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Review

Status of PSMA-targeted radioligand therapy in prostate cancer: current data and future trials

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***Abstract*:** Metastatic prostate cancer continues to be an incurable disease. Despite all the novel therapies approved in the past two decades, overall patient outcomes remain relatively poor, and these patients die on a regular basis. Clearly, improvements in current therapies are needed. Prostate-specific membrane antigen (PSMA) is a target for prostate cancer given its increased expression on the surface of the prostate cancer cells. PSMA small molecule binders include PSMA-617 and PSMA-I&T and monoclonal antibodies such as J591. These agents have been linked to different radionuclides including beta-emitters such as lutetium-177 and alpha-emitters such as actinium-225. The only regulatory-approved PSMA-targeted radioligand therapy (PSMA-RLT) to date is lutetium-177–PSMA-617 in the setting of PSMA-positive metastatic castration-resistant prostate cancer that has failed androgen receptor pathway inhibitors and taxane chemotherapy. This approval was based on the phase III VISION trial. Many other clinical trials are evaluating PSMA-RLT in various settings. Both monotherapy and combination studies are underway. This article summarizes pertinent data from recent studies and provides an overview of human clinical trials in progress. The field of PSMA-RLT is rapidly evolving, and this therapeutic approach will likely play an increasingly important role in the years to come.

Keywords: advanced prostate cancer, lutetium-177–PSMA-617, precision medicine, PSMA theranostics, radioligand therapy

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Introduction

An estimated 268,000 new cases of prostate cancer in the United States are expected in 2022.[1] Although the overall 5-year survival rate is over 95%, only about one in three patients live past 5 years if metastases are present,[2] and prostate cancer remains the second leading cause of cancer deaths in men after lung cancer.[1] Prostate cancer typically transitions from hormone sensitive to castration resistant, and patients with metastatic castration-resistant prostate cancer (mCRPC) survive for only about 2–3 years.[3–5] To improve longevity, in addition to androgen deprivation therapy (ADT), there have been a number of therapies approved in the mCRPC setting over the past two decades, including taxane chemotherapy (docetaxel and cabazitaxel), immunotherapy (sipuleucel-T and pembrolizumab), androgen receptor pathway inhibitors (ARPIs; abiraterone and enzalutamide), and targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib and rucaparib).[6] Despite the increasing size of this armamentarium, the vast majority of patients with CRPC progress and novel agents are urgently needed to improve survival while maintaining quality of life.

Radioligand therapy (RLT) has gained significant momentum in the last few years as oncology treatment continues to become more specific and personalized. RLT delivers radiation therapy (typically alpha and beta particles) at the cellular level to specifically target cancer cells and the surrounding microenvironment while sparing normal cells, in contrast to traditional external beam radiation therapy (EBRT).[7] Alpha particles

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(composed of two protons and two neutrons) are much larger than beta particles (similar in weight to electrons) and can inflict much more damage to DNA and other targets in cancer cells. RLT has been used in the past few decades in the form of bone-targeted radionuclides, including phosphorus-32, strontium-89, and samarium-153 lexidronam approved by the United States Food and Drug Administration (FDA) many decades ago to treat painful bone metastases, although none showed a survival benefit.[8–10] In 2013, radium-223 was approved for patients with CRPC and symptomatic bone metastases without visceral involvement, and it provided an overall survival (OS) advantage of about 3 months over placebo.[11] Phosphorus-32, strontium-89, and samarium-153 are beta-emitters, and radium-223 is an alpha-emitter.[12] These radionuclides are injected intravenously and are preferentially taken up by the osteoblastic metastases of prostate cancer but are not effective in targeting lymph node and visceral metastases.

Both small molecules and antibody radionuclide conjugates have been used to target cancer cells. For prostate cancer, prostate-specific membrane antigen (PSMA), a transmembrane protein, has become of significant interest in both diagnostic and therapeutic strategies for prostate cancer. Although its exact function in prostate cancer is unclear, PSMA is expressed at high concentrations on the surface of prostate cancer cells compared to benign prostate cells, and a positive correlation exists between the PSMA level and cancer severity.[13] Notably, PSMA is also expressed in several other benign tissues, such as the salivary and lacrimal glands, proximal renal tubular cells, and the duodenal mucosa.[14] PSMA-targeted radioligand therapy (PSMA-RLT) involves PSMA-targeted ligands or antibodies conjugated to radioactive isotopes. This review article summarizes the status of PSMA-RLT in prostate cancer, delves into optimal sequencing of this therapy whether in tandem or in combination, and touches on some ways to predict PSMA-RLT responses.

