any of the aforementioned radioligand therapies. [1]

4.5. Clinical outcome

A maximum PSA decline ≥50% (i.e. responders) showed longer PSA-PFS with a of median 4 months [95%CI 1.8-11.2] vs. a median of 1.9 months [95%CI 0.6-4.9]; p=0.02; HR 2.6) in patients with < 50% decline. In addition, a trend towards a longer cPFS (5 months [95%CI 3-14.8] and OS [12 months (95%CI 5.4–15.5)] was found in responders comparing to non-responder (PSA >50%) group [1.8 months (95%CI 1.1-5.6)]; p=0.054; HR 2.3) and [7.6 months (95%CI 2.4–7.7)]; p=0.09; HR 2.9, respectively). The corresponding Kaplan Meier curves are shown in Figure 7. No relevant differences of outcome parameters were observed for patients who received an initial ^{225}Ac-PSMA-617 activity (activity at first cycle) of <10 vs. ≥10 MBq.

Figure 7 **Maximum PSA decline with PSA-PFS (A), cPFS (B), and OS (C) after ^{225}Ac-PSMA-617 RLT**



A maximum PSA decline ≥50% showed a tendency towards better PSA PFS, cPFS and OS. Median PSA-PFS (A) was 4 months (95% CI 1.8-11.2) vs. 1.9 months (95% CI 0.6– 4.9, HR 2.6, p = 0.02). Median cPFS (B) was 5 months (95% CI 3-14.8) vs. 1.8 months (95% CI 1.1 – 5.6, HR 2.3, p = 0.054). Median OS (C) was 12 months (95% CI 5.4 – 15.5) vs. 7.6 months (95% CI 2.4–7.7, HR 2.9, p = 0.09). [1]

Figure 8 **PSA-PFS (A), cPFS (B), and OS (C) after intiation of ^{225}Ac-PSMA-617 RLT**

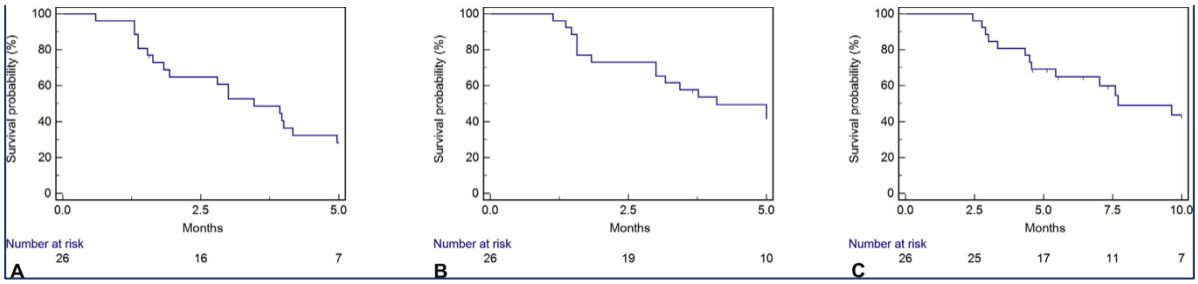
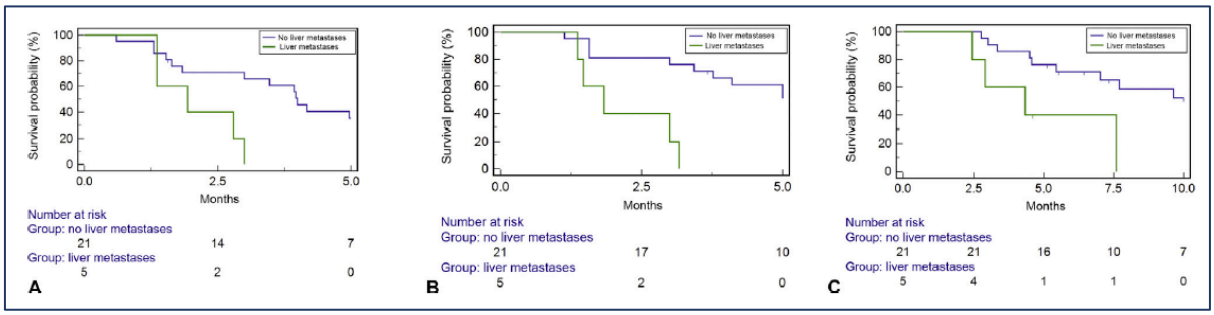


Figure 8 demonstrates the Kaplan-Meier curves after initiation of targeted alpha therapy (TAT). After a median follow-up of 7.6 months (range 2.4-16), 18/26 (95%CI 49-84%) patients were deceased. Median PSA-PFS was 3.5 months [95%CI 1.8-11.2], median cPFS was 4.1 months [95%CI 3.0-14.8] (Figure 9b) and median OS was 7.7 months [95%CI 4.5-12.1]. [1] Visceral metastases, in this case liver metastases, prior to initiation of treatment were seen in 11 of 26 (42%) of patients. These were recognized as a risk factor significantly associated with shorter PSA-PFS (1.9 vs 4.0 mo; p = 0.02, hazard ratio [HR] 3.01, 95% CI 0.7– _13.1), shorter cPFS (1.8 vs 5.2 mo; p = 0.001, HR 4.38, 95% CI 0.8–24.7), and shorter OS (4.3 vs 10.4 mo; p = 0.01, HR 9.35, 95% CI 1.5–56.9). The corresponding Kaplan Meier curves are shown in Figure 9.

Figure 9 **PSA-PFS, cPFS, and overall survival after initiation of Ac-225-PSMA-617 RLT in patients without (blue line) versus with (green line) liver metastases at the initiation of treatment**



Kaplan-Meier curve A visualizes longer median PSA-PFS (progression free survival) (4.0 vs 1.9 mo; p = 0.02; hazard ration (HR) 3.01, 95% CI 0.7–13.1). Figure 8B shows a longer median cPFS (clinical progression-free survival) (5.2 vs 1.8 mo; p = 0.001; HR 4.38, 95% CI 0.8–24.7), and (C) longer median overall survival (OS) (10.4 vs 4.3 mo; p = 0.01; HR 9.35, 95% CI 1.5–56.9).

The subgroup without liver metastases showed a significantly better outcome on PSA PFS, cPFS and OS. [1]

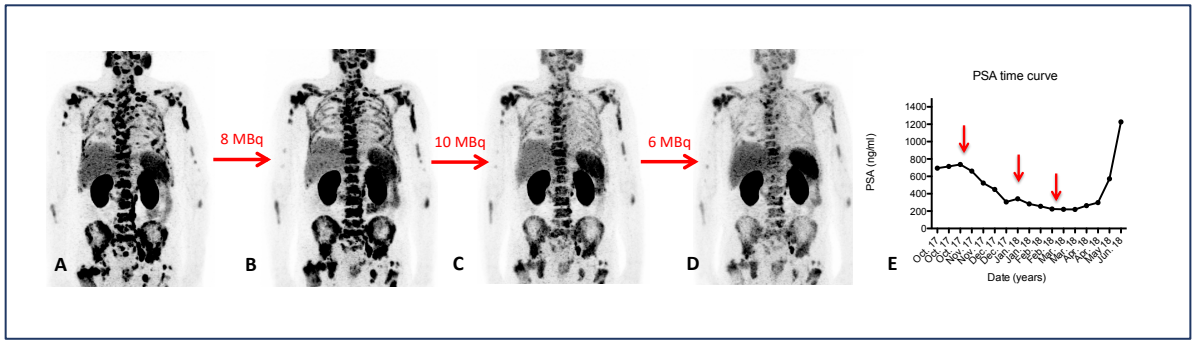
4.6. Imaging response

Out of 26 patients, 21 (81%) were also evaluated for morphological and/or molecular response to treatment using ^{68}Ga-PSMA PET/CT or ^{68}Ga-PSMA PET/MRI. For the remaining patients of the cohort, no data was available. In ^{68}Ga-PSMA PET/CT, 43% (9/21) of patients presented disease progression, 19% (4/21) showed mixed response and 10% (2/21) partial response. Stable disease was demonstrated in 14% (3/21) of patients and 10% (2/21) exemplified treatment response. Unfortunately, no patient was in complete remission [1]. Table 12 summarizes the above-mentioned response to treatment as seen in imaging procedures.

