PSMA theragnostics for metastatic castration resistant prostate cancer

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ABSTRACT

There has been tremendous growth in the development of theragnostics for personalized cancer diagnosis and treatment over the past two decades. In prostate cancer, the new generation of prostate specific membrane antigen (PSMA) small molecular inhibitor-based imaging agents achieve extraordinary tumor to background ratios and allow their therapeutic counterparts to deliver effective tumor doses while minimizing normal tissue toxicity. The PSMA targeted small molecule positron emission tomography (PET) agents ^{18}F-DCFPyL (2-(3-{1-carboxy-5-((6-(18)F-fluoro-pyridine-3-carbonyl)-amino)-pentyl}-ureido)-pentanedioic acid) and Gallium-68 (^{68}Ga)-PSMA-11 have been approved by the United States Food and Drug Administration (FDA) for newly diagnosed high risk prostate cancer patients and for patients with biochemical recurrence. More recently, the Phase III VISION trial showed that Lutetium-177 (^{177}Lu)-PSMA-617 treatment increases progression-free survival and overall survival in patients with heavily pre-treated advanced PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). Here, we review the PSMA targeted theragnostic pairs under clinical investigation for detection and treatment of metastatic prostate cancer.

Introduction

Prostate cancer (PC) is the second most common cancer and sixth leading cause of cancer related death among men in the world [1]. PC mortality rates declined since the 1990s, in large part due to earlier diagnosis from prostate specific antigen (PSA) testing and treatment advances; however, this decline has plateaued since 2013 [2]. At diagnosis, the most common stages of PC are localized (74%) and regional (13%); these can be treated effectively with surgery and radiation therapy and have an excellent prognosis with 5-year relative survival close to 100% [2,3]. However, 10–20% patients eventually develop castration resistant prostate cancer (CRPC) with 84% patients having metastases at the time of this diagnosis. The median survival of patients with CRPC based on a pooled review is about 14 months [4]. Recent advances in hormonal therapy, chemotherapy, immunotherapy, systemic radioisotopes and DNA damage repair inhibitors have provided new treatment options for mCRPC.

Novel theragnostic agents are currently under investigation for personalized diagnosis and treatment for cancer. The linking of diagnostic and therapeutic radioisotopes to the same (or very similar) targeting agents makes it possible to confirm the presence and abundance of the targeted molecule on tumors before initiating treatment. The development of imaging agents with high tumor to background ratios

allows their therapeutic counterparts to achieve a high therapeutic index. Such theragnostic strategy has been successful in the long-established radioiodine therapy for thyroid cancer and more recently in the ^{68}Ga/^{177}Lu-DOTATATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate) theragnostic pair for neuroendocrine tumors [5]. Several theragnostic agents are currently in clinical trials for prostate cancer. In this article, we review the PSMA based theragnostics for prostate cancer and related clinical trials.

PSMA as theragnostics target for prostate cancer

PSMA is a 750 amino-acid type II transmembrane glycoprotein with a 707-residue extracellular component that is highly expressed in the prostate [6,7]. While PSMA is expressed in all types of prostate tissue, the expression level increases 100 to 1000 fold in PC and correlates with the cancer grade [8]. In addition to prostate tissue, PSMA is expressed in other normal tissues including the salivary and lacrimal glands, proximal tubules of the kidneys, duodenum, liver, and spleen [9,10]. The salivary glands and kidneys are of particular interest, as they are typically the dose limiting organs in PSMA-targeted radiopharmaceutical therapy. Many studies have shown that PSMA is also expressed in neovasculature of solid tumors such as renal cell carcinoma, transitional cell carcinoma, and colonic adenocarcinoma, etc. [11,12], which could lead

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to false positive diagnostic imaging interpretation in the setting of PSMA positive malignancy.

The crystal structure of the PSMA extracellular component revealed a homodimer that is structurally similar to transferrin receptor, but with an additional protease domain [6]. Thus, PSMA demonstrates enzymatic activity as an N-acetylated-alpha-linked acidic dipeptidase I (NAALA-Dase I), also known as glutamate carboxypeptidase (GCPII) or folate hydrolase. However, the endogenous ligand for PSMA has not yet been identified. The known substrates and transition state analogues such as N-acetyl-aspartyl-glutamate (NAAG) of PSMA have become the scaffold for design of many small molecule PMSA inhibitors [13]. In addition, PSMA is internalized into cells through clathrin coated pits and into the cellular lysosomes, with transport affected in a dose dependent manner by PSMA binding monoclonal antibody [14]. The function of PSMA in normal prostate tissue and its role in PC progression remains unclear. Kaittani C et al. proposed that carboxypeptidase activity of PSMA may release glutamate and activated metabotropic glutamate receptor which in turn upregulates the oncogenic PI3K (Phosphoinositide 3-kinases) pathway [15]. Thus, PSMA expression increases with grade and is inversely correlated with survival. These properties of PSMA make it an ideal target for developing theragnostic agents that can detect and treat mCRPC.

PSMA targeted PC imaging

[111]In-capromab pendetide (ProstaScint®) was the first PSMA targeted imaging agent approved by the FDA in 1996. It is an ^{111}In-labeled murine anti-PSMA monoclonal antibody, 7E11-C5.3, that targets to the cytoplasmic epitope of PSMA. ^{111}In-capromab pendetide is a single-photon emission computed tomography (SPECT) imaging agent. In newly diagnosed PC patients, the pivotal phase 3 trial showed a sensitivity of 62%, specificity of 72%, positive predictive value (PPV) of 62% and negative predictive value (NPV) of 72% for pelvic node metastases, with an overall diagnostic accuracy of 68%. For patients with biochemical recurrence (BCR), a second pivotal phase 3 trial showed a sensitivity of 49%, specificity of 71%, PPV of 50% and NPV of 70% with an overall accuracy of 63% [16]. A recent study suggested that capromab pendetide single-photon emission computed tomography/computed tomography (SPECT/CT) may be used to detect pelvic lymph node metastases in newly diagnosed high risk PC patients with overall accuracy of 93% [17].

