PSMA-Targeted Radionuclide Therapy for Prostate Cancer

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There is now an increasing trend for targeting cancers to go beyond early diagnosis and actually improve Progression-Free Survival and Overall Survival. Identifying patients who might benefit from a particular targeted treatment is the main focus for Precision Medicine. Radiolabeled ligands can be used as predictive biomarkers which can confirm target expression by cancers using positron emission tomography (PET). The same ligand can subsequently be labeled with a therapeutic radionuclide for targeted radionuclide therapy. This combined approach is termed “Theranostics”. The prostate-specific membrane antigen (PSMA) has emerged as an attractive diagnostic and therapeutic target for small molecule ligands in prostate cancer. It can be labeled with either positron emitters for PET-based imaging or beta and alpha emitters for targeted radionuclide therapy.

PSMA prostate cancer theranostics PET/CT radionuclide therapy

1. PSMA-Targeted Radioligand Therapy

1.1. ^{177}Lu-PSMA Radioligand Therapy

Lutetium-177 (^{177}Lu) is a beta-emitting radioisotope with a half-life of 6.7 days. It has an average energy of 133.6 keV with a maximum penetration depth of <2 mm [1]. Because of its good physical properties and the possibility of post-treatment imaging, ^{177}Lu labeled PSMA has been extensively studied and it has emerged as a novel treatment for mCRPC. Until recently, the majority of PSMA-targeting tracers involve urea-based agents (small molecule inhibitors) including ^{177}Lu-PSMA-I&T (imaging and therapy) and ^{177}Lu-PSMA-617, with the latter being preferred due to lower renal uptake [2][3]. A previous study of Ruigrok et al. revealed that although ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T show similar binding characteristics in prostate tumors, ^{177}Lu PSMA-I&T has a lower tumor-to-kidney ratio than ^{177}Lu PSMA-617 [4].

Protecting the kidneys and salivary and lacrimal glands is the major challenge for PSMA-targeting radiotracers due to high uptake in these organs. Salivary gland toxicity has been documented as dose-limiting. This significantly reduced the quality of life of treated patients. Recently, there have been more reports and publications focusing on the safety and efficacy of ^{177}Lu-PSMA radioligand therapy.

The systematic review and meta-analysis of Yadav et al. focused on 17 retrospective/prospective reports, totaling 744 patients treated with ^{177}Lu PSMA-radioligand therapy and concluded that 75% of patients had a reduction of PSA levels, with 46% having a reduction of more than 50%. A radiographic partial remission was seen in 37%,

median overall survival (OS) was 13.8 months, and median progression-free survival (PFS) was 11 months. The most common treatment-related side effects were myelosuppression, nephrotoxicity, and salivary gland toxicity (pain, swelling, and dry mouth) [5].

(a)^{177}Lu-PSMA-617

The LuPSMA trial (prospective single-arm, single-center, phase II trial) was conducted between August 2015 and December 2016. Forty men with PSMA-avid metastatic CRPC were treated with ^{177}Lu-PSMA-617 (7.5 GBq/cycle). Seventeen (57%) of thirty patients had a reduction in PSA of 50% or more. There were no treatment-related deaths. The most common adverse effect associated with ^{177}Lu-PSMA-617 was grade 1 dry mouth (87%), and grade 3 or 4 thrombocytopenia that may have been caused by ^{177}Lu-PSMA-617 occurred in 13%. Objective response in LN or visceral disease was found in 82% of patients. Median PSA progression was 7.6 months, and median OS was 13.5 months [6].

The TheraP study (randomized phase 2 clinical trial at 11 centers in Australia) was conducted between February 2018 and September 2019 with 200 mCRPC patients. Treatment in the study was given to 98 (99%) of 99 men randomly selected to ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously every 6 weeks for up to 6 cycles) compared to 85 (84%) of 101 randomly assigned to cabazitaxel (20 mg/m^2). PSA responses were more common among men in the ^{177}Lu-PSMA-617 group than in the cabazitaxel group. Grade 3–4 adverse events occurred in 32 of 98 men (33%) in the ^{177}Lu-PSMA-617 group versus 45 of 85 men (53%) in the cabazitaxel group. No deaths were found in the ^{177}Lu-PSMA-617 group [7].