Table 12 **Overview of therapy response in imaging**

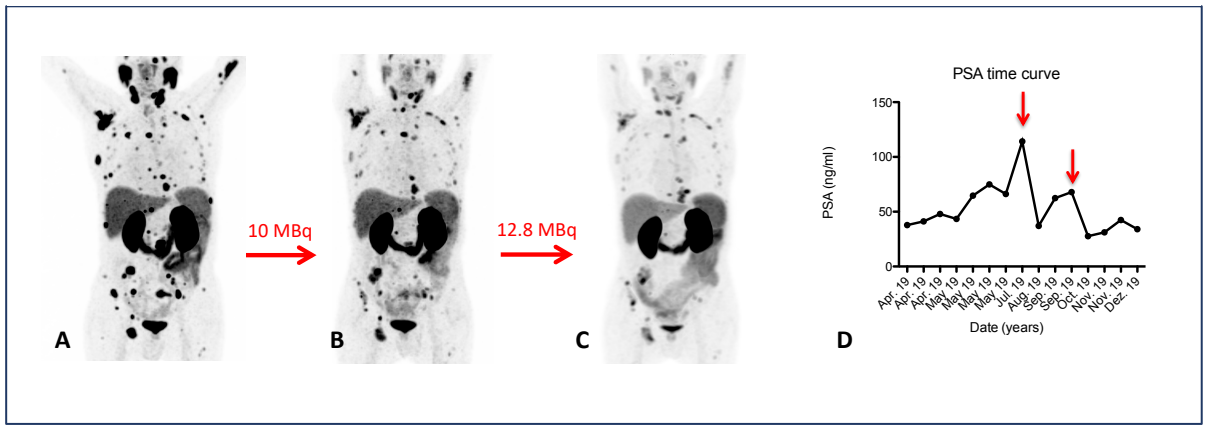
Pat. ID	PET response after 1st cycle	PET response after 2nd cycle	PET response after 3rd cycle	PET response after 4th cycle	PET response after 5th cycle
1	TR	TR	TR		
2	TR	TR	PD		
3	MR	SD	PD		
4	MR	MR	PD		
5	MR	MR			
6	MR				
7	MR				
8	MR				
9	SD	SD			
10	SD	TR			
11	PD				
12	PD				
13	SD	SD			
14	MR	MR	PD		
15	PD	SD	PR	SD	
16	MR	PD			
17	PD				
18	PR				
19	PR				
20	NA*	NA	NA	NA	NA
21	TR-SD	PD			

Figure 10 **71-year-old mCRPC patient after 4 prior mCRPC lines**



Favorable PSA-response was found after 3 cycles of ^{225}Ac-PSMA-617 with stable findings on PSMA-PET imaging and treatment was halted. The patient died approximately 5 months after the last treatment cycle. Baseline PSMA-PET exhibited high PSMA-ligand uptake in multiple tumor lesions (PSA 714 ng/ml, A) followed by decreasing activity after the first (PSA 449 ng/ml, B), second (PSA 255 ng/ml, C) and third cycle (PSA 219 ng/ml, D). Steep increase of the tumor marker PSA was observed after halt of treatment (red arrows indicate time of ^{225}Ac-PSMA-617 application).

Figure 11 **76-year-old mCRPC patient after 3 prior mCRPC lines**



Baseline ^{68}Ga-PSMA PET/CT MIP (maximum intensity projection) exhibited high ^{68}Ga-PSMA uptake in multiple bone and lymph node metastases (PSA 66 ng/ml, A) followed by decreasing activity after the first (PSA 37 ng/ml, B) and second cycle (PSA 26 ng/ml, C). Of note, the tumor marker PSA showed substantial drop with increase after a short period of time (red arrows indicate time of ^{225}Ac-PSMA-617 application).

The latest data on the use of ^{225}Ac-PSMA-617 RLT in various patient cohorts are shown in Table 13. The efficacy of the treatment on PSA levels, complete remission (CR) in PSMA-PET/CT and median overall survival (OS) have been summarized.

Table 13: **Use of ^{225}Ac-PSMA-617 RLT in various patient cohorts**

Cohort	Pretoria I	Pretoria II	Heidelberg	TUM
Characteristics	Chemo-naïve mHSPC/mCRPC	Early mCRPC	Intermediate mCRPC (7/40 post ^{177}Lu-PSMA-617)	Late mCRPC (all after ^{177}Lu-PSMA-I&T)
N	17	73	40	26
Prior mCRPC lines	No CTx, no second ADT, thrice ^{177}Lu-PSMA-617	1-2	Median 3 (range 1-7)	Median 6 (range 3-8)
Any PSA decline	94% (16/17)	83% (60/73)	93% (37/40)	88% (23/26)
max. ≥50% PSA decline	88% (15/17)	70% (51/73)	75% (30/40)	65% (17/26)
max. ≥90% PSA decline	82% (14/17)	58% * (42/73)	40% * (16/40)	12% (3/26)
CR in PSMA-PET/CT	65% (11/17)	29% (21/73)	NA	0%
Median cPFS	NA	15.2 months (est)	7 months	5.0 months
Median OS	NA	18 months (est)	>12 months	7.7 months
Source	[90]	[100]	[101]	[1]

*Data from water fall plot, NA: not available, ADT: androgen deprivation therapy, CTx: chemotherapy, est: estimated

4.7. Assessment of health status and quality of life

After the first and second cycle of radioligand therapy with ^{225}Ac-PSMA-617, no significant changes in global health status or quality of life could be noted. Even though after the first cycle some evidence was found to underline higher scores in social functioning, scores in pain were lower. Even scores of appetite loss were lower following the first and second cycle. Differences between groups do not meet conventional levels of statistical difference. Following the second cycle, significant differences in higher scores for nausea and vomiting (4.2 ± 2.9 vs. 13.9 ± 8.4, p = 0.002) were observed. All other functional and symptom scales indicated no substantial changes as demonstrated in Table 14.

As mentioned before in the materials and methods section, patients were asked to fill out a questionnaire regarding their quality of life. However, we are not able to proof the reliability of some questioners, which may cause a bias in the results. A summary of the questions and each respective answers can be seen in Table 14.

Table 14: **Assessment of Health status and Quality of Life (EORTC-QLQ 30) before and 4-8 weeks after 1 and 2 cycles of ^{225}Ac-PSMA-617 treatment.**

	Baseline cycle 1 [+]	4-8 weeks after treatment cycle 1 [+]	p-value	Baseline cycle 2 [++]	4-8 weeks after treatment cycle 2 [++]	p-value
Global health status / QoL	56.3±5.1	52.8±4.3	0.61	66.7±4.6	55.6±6.5	0.26
Functional scales						
Physical functioning	63.9± 5.0	58.3±5.7	0.47	71.1±6.6	68.3±5.3	0.48
Role functioning	45.8±7.9	45.8±7.7	1.0	58.3±8.6	54.2±11.5	0.35
Emotional functioning	70.8±7.6	68.1±6.2	0.78	75.0±6.4	75.7±6.8	0.83
Cognitive functioning [§]	80.3±4.4	87.8±5.5	0.29	86.1±4.5	86.1±5.6	0.58
Social functioning	59.7±8.3	76.4±7.5	0.15	70.8±6.5	69.4±6.4	0.96
Symptom scales/items						
Constipation	45.4±5.4	53.7±6.5	0.33	39.8±6.8	45.4±6.9	0.94
Nausea and vomiting	8.3±3.8	15.3±6.3	0.35	4.2±2.9*	13.9±8.4*	0.002*
Pain [§]	45.5±10. 3	18.2±9.3	0.06	16.7±7.7	19.4±5.7	0.35
Dyspnea	36.1±9.6	33.3±10.1	0.84	33.3±8.2	33.3±7.1	0.64
Insomnia	25.0±10. 9	22.2±7.5	0.83	22.2±9.5	25.0±7.3	0.39
Appetite loss	25.0±10. 2	44.4±9.5	0.17	16.7±5.0	33.3±8.2	0.12
Constipation [§]	18.2±8.2	6.1±4.1	0.20	21.2±11.3[§]	11.1±6.3	0.09
Diarrhea [§]	15.2±8.2	21.2±10.3	0.65	6.1±4.1 [§]	5.6±3.7	0.9
Financial difficulties	8.3±4.3	5.6±5.6	0.69	5.6±3.8	2.8±2.8	0.3

Answers of patients before (and 4-8 weeks after 1 and 2 cycles of ^{225}AcAc-PSMA-617 RLT using the EORTC-30 questionnaire. Data are presented as mean ± SEM. [+] n = 12, [++] n = 12, * $p < 0.05$

For global health status / QoL a high score indicates a high quality of life / health status. For functional scales a high score represents a healthy / high level of functioning. For symptom scales/items a high scale score indicates a high level of problems or symptoms. [§] data for n=11 patients (single items missing).

