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ANNUAL REVIEWS

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Prostate-Specific Membrane Antigen: Gateway to Management of Advanced Prostate Cancer

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Keywords

prostate-specific membrane antigen, prostate cancer, antibody therapy, radioligand therapy, precision oncology, PSMA imaging, positron emission tomography, PET

Abstract

Prostate-specific membrane antigen (PSMA) as a transmembrane protein is overexpressed by prostate cancer (PC) cells and is accessible for binding antibodies or low-molecular-weight radioligands due to its extracellular portion. Successful targeting of PSMA began with the development of humanized J591 antibody. Due to their faster clearance compared to antibodies, small-molecule radioligands for targeted imaging and therapy of PC have been favored in recent development efforts. PSMA positron emission tomography (PET) imaging has higher diagnostic performance than conventional imaging for initial staging of high-risk PC and biochemical recurrence detection/localization. However, it remains to be demonstrated how to integrate PSMA PET imaging for therapy response assessment and as an outcome endpoint measure in clinical trials. With the recent approval of ^{177}Lu-PSMA-617 by the US Food and Drug Administration for metastatic

castration-resistant PC progressing after chemotherapy, the high value of PSMA-targeted therapy was confirmed. Compared to standard of care, PSMA-based radioligand therapy led to a better outcome and a higher quality of life. This review, focusing on the advanced PC setting, provides an overview of different approved and nonapproved PSMA-targeted imaging and therapeutic modalities and discusses the future of PSMA-targeted theranostics, also with an outlook on non-radiopharmaceutical-based PSMA-targeted therapies.

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INTRODUCTION

Worldwide, prostate cancer (PC) is the second-most common cancer in men and the most frequently diagnosed noncutaneous cancer in men, with increasing morbidity and mortality. In 2020, PC was estimated to account for over 1,414,000 new cases and over 375,000 cancer-related deaths worldwide (1).

In patients with advanced PC, disease initiation and progression are driven by androgen receptor (AR) signaling, leading to treatment with androgen deprivation therapy. AR signaling inhibitors (ARSi) such as abiraterone and enzalutamide or taxane-based chemotherapy have improved outcome in hormone-sensitive PC (HSPC) (2, 3). In metastatic castration-resistant PC (mCRPC), in which PC cells become resistant to androgen deprivation therapy, the implementation of ARSi therapy, chemotherapy with docetaxel or cabazitaxel, radiopharmaceutical therapy with an alpha-emitting bone-seeking radioisotope (^{223}Ra), and the immunotherapeutic sipuleucel-T have demonstrated prolonged overall survival. In addition, since 2020, poly(ADP-ribose) polymerase (PARP) inhibitors have received US Food and Drug Administration (FDA) approval for mCRPC patients with a *BRCA1/2* mutation who underwent treatment with both a second-generation hormonal agent and taxane-based chemotherapy (4).

The theranostic approach describes a specific molecular targeting for diagnostics and therapy. In nuclear medicine, theranostics is the combined use of imaging and therapeutic radiopharmaceuticals with the same molecular target: The visualization of potential targets by imaging can help predict the benefit from target-specific treatment in the context of a preselection of suitable patients.

Imaging and therapy modalities that target prostate-specific membrane antigen (PSMA) have recently been approved and are changing the landscape of patient management in advanced PC. Here we focus on the role of PSMA-targeted approaches in nonmetastatic CRPC, mHSPC, and mCRPC.

AR: androgen receptor

ARSi: androgen receptor signaling inhibitors

(m)HSPC: (metastatic) hormone-sensitive prostate cancer

(m)CRPC: (metastatic) castration-resistant prostate cancer

PROSTATE-SPECIFIC MEMBRANE ANTIGEN

In 1987, Horoszewicz et al. (5) described a prostate-specific antigen that was later designated prostate-specific membrane antigen (PSMA). This type II transmembrane protein is also known as folate hydrolase 1 (FOLH1), glutamate carboxypeptidase II (GCPII), or N-acetyl-α-linked acidic dipeptidase I. The function of PSMA in PC remains unclear. PSMA is expressed by prostate epithelial cells, but more importantly, it is highly overexpressed by PC cells in more than 85% of PC patients (6). Higher PSMA expression carries prognostic value and has been associated with decreased survival (7). Despite its designation, PSMA was subsequently found to be expressed in some normal tissues such as renal proximal tubules, small bowel, and salivary and lacrimal glands, as well as in the neovasculature in many solid tumors (8).

PSMA-targeted agents can be internalized into the targeted cells, to deliver their payloads into the PC cells (9, 10).