The VISION study was a phase 3 randomized trial from June 2018 to mid-October 2019. The study enrolled 831 mCRPC patients with a median follow-up of 20.9 months. ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks × 6 cycles) combined standard of care (SOC) compared to SOC alone and revealed significant improvement in OS by a median of 4.0 months and PFS based on imaging was significantly longer. The incidence of grade 3 or above adverse events was higher with ^{177}Lu-PSMA-617 than the other arm but the quality of life was not affected. Due to the favorable treatment outcome with low incidence of adverse events in this study, the promotion of ^{177}Lu-PSMA-617 as a standard protocol in advanced PSMA-positive mCRPC is suggested [8].

The LuTectomy trial (open label, phase 1/2, non-randomized clinical trial) evaluated the dosimetry, efficacy, and toxicity of ^{177}Lu-PSMA in men with high PSMA-expressing high-risk localized or locoregional advanced PCa who underwent radical prostatectomy (RP) and pelvic lymph node dissection (PLND). This study started enrollment in August 2020 and is expected to be completed in June 2023 (NCT04430192) [9].

The UpFrontPSMA trial (open label, randomized, phase 2 trial) of sequential ^{177}Lu-PSMA 617 and docetaxel Versus docetaxel alone in 140 newly diagnosed metastatic PCa. The objective of this study was to evaluate response to treatment by measuring PSA levels and radiological response and safety of ^{177}Lu-PSMA 617. This study started enrollment in April 2020 and is expected to be completed in April 2024 (NCT04343885) [10].

(b) ^{177}Lu-PSMA-I&T

^{177}Lu-labeled PSMA ligand (DOTAGA-(I-y) fk (Sub-KuE), also known as PSMA I&T, for “imaging and therapy”) is now considered essential for the treatment of advanced PCa [11]. PSMA-I&T was first developed in Germany in 2015. There are similar properties between ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-617. In a study of 56 mCRPC patients who received an average dose of 5.76 GBq per cycle (total of 125 cycles), the PSA PFS was approximately 14 months with 59% of patients having >50% reduction in PSA levels [12].

In a previous large cohort study in 2019 involving100 patients treated with a total 319 cycles of ^{177}Lu-PSMA-I&T (median 2 cycles, range 1–6), 6–8 weekly with mean activity of 7.4 GBq, PSA decreased ≥50% within 12 weeks of treatment. Longer PFS and OS was observed in 38 patients, PFS was 4.1 mo and OS was 12.9 mo. Hematologic grade 3/4 toxicities were anemia (9%), thrombocytopenia (4%), and neutropenia (6%). Grade 3/4 non-hematologic toxicities were not found [13].

The SPLASH trial (a phase 3, open-label, randomized study) evaluated the efficacy of ^{177}Lu PSMA-I&T (AKA. ^{177}Lu-PNT2002) versus abiraterone or enzalutamide in slowing the progression of radiographic findings in mCRPC patients. The study will begin with a safety and dosimetry arm involving 25 patients (Part 1) and Part 2 involves a randomized therapeutic phase in 390 patients. All patients will have long-term follow-up for at least 5 years, death, or loss to follow-up (Part 3). This study began enrollment in March 2021 with approximately 415 patients (NCT04647526) [14].

(c) Combination of ^{177}Lu-PSMA 617 with androgen receptor-axis-targeted therapies (ARAT)

ARAT was only approved for patients with metastatic castration. Systemic ARAT is now FDA-approved even in PCa without evidence of mCRPC. ARAT administration increases PSMA expression. In addition, ARAT may cause radiosensitization. It is hypothesized that combined ^{177}Lu-PSMA radioligand treatment and ARAT might result in better tumor control in patients with CRPC [15].

The PSMAddition study is an international open-label, randomized, phase III study in 1126 metastatic hormone-sensitive PCa patients. The objective of this study was to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 combined with SOC, versus SOC alone. The SOC was determined as a combination of ARAT with ADT. Participants received approximately 7.4 GBq of ^{177}Lu-PSMA-617, every 6 weeks for 6 planned cycles. The primary outcome was to assess radiographic PFS (rPFS) and estimated final OS analysis. This study started enrollment in June 2021 and is expected to be completed in December 2025 (NCT04720157) [16].

The ENZA-p trial (open label, randomized phase 2, multicenter) was to compare the efficacy and safety of 160 mg enzalutamide daily + 177Lu-PSMA-617 (up to 4 cycles of 7.5 GBq) versus enzalutamide alone in 160 mCRPC patients who were deemed at high-risk for early failure on enzalutamide monotherapy. This study started enrollment in August 2020 and is expected to be completed in June 2023 (NCT04419402) [17].