Table 15: **Life quality questionnaire**

Question	Treatment	6 weeks post treatment
Did you experience any pain?	16% (1/4) 0% (2/4) 50% (3/4) 33% (4/4)	20% (1/4) 20% (2/4) 40% (3/4) 20% (4/4)
Did you feel any weakness?	0% (1/4) 50% (2/4) 50% (3/4) 0% (4/4)	0% (1/4) 0% (2/4) 80% (3/4) 20% (4/4)
Did you feel nauseous?	50% (1/4) 50% (2/4) 0% (3/4) 0% (4/4)	80% (1/4) 0% (2/4) 20% (3/4) 0% (4/4)
Did your current health status affect your personal/family life?	16% (1/4) 16% (2/4) 50% (3/4) 16% (4/4)	20% (1/4) 80% (2/4) 0% (3/4) 0% (4/4)
How would you rate your health status?	33% (3/7) 66% (4/7)	33% (3/7) 50% (4/7) 17% (5/7)
How would you rate your quality of life?	33% (3/7) 50% (4/7) 17% (5/7)	33% (3/7) 50% (4/7) 17% (5/7)

*All questions regard the patients' experience during the last week prior to answering the questionnaire.

4.8. Treatment withdrawal

Overall, 21 patients were not able to complete all treatment courses. This was related to hematological, non-hematological toxicities. However, intolerable xerostomia was one of the main reasons for incomplete therapy. In two patients (2/26, 8%), treatment had to be terminated because of thrombocytopenia grade 4. Clinical and/or radiographic disease progression was seen in ten patients. At the time of the analysis, 16 patients (16/26, 62%) had deceased. Nine patients (9/26, 35%) withdrew the treatment or were under surveillance and one patient was still in active therapy. Table 15 demonstrates the above-mentioned reasons for withdrawal of ^{225}Ac-PSMA-617 RLT.

Table 16: **Overview justification for treatment stop**

Reasons to halt treatment	Number of patients (n)
Xerostomia	6/21 (29%)
Progressive disease (clinical or imaging)	1/21 (5%), 9/21 (43%)
Patient's request	3/21 (14%)
To prevent further adverse events (other than xerostomia)	2/21 (10%)

5. Discussion

In this thesis, we have retrospectively analyzed the safety, tolerability, and therapeutic efficacy of radioligand therapy with ^{225}Ac-PSMA-617, as a novel treatment approach, in metastatic castration-resistant prostate cancer patients with disease progression after failure of ^{177}Lu-PSMA-I&T RLT (and other preceding treatment lines). Previous experiences with radioligand therapy have been made in other oncological entities, such as leukemia [102, 103], melanoma [104-106], bladder cancer [107], glioma [108, 109], neuroendocrine tumors [87, 110] and prostate cancer [84, 86, 90, 101].

Early investigations on targeted alpha therapy (TAT) with ^{225}Ac-PSMA-617 revealed some limitations, yet effective potential to cause anti-tumor effects, despite mCRPC patients having been pretreated with a median of six lines of prior treatment approaches, including hormone- and chemotherapy.

In this study, 65% of our patients showed a maximum PSA-decline ≥50%. The most prominent side effect of this therapy was xerostomia, which in many cases was irreversible. Hematological and non-hematological toxicities were observed to be moderate however more frequent than previous experiences. [1, 90, 100, 101]

Our treatment plan consisted of administering an average dose of 8 MBq ^{225}Ac-PSMA-617 per cycle. The applied activity for the subsequent cycles was eventually modified based on clinical re-assessment and possible toxicities. We derived dosimetry and therapy notion from initial experiences published by Kratochwil et. al, which demonstrated that 100 kBq/kg/bw was a justifiable treatment concept, balancing intolerable side effects and effective treatment. [86] Therefore, a mean dose of 8 MBq was administered to achieve optimal therapeutic efficacy while limiting related toxicities.

5.1. Response to treatment

Our results were in consistent with the previous published data as seen in Table 13. However, due to heterogeneous patients' populations, the therapeutic outcomes of ^{225}Ac-PSMA-617 in each study should be interpreted with caution. Kratochwil et al. in Heidelberg (Germany) in 2018 examined 38 mCRPC patients of which only 7 received ^{177}Lu-PSMA-617 RLT prior to ^{225}Ac-PSMA-617 therapy. [101] Our study exhibits mCRPC patients who had all received prior ^{177}Lu-PSMA-I&T RLT before receiving targeted alpha emitter therapy.

Therefore, for better classification of the study cases, we categorized the cohort of the latter study as “intermediate mCRPC” patients. To keep an overview of the others as well, we chose to define the cohort of the authors Sathekge et al as Pretoria I („chemo-naive mHSPC/mCRPC“) [90] and the second trial of the same group as Pretoria II (early mCRPC)[100]. Any PSA-decline was observed in 87% of these intermediate mCRPC patients, while a maximum PSA-decline ≥50% was measured in 75% cases. Overall survival was reported as more than 12 months.[84] PSA progression free survival was estimated at around 7 months. Moreover, two cases were observed to have benefited from the therapy over an extended follow-up period of two years. [1, 101] The Heidelberg patient cohort differed to ours in the aspect of mCRPC therapy lines prior to ^{225}Ac-PSMA-617. As mentioned before, only 7 of 38 Heidelberg patients had prior therapies with beta emitting ^{177}Lu-PSMA-617 [101]. Many other mCRPC patients had received less therapy lines (median of 3) prior to ^{225}Ac-PSMA-617 RLT. This might explain the smaller number of patients (i.e. 65%) achieved PSA-decline ≥50% from baseline, as our patients received ^{225}Ac-PSMA-617 as a salvage therapy succeeding prior mCRPC treatment lines. A recent experimental study [111] examined different biological mechanisms for tumor responsiveness to PSMA RLT such as alteration and/or activation of genotoxic stress response pathways, including deregulation of DNA damage/replication stress response, TP53, androgen receptor, phosphatidylinositol-3-kinase/AKT, and MYC signaling. They showed a 2.5% alteration in the total identified proteomes and phosphoproteomes of ^{177}Lu-PSMA RLT-treated tumor cells. Thus, previous ^{177}Lu-PSMA-I&T RLT might be a potential factor limiting the therapeutic efficacy of ^{225}Ac-PSMA-617 RLT.

On the other hand, approximately 70% of their patients studied by Kratochwil et al. [84] had received chemotherapy prior to radioligand therapy (^{177}Lu-PSMA-617 and/or ^{225}Ac-PSMA-617). This may also improve the therapeutic efficacy of ^{225}Ac-PSMA-617 RLT due to the known radiosensitizing effect of chemotherapy.

In addition, assessment of the time to PSA response after ^{225}Ac-PSMA-617 RLT was different among the published studies. In our study, clinical and laboratory follow-up assessments were performed at an average of six weeks post therapy, whereas the Heidelberg group did so at eight weeks post treatment. This may also explain the difference between the number of cases with ≥50% PSA decline in each study.

Concerning the outcome of the patients in our trial, unfortunately, no complete remission could be observed on ^{68}Ga-PSMA PET/CT. Despite the observation of biochemical anti-tumor effects, the data also suggests that the extent of these are timely limited. [1, 101]

In another RLT study conducted by Sathegke et al. in South Africa, chemotherapy-naïve mCRPC and mHSPC patients who received ^{225}Ac-PSMA-617 showed outstanding response to treatment. [90] The South African cohort consisted of 17 patients, of which 14 (82%) showed a PSA decline >90% post treatment and any PSA-decline was seen in 94% of patients. Amongst these 14 patients, further seven had no traceable PSA values in their blood works after the second (of three) ^{225}Ac-PSMA-617 cycle. The results of this study were very promising. In 15 of 17 (88%) patients a >50% decrease in lesion ^{68}Ga-PSMA avidity was seen on PET/CT. Moreover, 11 chemotherapy-naïve mCRPC patients showed complete remission on ^{68}Ga-PSMA PET/CT. In 7 of 17 patients (42%) PSA-levels were even undetectable after two or three cycles of ^{225}Ac-PSMA-617 RLT.[90] However, the reported findings were in contrast to our study, as no complete response was seen in our patient cohort on ^{68}Ga-PSMA PET/CT and only a fraction showed partial response. Hence, the question arises again whether the number and entity of the preceding treatments might influence the outcome of ^{225}Ac-PSMA-617 RLT. [90] One could argue that radioligand therapy may be indicated at an earlier stage of mCRPC disease rather than in more advanced ones.