In rapid development in the past two decades, small molecular PSMA inhibitor PET agents have demonstrated superior detection rates and accuracy compared to anatomical imaging. Two small molecular PSMA inhibitor PET agents, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL were approved by the FDA in 2020 and 2021, respectively, for newly diagnosed biopsy-proven PC patients at high risk for pelvic nodal metastases, as well for BCR PC [18-21].

PSMA PET for BCR PC

Thus far, PSMA targeted PET agents have primarily been used in the setting of BCR. In one of the two pivotal prospective trials that led to FDA approval, Fendler *et al.* found that ^{68}Ga-PSMA-11 PET localized recurrent PC in 475 of 635 (75%) patients with BCR disease, demonstrating a PPV of 0.84 (95% CI, 0.75–0.90) by histopathologic validation [18]. The detection rate increased with PSA levels, 38% for PSA < 0.5 ng/mL, 57% for 0.5 ≤ PSA < 1 ng/mL, 84% for 1≤ PSA < 2 ng/mL, and 86% for 2 ≤ PSA < 5 ng/mL and 97% for PSA ≥ 5 ng/mL. Similar detection rates were observed with the other FDA approved PSMA imaging agent, ^{18}F-DCFPyL. In a cohort of patients with BCR in the pivotal phase II/III OSPREY study, sensitivity was 95.8% and positive predictive value was 81.9% [21]. In the second pivotal phase III CONDOR trial of 208 patients, the detection efficiency among three central reviewers ranged from 59 to 66%, with correct localization rate (CLR) of 84.8 to 87.0% [20]. In several additional prospective studies evaluating

^{18}F-DCFPyL-PET in BCR PC, the overall detection rate was found to be 80.2%, and increased with higher PSA levels [22-26].

Another small molecule PSMA agent ^{18}F-PSMA-1007 is excreted mainly through the hepatobiliary system and may improve detection of small lesions adjacent to the urinary tract, although it demonstrated a higher rate of false positive bone lesions [27]. Overall, ^{18}F-PSMA-1007 was found to have a comparable detection rate of 81.3% in a retrospective study of 251 patients with BCR PC [28]. In a meta-analysis of 43 studies with 5113 patients evaluating PSMA imaging agents including ^{68}Ga-PSMA-11, ^{18}F-DCFPyL and PSMA-1007, the pooled detection rate was 70.2% for the entire cohort [29]. PSMA PET had a higher detection rate in patients with BCR when compared with imaging modalities such as CT and bone scan [22,30,31]. In a head-to-head prospective comparison to ^{18}F-fluciclovine PET/CT in 50 patients, ^{68}Ga-PSMA-11 PET/CT showed a significantly higher detection rate overall (56% vs 26%), particularly in pelvic lymph nodes (30% vs 8%), extra-pelvic lymph nodes (6% vs 0%), and bone lesions (8% vs 0%) [32]. In a meta-analysis of 482 ^{18}F-fluciclovine PET scans and 3217 PSMA PET scans in patients with biochemical recurrence and PSA levels < 2 ng/mL, PSMA PET showed a higher per-patient detection rate compared to ^{18}F-fluciclovine PET for PSA levels of 1.0 −1.9 ng/mL. For PSA levels < 1.0 ng/mL, there were no statistically significant differences between the two agents [33].

PSMA PET for high risk newly diagnosed PC

Accurate staging in newly diagnosed, high risk PC is crucial for appropriate treatment planning. Anatomical imaging modalities are limited in detecting regional nodal metastases, and PSMA agents have shown improved specificity. In a phase III study of 764 patients with intermediate to high-risk prostate cancer prior to prostatectomy and pelvic nodal dissection, ^{68}Ga-PSMA-11 PET showed a sensitivity of 40% and specificity of 95% for detecting pelvic nodal metastases [19]. A ^{68}Ga-PSMA-11 PET/MR study of 33 patients found similar sensitivity of 50% and specificity of 98.4% [34]. The phase II/III OSPREY trial reported similar performance for ^{18}F-DCFPyL in 252 patients with high-risk prostate cancer prior to radical prostatectomy with median sensitivity of 40.3% and specificity of 97.9% among three central reviewers [21]. In a prospective, randomized multicenter study of 339 patients, ^{68}Ga-PSMA-11 was found to be more accurate in detecting regional nodal and distant metastases than combined findings of both CT and bone scan [35]. Androgen levels have been shown to negatively regulate PSMA expression in vitro [36]; however, reports of PSMA uptake after androgen deprivation therapy in clinical practice remain mixed. Some studies found PSMA uptake was dependent on duration of androgen blockade and castration status [37-39].

Overall, the various PSMA imaging agents have shown similar diagnostic performance in both BCR and high risk newly diagnosed PC. [18]F labeled imaging agents have a longer half-life which allows for centralized production and distribution and eliminates the needs for an on-site [68]Germanium/[68]Gallium ([68]Ge/^{68}Ga) generator, although cyclotron-produced ^{68}Ga is now feasible.