Even though there is a biological basis to promote combined ARAT and ^{177}Lu-PSMA 617, key questions to answer will include the optimal dose, period of administration, and long-term safety of use of ^{177}Lu-PSMA-617 in the early stage of subsequent lines of treatment.

(d) Combination of ^{177}Lu PSMA-617 with DNA damage repair inhibitor

Transcription active sites are often unstable and susceptible to breakage since the torsional stress and local depletion of nucleosomes allow DNA to be more accessible to damaging substances. A dedicated DNA damage response (DDR) is necessary to preserve genome integrity at the exposed sites. The DDR is a complex system of DNA damage sensor proteins, for example, the poly (ADP-ribose) polymerase 1 (PARP-1). It is important in repairing radiation-induced single-stranded DNA breaks, which permit cancer cells to become resistant to radiation [18]. Therefore, PARP-1 inhibition may cause radiosensitization when combined with radioligand treatment. PARP inhibitors, such as olaparib and rucaparib, have been described as effective against mCRPC [9][10].

LuPARP is an Australian phase 1, open-label, multicenter, dose-escalation and dose-expansion study to investigate the use of ^{177}Lu-PSMA 617 with olaparib in 52 mCRPC patients who have progressed on novel AR targeted drugs and have PSMA-avid disease on imaging. Patients received fixed 7.4 GBq of ^{177}Lu-PSMA-617 every 6 weeks plus olaparib. The primary endpoints were dose-limiting toxicity and maximum tolerated dose. Secondary endpoints were adverse events, rPFS, and OS. This study started enrollment in July 2019 and is expected to be completed in October 2022 (NCT03874884) [19].

(e) Combination of ^{177}Lu PSMA-617 with checkpoint inhibitor immunotherapy

Immunotherapy has changed the therapeutic strategy of many hematological and solid cancers. However, several phase I and II trials evaluating programmed death receptor 1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors have reported limited usage for mCRPC. Additionally, although sipuleucel-T represents the only FDA-approved cancer vaccine for mCRPC according to IMPACT trial results [20], its use is relatively limited in daily clinical practice. There are several ongoing clinical trials in various immunotherapy approaches either alone or combined with other therapies in mCRPC. Different mAb against PD-1, PD-L1, or CTLA-4 were tested for mCRP treatment with unsatisfactory results [21].

PRINCE is the phase Ib/II study of ^{177}Lu-PSMA-617 combined with pembrolizumab for treatment in 37 mCRPC patients who have progressed on ARAT. Patients with PSMA-avid disease were enrolled to receive ^{177}Lu-PSMA for up to 6 doses (starting at 8.5 GBq with a decrease of 0.5 GBq for each cycle) and pembrolizumab for up to 35 cycles (every 3 weeks). The primary objectives were PSA response rate and safety. Secondary objectives were rPFS, PSA-PFS, and OS. This study started recruitment in July 2019 and was completed in October 2021 (NCT03658447) [22].

1.2. Alpha-Emitting PSMA-Targeted Radioligand Therapy

For mCRPC treatment, multiple studies have confirmed that ^{177}Lu-PSMA-617 has a favorable dosimetry and good objective response, including improvement in PSA levels and radiological findings [23][24]. However, approximately 30% of patients did not respond to ^{177}Lu-labeled PSMA ligands. Targeted α-radiation therapy may be more effective for mCRPC treatment and has been reported in a limited number of patients to be effective in patients resistant to ^{177}Lu-PSMA-617 therapy. Despite having good tolerability, high radioactivity accumulations in bone metastases which lie near to or within the red marrow, indicate that the actual absorbed dose to some domains of active marrow may be rather higher than estimated in the previous study due to spillover resulting in associated developmental risk factor for hematologic toxicity. Recent studies have shown that targeted α-radiation therapy is highly beneficial for mCRPC patients in this setting [25].