Another study published by Sathegke et al in South Africa (Table 13, Pretoria II) included a total of 73 early mCRPC patients. The cohort included patients who had undergone first or second line therapies prior to TAT with ^{225}Ac-PSMA-617. Despite prior treatments, any PSA-decline was achieved in 83% and maximum PSA-decline ≥ 50% in 70% of patients. [100] ^{68}Ga-PSMA PET/CT showed complete remission in 29% of patients and median overall survival was estimated at 18 months. [89]

Evaluating all these ^{225}Ac-PSMA-617 RLT studies, it can be concluded that the number of patients with any PSA-decline were quite similar in all cohorts reaching from 83% to 94%, in consistent with our findings of 88%. [1, 84, 90] Despite ^{177}Lu-PSMA-I&T failure, targeted alpha therapy with ^{225}Ac-PSMA-617 still demonstrates an anti-tumor effect. Nonetheless, whilst comparing PSA response, we observed a trend towards lower efficacy of ^{225}Ac-PSMA-617 RLT at later onset of the therapy in advanced mCRPC. [1] To demonstrate this difference, the South African cohort can be compared to the TUM patients' population. A PSA-decline ≥50%

was achieved in 88% (15/17) of chemo-naïve patients, whereas only 65% (17/26) of our late mCRPC patients achieved this. The maximum PSA decline ≥90% displayed strongest contrast between the four cohorts in question. PSA reduction occurred in 82% (14/17), 58% (42/73; data extrapolated), 40% (16/40) and only 12% (3/26) of patients in the chemo-naïve, early, intermediate, and our late mCPRC cohorts, respectively. [1]

Furthermore, the duration of responses had clear distinctions in different cohorts. Our patients had a median cPFS of 5.0 months whereas the Pretoria II group was estimated to have around 15.2 months (Table 12). The Heidelberg cohort reported a median cPFS of 7.0 months. [1, 84, 100] It is important to note that we performed a ^{68}Ga-PSMA PET/CT scan 6 weeks after every cycle prior to the next one. This was included in our cPFS calculations and can cause significant bias as diseases progression can be detected earlier than in conventional imaging. [1] On the other hand, Kratochwil et al analyzed imaging response through PSMA-PET/CT after six months. [84] To highlight differences between the cohorts further, we assessed an overall survival of 7.7 months in our group (late mCRPC) [1] whilst Pretoria II (early mCRPC) calculated their OS at 18 months [100], and Kratochwil et al reported that at least 50% of their intermediate mCRPC patients were alive after 12 months and assessed their OS >12 months [84]. Nevertheless, compared to a multicenter study performed in 2015 by Caffo et al in Italy, our cohort still had a higher median OS (7.7 months) than patients who underwent third- and fourth-line therapies with novel agents (such as abiraterone, enzalutamide, cabazitaxel). The authors reported a median OS of 5 months for their patient cohort. [112]

Like ^{177}Lu-PSMA-617 RLT [113], the presence of visceral metastases proved to be unfavorable as it resulted in shorter cPFS, PSA-PFS, and OS in mCRPC patients undergoing ^{225}Ac-PSMA-617 RLT. We observed that a maximum PSA-decline ≥50% was linked to a statistically not significant, yet clearly longer cPFS median of 5 vs. 1.8 months (p=0.054) and OS of 12 vs. 7.6 months (p=0.09). [1] Nevertheless, clinicians in South Africa (Pretoria II, early mCRPC) reported better disease outcome after ^{225}Ac-PSMA-617 RLT. Median cPFS was calculated at 17.9 vs. 6.6 months (p<0.001) and median OS at 20.1 vs. 10.5 months (p<0.001). [100] Furthermore, Sathegke et al reported that prior treatment with ^{177}Lu-PSMA-617 could be a negative predictive factor for progression free survival. [100] This is in line with the hypothesis examined in an experimental study mentioned before. [111] Prognostic factors influencing the outcome of different mCRPC therapies, such as ^{177}Lu-PSMA-I&T RLT, as reported in studies

performed by Heck et al [113] and Kessel et al [114] were also seen with ^{225}Ac-PSMA-617 RLT. Hepatic metastases specifically were negative prognostic factors for cPFS, PSA-PFS, and OS, seen in the aforementioned cohorts. [113, 114] as well as in ours. [1] Through multivariate analysis we concluded that a higher ECOG baseline score served as an independent predictor of shorter overall survival. A factor possibly attributing to the short OS in our cohort could have been that nearly 20% of our patients had metastatic liver lesions. One might consider liver metastases and/or reduced overall performance as an exclusion criterion for further studies. [1] Bone metastases were also noticed to influence PFS. Patients with only lymph node metastases were seen with a significant longer PFS than patients with additional bone involvement. [100] Similar results have been published in previous studies with ^{177}Lu-PSMA-labeled RLT with overall longer OS in stage IVa versus IVb. [115]

Furthermore, efficacy of treatment was observed to be different in beta-emitting ^{177}Lu-PSMA-labeled RLT and alpha-emitting ^{225}Ac-PSMA-617 as well. Targeted alpha therapy in our TUM cohort yielded a maximum PSA-decline ≥50% in 65% (17/26) of late mCRPC patients [1]. Data from other studies report a maximum PSA-decline ≥50% through radioligand therapy with ^{177}Lu-PSMA-I&T in 38% of patients [113], 43% of patients treated at median dose of 4-6 GBq [84], and 44% of patients who received a dose of 6 GBq [116]. Comparing our data to the radioligand therapies with ^{177}Lu-PSMA-I&T, we can see that a biochemical response can even be obtained in late mCRPC patients.

As promising as this new theranostic approach with ^{225}Ac-PSMA-617 might be, side effects such as xerostomia and the associated loss of quality of life must be kept in mind. There is a dire need for new resolutions to tackle adverse events to allow further development and use of ^{225}Ac-PSMA-617 in the field of mCRPC.

5.2. Adverse events

Initial experiences made by Sathegke et al. revealed that xerostomia is a prominent side effect of targeted alpha therapy (TAT), in this instance ^{225}Ac-PSMA-617 RLT. They reported grade 1-2 xerostomia in 85% to 100% in their cohort without halt of treatment. [90] Our cohort did not vary in this aspect as xerostomia grade 1 was experienced by all 26 mCRPC patients (100%). According to the CTCAE v5.0 criterions, this is defined as symptomatic dryness of the mouth with thick or dry saliva. As it can be imagined, this had a drastic impact on the quality

of life of the cohort. Therefore, 23% of our patients withdrew treatment due to unendurable symptomatic xerostomia.[1] In comparison, the cohort in Heidelberg by Kratochwil et al reported discontinued treatment in 10% of the patients. [86] Another cohort published by Yadav et al in India reported grade 1-2 in 29%. [117] As far as the pathophysiology behind TAT-induced xerostomia because of higher salivary gland uptake and the higher toxicity of toxicity of ^{225}Ac-PSMA-617 than subsequent ^{117}Lu-PSMA-I&T are not understood fully. [1]

In 2019, Rathke et al. made initial clinical experiences to reduce xerostomia by sialendoscopy with saline flushing of the salivary tracts, extraction of mucus plugs within major salivary glands, and corticosteroid injections. The results differed individually but an overall favorable effect was observed. Despite initial benefits, minimal interventional support through sialendoscopy could not outweigh the inflammation and consequences of radiation as both were contributors to reduced salivary gland function. [118] As mentioned before, our cohort was asked to use Glandomed solution throughout the therapy regime to reduce xerostomia side effects. We observed that some patients experienced an improvement in their symptoms. Further attempts to reduce xerostomia included manual therapy, cooling of the salivary glands with ice collars, eating cold nourishments (such as ice cream) and frequent simulation through chewing gums or sour food. However, xerostomia could not be prevented completely. [1] Our patients experienced an overall higher exposition to cumulative toxicity due to previous chemotherapies or ^{117}Lu-PSMA-I&T RLT. It can be argued that radiation or chemotherapy induced damage (through prior mCRPC line) might affect and contribute further damage to the salivary glands. This could explain the increased frequency and severity of xerostomia in our patient population. An interesting aspect is that in patients who underwent ^{225}Ac-PSMA-617 RLT in earlier phases of disease, less xerostomia was observed. [90] Permanent xerostomia after prior ^{117}Lu-PSMA-I&T RLT did not occur in our patient cohort. Heck et al however reported cases of temporary xerostomia ^{117}Lu-PSMA-I&T RLT. [113]. A quantitative comparison of irradiation from ^{117}Lu-PSMA-I&T and ^{225}Ac-PSMA-617 is currently not possible due to the limitation of alpha-emitter dosimetry. [1]