PSMA targeted radiopharmaceutical therapy (RPT)

PSMA targeted radiolabeled antibodies

The earliest PSMA targeted radiopharmaceutical therapy was Yttrium-90 (^{90}Y)-labeled capromab pentide, the therapeutic counterpart of the diagnostic agent Indium-111 (^{111}In)-capromab pentide. A phase II study found significant hematologic toxicity in 6 of 8 patients treated with ^{90}Y-capromab pentide at dose of 9 mCi/m^2 without lowering serum PSA level [40]. To improve targeting and minimize effects of human anti-mouse antibodies (HAMA), a humanized monoclonal antibody, J591, targeting the extracellular domain of PSMA was developed [41]. Following preclinical and early clinical studies of ^{111}In, ^{177}Lu, ^{90}Y and

Iodine-131 (^{131}I) labeled J591 [42,43], ^{177}Lu-J591 was selected for further evaluation in a phase II trial in CRPC patients. Overall, 10.6% patients had ≥ 50% decline in PSA and 36.2% of patients experienced ≥ 30% decline in PSA after a single dose of ^{177}Lu-J591 at 65 mCi/m^2 and 70 mCi/m^2. Myelosuppression was the dose limiting toxicity, with 46.8% of patients showing grade 4 thrombocytopenia and 25.5% of patients showing grade 4 neutropenia after treatment [44]. In a more recent Phase I/II study of fractionated ^{177}Lu-J591, both efficacy and hematologic toxicity were increased with higher doses ranging from 20 to 45 mCi/m^2. The highest dose group received 2 doses of ^{177}Lu-J591 given 2 weeks apart at 45 mCi/m^2; nearly a third of patients (29.4%) of the patients had > 50% PSA decrease with medial overall survival of 42.3-month [45]. Furthermore, combining fractionated ^{177}Lu-J591 with docetaxel/prednisone has shown >50% PSA decline in 73.3% of the patients [46]. Similar to prior studies, reversible myelosuppression was the main toxicity observed. Although longer serum half-life of radiolabeled antibody increases the risk of hematologic toxicity, it may also increase accumulation of radiotracer leading to higher tumor dose. Poor penetration of large solid tumors by large molecules such as antibodies may lead to heterogeneous tumor dose and decreased probability of tumor control. Further optimization of PSMA targeted radiopharmaceuticals is needed to improve their therapeutic index.

PSMA targeted radiolabeled small molecular inhibitors

The small molecule PSMA inhibitors developed over the last two decades offer high PSMA inhibition potency, efficient internalization after binding, as well as better penetration of solid tumors with rapid clearance from the blood and normal soft tissues. The successful development and clinical application of analogous small molecule theragnostic agents for neuroendocrine tumor such as ^{68}Ga-and ^{177}Lu-DOTATATE has paved the way for new treatment strategies. In a similar fashion, PSMA imaging agents can be used to screen patients for PSMA expression and eligibility for treatment, with the therapeutic PSMA agent then being administered in multiple cycles. Utilization of multiple cycles minimizes toxicity from each administration and allows for normal tissue recovery over 6 to 8 weeks before the next cycle of treatment is administered.

Beta-particle emitter labeled PSMA small molecular inhibitors

The first small molecule PSMA theragnostic agent used in a clinical study was Iodine-124/Iodine-131 (^{124}I/^{131}I)-MIP-1095 [47]. After a ^{124}I PET/CT based dosimetry study, 28 patients were treated with a single cycle of ^{131}I-MIP-1095 with mean activity of 4.8 GBq. Over 60% of patients demonstrated a PSA decline > 50%. The dose limiting organ was the salivary gland, with 25% patients experiencing mild to moderate xerostomia. Only mild hematologic toxicities were observed. Subsequent clinical studies mainly focused on ^{177}Lu-based PSMA inhibitors such as PSMA-617 and PSMA I&T [48–50]. A retrospective multicenter analysis of 145 patients treated with 1 to 4 cycles of ^{177}Lu-PSMA-617 at 2–8 GBq per cycle showed that 45 of 99 (45%) patients had > 50% decline in PSA. In terms of toxicities, 18 of 145 patients (12%) experienced Grade 3–4 hematologic adverse events and 11 (8%) patients had mild to moderate xerostomia. No grade 3 or 4 nephrotoxicity was reported. In a separate single center phase II trial, 30 patients were treated with ^{177}Lu-PSMA-617 at 7.5 GBq per cycle for up to 4 cycles. All patients had history of progression after taxane based chemotherapy and second-generation anti-androgen treatment. A ^{68}Ga-PSMA-11 PET scan was used to screen for PSMA expression. More than half (57%) of patients achieved > 50% decline in PSA. Approximately 13% patients had Grade 3 or 4 thrombocytopenia and 87% of patients had grade 1 xerostomia [51]. In a second randomized, open-label, phase II trial, 98 patients with metastatic CRPC, for whom cabazitaxel was considered the next appropriate standard treatment, were randomized to be treated with either ^{177}Lu-PSMA 617 at 6.0–8.5 GBq per cycle for up to 6 cycles versus more traditional therapy with

cabazitaxel [52]. ^{68}Ga-PSMA-11 and ^{18}F-FDG PET were used for screening. Overall, 66% patients in the ^{177}Lu-PSMA 617 group demonstrated PSA response (> 50% decline), while only 37% showed PSA response in the cabazitaxel group. A third (33%) of patients in the ^{177}Lu-PSMA-617 group had Grade 3–4 adverse effects, fewer than the 53% adverse events reported in the cabazitaxel group.