Regulatory-approved PSMA-RLTs

Just one RLT involving PSMA has been approved thus far for patients with advanced prostate cancer, lutetium-177–PSMA-617 (^{177}Lu-PSMA-617, also known as lutetium-177 vipivotide tetraxetan), based on the phase III VISION trial (NCT03511664).[15] This trial randomized 831 patients from 84 sites across North America and Europe in a 2:1 ratio (551 to the experimental group and 280 to the control group) to either four to six cycles of 7.4 GBq of ^{177}Lu-PSMA-617 every 6 weeks with standard of care (SoC) *versus* SoC alone. SoC excluded chemotherapy, immunotherapy, radium-223, and experimental agents not approved at the time of study design such as PARP inhibitors. The eligibility criteria included PSMA-positive mCRPC (at least one PSMA-positive metastatic lesion, defined as ^{68}Gallium-PSMA-11 uptake greater than the physiologic radiotracer uptake of the liver parenchyma, with no PSMA-negative lesions), disease progression after treatment with at least one ARPI and one or two taxane regimens, Eastern Cooperative Oncology Group performance status of 0–2, and life expectancy of $\geq$6 months. The primary endpoints included imaging-based progression-free survival (PFS) and OS. Secondary endpoints included objective response, time to first symptomatic skeletal event, adverse events, and health-related quality of life (HRQoL).

The results overwhelmingly favored the patients randomized to the experimental group. The median OS (mOS) was 15.3 months in the SoC plus ^{177}Lu-PSMA-617 group compared to 11.3 months in the SoC control group [hazard ratio (HR), 0.62; 95% confidence interval (CI), 0.52–0.74; $p < 0.001$], and the median radiographic PFS (rPFS) or death was 8.7 months *versus* 3.4 months (HR 0.40; 99.2% CI, 0.29–0.57; $p < 0.001$), respectively. A complete response of 9.2% and a partial response of 41.8% were seen for patients in the experimental group, compared to 0% and 3%, respectively, in the control group. Time to first symptomatic skeletal event or death was 11.5 months in the experimental group compared to 6.8 months in the SoC group (HR 0.50; 95% CI, 0.40–0.62; $p < 0.001$). Adverse events were higher in the experimental group (98.1% *versus* 82.9% for any adverse event, and 52.7% *versus* 38.0% for grade $\geq$3). The most common adverse events included fatigue, dry mouth, anemia, and back pain. HRQoL data presented at the ESMO Congress 2021 demonstrated patients tolerated the radiopharmaceutical well despite more grade $\geq$3 adverse events, based on the FACT-P and BPISF pain intensity scores which were significantly lower in the experimental arm.[16] The overwhelming success of the VISION trial allowed ^{177}Lu-PSMA-617 to be approved by the FDA in March 2022 and by the European Commission in December 2022 for patients with PSMA-positive

Table 1. Current active and recruiting phase III prostate cancer trials involving PSMA-RLT with lutetium-177. Search performed using clinicaltrials.gov on 15 October 2022 and updated on 21 January 2023.

Trial number (name)	Type of prostate cancer	Intervention	Total enrollment	Primary outcome measures
NCT0351164 (VISION)	mCRPC previously treated with ARPI and taxane chemotherapy	^{177}Lu-PSMA-617 with SoC *versus* SoC	831	rPFS and OS
NCT04876651 (PROSTACT)	mCRPC previously treated with ARPI	^{177}Lu-TLX591 with SoC *versus* SoC	387	rPFS
NCT04689828 (PSMAfore)	mCRPC previously treated with ARPI and without prior taxane therapy	^{177}Lu-PSMA-617 *versus* switch of ARPI	450	rPFS
NCT05204927 (ECLIPSE)	mCRPC previously treated with ARPI and without prior taxane therapy	^{177}Lu-PSMA-I&T *versus* abiraterone or enzalutamide	400	rPFS
NCT04647526 (SPLASH)	mCRPC previously treated with second-line ARPI	^{177}Lu-PSMA-I&T *versus* abiraterone or enzalutamide	415	rPFS
NCT04720157 (PSMAddition)	mHSPC	^{177}Lu-PSMA-617 with SoC *versus* SoC alone	1126	rPFS

ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PSMA-RLT, prostate-specific membrane antigen-radioligand therapy; rPFS, radiographic progression-free survival; SoC, standard of care.

mCRPC previously treated with ARPI and taxane-based chemotherapy.