Hematological and non-hematological toxicities except xerostomia were also observed in our patient collective. Thrombocytopenia, leucopenia, and grade 3-4 anemia occurred in 19% (5/26), 27% (7/26) and 35% (9/26) patients, respectively. Patients with critical anemia received single unit blood transfusions. Frequencies of thrombocytopenia, leucopenia, and grade 3-4 anemia in ^{117}Lu-PSMA-labeled RLT cohorts [78, 113, 119-121] were observed to be

2-13%, 3-32%, and 9-10%, respectively. It's important to remember that our patients received TAT at a significant later phase of their disease and yet had less adverse events than advanced mCRPC cohorts treated with investigational agents [122] or Carboplatin/Etoposide [123].

Impairment of renal functions, measured through creatinine and GFR, were seen in 19% (5/26) of patients without clinical impact, alike experiences made by Sathekge et al in South Africa. [90]

As mentioned before, an initial dose of 100 kBq/kg body weight was applied in our cohort. This approximates 8 MBq for an average, standard patient as an adequate trade-off between toxicity and efficacy. [1, 84] The study conducted by Kratochwil et al in Heidelberg yielded moderate antitumor effects and, in some cases, even disease progression during treatment. Given our advanced mCRPC cohort and initial suboptimal antitumor effects, we applied higher initial doses. Propositions were made to reduce activity dosage in patients with good therapy response, in order to encounter salivary gland toxicity. [124] Unfortunately, only 34% (9/26) of patients were eligible for subsequent dose reductions after initial antitumor response. The antitumor effect and its adverse events of ^{225}Ac-PSMA-617 could be optimized by introducing a patient-oriented treatment schedule. In some patients with good treatment response a rise of PSA six weeks after each TAT injection was seen. Shorter treatment intervals or patient adapted (based on response, adverse events, and quality of life) cycles with less activity per cycle might increase efficacy and antitumor effect. [1] Thus, one of the main challenges remains in dosimetry, and with it clinically relevant side effects like hematological toxicity and dose limiting organs such as the salivary glands, which should be addressed in future researches.

5.2.1. Impact on health and quality of life

Quality of life was quantified by the EORTC-30 questionnaire. After six weeks of treatment with ^{225}Ac-PSMA-617 RLT no significant impact was observed. Minimal loss of strength and limitations in daily activities were noted. These might have been caused by the clinical progression of the disease as well. One must keep in mind that the evaluation of xerostomia cannot be fully assessed by the EORTC-30 questionnaire. Loss of appetite and hence weight loss were seen in almost one-third of our collective, potentially leading back to xerostomia as the beginning of the causal chain. The exact etiology remains yet unclear. Effects of radiation

on bowel movements, cancer progress can be potential factors as well. These side effects were not observed using the questionnaire, most likely due to its lack of sensitivity toward cancer-related adverse events. Furthermore, a review of current databases and literatures could not identify other studies conducted with ^{177}Lu-PSMA-I&T or ^{225}Ac-PSMA-617 assessing quality of life through the EORTC-30 questionnaire. [1]

5.3. Restrictions and limitations

As in every area of medicine, one always faces restrictions and limitations. Our study was confronted with challenges such as a small patient cohort and the nature of the retrospective design. Moreover, many patients had passed away at the time of follow-up due to the gravity of the mCRPC and its mortality. Given the advanced stage of the disease in most of the patients, many did not continue treatment according to protocol and others did not answer the EORTC-Q questionnaires. This limited our data acquisitions, which further disallowed significant conclusions. Despite these limitations, our patient group was more homogenous than previous studies conducted with ^{225}Ac-PSMA-617 RLT after ^{177}Lu-PSMA-I&T failure. [1]

5.4. Prospects of radioligand therapy

As seen in recent studies such as VISION by Sartor et al ^{177}Lu-PSMA-617, a significant prolonged imaging-based progression-free survival and overall survival were observed in mCRPC patients, who received additional ^{177}Lu-PSMA-617 RLT treatment to standard care. Another multicentre, unblinded, randomised phase 2 trial study by Hofman et al (TheraP) [125] showed a higher PSA response and with fewer high-grade adverse events in mCRPC patients underwent ^{177}Lu-PSMA-617 RLT in comparison to second line cabazitaxel therapy. [126] Radioligand therapy has opened paths to more efficient therapy approaches with higher antitumor efficacy and often less adverse events. Moreover, we can see a certain trend towards combination therapy approaches such combining two radioligand agents. Approaches like these were seen in the combination of ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617 radioligand therapy by Khreish et al. [127]. Limited side effects while maintaining promising antitumor effects were seen in this study. Nonetheless, this must be further addressed in future studies whilst focusing on adverse events, like xerostomia. Other recent studies

focusing on combination therapy described xerostomia without further information on treatment discontinuation. [128-130] Not only different therapy approaches are aspects to be considered, but also patient collectives. As mentioned before, patients with earlier treatment onset with ^{225}Ac-PSMA-617 showed better antitumor effects in OS or PSA-PFS. [1] There are ongoing trials, such as PSMAfore (NCT04689828), to determine whether RLT with ^{177}Lu-PSMA-617 improves rPFS or death compared to a change in ADT in mCRPC patients who were previously treated with an alternative ADT and have not been exposed to a taxane-containing regimen in either CRPC or mHSPC.

Nevertheless, the question arises which different factors could influence this therapy efficacy. One prognostic factor mentioned before was that patients without bone or visceral (i.e. liver) involvement showed better therapy outcomes. One might consider for future approaches to begin TAT with ^{225}Ac-PSMA-617 at an earlier disease stage, maybe even prior to progression. One way to ascertain this hypothesis would be to consider bone or liver metastases as exclusion criterion for future analysis.

6. Conclusion

^{225}Ac-PSMA-617 RLT showed promising salvage therapy approach with measurable anti-tumor effects in mCRPC patients with advanced, late-stage disease, who failed response to ^{177}Lu-PSMA-I&T. However, the duration of these effects was observed to be timely limited. [1] Despite of advanced stages of the disease and extensive previous therapies more than half of our cohort showed a maximum PSA-decline ≥50% to baseline. Nevertheless, a significantly shorter overall survival was seen at the presence of visceral metastases as well. Hematological and non-hematological adverse events were within ordinary ranges for this late stage of the disease, except xerostomia. This particularly was omnipresent throughout all patients and might pose a restriction for further and broader use of ^{225}Ac-PSMA-617 RLT, given the fact that it substantially impacted the patients' quality of life. Reviewing our data, one can propose that the use of this treatment regime could be limited to cohorts without visceral metastases, as this imposed shorter response durations in comparison to patients in earlier phases of the disease. The significance and gravity of ^{225}Ac-PSMA-617 radioligand therapy as well as side effect profiles in different phases of prostate cancer, especially in advanced mCRPC, need to be more investigated and defined. Prospective studies systematically deducing its importance are recommended to highlight the clinical benefit of ^{225}Ac-PSMA-617. [1]