An international, randomized open label phase III trial (VISION) was conducted based on the encouraging PSA response and low toxicity profile reported in the early phase clinical studies [53] (Table 1). A ^{68}Ga-PSMA-11 PET scan was used to screen patients. All eligible patients had at least one PSMA positive metastatic lesion and no PSMA-negative lesions. A total of 831 patients were randomized in a 2:1 ratio to be treated with ^{177}Lu-PSMA-617 plus standard care or standard care alone. The ^{177}Lu-PSMA-617 group received 7.4 GBq ^{177}Lu-PSMA-617 once every 6 weeks for at least four cycles, with two additional cycles allowed at the discretion of the treating physician. Overall, patients treated with ^{177}Lu-PSMA-617 plus standard care had prolonged median progression-free (as determined by imaging) survival of 8.7 months vs. only 3.4 months in the standard care group (P<0.001). Moreover, median overall survival was higher at 15.3 months in the PSMA group vs. 11.3 months in the standard care group (P<0.001). Nearly half (46%) of patients in the ^{177}Lu-PSMA-617 group had ≥ 50% PSA decline compared to only 7.1% in the standard care group. On the other hand, the ^{177}Lu-PSMA-617 group experienced higher adverse events with 52.7% having Grade ≥ 3 adverse events including 23.4% with hematological toxicity versus 38.0% and 6.8% in the standard care group, respectively. Mild (grade < 3) dry mouth was reported by 39.3% of patients in the ^{177}Lu-PSMA-617 group vs 1.0% in the standard care group.

Table 1
Clinical trials of ^{177}Lu-PSMA-617 in mCRPC patients.

Trials	VISION [53]	TheraP [52]	LuPSMA [51]
Study design	International, open label, randomized, phase 3 trial	Multicenter, unblinded, randomized phase 2 trial	Single-arm, single-center, phase 2 trial
Number of patients	831	200	30
Patient population	mCRPC progressed on ADT and taxane chemotherapy	mCRPC for whom cabazitaxel was considered the next appropriate standard treatment.	mCRPC progressed on ADT and taxane chemotherapy
Imaging screening	^{68}Ga-PSMA-11	^{68}Ga-PSMA-11	^{68}Ga-PSMA-11
Positive lesion criteria	Uptake > liver	SUV max ≥ 20 at a site of disease and > 10 at all other sites	Uptake ≥ 1.5 x liver uptake
Negative lesion criteria	Uptake ≤ liver [a]	Low uptake. PSMA neg/FDG pos lesion.	Low uptake. PSMA neg/FDG pos lesion.
Treatment protocol	7.4 GBq every 6 weeks for 4 to 6 cycles	6.0–8.5 GBq every 6 weeks for up to 6 cycles	7.5 GBq every 6 weeks for 4 cycles
Control group	Standard care [b]	Cabazitaxel	N/A
% patients ≥ 50% PSA decline vs control	46% vs 7.1%	66% vs 37%	57%
Median PFS (months) vs control	8.7 vs 3.4	5.1 vs 5.1	7.6
Median OS (months) vs control	15.3 vs 11.3	N/A	13.5

[a] Lymph nodes ≥ 2.5 cm, solid organ lesion ≥ 1.0 cm, bone lesion with soft tissue component ≥ 1.0 cm.

[b] No cytotoxic chemotherapy, systemic radioisotopes, immunotherapy, or investigational drugs.

Alpha-particle emitter labeled PSMA small molecular inhibitors

Failure to eradicate micrometastatic disease using systemic therapy is the main cause of PC recurrence. Alpha particle emitter labeled radiopharmaceuticals are promising treatment modalities for targeting micrometastases as their energy is highly concentrated on a short path length of ~100 μm with high linear energy transfer (LET) of ~100 keV/μm. High LET alpha particles can cause severe DNA double-strand breaks independent of dose rate, cell cycle or oxygenation status. Thus, it is possible to overcome the resistance to beta particles and induce cellular death even when only a few alpha particles traverse the cell nucleus [54].

Several alpha particle emitter labeled PSMA agents have been studied in both preclinical and clinical settings, including ^{213}Bi, ^{225}Ac, ^{211}At, and ^{227}Th [55-58]. In the initial clinical study of ^{225}Ac-PSMA-617, two patients who progressed on ^{177}Lu-PSMA-617 received 3 cycles of ^{225}Ac-PSMA-617 bimonthly at 100 kBq per kilogram of body weight. Both patients had a dramatic decline in PSA and showed complete response on follow up imaging [59]. In a subsequent retrospective evaluation of a larger cohort of mCRPC patients with history of progression on approved treatments, 24 of 38 patients (63%) treated with ^{225}Ac-PSMA-617 had a PSA decline > 50%. The median duration of tumor control was 9.0 months. However, 5 of the initially 40 treated patients dropped out of the treatment due to intolerable xerostomia. In chemotherapy naïve patients with advanced PC, one study showed that 14 of 17 patients (82%) had PSA decline ≥ 90% after 2–3 cycles of ^{225}Ac-PSMA-617 bimonthly with a de-escalation dosing scheme based on patient response [60]. In a follow-up retrospective analysis of 73 patients treated with ^{225}Ac-PSMA-617 by the same group, 70% patients had >50% PSA decline. The median progression free survival was 15.2 months and overall survival was 18 months [61].