Despite the success, there are several limitations in the VISION trial. The SoC control arm only allowed non-chemotherapeutic agents as the SoC. No chemotherapy was allowed in the VISION trial participants. The dropout rate in the control group was high and the endpoints other than survival are based on smaller numbers than might be anticipated. Radiographic PFS is limited in many ways – those with clinical deterioration may or may not have radiographic progression. The role of SoC in the ^{177}Lu-PSMA-617 group remains undefined. Adverse events were defined in the study as occurring during the treatment period for only up to 30 days after the last dose of treatment.

Several unanswered questions remain despite the VISION trial's success. These include the optimal dose and schedule of ^{177}Lu-PSMA-617 infusions, the optimal selection criteria based on imaging for patients, the optimal role of predictive biomarkers such as PSMA uptake, long-term safety, and the effectiveness of the combination therapy with SoC. It is unknown whether using ^{177}Lu-PSMA-617 as an earlier treatment regimen such as first-line mCRPC setting or even in the setting of metastatic hormone-sensitive prostate cancer (mHSPC) and localized disease would be effective. Phase III trials are summarized in Table 1, and phase I/II trials are summarized in Table 2.

Other PSMA-RLT studies

Besides this regulatory approval, there is currently no current data addressing optimal sequence for PSMA-RLT with respect to other approved agents. Many clinical trials are underway with PSMA-RLT being tested in various stages of prostate cancer and being included in earlier lines of therapy, in combination with other targeted therapies, and in combination with other PSMA-RLT agents. Different radioisotopes and different PSMA binders and antibodies are being used. Although lutetium-177 and actinium-225 continue to be the most heavily studied, other radioisotopes including thorium-227 and terbium-161 are being used in early phase clinical trials.

^{177}Lu-PSMA-617 monotherapy

TheraP (NCT03392428) is a phase II trial conducted in Australia that randomized 200 patients with mCRPC and prior docetaxel treatment in a 1:1 fashion to either ^{177}Lu-PSMA-617 or cabazitaxel.[17] The patients were required to have

Table 2. Current active and recruiting phase I/II prostate cancer trials involving PSMA-RLT with lutetium-177 and/or actinium-225 and other novel radionuclides terbium-161 and thorium-227. Search performed using clinicaltrials.gov on 15 October 2022 and updated on 21 January 2023.

Trial number (name)	Notable characteristics	Intervention	Total enrollment	Primary outcome measures
^{177}Lu monotherapy				
NCT05079698	Hormone sensitive, oligometastatic	^{177}Lu-PSMA-617 with SBRT	6	DLTs
NCT04443062 (BULLSEYE)	Hormone sensitive, oligometastatic	^{177}Lu-PSMA-617 *versus* SoC	58	Disease progression
NCT05114746	mCRPC	^{177}Lu-PSMA-617 with SoC	28	DLTs and ORR
NCT05458544	mCRPC	^{177}Lu-Ludotadipep	26	DLTs and ORR
NCT05579184	mCRPC	^{177}Lu-Ludotadipep	30	PSA response rate
NCT04509557	mCRPC	^{177}Lu-Ludotadipep	30	DLTs
NCT05340374	mCRPC previously treated with docetaxel and ARPI	^{177}Lu-PSMA-617 with cabazitaxel	44	DLTs and MTD
NCT03454750	mCRPC	^{177}Lu-PSMA-617 with radiometabolic therapy	210	DCR, treatment-emergent adverse events
NCT03042468	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617	50	DLTs and MTD
NCT03874884 (LuPARP)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with olaparib	52	DLTs and MTD
NCT04343885 (UpFrontPSMA)	mHSPC	^{177}Lu-PSMA-617 followed by docetaxel *versus* docetaxel	140	Undetectable PSA rate at 12 months
NCT05383079 (AlphaBet)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-I&T with radium-223	36	DLTs, MTD, 50% PSA response rate
NCT04786847 (ProstACTSelect)	mCRPC previously treated with ARPI	^{177}Lu-DOTA-TLX591	50	Treatment-related adverse events
NCT05146973 (ProstACT TARGET)	Biochemically recurrent oligometastatic prostate cancer	^{177}Lu-DOTA-TLX591 with EBRT	50	PSA PFS
NCT03780075	mCRPC	^{177}Lu-EB-PSMA-617	50	PSA change, SUV change
NCT00859781	Biochemically relapsed prostate cancer after local therapy	^{177}Lu-J591 with ketoconazole	55	Proportion of subjects free of radiographically evident metastases
NCT03658447 (PRINCE)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with pembrolizumab	37	PSA response, treatment-related adverse events, tolerability
NCT04430192 (LuTectomy)	High-risk localized prostate cancer	^{177}Lu-PSMA-617	20	Radiation absorbed dose
NCT05547061	mCRPC	^{177}Lu-DGUL	73	ORR
NCT04663997	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 *versus* docetaxel	200	PFS
NCT05113537 (UPLIFT)	mCRPC previously treated with ARPI	Abemaciclib followed by ^{177}Lu-PSMA-617	30	DLTs and MTD