Bibliography

1. Feuerecker, B., et al., *Activity and Adverse Events of Actinium-225-PSMA-617 in Advanced Metastatic Castration-resistant Prostate Cancer After Failure of Lutetium-177-PSMA.* Eur Urol, 2021. **79**(3): p. 343-350.
2. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA Cancer J Clin, 2018. **68**(6): p. 394-424.
3. Rawla, P., *Epidemiology of Prostate Cancer*. 2019. 2019.
4. Cancer, I.A.f.R.o. *Estimated age-standardized mortality rates (World) in 2020, prostate, males, all ages*. 2020 [cited 2022 January 17th]; Available from: https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=population&mode_population=countries&population=900&populations=900&key=total&sex=1&cancer=27&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Afalse%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D.
5. Panigrahi, G.K., et al., *Exosome proteomic analyses identify inflammatory phenotype and novel biomarkers in African American prostate cancer patients.* Cancer Med, 2019. **8**(3): p. 1110-1123.
6. Wirth, *Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms.* 2019, Deutsche Gesellschaft für Urologie (DGU). p. 1-352.
7. Mottet, N., et al., *EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent.* Eur Urol, 2017. **71**(4): p. 618-629.
8. Beheshti, M., W. Langsteger, and A. Rezaee, *PET/CT in cancer : an interdisciplinary approach to individualized imaging*. 2017, Philapelphia, PA: Elsevier. xii, 261 pages.
9. De Angelis, R., et al., *Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study.* Lancet Oncol, 2014. **15**(1): p. 23-34.
10. Shipley, W.U., et al., *Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer.* N Engl J Med, 2017. **376**(5): p. 417-428.
11. Lowrance, W.T., et al., *Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART I.* J Urol, 2021. **205**(1): p. 14-21.
12. N. Mottet (Chair), P.C.V.-c., R.C.N. van den Bergh, E. Briers (Patient Representative), M. De Santis, S. Fanti, S. Gillessen, J. Grummet, A.M. Henry, T.B. Lam, M.D. Mason, T.H. van der Kwast, H.G. van der Poel, O. Rouvière, I.G. Schoots, D. Tilki, T. Wiegel. *EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020*. 2020 [cited 2020 April 15th]; Available from: https://uroweb.org/guideline/prostate-cancer/#11.
13. Hugosson, J., et al., *A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer.* Eur Urol, 2019. **76**(1): p. 43-51.
14. Ilic, D., et al., *Screening for prostate cancer.* Cochrane Database Syst Rev, 2013. **2013**(1): p. Cd004720.
15. e.V., D.G.f.U., *S3-Leitlinie Prostatakarzinom* 2021, Deutsche Krebsgesellschaft e.V. .

16. Mistry, K. and G. Cable, *Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma.* J Am Board Fam Pract, 2003. **16**(2): p. 95-101.
17. Beheshti, M., S. Haim, and W. Langsteger, *Nuklearmedizin der Prostata und des äußeren Genitale*, in *Die Urologie*, M.S. Michel, et al., Editors. 2016, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1265-1275.
18. Wirth, M., et al., *Prostatakarzinom: Diagnostik*, in *Die Urologie*, M.S. Michel, et al., Editors. 2016, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1305-1320.
19. Brierley, J.D.G., Mary K.; Wittekind, Christian *TNM Classification of Malginant Tumours*. Vol. 8. 2017: Wiley-Blackwell.
20. Baretton, G.B. and M. Toma, *Prostatakarzinom: Histopathologie*, in *Die Urologie*, M.S. Michel, et al., Editors. 2016, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1321-1339.
21. Humphrey, P.A., *Histopathology of Prostate Cancer.* Cold Spring Harb Perspect Med, 2017. **7**(10).
22. Kendal, W.S. and K.T. Mai, *Histological subtypes of prostatic cancer: a comparative survival study.* Can J Urol, 2010. **17**(5): p. 5355-9.
23. Buhmeida, A., et al., *Prognostic factors in prostate cancer.* Diagn Pathol, 2006. **1**: p. 4.
24. Heidenreich, A., et al., *EAU guidelines on prostate cancer.* Eur Urol, 2008. **53**(1): p. 68-80.
25. Hausmann, D. and S. Schönberg, *MRT der Prostata*, in *Die Urologie*, M.S. Michel, et al., Editors. 2016, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1241-1263.
26. Hersh, M.R., E.L. Knapp, and J. Choi, *Newer imaging modalities to assess tumor in the prostate.* Cancer Control, 2004. **11**(6): p. 353-7.
27. Szigeti, F., et al., *Incremental Impact of [(68) Ga]Ga-PSMA-11 PET/CT in Primary N and M Staging of Prostate Cancer Prior to Curative-Intent Surgery: a Prospective Clinical Trial in Comparison with mpMRI.* Mol Imaging Biol, 2022. **24**(1): p. 50-59.
28. NCCN, N.C.C.N. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prostate Cancer*. 2018 [cited 2021 December 6th]; Version 2.2018:[Available from: www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
29. Wirth, M., et al., *Prostatakarzinom: Kurative Therapie*, in *Die Urologie*, M.S. Michel, et al., Editors. 2016, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1341-1362.
30. Huber, J., et al., *Prostatakarzinom: Palliative Therapie*, in *Die Urologie*, M.S. Michel, et al., Editors. 2016, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1363-1383.
31. Sandhu, S., C. Guo, and M.S. Hofman, *Radionuclide Therapy in Prostate Cancer: from standalone to combination PSMA theranostics.* J Nucl Med, 2021.
32. Beheshti, M., et al., *Prostate-specific membrane antigen radioligand therapy of prostate cancer.* Q J Nucl Med Mol Imaging, 2019. **63**(1): p. 29-36.
33. Cornford, P., et al., *EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer.* Eur Urol, 2017. **71**(4): p. 630-642.
34. Rice, M.A., S.V. Malhotra, and T. Stoyanova, *Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer.* Front Oncol, 2019. **9**: p. 801.
35. Heidegger, I., et al., *Novel therapeutic approaches for the treatment of castration-resistant prostate cancer.* J Steroid Biochem Mol Biol, 2013. **138**: p. 248-56.

36. Heck, M.M., et al., *[PSMA-targeted radioligand therapy in prostate cancer].* Urologe A, 2017. **56**(1): p. 32-39.
37. Pal, S.K., et al., *Identification of mechanisms of resistance to treatment with abiraterone acetate or enzalutamide in patients with castration-resistant prostate cancer (CRPC).* Cancer, 2018. **124**(6): p. 1216-1224.
38. Hurwitz, M., *Chemotherapy in Prostate Cancer.* Curr Oncol Rep, 2015. **17**(10): p. 44.
39. Sathianathen, N.J., et al., *Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis.* Eur Urol, 2020. **77**(3): p. 365-372.
40. Armstrong, A.J., et al., *Efficacy of Enzalutamide plus Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer by Pattern of Metastatic Spread: ARCHES Post Hoc Analyses.* J Urol, 2021. **205**(5): p. 1361-1371.
41. Davis, M.I., et al., *Crystal structure of prostate-specific membrane antigen, a tumor marker and peptidase.* Proc Natl Acad Sci U S A, 2005. **102**(17): p. 5981-6.
42. Chakravarty, R., et al., *Targeted α-therapy of prostate cancer using radiolabeled PSMA inhibitors: a game changer in nuclear medicine.* Am J Nucl Med Mol Imaging, 2018. **8**(4): p. 247-267.
43. Udovicich, C., et al., *(68)Ga-prostate-specific membrane antigen-positron emission tomography/computed tomography in advanced prostate cancer: Current state and future trends.* Prostate Int, 2017. **5**(4): p. 125-129.
44. Pillai, M.R.A., et al., *Radiolabeled enzyme inhibitors and binding agents targeting PSMA: Effective theranostic tools for imaging and therapy of prostate cancer.* Nucl Med Biol, 2016. **43**(11): p. 692-720.
45. Lütje, S., et al., *PSMA Ligands for Radionuclide Imaging and Therapy of Prostate Cancer: Clinical Status.* Theranostics, 2015. **5**(12): p. 1388-401.
46. Schwarzenboeck, S.M., et al., *PSMA Ligands for PET Imaging of Prostate Cancer.* J Nucl Med, 2017. **58**(10): p. 1545-1552.
47. Barrett, J.A., et al., *First-in-man evaluation of 2 high-affinity PSMA-avid small molecules for imaging prostate cancer.* J Nucl Med, 2013. **54**(3): p. 380-7.
48. Zechmann, C.M., et al., *Radiation dosimetry and first therapy results with a (124)I/ (131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy.* Eur J Nucl Med Mol Imaging, 2014. **41**(7): p. 1280-92.
49. Vallabhajosula, S., et al., *99mTc-labeled small-molecule inhibitors of prostate-specific membrane antigen: pharmacokinetics and biodistribution studies in healthy subjects and patients with metastatic prostate cancer.* J Nucl Med, 2014. **55**(11): p. 1791-8.
50. Eder, M., et al., *Novel Preclinical and Radiopharmaceutical Aspects of [68Ga]Ga-PSMA-HBED-CC: A New PET Tracer for Imaging of Prostate Cancer.* Pharmaceuticals (Basel), 2014. **7**(7): p. 779-96.
51. Cho, S.Y., et al., *Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer.* J Nucl Med, 2012. **53**(12): p. 1883-91.
52. Szabo, Z., et al., *Initial Evaluation of [(18)F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer.* Mol Imaging Biol, 2015. **17**(4): p. 565-74.
53. Giesel, F.L., et al., *F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients.* Eur J Nucl Med Mol Imaging, 2017. **44**(4): p. 678-688.