PSMA-TARGETED IMAGING IN ADVANCED PROSTATE CANCER

Since the largest proportion of the PSMA molecule is extracellular, it is accessible for binding of antibodies or low-molecular-weight ligands. There was a first attempt to image PSMA with gamma scintigraphy via a monoclonal antibody labeled with ^{111}In: ProstaScint® (7E11-C5), FDA approved in 1996 (11); however, 7E11-C5 targets an intracellular epitope of PSMA that provided low-quality images, and its clinical use was abandoned (12). Successful demonstration of clinical targeting of the external portion of PSMA began with the development of the humanized J591 antibody (13). First gamma planar scintigraphy images obtained with ^{111}In-J591 and ^{177}Lu-J591 demonstrated the ability of a PSMA-targeted agent to accurately target bone and soft tissue PC lesions in patients with metastatic PC (13, 14). Furthermore, some lesions were detected prior to visibility on conventional imaging (13), which presaged the development of substantial imaging improvement with positron emission tomography (PET). About a decade later, PET imaging using ^{89}Zr-J591 was able to detect many more lesions than conventional imaging techniques in metastatic PC, especially bone lesions (13a). However, because of the relatively long clearance time of antibodies, the ideal imaging time to provide the highest tumor-to-background ratio was 7 days postinjection (13a). In contrast, small-molecule ligands that bind to PSMA have much faster clearance and are more practical for clinical imaging.

PSMA-Based Radioligands for PET

PSMA small-molecule ligands have a fast clearance from blood plasma and are rapidly internalized and accumulated into PC cells (15, 16). The first-in-human PET image of a PSMA small molecule ligand was performed in Heidelberg, Germany in 2012 (17). In recent years, multiple different PSMA-targeted small molecules, most sharing the same glutamate-urea-lysine binding motif but slightly differing in their linker-chelate, were developed (15). They can be radiolabeled with positron emitter isotopes such as ^{68}Ga, ^{18}F, or ^{64}Cu. These positron emitters differ in their half-lives (^{68}Ga: 68 min, ^{18}F: 110 min, ^{64}Cu: 12.7 h), their positron energy, and their synthesis methods. Among others, the following PSMA-targeted PET tracers should be highlighted: ^{18}F-DCFPyL, ^{18}F-rhPSMA7.3, ^{68}Ga-PSMA-I&T, ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, ^{18}F-PSMA-1007, and ^{64}Cu-PSMA-I&T. Within these, ^{68}Ga-PSMA-11 (manufactured by UCLA-UCSF; or as Illuccix® by Telix and Locametz® by Novartis), ^{18}F-DCFPyL (PYLARIFY®, Lantheus), and ^{18}F-rhPSMA7.3 (POSLUMA®, Blue Earth Diagnostics) have been approved by the FDA since 2020.

Overall, the FDA-approved PSMA ligands have similar diagnostic efficacy for both initial staging and restaging. In high-risk patients, the sensitivity is ~40% and the specificity of PSMA PET for detection of pelvic nodal disease ranges between 95% and 98% as validated by histopathology (positive predictive value 75–87%, negative predictive value 81–83%) (18, 19). In patients with biochemically recurrent PC, detection rates for disease between both these tracers were similar with a high positive predictive value (92–93%) (20, 21). In HSPC patients with biochemical recurrence, the detection rate depends mostly on the prostate-specific antigen (PSA) value at the time of the scan. Some reports suggest a slight superiority of ^{18}F tracers, but no statistically robust prospective comparison has been conducted (22–24).

Use of PSMA-Based PET Radioligands for the Clinical Management of Prostate Cancer

The National Comprehensive Cancer Network guidelines and the Appropriate Use Criteria recommend the use of the FDA-approved PSMA-targeted PET radioligands as a first-line imaging

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tool for initial staging of a newly diagnosed intermediate and high-risk/very high-risk PC, the detection of biochemical recurrence, and as a work-up for progression in recurrent PC (12, 25). Similarly, the American Urological Association, the European Association of Urology, and the European Society for Medical Oncology recommend PSMA PET imaging in their guidelines (26–29). Standardized frameworks for (initial) staging, such as PROMISE V2, can provide in this context a modified TNM (tumor, node, metastasis) staging based on molecular imaging (30).

The majority of trials have studied the impact of PSMA PET on recurrence after primary therapy and reported higher detection rates than conventional imaging with a high impact on treatment management (31–33). For initial staging, studies also demonstrated the superiority to conventional imaging and the impact on patient management of PSMA PET for extraprostatic disease detection (34, 35). Additionally, PSMA PET might have an impact on the intraprostatic evaluation of PC lesion(s). The combination of PSMA PET with magnetic resonance imaging (MRI) provides additive information for intraprostatic tumor delineation. Combining PSMA PET/CT (computed tomography) with MRI can decrease the rate of false-negative results, thereby potentially avoiding unnecessary prostate biopsies (36, 37). PSMA PET may also be used to guide prostate biopsy in cases of high suspicion of PC and prior inconclusive/negative MRI-guided/systematic biopsy (38, 39).