(a)^{225}Ac-PSMA-617

^{225}Ac is an alpha emitter with a relatively long half-life (9.9 days) [26][27]. Actinium-225 (^{225}Ac)-PSMA-617 has a significantly higher linear energy transfer (LET) compared to beta particles. With reference to a preliminary report from a single-center study, ^{225}Ac-PSMA-617 (100 kBq/kg every two weeks) resulted in decreased PSA levels below measurable levels and showed complete response on imaging. No related hematologic toxicity was found. Xerostomia was the only clinical side effect mentioned [28]. In the previous study of Kratochwil et al. of fourteen PCa patients with metastasis, therapeutic activity of 100 kBq/kg of ^{225}Ac PSMA-617 per cycle repeated every eight weeks demonstrated proper trade-off between toxicity and biochemical response. Low grade hematological toxicity was found in six patients and xerostomia was found in eight patients. Xerostomia was the dose-limiting factor with 100 kBq/kg considered the maximum tolerated dose [29]. A recent study of Sathekge M et al. assessed the therapeutic outcome of ^{225}Ac-PSMA-617 in seventeen advanced PCa patients of which the results showed a good anti-tumoral effect assessed by serum PSA level and ^{68}Ga-PSMA-PET/CT as seen in 94.1% of patients. A PSA decrease by ≥90% after treatment was found in 82.4% of patients. All patients experienced grade 1/2 xerostomia without severe symptoms [30]. Although targeted α-therapy with ^{225}Ac-PSMA-617 is still considered experimental, it clearly has the potential to be of great benefit to advanced-stage PCa patients.

(b)^{213}Bi-labeled PSMA-617

Bismuth-213 (^{213}Bi) is a short half-life (45.6 min) mixed alpha and beta emitting agent [27][31]. Sathekge et al. reported a 1st treatment case with ^{213}Bi-PSMA-617 (two cycles with a cumulative activity of 592 MBq) in mCRPC patients who had progressed under conventional therapy gained PSMA-imaging response and biochemical response with a declined PSA level from 237 µg/L to 43 µg/L [32]. The previous study of Kratochwil et al. revealed that dosimetry of ^{213}Bi-PSMA-617 is suitable for clinical application. However, when compared with ^{225}Ac-PSMA-617, it suffers from higher perfusion-dependent off-target radiation, and a biological half-life of PSMA-617 in dose-limiting organs is longer than the physical half-life of ^{213}Bi, making this agent a second-choice radiolabel for the targeted alpha therapy of PCa [33].

2. Anti-PSMA Radioimmunotherapy

J591 was the first monoclonal antibody (mAb) targeting the extracellular domain of PSMA that was derived from the original murine J591 (muJ591) by substituting epitopes of the B and T cell [34][35]. This led to differences in kinetics and biodistribution, the adverse events observed following two agents were often different. The prospective study of Tagawa concluded that the PSMA-targeted ^{177}Lu antibody J591 was related with greater hematologic effects than with PSMA-617. However, ^{177}Lu PSMA-617 is related with more non-hematological toxicity than ^{177}Lu-J591. ^{177}Lu-PSMA-617 was observed to be related with more PSA decline than ^{177}Lu-J591, but no difference in OS was found on multivariable analysis [36]. The difference between mAb and Ligand are described in **Table 1**.

Table 1. Differences between mAb and Ligands.

Ligand (PSMA 617)	mAb (J591)
Small (mw 1400)	Large (mw 150,000)
Short circulation time	Long circulation time (days)
• optimal tumor imaging within hours	• optimal tumor imaging at 3–8 days
Rapidly diffuse to all sites of expression	Mostly target via vasculature
Toxicities	Toxicities
• Kidney • Salivary glands • Small intestine	• Bone marrow • Liver

2.1. ^{177}Lu-J591 Antibody

J591 is typically labeled with lutetium-177 (^{177}Lu-J591) to target PCa cells and deliver radioimmunotherapy. It has been studied extensively in phase I/II clinical trials. ^{177}Lu-J591 was first studied in a phase I trial in 2005 in 35 mCRPC patients receiving up to three doses. Myelosuppression was a dose limited to 75 mCi/m^2, and a dose level of 70-mCi/m^2 was defined as the single-dose maximum tolerated dose. The biologic activity was observed in four patients with >50% reduction in PSA levels for between 3 and 8 months. No patient developed a human anti-J591 antibody response to deimmunized J591 [37]. In a phase 2 study of Tagawa et al., single doses of ^{177}Lu-J591 were studied in forty-seven patients with progression after hormonal treatment. A total of 10.6% experienced ≥50% reduction in PSA, 36.2% experienced ≥30% decline, and 59.6% experienced any PSA decline after single treatment. Median OS was approximately 22 vs. 12 months in mCRPC treated with a single-dose of 70 mCi/m^2 and 65 mCi/m^2, respectively. However, a higher dose resulted in a higher grade of thrombocytopenia and neutropenia [38]. In a phase 1/2 study, forty-nine mCRPC patients received ^{177}Lu-J591 doses ranging between 20 and 45 mCi/m^2 × 2 two weeks apart. The recommended doses at phase 2 were 40 mCi/m^2 and 45 mCi/m^2 × 2.