54. Afshar-Oromieh, A., et al., *The Theranostic PSMA Ligand PSMA-617 in the Diagnosis of Prostate Cancer by PET/CT: Biodistribution in Humans, Radiation Dosimetry, and First Evaluation of Tumor Lesions.* J Nucl Med, 2015. **56**(11): p. 1697-705.
55. Weineisen, M., et al., *68Ga- and 177Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies.* J Nucl Med, 2015. **56**(8): p. 1169-76.
56. Calais, J., et al., *Potential Impact of (68)Ga-PSMA-11 PET/CT on the Planning of Definitive Radiation Therapy for Prostate Cancer.* J Nucl Med, 2018. **59**(11): p. 1714-1721.
57. Farolfi, A., et al., *(68)Ga-PSMA-11 PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy and PSA <0.5 ng/ml. Efficacy and impact on treatment strategy.* Eur J Nucl Med Mol Imaging, 2019. **46**(1): p. 11-19.
58. Wang, Z., et al., *Radioligand Therapy of Prostate Cancer with a Long-Lasting Prostate-Specific Membrane Antigen Targeting Agent (90)Y-DOTA-EB-MCG.* Bioconjug Chem, 2018. **29**(7): p. 2309-2315.
59. Paganelli, G. and U. De Giorgi, *[(177)Lu]-PSMA-617 for targeted prostate cancer treatment: a magic bullet?* Lancet Oncol, 2018. **19**(6): p. 725-726.
60. Afshar-Oromieh, A., et al., *Repeated PSMA-targeting radioligand therapy of metastatic prostate cancer with (131)I-MIP-1095.* Eur J Nucl Med Mol Imaging, 2017. **44**(6): p. 950-959.
61. Lütje, S., et al., *PSMA ligands in prostate cancer - Probe optimization and theranostic applications.* Methods, 2017. **130**: p. 42-50.
62. Colombatti, M., et al., *The prostate specific membrane antigen regulates the expression of IL-6 and CCL5 in prostate tumour cells by activating the MAPK pathways.* PLoS One, 2009. **4**(2): p. e4608.
63. Conway, R.E., et al., *Prostate-specific membrane antigen regulates angiogenesis by modulating integrin signal transduction.* Mol Cell Biol, 2006. **26**(14): p. 5310-24.
64. Grant, C.L., et al., *Prostate specific membrane antigen (PSMA) regulates angiogenesis independently of VEGF during ocular neovascularization.* PLoS One, 2012. **7**(7): p. e41285.
65. Kasperzyk, J.L., et al., *Prostate-specific membrane antigen protein expression in tumor tissue and risk of lethal prostate cancer.* Cancer Epidemiol Biomarkers Prev, 2013. **22**(12): p. 2354-63.
66. Paschalis, A., et al., *Prostate-specific Membrane Antigen Heterogeneity and DNA Repair Defects in Prostate Cancer.* Eur Urol, 2019. **76**(4): p. 469-478.
67. Eiber, M., et al., *Prospective head-to-head comparison of (11)C-choline-PET/MR and (11)C-choline-PET/CT for restaging of biochemical recurrent prostate cancer.* Eur J Nucl Med Mol Imaging, 2017. **44**(13): p. 2179-2188.
68. Heck, M.M., et al., *Systemic Radioligand Therapy with (177)Lu Labeled Prostate Specific Membrane Antigen Ligand for Imaging and Therapy in Patients with Metastatic Castration Resistant Prostate Cancer.* J Urol, 2016. **196**(2): p. 382-91.
69. Kratochwil, C., et al., *PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with 177Lu-Labeled PSMA-617.* J Nucl Med, 2016. **57**(8): p. 1170-6.
70. Ahmadzadehfar, H., et al., *Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer.* Oncotarget, 2016. **7**(11): p. 12477-88.

71. Ahmadzadehfar, H., et al., *Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study.* EJNMMI Res, 2015. **5**(1): p. 114.
72. Rahbar, K., et al., *Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis.* J Nucl Med, 2016. **57**(9): p. 1334-8.
73. Yadav, M.P., et al., *(177)Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment.* Eur J Nucl Med Mol Imaging, 2017. **44**(1): p. 81-91.
74. Baum, R.P., et al., *177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy.* J Nucl Med, 2016. **57**(7): p. 1006-13.
75. Fendler, W.P., et al., *Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer.* Oncotarget, 2017. **8**(2): p. 3581-3590.
76. Schuchardt, C., et al., *The Bad Berka dose protocol: comparative results of dosimetry in peptide receptor radionuclide therapy using (177)Lu-DOTATATE, (177)Lu-DOTANOC, and (177)Lu-DOTATOC.* Recent Results Cancer Res, 2013. **194**: p. 519-36.
77. Benesova, M., et al., *Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer.* J Nucl Med, 2015. **56**(6): p. 914-20.
78. Rahbar, K., et al., *German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients.* J Nucl Med, 2017. **58**(1): p. 85-90.
79. Bräuer, A., et al., *(177)Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer.* Eur J Nucl Med Mol Imaging, 2017. **44**(10): p. 1663-1670.
80. Kratochwil, C., et al., *Joint EANM/SNMMI procedure guideline for the use of (177)Lu-labeled PSMA-targeted radioligand-therapy ((177)Lu-PSMA-RLT).* Eur J Nucl Med Mol Imaging, 2023. **50**(9): p. 2830-2845.
81. Sartor, O., et al., *Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer.* N Engl J Med, 2021. **385**(12): p. 1091-1103.
82. Hofman, M.S., et al., *[(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial.* Lancet, 2021. **397**(10276): p. 797-804.
83. McDevitt, M.R., et al., *An alpha-particle emitting antibody ([213Bi]J591) for radioimmunotherapy of prostate cancer.* Cancer Res, 2000. **60**(21): p. 6095-100.
84. Kratochwil, C., et al., *225Ac-PSMA-617 for PSMA-Targeted alpha-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer.* J Nucl Med, 2016. **57**(12): p. 1941-1944.
85. Kassis, A.I., *Therapeutic radionuclides: biophysical and radiobiologic principles.* Semin Nucl Med, 2008. **38**(5): p. 358-66.
86. Kratochwil, C., et al., *Targeted alpha-Therapy of Metastatic Castration-Resistant Prostate Cancer with (225)Ac-PSMA-617: Dosimetry Estimate and Empiric Dose Finding.* J Nucl Med, 2017. **58**(10): p. 1624-1631.