However, the role of PSMA for the restaging of advanced PC is not clearly defined, and it remains unknown how to use the data of clinical trials based on conventional imaging staging. Disease stage migration from M0-conventional imaging to M1-PSMA PET occurs frequently in nonmetastatic CRPC (21, 40). Some reports showed a potential role of PSMA PET for oligometastatic CRPC (41). In advanced PC, precise disease localization and staging are often less important than evaluation of disease volume (high versus low) for prognostication and therapy management (2, 42). PSMA PET will also redefine high- and low-volume disease. Further studies are needed to understand how to incorporate new PSMA PET information into treatment algorithms. Similarly, PSMA PET–based therapy response assessment is not clearly defined yet and the CT/bone scan-based Prostate Cancer Working Group 3/Response Evaluation Criteria in Solid Tumors (PCWG3/RECIST) criteria remain the methods of reference.

Finally, PSMA PET offers the possibility to visualize and quantify PSMA target expression before administering PSMA-targeted therapy. Due to the approval of ^{177}Lu-PSMA-617 (Pluvicto®) by the FDA and European Medicines Agency, the use of PSMA PET is likely to increase in patients with advanced PC.

PSMA-Targeted PET Radioligands: Future Directions

Within the next few years, the whole-body (WB) PSMA tumor volume as well as the role of PSMA-targeted PET for response assessment will gain increasing importance.

The value of whole-body PSMA tumor volume segmentation. WB imaging biomarkers such as the bone scan index in bone scintigraphy can be associated with outcome in advanced PC (43). PET imaging provides the ability to obtain WB images with quantitative parameters such as the WB PSMA-positive total tumor volume (PSMA TV) or the average WB standardized uptake value (SUV_{mean}). The WB SUV_{mean} reflects the tumor biology heterogeneity at the WB patient level, unlike the SUV_{max} (highest SUV), which is more subject to the sampling bias of the lesion-based assessment.

Manual segmentation of WB PSMA TV is time consuming, which limits its widespread use in clinical routine. Additionally, there is no standardized recommendation for the segmentation method of WB tumor delineation. Artificial intelligence and/or semiautomated methods for WB

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PSMA TV measurement are under clinical development to provide fast and reproducible tools (44, 45).

As shown recently, a WB PSMA-TV-derived risk score can provide a model for patient outcome across all disease stages (46). The WB PSMA SUV_{mean} reflecting the overall PSMA expression of the disease was reported to be of strong predictive value before ^{177}Lu-PSMA therapy (47) and has been integrated among other clinical parameters into a clinical nomogram available online (*LuPSMA Prognostic Model*) (48, 49). Recently, an alternative to assessing WB PSMA SUV_{mean} quantitatively before ^{177}Lu-PSMA was proposed: the PSMA PET tumor-to-salivary glands ratio, a visual grading system that can be obtained rapidly from the PET maximum intensity projection (MIP) to provide a WB target expression assessment without requiring WB TV segmentation (50). Outside of research environments, this novel score in combination with the VISION criteria can assist individual clinical decision-making in patients considered for ^{177}Lu-PSMA-targeted therapy (51).

The role of PSMA-targeted PET imaging for therapy response assessment. RECIST and PCWG3 criteria are established criteria to assess response to systemic therapy in advanced PC. However, they rely on changes that occur late after treatment initiation. These criteria are also limited for sclerotic bone lesion assessment. In this context, PSMA PET/CT may be a useful method for evaluating response to therapy.

Retrospective studies on the use of PSMA PET for assessing response to systemic therapy applied different methods to determine response, included heterogeneous treatment modalities and different time frames between therapy initiation and follow-up with PSMA PET/CT (52–54): Some reported that changes of PSMA PET parameters under taxane-based chemotherapy might be used as predictive biomarkers for overall survival (54). PSMA expression is correlated with AR activity, and studies suggest that short-term antiandrogen therapy may upregulate PSMA expression (flare phenomenon) (55). Of note, when the follow-up scans are performed with different PSMA ligands (e.g., ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL), SUVs are not comparable and cannot be used for therapy response assessment (24).

The EANM consensus statements on PSMA PET/CT response assessment criteria in PC underline that an evaluation of treatment response should be performed only if a potential change in patient management is expected from the imaging, and defined categories for response and progression to treatment (56) (**Table 1**).

Table 1 European Association of Nuclear Medicine consensus statements on PSMA PET/CT response assessment (56)

Complete response	Partial response	Stable disease	Progressive disease
Disappearance of any lesion with tracer uptake	Reduction of uptake and tumor volume >30%	Change of uptake and tumor volume ± ≤30 and no new lesions	Appearance of ≥2 lesions[a] and/or increase of uptake of tumor PET volume ≥30% Appearance of 2 or more new lesions should not necessarily be rated as progressive disease if total tumor volume or uptake does not increase >30%

Abbreviations: CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

[a]Identification based on appearance of new focal area of PSMA uptake at PET with or without CT change.