In a prospective study of ^{225}Ac-PSMA-617, 28 mCRPC patients received 2 cycles of ^{225}Ac-PSMA-617 every two months at 100 KBq per kilogram body weight. Patients with PSA response or stable disease on interim ^{68}Ga-PSMA-11 PET after 2 cycles received additional cycles of ^{225}Ac-PSMA-617 (median 3 cycles, range 1–7 cycles). Approximately 39% patients had >50% PSA decline at the end of follow up. The median progression free survival and overall survival were 12 months and 17 months, respectively. Only 29% patients reported mild (grade I/II) xerostomia. No grade 3 or 4 toxicities were observed [61]. Two additional recent retrospective studies showed similar findings of ^{225}Ac-PSMA-617 treatment in mCRPC patients with > 50% PSA decline in 69% (9 of 13) and 65% (17/26) of patients, respectively [62] [61]. Zacherl et al. reported the first retrospective study of ^{225}Ac-PSMA-I&T in mCRPC patients with history of progression on approved therapy. A total of 14 patients received 100 KBq per kilogram body weight ^{225}Ac-PSMA-I&T in 1–5 cycles. Half of the patients (7 of 14) experienced a PSA decline of >50%, similar to the results observed with other studies with ^{225}Ac-PSMA-617. In a meta-analysis of 256 patients treated with ^{225}Ac-PSMA agents, 62.8% of patients achieved > 50% PSA decline. The pooled median progression free survival was 9.1 months and overall survival was 12.8 months. Clinically significant (grade ≥ 3) xerostomia and bone marrow suppression was observed in 1.2% and 25.9% of patients, respectively [63] (Table 2).

To date, there are no published clinical studies directly comparing the efficacy of ^{225}Ac-PSMA-617 to ^{177}Lu-PSMA-617. Given that many of the patients treated with ^{225}Ac-PSMA-617 had previously progressed on ^{177}Lu-PSMA-617, the biochemical response rate observed in this patient population is quite impressive. It remains unclear, however, what (if any) survival benefits ^{225}Ac-PSMA-617 will add. Xerostomia remains the dose limiting toxicity for ^{225}Ac-PSMA-617 and 100 kBq/kg was determined to be the maximal tolerated doses in early dose escalation studies. Several strategies have been proposed to prevent or treat radiation induced xerostomia, ranging from local cooling with an ice pack [64], local injection of Botulinum toxin [65], oral monosodium glutamate [66] to transplantation of artificial salivary glands [67]. As of yet, no clinical studies have been reported on the incorporation of these

Table 2
Clinical trials of ^{225}Ac-PSMA-617 in mCRPC patients (>20 patients).

Trials	Kratochwil C et al. [56]	Sathekge M et al. [97]	Yadav MP et al. [61]
Study design	Retrospective	Retrospective	Prospective
Number of patients	40	73	28
Patient population	mCRPC progressed and resistant against or ineligible for approved treatments	mCRPC [a]	mCRPC [b]
Imaging screening	^{68}Ga-PSMA-11 or ^{99m}Tc-MIP-1427	^{68}Ga-PSMA-11	^{68}Ga-PSMA-11
Positive lesion criteria	Uptake > liver	Uptake ≥ 2 x liver uptake	Uptake ≥ liver
Negative lesion criteria	Uptake <liver	Uptake < 2 x liver uptake	Uptake < liver
Treatment protocol	100 kBq/kg b.w. every 2 months, 1 or 2 cycles	8, 7, 6, 4 MBq/cycle, every 8 weeks, 1 to 8 cycles	100 kBq/kg b.w. every 8 weeks, 1 to 7 cycles
Control group	N/A	N/A	N/A
% patients with ≥ 50% PSA decline	63% [c]	70%	39%
Median PFS (months)	7.0	15.2	12.0
Median OS (months)	> 12.0	18.0	17.0

[a] Relapsed after GnRH analog, completed or refused chemotherapy, no access to 2nd gen. hormonal therapy.

[b] Received prior 2nd gen. hormonal therapy, complete or unfit for chemotherapy, refractory to ^{177}Lu-PSMA-617 or directly opted ^{225}Ac-PSMA-617.

[c] Patients who survived at least 8 weeks after first treatment.

strategies to escalate maximal tolerable dose.

Dosimetry

Unlike anti-CD20 antibody for non-Hodgkins' lymphoma, it is unclear whether unconjugated anti-PSMA antibody and small molecular inhibitors themselves have any clinically significant anti-tumor effects which could complicate dose response evaluation for radiolabeled agents [68]. So far, several post-therapy dosimetry studies have shown a trend of dose response to ^{177}Lu-PSMA-617 treatment in mCRPC patients [69-72]. Violet *et al.* performed post-therapy dosimetry in patients in the phase II LuPSMA trial. Patients who achieved PSA decline > 50% had a median "whole body" tumor dose of 14.1 Gy versus 9.6 Gy in patients with ⟨ 50% PSA decline. Patients with tumor dose < 10 Gy were unlikely to achieve PSA response ⟩ 50%. The salivary glands, lacrimal glands, and kidneys received the highest normal organ doses but these remained below the maximal tolerated level for these organs, consistent with mild toxicity profile observed in the clinical trials of ^{177}Lu-PSMA-617. Traditional index lesion dosimetry however was not performed and it is unclear if the "whole body" tumor dose can be correlated with traditional external beam radiation therapy dose. Schuchardt *et al.* performed dosimetry on 138 patients that were treated with either ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T. The mean tumor absorbed doses were 5.8 Gy/GBq and 5.9 Gy/GBq for ^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617, respectively [73]. The most common tumor doses for ^{177}Lu labeled small molecular PSMA agents range from 2 to 6 Gy/GBq in the majority of dosimetry studies [74]. Assuming a dose of 7.4 GBq per cycle as used in the VISION trial, ^{177}Lu-PSMA-617 would deliver between 15- 44 Gy to the tumor per cycle and accumulate 60–170 Gy after 4 cycles, which is above the typical dose that prostate tumor will respond to in traditional external beam radiation therapy. In comparison, solid tumors targeted by most radiolabeled antibodies received less than 50 Gy [75].