87. Kratochwil, C., et al., *(2)(1)(3)Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience.* Eur J Nucl Med Mol Imaging, 2014. **41**(11): p. 2106-19.
88. Seidl, C., *Radioimmunotherapy with alpha-particle-emitting radionuclides.* Immunotherapy, 2014. **6**(4): p. 431-58.
89. Teiluf, K., et al., *alpha-Radioimmunotherapy with (2)(1)(3)Bi-anti-CD38 immunoconjugates is effective in a mouse model of human multiple myeloma.* Oncotarget, 2015. **6**(7): p. 4692-703.
90. Sathekge, M., et al., *(225)Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study.* Eur J Nucl Med Mol Imaging, 2019. **46**(1): p. 129-138.
91. Sathekge, M., et al., *(213)Bi-PSMA-617 targeted alpha-radionuclide therapy in metastatic castration-resistant prostate cancer.* Eur J Nucl Med Mol Imaging, 2017. **44**(6): p. 1099-1100.
92. Morgenstern, A., et al., *An Overview of Targeted Alpha Therapy with (225)Actinium and (213)Bismuth.* Curr Radiopharm, 2018. **11**(3): p. 200-208.
93. Apostolidis, C., et al., *Production of Ac-225 from Th-229 for Targeted α Therapy.* Analytical Chemistry, 2005. **77**(19): p. 6288-6291.
94. Fanti, S., et al., *Consensus statements on PSMA PET/CT response assessment criteria in prostate cancer.* Eur J Nucl Med Mol Imaging, 2021. **48**(2): p. 469-476.
95. Grubmüller, B., et al., *Response assessment using (68)Ga-PSMA ligand PET in patients undergoing (177)Lu-PSMA radioligand therapy for metastatic castration-resistant prostate cancer.* Eur J Nucl Med Mol Imaging, 2019. **46**(5): p. 1063-1072.
96. Pinker, K., C. Riedl, and W.A. Weber, *Evaluating tumor response with FDG PET: updates on PERCIST, comparison with EORTC criteria and clues to future developments.* Eur J Nucl Med Mol Imaging, 2017. **44**(Suppl 1): p. 55-66.
97. Seitz, A.K., et al., *Preliminary results on response assessment using (68)Ga-HBED-CC-PSMA PET/CT in patients with metastatic prostate cancer undergoing docetaxel chemotherapy.* Eur J Nucl Med Mol Imaging, 2018. **45**(4): p. 602-612.
98. Dabrowska-Bender, M., et al., *Analysis of Quality of Life Subjective Perception by Patients Treated for Prostate Cancer with the EORTC QLQ-C30 Questionnaire and QLQ-PR25 Module.* J Cancer Educ, 2017. **32**(3): p. 509-515.
99. Institute, N.C. *Common Terminology Criteria for Adverse Events (CTCAE)*. 2017; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
100. Sathekge, M., et al., *Predictors of Overall and Disease-Free Survival in Metastatic Castration-Resistant Prostate Cancer Patients Receiving (225)Ac-PSMA-617 Radioligand Therapy.* J Nucl Med, 2020. **61**(1): p. 62-69.
101. Kratochwil, C., et al., *Targeted alpha-Therapy of Metastatic Castration-Resistant Prostate Cancer with (225)Ac-PSMA-617: Swimmer-Plot Analysis Suggests Efficacy Regarding Duration of Tumor Control.* J Nucl Med, 2018. **59**(5): p. 795-802.
102. Rosenblat, T.L., et al., *Sequential cytarabine and alpha-particle immunotherapy with bismuth-213-lintuzumab (HuM195) for acute myeloid leukemia.* Clin Cancer Res, 2010. **16**(21): p. 5303-11.
103. Jurcic, J.G., et al., *Targeted alpha particle immunotherapy for myeloid leukemia.* Blood, 2002. **100**(4): p. 1233-9.

104. Allen, B.J., et al., *Intralesional targeted alpha therapy for metastatic melanoma.* Cancer Biol Ther, 2005. **4**(12): p. 1318-24.
105. Allen, B.J., et al., *Analysis of patient survival in a Phase I trial of systemic targeted alpha-therapy for metastatic melanoma.* Immunotherapy, 2011. **3**(9): p. 1041-50.
106. Raja, C., et al., *Interim analysis of toxicity and response in phase 1 trial of systemic targeted alpha therapy for metastatic melanoma.* Cancer Biol Ther, 2007. **6**(6): p. 846-52.
107. Autenrieth, M.E., et al., *Treatment of carcinoma in situ of the urinary bladder with an alpha-emitter immunoconjugate targeting the epidermal growth factor receptor: a pilot study.* Eur J Nucl Med Mol Imaging, 2018. **45**(8): p. 1364-1371.
108. Kneifel, S., et al., *Local targeting of malignant gliomas by the diffusible peptidic vector 1,4,7,10-tetraazacyclododecane-1-glutaric acid-4,7,10-triacetic acid-substance p.* Clin Cancer Res, 2006. **12**(12): p. 3843-50.
109. Cordier, D., et al., *Targeted alpha-radionuclide therapy of functionally critically located gliomas with 213Bi-DOTA-[Thi8,Met(O2)11]-substance P: a pilot trial.* Eur J Nucl Med Mol Imaging, 2010. **37**(7): p. 1335-44.
110. Kratochwil, C., et al., *Ac-225-DOTATOC-an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors.* Journal of Nuclear Medicine, 2015. **56**(supplement 3): p. 1232-1232.
111. Stuparu, A.D., et al., *Mechanisms of Resistance to Prostate-Specific Membrane Antigen-Targeted Radioligand Therapy in a Mouse Model of Prostate Cancer.* J Nucl Med, 2021. **62**(7): p. 989-995.
112. Caffo, O., et al., *Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study.* Eur Urol, 2015. **68**(1): p. 147-53.
113. Heck, M.M., et al., *Treatment Outcome, Toxicity, and Predictive Factors for Radioligand Therapy with (177)Lu-PSMA-I&T in Metastatic Castration-resistant Prostate Cancer.* Eur Urol, 2019. **75**(6): p. 920-926.
114. Kessel, K., et al., *Second line chemotherapy and visceral metastases are associated with poor survival in patients with mCRPC receiving (177)Lu-PSMA-617.* Theranostics, 2019. **9**(17): p. 4841-4848.
115. von Eyben, F.E., et al., *(177)Lu-PSMA radioligand therapy of predominant lymph node metastatic prostate cancer.* Oncotarget, 2019. **10**(25): p. 2451-2461.
116. Ahmadzadehfar, H., et al., *Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using [(177)Lu]Lu-PSMA-617.* Eur J Nucl Med Mol Imaging, 2017. **44**(9): p. 1448-1454.
117. Yadav, M.P., et al., *Efficacy and safety of (225)Ac-PSMA-617 targeted alpha therapy in metastatic castration-resistant Prostate Cancer patients.* Theranostics, 2020. **10**(20): p. 9364-9377.
118. Rathke, H., et al., *Initial clinical experience performing sialendoscopy for salivary gland protection in patients undergoing (225)Ac-PSMA-617 RLT.* Eur J Nucl Med Mol Imaging, 2019. **46**(1): p. 139-147.
119. Hofman, M.S., et al., *[(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study.* Lancet Oncol, 2018. **19**(6): p. 825-833.

120. Rahbar, K., et al., *PSMA targeted radioligandtherapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival.* Eur J Nucl Med Mol Imaging, 2018. **45**(1): p. 12-19.
121. Violet, J., et al., *Long-Term Follow-up and Outcomes of Retreatment in an Expanded 50-Patient Single-Center Phase II Prospective Trial of (177)Lu-PSMA-617 Theranostics in Metastatic Castration-Resistant Prostate Cancer.* J Nucl Med, 2020. **61**(6): p. 857-865.
122. Karzai, F., et al., *Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations.* J Immunother Cancer, 2018. **6**(1): p. 141.
123. Caubet, M., et al., *Carboplatin-etoposide combination chemotherapy in metastatic castration-resistant prostate cancer: A retrospective study.* Mol Clin Oncol, 2015. **3**(6): p. 1208-1212.
124. Bruchertseifer, F., et al., *Optimizing the treatment regimen for targeted alpha therapy of mCRPC with ²²⁵Ac-PSMA-617.* Journal of Nuclear Medicine, 2019. **60**(supplement 1): p. 466-466.
125. Hofman, M.S., et al., *[(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial.* Lancet, 2021. **397**(10276): p. 797-804.
126. Sartor, O., et al., *Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer.* N Engl J Med, 2021. **385**(12): p. 1091-1103.
127. Khreish, F., et al., *(225)Ac-PSMA-617/(177)Lu-PSMA-617 tandem therapy of metastatic castration-resistant prostate cancer: pilot experience.* Eur J Nucl Med Mol Imaging, 2020. **47**(3): p. 721-728.
128. Kratochwil, C., U. Haberkorn, and F.L. Giesel, *(225)Ac-PSMA-617 for Therapy of Prostate Cancer.* Semin Nucl Med, 2020. **50**(2): p. 133-140.
129. Langbein, T., et al., *Salivary Gland Toxicity of PSMA-Targeted Radioligand Therapy with (177)Lu-PSMA and Combined (225)Ac- and (177)Lu-Labeled PSMA Ligands (TANDEM-PRLT) in Advanced Prostate Cancer: A Single-Center Systematic Investigation.* Diagnostics (Basel), 2022. **12**(8).
130. Langbein, T., et al., *Combined PRLT using Ac-225 and Lu-177 labeled PSMA-617 (TANDEM-PRLT) in end-stage metastatic prostate cancer: a concept to reduce salivary gland toxicity?.* Journal of Nuclear Medicine, 2019. **60**(supplement 1): p. 77-77.