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Table 2 Modified PSMA PET progression criteria (57)

Category A	Category B	Category C
≥2 new metastases	1 new metastasis and increase of ≥25% in PSA or LDH or ALP or NSE	Distinct increase in tumor volume by visual assessment and increase of ≥25% in PSA or LDH or ALP or NSE

Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; PSA, prostate-specific antigen.

In the modified PSMA PET progression (PPP) criteria, three categories define disease progression in PC as listed in **Table 2**, the main parameter being the appearance of new lesions on PSMA PET (57).

RECIP (Response Evaluation Criteria In PSMA Imaging) 1.0 integrates both the WB PSMA TV changes, as assessed quantitatively, and the appearance of new lesions (**Table 3**). RECIP 1.0 is a biomarker that is prognostic for overall survival after ^{177}Lu-PSMA (58, 59) and potentially also under other systemic therapies, such as chemo- or AR-targeted therapies (60). RECIP 1.0 was reported to be more reproducible than RECIST 1.1, aPCWG3, aPERCIST (PET Response Criteria in Solid Tumors), and PPP (60). As automatic segmentation tools are not yet widely available outside of the research setting, the use of nomograms for visual assessment of WB PSMA TV such as Visual RECIP may assist individual clinical decision-making in patients treated with systemic therapy and evaluated with PSMA PET (61).

PSMA-TARGETED THERAPY IN PROSTATE CANCER

PSMA-Targeted Therapy Agents

Targeting of PSMA can be performed by radionuclide-based therapeutics as well as by antibodies.

Radionuclide-based therapy agents. Radionuclide therapy (also radiopharmaceutical therapy or molecular radiotherapy) aims to deliver radiation (usually emitted as alpha or beta particles) to tumor lesions via intravenous administration of a radiopharmaceutical agent. The radiation can be delivered to the cancer cells directly via specific targets (sodium/iodide symporter for thyroid cancer, somatostatin receptor for neuroendocrine tumors, CD20 for lymphoma, PSMA for PC) or indirectly via osteoblasts for ^{153}Sm or ^{223}Ra. Most approved therapeutic radiopharmaceuticals are currently labeled with beta-emitting isotopes. The most commonly used beta emitter for radioligand therapy (RLT) in PC is ^{177}Lu (mean tissue penetration 0.5–0.6 mm, maximum 2 mm, 498 keV, half-life 6.7 days). Also regularly used in clinical or investigational settings are the beta-emitting isotopes ^{131}I and ^{90}Y and the alpha-emitting isotopes ^{225}Ac and ^{223}Ra.

Table 3 RECIP 1.0 criteria for response assessment (59, 60)

Response	Complete	Partial	Stable	Progressive
PET	Absence of any PSMA-positive lesion	Decline of ≥30% in whole-body tumor volume without appearance of new lesions	Any condition not rated as complete, partial, or progressive	Increase ≥20% in whole-body tumor volume with appearance of new lesions

Abbreviations: PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

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Antibodies. As with imaging, the first efforts at PSMA-targeted radionuclide therapy were investigator-initiated trials utilizing the J591 antibody. Two prospective phase I trials at Weill-Cornell Medicine of a single dose of ^{90}Y-J591 (62) and ^{177}Lu-J591 (14), respectively, established that the dose-limiting toxicity was myelotoxicity, primarily thrombocytopenia, as with previous beta particle–labeled antibodies in other tumor types. This was attributed to the relatively long circulating time of an antibody and resulting marrow exposure. These trials confirmed antitumor activity with PSA response and symptomatic improvement of bone pain and served to validate PSMA as a clinically addressable and potentially valuable target. The subsequent phase II trial of a single dose of ^{177}Lu-J591 confirmed that it was well tolerated with reversible myelosuppression. Subsequently, PSA responses were seen, with evidence of a ^{177}Lu-J591 dose-response relationship. A two-dose fractionated regimen was tested in mCRPC patients in a phase Ib/IIa trial (63). The goal of fractionation was to increase the cumulative dose of radiation administered by dividing the regimen into 2 doses 2 weeks apart. The 2-week timing was chosen to coordinate with the platelet recovery kinetics (14). Fractionated administration of ^{177}Lu-J591 allowed higher cumulative radiation dosing. The frequency and depth of PSA decrease, overall survival, and also toxicity (dose-limiting myelosuppression) increased with higher doses. In 2013, the long-term follow-up of 150 patients treated with ^{177}Lu-J591 or ^{90}Y-J591 showed that all patients had complete neutrophil count recovery and 97% had platelet count recovery to grade 0–1. It was also shown that ^{177}Lu-J591 radionuclide therapy did not preclude subsequent chemotherapy (64). Currently, the phase I ProstACT SELECT study (NCT04786847) is aiming to assess the safety and tolerability of targeted radiotherapy with ^{177}Lu-J591 (^{177}Lu-DOTA-TLX591) administered in two cycles in patients with PSMA-expressing mCPRC (65). A phase III randomized registration trial is underway (ProstACT Global).