Kratochwil et al. estimated ^{225}Ac-PSMA-617 doses using extrapolation of pre-existing serial post-treatment ^{177}Lu-PSMA-617 scans [76]. Assuming a relative biologic effect of 5 for alpha particles, the effective

doses of ^{225}Ac-PSMA-617 received by the salivary glands, kidneys and red marrow were similar to those obtained for ^{131}I-MIP-1095 and ^{177}Lu-PSMA-617. Gosewisch *et al.* showed post-therapy quantitative ^{225}Ac-SPECT based dosimetry was feasible for ^{225}Ac-PSMA-I&T; for example, tumor absorbed dose for a small lesion in the right hip was 0.26Sv$_{RBE=5}$/MBq for ^{225}Ac-PSMA-I&T versus 0.35 Gy/GBq for ^{177}Lu-PSMA-I&T [77]. Despite the feasibility of dosimetry, pre-therapy dosimetry was not utilized in the Phase III VISION trial for ^{177}Lu-P-SMA-617. Instead, the number of treatment cycles patients received were adjusted based on clinical indicators such as adverse events and PSA response. Whether dosimetry-based treatment planning could improve clinical outcome compared to the current dosing scheme remains to be investigated.

PSMA PET guided radiotherapy of oligometastases

In some cases of BCR PC, only a small number of metastases are detected, described as an oligometastatic state which falls between localized disease and wide-spread metastases. In such cases, stereotactic ablative body radiotherapy (SABR) can be used to deliver high radiation

Table 3
Ongoing clinical trials of radiolabeled PSMA targeted small molecule inhibitors.

Intervention	Clinical Trials.gov Identifier	Study Title	Phase	Primary outcomemeasures
^{177}Lu-PSMA-617	NCT04430192	Dosimetry, Safety and Potential Benefit of ^{177}Lu-PSMA-617 Prior to Prostatectomy	1/2	To determine the radiation absorbed dose in the prostate and involved lymph nodes prior to radical prostatectomy
	NCT04443062	Lutetium-177-PSMA-617 in Oligo-metastatic Hormone Sensitive Prostate Cancer	2	Fraction of patients and time to disease progression in treatment arm vs standard of care arm
	NCT04720157	An International Prospective Open-label, Randomized, Phase III Study Comparing ^{177}Lu-PSMA-617 in Combination With Soc, Versus SoC Alone, in Adult Male Patients With mHSPC	3	Radiographic Progression Free Survival (rPFS)
	NCT04663997	^{177}LuPSMA-617 vs Docetaxel in Metastatic Castration Resistant and PSMA-Positive Prostate Cancer	2	Progression-free survival (PFS)
	NCT04689828	^{177}Lu-PSMA-617 vs. Androgen Receptor-directed Therapy in the Treatment of Progressive Metastatic Castrate Resistant Prostate Cancer	3	Radiographic Progression Free Survival (rPFS)
	NCT03042468	Phase I Dose-escalation Study of Fractionated ^{177}Lu-PSMA-617 for Progressive Metastatic CRPC	1/2	Dose limiting toxicity (DLT); Cumulative maximum tolerated dose (MTD)
	NCT05114746	Study of ^{177}Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer in Japan	2	Dose Limiting Toxicity (DLT) during 1 cycle; Overall Response Rate (ORR)
^{225}Ac-PSMA-617	NCT04597411	Study of ^{225}Ac-PSMA-617 in Men With PSMA-positive Prostate Cancer	1	Recommended Phase 2 Dose (RP2D)
^{177}Lu-PSMA-I&T	NCT04647526	Study Evaluating mCRPC Treatment Using PSMA Lu-177-PNT2002 Therapy After Second-line Hormonal Treatment (SPLASH)	3	Radiographic Progression Free Survival (rPFS)
	NCT05204927	Lu-177-PSMA-I&T for Metastatic Castration-Resistant Prostate Cancer	3	Radiographic Progression Free Survival
	NCT04297410	^{177}Lu-PSMA-I&T Prior to Radical Prostatectomy for Locally Advanced Disease	0	Surgical safety; Early oncological outcomes
^{225}Ac-PSMA-I&T	NCT05219500	Targeted Alpha Therapy With ^{225}Actinium-PSMA-I&T of Castration-resISTant Prostate Cancer (TATCIST).	2	Determination safety and efficacy after ^{225}Ac-PSMA-I&T
^{177}Lu-EB-PSMA-617	NCT04996602	Therapeutic Efficiency and Response to ^{177}Lu-EB-PSMA-617 in Comparison to ^{177}Lu-PSMA-617 in Patients With mCRPC	1	Therapeutic effect: PSA Response, ^{68}Ga-PSMA PET/CT Response
CTT1403	NCT03822871	A Trial of CTT1403 for Metastatic Castration Resistant Prostate Cancer	1	Frequency of DLTs at escalating dose levels of CTT1403
^{177}Lu-Ludotadipep	NCT04509557	^{177}Lu-Ludotadipep Treatment in Patients With Metastatic Castration-resistant Prostate Cancer.	1	Dose-limiting toxicity (DLT)
^{67}Cu-SAR-bisPSMA	NCT04868604	^{64}Cu-SAR-bisPSMA and ^{67}Cu-SAR-bisPSMA for Identification and Treatment of PSMA-expressing Metastatic Castrate Resistant Prostate Cancer (SECuRE)	1/2	Biodistribution, dosimetry of ^{64}Cu-SAR-bisPSMA; MTD, efficacy, adverse events, safty and tolerability of ^{67}Cu-SAR-bisPSMA
^{177}Lu-PSMA-617, Enzalutamide	NCT04419402	Enzalutamide With Lu PSMA-617 Versus Enzalutamide Alone in Men With Metastatic Castration-resistant Prostate Cancer (ENCA-p)	2	Prostate Specific Antigen (PSA) Progression-Free Survival
^{177}Lu-PSMA-617, Abemaciclib	NCT05113537	Abemaciclib Before ^{177}Lu-PSMA-617 for the Treatment of Metastatic Castrate Resistant Prostate Cancer	1/2	Recommended phase 2 dose, Proportion of participants with DLTs, Change in SUVmax on ^{68}Ga-PSMA-11
^{177}Lu-PSMA-617, Docetaxel	NCT04343885	In Men With Metastatic Prostate Cancer, What is the Safety and Benefit of Lutetium-177 PSMA Radionuclide Treatment in Addition to Chemotherapy (UpFrontPSMA)	2	Undetectable prostate specific antigen (PSA) rate at 12 months after commencement of protocol therapy
^{177}Lu-PSMA, Ipilimumab, Nivolumab	NCT05150236	^{177}Lu-PSMA Therapy Versus ^{177}Lu-PSMA in Combination With Ipilimumab and Nivolumab for Men With mCRPC (EVOLUTION)	2	PSA progression free survival (PSA-PFS) at 1 year
^{177}Lu-PSMA-617, Pembrolizumab	NCT03805594	^{177}Lu-PSMA-617 and Pembrolizumab in Treating Patients With Metastatic Castration-Resistant Prostate Cancer	1	Recommended phase 2 dose; Objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria
^{177}Lu-PSMA-617, Olaparib	NCT03874884	^{177}Lu-PSMA-617 Therapy and Olaparib in Patients With Metastatic Castration Resistant Prostate Cancer (LuPARP)	1	Dose Limiting toxicities (DLTs); Maximum Tolerated dose (MTD); Recommended Phase 2 Dose (RP2D)
I-131–1095, Enzalutamide	NCT03939689	Study of I-131–1095 Radiotherapy in Combination With Enzalutamide in Patients With Metastatic Castration-resistant Prostate Cancer Who Are Chemotherapy Naive and Have Progressed on Abiraterone	2	PSA Response Rate
^{177}Lu-PSMA-I&T/ PNT2002, Brachytherapy	NCT05230251	Radioligand fOr locAl raDiorecurrent proStaTe cancER (ROADSTER)	2	Safety and Efficacy of ^{177}Lu-PNT2002, 2 weeks prior to the planned HDR