Median OS was 42.3 months vs. 19.6 months in patients receiving higher vs. lower doses. The higher grade of thrombocytopenia and neutropenia were found in higher doses than lower doses [39].

2.2. ^{225}Ac-J591 Antibody

The reason for higher hematological toxicity for ^{177}Lu-J591 is possibly because mAb is a large molecule with slower circulating clearance compared to smaller molecules, for example, PSMA-617. However, compared to PSMA-617, J591 shows no uptake in the salivary gland or kidneys [40]. Because of this character, it has been hypothesized that ^{225}Ac-J591 can reduce the incidence of salivary and renal toxicity found in ^{225}Ac-PSMA-617. In the previous phase 1 trial of Tagawa, twenty-two mCRPC patients received seven dose levels of ^{225}Ac-J591, and only one patient who received 80 KBq/kg had grade 4 thrombocytopenia and anemia. Xerostomia was seen only in patients receiving ^{177}Lu-PSMA-617 treatment. PSA reduction was observed in 64% with 41% of patients having ≥50% PSA reduction (Clinical trial information: NCT03276572) [41].

2.3. ^{227}TH-PSMA-TTC Antibody

PSMA-Targeted Thorium-227 Conjugate (PSMA-TTC) is a targeted alpha therapy for PCa. Thorium-227 (^{227}Th) is a long half-life (18.7 days) α-particle emitter which is the parent nuclide of radium-223. ^{227}Th-PSMA-TTC is a novel human antibody attached to ^{227Th} and has shown very strong antitumor efficacy in animal models with PCa [42]. A phase I clinical trial of PSMA-TTC in mCRPC is currently ongoing based on promising preclinical data. It is planned with a recruitment of one hundred ninety-eight patients and is expected to be completed in September 2024 [43] (NCT03724747). Clinical trials of PSMA-targeted radioligand therapy is described in **Table 2**.

Table 2. Clinical trials of PSMA-targeted radioligand therapy.

Clinical Trial	Status	Phase	Patients	Interventions
ACTRN12615000912583 (LuPSMA) [6]	completed	2	40	^{177}Lu-PSMA-617 in progressive mCRPC
NCT03392428 (TheraP) [7]	active, not recruiting	2	200	^{177}Lu-PSMA-617 vs. cabazitaxel in progressive mCRPC
NCT03511664(VISION) [8]	active, not recruiting	3	831	^{177}Lu-PSMA-617 + SOC vs. SOC in progressive mCRPC
NCT04430192 (LuTectomy) [9]	recruiting	1/2	20	^{177}Lu-PSMA-617 followed by prostatectomy
NCT04343885 (UpFrontPSMA) [10]	recruiting	2	140	Sequential ^{177}Lu-PSMA-617 + docetaxel vs. docetaxel in metastatic hormone-naive PCa
NCT04419402 (ENZA-P) [17]	recruiting	2	160	Enzalutamide + ^{177}Lu-PSMA-617 vs. Enzalutamide alone in mCRPC

Clinical Trial	Status	Phase	Patients	Interventions
NCT04647526 (SPLASH) [14]	recruiting	3	415	^{177}Lu-PSMA-I&T vs. ARAT in progressive mCRPC
NCT04720157 (PSMAddition) [16]	recruiting	3	1126	^{177}Lu-PSMA-617 + SOC vs. SOC alone in mHSPC
NCT03874884 (LuPARP) [19]	recruiting	1	52	^{177}Lu-PSMA-617 + olaparib in progressive mCRPC
NCT03658447 (PRINCE) [22]	active, not recruiting	1/2	37	^{177}Lutetium-PSMA-617 + pembrolizumab (mCRPC)
NCT03276572 [41]	active, not recruiting	1	31	^{225}Ac-J591 in mCRPC
NCT03724747 [43]	recruiting	1	198	^{227}Th-PSMA-TTC in progressive mCRPC

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