Radio-labeled low-weight molecules. The first PSMA-based therapeutic small-molecule radioligand introduced in the clinic was ^{131}I-labeled PSMA-1095 in 2008 (16, 66). ^{131}I-MIP1095 showed promising results with good PSA responses (66). A multicenter phase II study (ARROW, NCT03939689) is currently evaluating the safety and efficacy of ^{131}I-labeled PSMA-1095 plus enzalutamide compared to enzalutamide alone in patients with mCRPC who have progressed under abiraterone (67). However, compared to ^{177}Lu-PSMA, ^{131}I-MIP1095 was associated with a higher percentage of adverse effects (66, 68). Also, ^{131}I emits gamma radiation that requires more radiation safety precautions than the beta emissions of ^{177}Lu. Therefore, ^{177}Lu proved to be the beta-emitting radionuclide of choice for the clinical development of PSMA-targeted radioligand therapy.

^{177}Lu-PSMA-617 is the most investigated PSMA ligand for the treatment of mCRPC. After the first patient was treated with ^{177}Lu-PSMA-617 in 2014 (69), many clinical reports and phase II trials have demonstrated promising results: Early clinical studies showed significant treatment responses and low-grade toxicities, and reported that patients who received multiple treatments continued to respond in subsequent therapy cycles (70–74).

The phase III multicenter VISION trial confirmed the results of the earlier studies, reporting a significant improvement in patients undergoing ^{177}Lu-PSMA-617 plus standard of care compared to standard of care alone. Overall survival (median 15.3 versus 11.3 months), radiographic progression-free survival (median 8.7 versus 3.4 months), and PSA response were all improved with ^{177}Lu-PSMA-617 (66, 75). Additionally, ^{177}Lu-PSMA-617 delayed time to worsening of pain and increased health-related quality of life (76).

Another small-molecule PSMA inhibitor is ^{177}Lu-PSMA-I&T (see **Figure 1**), which has PSMA affinity, dosimetry, and pharmacokinetics close to that of ^{177}Lu-PSMA-617. ^{177}Lu-PSMA-I&T demonstrated significant PSA response and a prolonged overall survival in mCRPC in retrospective study designs (77, 78): Two multicenter phase III studies, SPLASH (NCT04647526)

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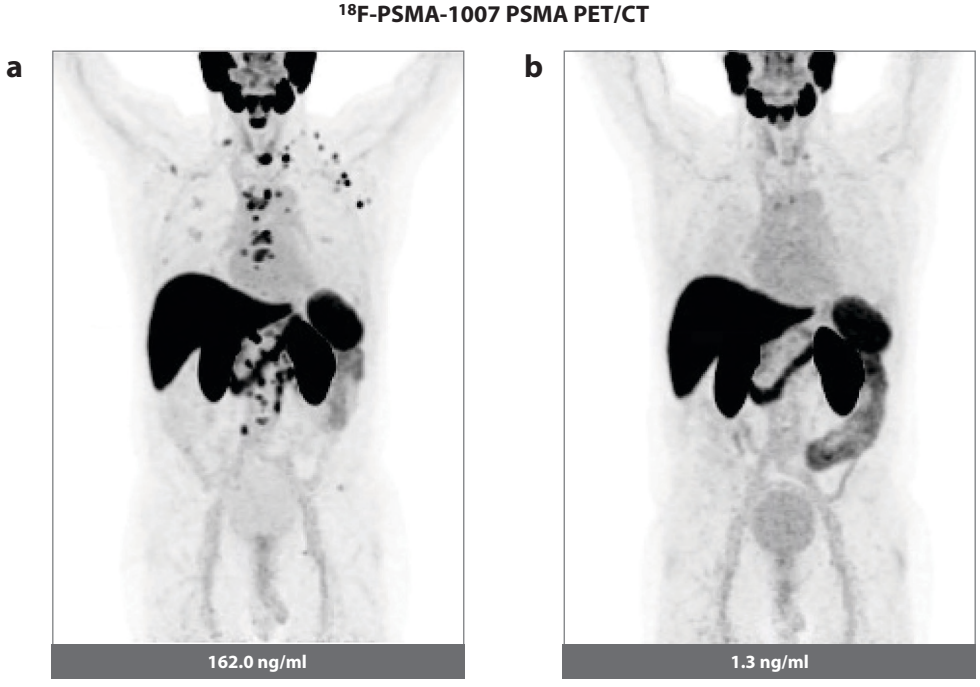


Figure 1

WB PET/CT images of a mCRPC patient who underwent four cycles of ^{177}Lu-PSMA-I&T and showed a significantly reduced post-therapeutic PSMA WB tumor volume (*b*) compared to the pretherapeutic PET (*a*) as well as a significant PSA response. Abbreviations: CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; WB, whole body.

and ECLIPSE (NCT05204927), are investigating the efficacy of ^{177}Lu-PSMA-I&T versus ARSi therapy regarding outcome parameters in the second-line setting after progression on the first ARSi therapy in mCRPC. The first studies comparing ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T suggested that the rate of adverse effects and overall survival did not differ between these radioligands (79). Further studies comparing both ligands, also including dosimetry models, may be needed.