dose to the tumor while minimizing exposure of surrounding normal tissues. Early clinical studies have shown that treating oligometastases with SABR could delay the use of systemic therapy and improve progression free survival. In the phase 2 ORIOLE trial, 54 patients with recurrent hormone sensitive prostate cancer that had 1 to 3 metastases on conventional imaging were randomized for SABR vs observation. These patients had not received ADT within 6 months of enrollment or 3 or more years total. Disease progression at 6 months occurred in only 19% (7 of 36 patients) in the SABR group compared with 61% (11 of 18 patients) in the observation group [78].

Bowden *et al.* reported SBRT for oligometastatic disease (< 5 metastatic lesions) in 138 PC patients. Using PSMA PET for restaging, 74 of 138 patients (53.6%) did not require treatment escalation over 2 years follow-up after SBRT [79]. In another prospective study, 57 patients with PSMA PET confirmed oligometastatic disease (< 3 lesions) were treated with SBRT. The median biochemical disease-free survival was 11 months. All patients underwent follow up PSMA PET after SBRT and no in-field failures were observed [80]. These findings support the use of SBRT to treat oligometastases identified on PSMA PET.

Future directions

^{177}Lu-PSMA-617 is currently under evaluation to compare its efficacy with Docetaxel and hormonal therapy in mCRPC. In addition, ^{177}Lu-PSMA-617 is being studied for clinical scenarios other than mCRPC, for example, in patients prior to prostatectomy and in patients with oligometastatic or metastatic hormonal sensitive prostate cancer (mHSPC) (Table 3). Additional radiolabeled PSMA small molecule inhibitors are also being investigated. ^{177}Lu-PSMA-I&T is being evaluated in a phase 3 trial to treat mCRPC (SPLASH trial). [225]Ac-PSMA-I&T is being studied in a phase II trial in CRPC patients (TATCIST trial) based on promising results from an initial clinical study [81]. Insertion of an albumin binding motif into PSMA targeted small molecules prolongs the blood clearance time thereby increasing the tumor doses. Two PSMA targeted molecules containing the albumin binding motif, CTT1403 and ^{177}Lu-Ludotadipep, are currently under evaluation in two phase I trials [82]. Small molecule theragnostic analogues with two PSMA binding motifs, ^{64}Cu/[67]Cu-SAR-bisPSMA, theorized to have higher specificity and in vivo stability are being investigated in a phase I/II trial for diagnosis and treatment of mCRPC (SECuRE trial).