^{177}Lu-PSMA-Targeted Radioligand Therapy

Following the VISION trial results, ^{177}Lu-PSMA-617 was approved by the FDA in 2022 as ^{177}Lu-vipivotide tetraxetan (Pluvicto®) for men with PSMA-positive progressing mCRPC after taxane-based chemotherapy who have been treated with androgen receptor pathway inhibition. Pluvicto® should be given once every 6 weeks for four cycles (injected activity 7.4 GBq/cycle) with the potential to increase up to six cycles if the patient is tolerating it.

The TheraP trial, comparing ^{177}Lu-PSMA RLT to cabazitaxel, showed a higher PSA response (66% versus 37%), fewer adverse events (33% versus 53%) and better quality of life in the ^{177}Lu-PSMA arm with similar overall survival in both arms under RLT (80). Addressing potential concerns using ^{177}Lu-PSMA RLT after ^{223}Ra therapy, the RALU (Radium Lutetium) study showed that ^{177}Lu-PSMA RLT was well tolerated in patients who had received prior ^{223}Ra before or after docetaxel and could consequently follow this therapy in PC treatment sequence (81).

A pretherapeutic PSMA-targeting imaging method is required to show at least one tumoral lesion with PSMA uptake above the liver, assessed visually, and the absence of PSMA-negative lesions (PSMA uptake equal or below liver) measurable by CT (bone with soft tissue component $\geq$1.0 cm, lymph node $\geq$2.5 cm, and solid organ $\geq$1.0 cm). As shown recently, patients with PSMA-negative lesions or low PSMA expression have a poor response to ^{177}Lu-PSMA RLT (82). VISION criteria and the subsequent FDA-approved Pluvicto® indications do not require a pretherapeutic ^{18}F-fluorodeoxyglucose (FDG) PET/CT evaluate potential FDG-positive PSMA-negative lesions, even if dual-tracer PET may assist in primary staging and restaging (83).

Several guideline documents have been recently generated, such as the joint European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging (EANM/SNMMI) guidelines for incorporating ^{177}Lu-PSMA RLT in clinical practice with site-specific standard operating procedure (84, 85). A questionnaire specific to ^{177}Lu-PSMA RLT has been developed to help monitor toxicities and symptoms: The Functional Assessment of Cancer Therapy-Radionuclide Therapy (FACT-RNT) score (84, 86).

Future and Development of PSMA-Targeted Radioligand Therapy

Studies continue to explore the optimal use of ^{177}Lu-PSMA, as well as alpha-emitting therapeutics, combination therapies, and non-radiopharmaceutical-based therapies.

Beyond VISION. Many practical questions regarding ^{177}Lu-PSMA RLT still remain to be answered. Follow-up reports may suggest that safety thresholds in patients with low kidney function and bone marrow function may be lowered.

The number of cycles, amount of injected activity, and time intervals between cycles were derived empirically, and further trials may be required for additional optimization. First studies demonstrated that a rechallenge RLT after this number of cycles showed acceptable safety profiles and higher response rates than other systemic therapies and provided a rationale to pursue this salvage RLT approach further (87, 88).

A recent study reported that a treatment holiday (i.e., break) for patients with marked reduction in PSA and partial response based on ^{177}Lu-PSMA and 24-h single photon emission computed tomography (SPECT)/CT images may lead to superior survival times compared with a fixed standard regimen of 6 cycles every 6 weeks. This study substantiates flexible dosing regimens as a promising approach (89).

The criteria to define disease progression using PSMA-targeted imaging and discontinue therapy remain to be defined. The value of gamma scintigraphy SPECT/CT images obtained after administration of ^{177}Lu-PSMA for response assessment or individualized dosimetry is under early investigation.

Multiple randomized phase III registration trials aim at moving ^{177}Lu-PSMA to earlier disease stages, i.e., prior to docetaxel and/or in the HSPC stage [PSMAfore (NCT04689828), PSMAddition (NCT04720157)]. ^{177}Lu-PSMA-I&T trials are testing ^{177}Lu-PSMA in taxane-naïve mCRPC patients (see the section titled Radio-Labeled Low-Weight Molecules).

From beta- to alpha-emitting therapeutics. As investigators strive to improve the therapeutic results with targeted radiopharmaceutical therapy, interest has surged in the use of alpha particles. Radioisotopes emitting alpha particles have much higher linear energy transfer and shorter penetration range than beta emitters, increasing the probability of DNA double-strand breaks (90), while DNA damage incidence is proportional to the absorbed dose. Alpha emitters' short range of $<$100 μm in human tissue minimizes the potential damage to surrounding healthy tissue. While interest in PSMA-targeted alpha particles is not new (91), development of these agents has been hampered by their limited availability, questions about the appropriate chelate, and concerns about

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potential toxicity. Currently, the most commonly used alpha emitter is ^{225}Ac (5.8 MeV, half-life 9.9 days). PSMA-617 and PSMA-I&T were tested with ^{225}Ac (92–94). ^{225}Ac PSMA-617 led to PSA responses (≥90% decline in chemotherapy-naïve patients, ≥50% decline in CPRC patients) and increased radiographic progression-free survival in mCRPC patients who had progressed under ^{177}Lu-PSMA (93–95), with an acceptable hematologic safety profile (92).

AcTION (NCT04597411) and TATCIST (NCT05219500) evaluated the safety profile of ^{225}Ac-PSMA-617 and ^{225}Ac-PSMA-I&T, respectively. In addition, tandem therapies combining ^{225}Ac-PSMA and ^{177}Lu-PSMA ligands within one cycle will be further evaluated in the coming years and have the potential to reduce the incidence of dry-mouth syndrome—the most prominent adverse event of ^{225}Ac-PSMA RLT as a result of the high radiobiological effect of alpha emitters (96, 97).

Antibodies can also be used to deliver alpha particles and may have a potential benefit with a different normal tissue biodistribution pattern compared to small ligands. For example, whereas small ligands deliver a high dose to the salivary and lacrimal glands and to the kidneys (their excretory route), antibodies show no detectable uptake in the salivary or lacrimal glands (98). The reason for the differing biodistribution of these two classes of PSMA-targeted agents is believed to be based on molecular size. J591 has been used to target ^{225}Ac in a prospective, investigator-initiated single ascending dose trial (NCT03276572) involving 32 patients with progressive, heavily pretreated mCRPC after ARSi and taxane-based chemotherapy including prior ^{177}Lu-PSMA RLT (99). In this trial, 47% of the patients experienced a >50% decline in PSA, and the PSA50 (a PSA response of >50% compared to baseline) response rate was similar in the ^{177}Lu-PSMA-617-naïve patients as in those with ^{177}Lu-PSMA-617 pretreatment. This agent is currently in a phase I/II multiple ascending dose trial (NCT04506567), a phase I/II trial in combination with ^{177}Lu-PSMA-I&T (NCT04886986), and a phase I/II trial in combination with pembrolizumab (NCT04946370).

Multiple radionuclides besides ^{131}I, ^{177}Lu, and ^{225}Ac are being investigated for PSMA-targeted therapies, such as ^{67}Cu (100), ^{213}Bi, ^{212}Pb, and ^{161}Tb (101).

Combination therapies with PSMA RLT: current trials and future perspectives. Even if patients initially respond to PSMA-based RLT, the response is often short-lived. The mechanisms of how tumors develop resistance to PSMA-based RLT are currently not well understood. Combining PSMA-based RLT with potentially synergistic agents may improve responses. Mechanisms for this include upregulating PSMA expression through AR-targeted agents, increasing tumor radiosensitivity through DNA repair inhibitors or agents causing additional DNA damage, targeting different PSMA-binding sites, and combining RLT with immune checkpoint inhibitors (102). Several potential combinations are being evaluated in ongoing clinical studies. The ENZA-p study (NCT04419402) is evaluating the efficacy of combined ^{177}Lu-PSMA-617 RLT with the ARSi enzalutamide. In the context of the current discussion on upregulation of PSMA expression by androgen deprivation therapy and ARSi, this trial aims to demonstrate if antiandrogen therapy may be a potential enhancer for PSMA-targeted RLT (103). The UpFrontPSMA study (NCT04343885) and the LuCAB study (NCT05340374) evaluate the combination/sequential use of ^{177}Lu-PSMA-617 with docetaxel or cabazitaxel, respectively, as radiosensitizers (104). The UPLIFT study (NCT05113537) inquires if abemaciclib, an CDK4/CDK6 inhibitor, may increase the efficacy of ^{177}Lu-PSMA-617. Addressing the increasing value of PARP inhibitors in mCRPC with *BRCA1/2* mutation, the LuPARP phase I study (NCT03874884) investigates the combination of olaparib and ^{177}Lu-PSMA-617. Studies such as EVOLUTION (NCT05150236) and PRINCE (NCT03658447) are evaluating combinations of ^{177}Lu-PSMA-617 with pembrolizumab or ipilimumab + nivolumab, respectively (^{177}Lu-PSMA to potentiate an immunogenic response) (104). The AlphaBet study (NCT05383079) evaluates the combination therapy of ^{23}Ra and ^{177}Lu-PSMA-I&T.