In the phase III VISION trial, the protocol permitted standard care but did not include some recent FDA approved treatments such as cytotoxic chemotherapy, systemic radioisotopes (such as [223]Ra), immunotherapy, or PARP-inhibitors, out of concern for possible unexpected toxicities related to combination therapy. Currently, many studies are underway to evaluate combined therapy with ^{177}Lu-PSMA-617 and these novel treatments (Table 3). One such example is Olaparib, a poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor approved by the FDA for germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC. In a phase 3 trial, Olaparib prolonged median progression-free survival to 7.4 months vs 3.6 months in the control group and increased overall survival to 18.5 months vs 15.1 months in the control group [83]. Treating mCRPC with Olaparib could potentially radiosensitize cancer cells to radiation from ^{177}Lu-PSMA-617. This approach could potentially be more effective with [225]Ac-PSMA-617, which causes more effective double strand DNA breaks. Interestingly, in 10 patients who had a poor response to [225]Ac-PSMA-617, tumor samples from 7 patients harbor mutations in DNA damage repair genes [84], suggesting the potential of combining DNA damage repair inhibition with targeted alpha therapy.

For PC patients with metastatic disease, conventional external beam radiotherapy is limited to a small number of metastases (oligometastases). A novel Biology-guided radiotherapy (BgRT) system combines PET/CT with linear accelerator to allow delivering radiation doses to PET positive tumor in real time. With improvement in feedback latency, BgRT can potentially treat multiple metastases in a single session.

Gaudreault M et al. showed that it is feasible to identify PSMA positive metastases in PC patients up to 11 lesions per patients in the setting of BgRT [85].

Two immunotherapies have been approved by the FDA for prostate cancer so far, Sipuleucel-T, an autologous cell-based immunotherapy, and pembrolizumab, an immune checkpoint inhibitor, for patients with high microsatellite instability, mismatch repair deficiency or high tumor mutational burden [86,87]. Several clinical trials are currently underway to evaluate combining ^{177}Lu-PSMA-617 with pembrolizumab. The hypothesis is that ^{177}Lu-PSMA-617 could make the tumor microenvironment more immunogenic for subsequent immunotherapy. On the other hand, however, bone marrow suppression from systemic ^{177}Lu-PSMA-617 treatment may be seen in some patients and could mitigate immune response. Aggarwal et al. evaluated immunogenic priming with a single dose of ^{177}Lu-PSMA-617 in mCRPC patients in a phase 1b study [88]. Nearly a third (28%) of patients had > 50% PSA decline and median progression free survival was 6.5 months. No dose-limiting toxicities and only one treatment related grade 3 adverse event (inflammatory arthritis) was reported. New immunotherapy approach using PSMA targeted chimeric antigen receptor-modified T-cell (CAR-T) therapy in mCRPC is being actively investigated. In a first-in-human phase 1 clinical trial of PSMA-directed/TGFβ-insensitive CAR-T cells (CART-PSMA-TGFβRdn) in mCRPC, 6 of 10 patients reported PSA response and PSA30 response occurred in 40% patients [89]. Several bispecific antibodies targeting both PSMA and CD3 thereby linking tumor cells and cytotoxic T-cells are being evaluated to assess recruitment of T-cells to kill tumor cells.

In addition to PSMA radiopharmaceuticals, other PSMA directed therapeutics are currently under investigation. PSMA targeted antibody drug conjugate (ADC) had been evaluated in mCRPC. In a phase I/II trial of MLN2701, an ADC of anti-PSMA monoclonal antibody MLN591 conjugated with maytansinoid (DM1), 62 patients were treated with escalating doses. Only 5 of 62 (8%) patients experienced PSA decline ≥ 50%. Overall, 44 of 62 patients (71%) reported peripheral neuropathy and 6 of these (10%) were grade 3/4 adverse events [90]. In a phase II trial of PSMA ADC, a monoclonal antibody conjugated to monomethylauristatin E, 113 patients were treated for 8 cycles, with 14% of patients showing a PSA decline ≥ 50% [91]. In addition, engineered antibody fragments such as PSMA targeted Fab and scFv fragments [92] and nanobody [93] have been developed, which maintain high binding affinity while their smaller size (~15 kDa for nanobody to 55 kDa for Fab) compared to full-size antibodies (~150 kDa) allows for fast renal clearance and better tumor penetration. These engineering antibody fragments however are relatively larger than PSMA small molecule inhibitors, and therefore may have a longer blood circulation time. Clinical studies for normal tissue and marrow toxicity with radiation dosimetry are needed to better understand their potential in targeted radionuclide therapy.

Given that PSMA is frequently expressed in the neovasculature of other solid tumors, PSMA targeted therapeutics are also being evaluated for other solid tumors, including renal cell carcinoma [94], adenoid cystic carcinoma of the salivary glands [95], and bladder cancer [96]. Kelin Nulent et al. reported their first experience with ^{177}Lu-PSMA-617 in patients with recurrent or metastatic salivary gland who were not candidates for traditional treatment. A total of 6 patients were treated with 4 cycles of 6.0–7.4 GBq ^{177}Lu-PSMA-617 at 6–8 week intervals, with 2 of 6 patients showing stable disease or partial response. 3 of 6 patients showed disease progression and one patient discontinued treatment due to grade 1 side effect.

Conclusion

PSMA targeted theragnostic agents have shown tremendous potential in detecting and treating metastatic prostate cancer. The PSMA small molecular inhibitor-based imaging agents achieve extraordinary tumor to background ratios and the PSMA small molecule therapeutic agents

have shown impressive therapeutic index in mCRPC. Moreover, the development and optimization of PSMA theragnostic agents provides invaluable information that may help guide development of future theragnostics for other solid tumors.

Authors contributions statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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