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Non-radiopharmaceutical-based PSMA-targeted therapies: bispecific antibodies, antibody-drug conjugates, and CAR T cells. The accurate visualization of PC tumors, along with the antitumor effect resulting from PSMA targeting with radiopharmaceuticals, has spawned efforts to develop multiple other targeted treatment approaches. Non-radiolabeled treatment approaches targeting PSMA can be divided into three major categories: antibody-drug conjugates (ADCs), chimeric antigen receptor T (CAR-T) cells, and bispecific T cell–redirected therapy (105). ADCs consist of monoclonal antibodies targeted at selective antigens that are overexpressed on cancer cells. A cytotoxic payload (such as microtubule-targeting or DNA-damaging cytotoxins) is attached to the monoclonal antibody via a stable linker (106, 107). Early-phase studies investigating PSMA-targeted ADCs for PC reported an unfavorable toxicity profile: 31% of patients discontinued treatment due to clinically significant adverse effects, such as grade 3+ neutropenia in a phase II study of 119 patients using a PSMA-targeted antibody conjugated to monomethyl auristatin E (105, 108). Similarly, 39.4% of patients developed severe adverse effects such as capillary leak syndrome and skin toxicities in a phase I study of 33 patients with another PSMA-targeted ADC using a pyrrolobenzodizepine dimer payload (109). Future studies will indicate whether the limited therapeutic window in these cases resulted from the nature of PSMA as a target or from suboptimal linker/payload engineering.

ADC: antibody drug conjugate

CAR-T cells are genetically engineered T cell receptors consisting of three parts: an extracellular antigen recognition domain, a transmembrane domain, and an intracellular T cell activation domain (110). The antibody-based extracellular domain recognizes specific tumor antigens such as PSMA. CAR-T cells have become a mainstay of therapy for hematological malignancies but, until very recently, have demonstrated little success in solid tumor therapy (105). Several early phase I studies are evaluating PSMA-targeted CAR-T cells in PC. A study combining low-dose interleukin-2 chemotherapy and PSMA-targeted CAR-T cells found a PSA50 response in 2/5 patients (105, 111). A study investigated PSMA-targeted transforming growth factor β–insensitive armored CAR-T cells in 13 mCRPC patients: Treatment reduced PSA by ≥30% in 4 patients; however, immune effector cell–associated neurotoxicity syndrome, which is a known adverse effect associated with CAR-T cell therapies, resulted in two deaths, causing the trial to be halted (112). Ongoing research efforts and further phase I studies are aimed at exploring patient-specific factors and tumor microenvironment factors that may influence the safety profile (e.g., avoiding severe adverse effects such as macrophage activation syndrome or higher-grade cytokine release syndrome) and efficacy profile of PSMA CAR-T cell therapy (113, 114).

Bispecific T cell–redirected therapies involve a bispecific antibody that targets a tumor-associated antibody such as PSMA, in addition to CD3 or CD28 on T cells. This leads to an activation of T cells and induces targeted tumor cell death (105, 115). One advantage of antibody therapies compared to cellular therapies might be the different tumor-penetrating capabilities; on the other hand, a disadvantage is the requirement of repeated dosing on a (bi-)weekly basis (116). AMG 212 and AMG 160 are such PSMA-targeted bispecific T cell engagers (BiTEs) under investigation, while AMG 160 is a next-generation BiTE molecule with an improved serum half-life and is also being tested in combination with pembrolizumab (105, 115, 117). Other exemplary bispecific therapeutic candidates targeting PSMA and CD3 for redirection of T cell responses against PSMA-expressing cells are APVO442 (118), JNJ-081 (119), BAY 2010112 (120), and CC-1 (116). Similarly, REGN5678 (PSMA × CD28) is another PSMA-targeting bispecific antibody designed to target and augment CD28 signaling. CD28 can act as a costimulatory receptor to increase CD3-mediated T cell activation and/or the antitumor activity of anti-PD-1 immunotherapy agents. It is currently being tested in a phase I/II study for its safety, tolerability, and pharmacokinetics as monotherapy or in combination with cemiplimab (anti-PD-1) in mCRPC (121, 122), where it has shown promising initial response rates.

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The value of PSMA expression assessment by PET imaging for selecting patients for non-radiopharmaceutical-based PSMA-targeted therapies still has to be evaluated. Although it seems logical that target expression is required for the targeted therapy to reach the PC cells, the amount of target expression to obtain treatment effect may be different than with radiopharmaceuticals and may be undetectable at the spatial resolution of PET.

CONCLUSION

PSMA-targeted imaging and therapy have recently been approved and are changing the landscape of patient management in advanced PC. Further studies are needed to understand how to integrate PSMA PET into treatment algorithms and as an endpoint measure in clinical trials. The approval of ^{177}Lu-PSMA-617 (Pluvicto®) as PSMA-targeted RLT for mCSPC paved the way for other PSMA-targeted approaches. Multiple innovative approaches in the field of PSMA-targeted therapy are under investigation, such as using PSMA RLT in earlier disease stages than mCRPC, combination therapies, alpha emitters, and the antibody J591. Also, some early-phase studies are investigating PSMA as a target for ADCs, bispecific antibodies, or CAR-T cells. PSMA will assume an important role in PC alongside the AR as a critical diagnostic and therapeutic target.

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