(Continued)

Table 2. (Continued)

Trial number (name)	Notable characteristics	Intervention	Total enrollment	Primary outcome measures
NCT05230251 (ROADSTER)	Localized prostate cancer with biochemical failure, previously treated with radiation therapy	^{177}Lu-PSMA-I&T with high-dose radiation *versus* high-dose radiation	12	Safety and efficacy
NCT03805594	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with pembrolizumab	43	ORR
NCT05162573 (PROQURE-1)	N1M0	^{177}Lu-PSMA-617 with EBRT	18	MTD
NCT05413850	mCRPC	^{177}Lu-rhPSMA-10.1	150	DLTs, treatment-related adverse events, 50% PSA response rate
NCT05496959 (LUNAR)	Oligorecurrent	^{177}Lu-PSMA-I&T before SBRT	100	PSMA-PET/CT-based PFS
NCT03822871	mCRPC previously treated with ARPI	CTT1403	40	DLTs
NCT05150236 (EVOLUTION)	mCRPC previously treated with ARPI	^{177}Lu-PSMA-617 with nivolumab and ipilimumab *versus* ^{177}Lu-PSMA-617	110	PSA-PFS at 1 year
NCT04419402 (ENZA-p)	mCRPC	^{177}Lu-PSMA-617 with enzalutamide *versus* enzalutamide	160	PSA PFS
^{225}Ac monotherapy				
NCT03276572	mCRPC previously treated with ARPI	^{225}Ac-J591	32	DLTs and MTD
NCT04506567	mCRPC previously treated with ARPI	^{225}Ac-J591	105	DLTs and MTD
NCT04946370	mCRPC previously treated with ARPI	^{225}Ac-J591 with pembrolizumab	76	DLTs, optimal dose, response rates
NCT05219500 (TATCIST)	mCRPC previously treated with ARPI	^{225}Ac-PSMA-I&T	100	Efficacy and safety
NCT04597411 (AcTION)	Both prior exposure and naïve to ^{177}Lu acceptable	^{225}Ac-PSMA-517	60	MTD
Combination of ^{177}Lu and ^{225}Ac				
NCT04886986	mCRPC previously treated with ARPI	^{225}Ac-J591 with ^{177}Lu-PSMA-I&T	33	DLTs, MTD, 50% PSA response rate
^{161}Tb				
NCT05521412 (VIOLET)	mCRPC previously treated with ARPI	^{161}Tb-PSMA-I&T	36	DLTs, MTD, treatment-related adverse events
^{227}Th				
NCT03724747	mCRPC previously treated with ARPI	BAY2315497 with or without darolutamide	63	MTD

ARPI, androgen receptor pathway inhibitor; DCR, disease control rate; DLTs, dose-limiting toxicities; EBRT, external beam radiation therapy; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PSA, prostate-specific antigen; PSMA-RLT, prostate-specific membrane antigen-radioligand therapy; SBRT, stereotactic body radiation therapy; SoC, standard of care.

PSMA-positive disease with SUVmax ⩾ 20, SUVmax ⩾ 10 at other sites of metastases on the ^{68}Ga-PSMA-11 PET-CT scan and have non-discordant findings between the PSMA PET-CT and fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scans. In all, 91 of 291 screened patients were excluded, with the majority either having low ^{68}Ga-PSMA-11 uptake on imaging or discordant disease when compared to FDG PET imaging. Dosage of ^{177}Lu-PSMA-617 was 8.5 GBq the first cycle and decreased by 0.5 GBq per cycle every 6 weeks, with a maximum of six cycles. Thus, a different dosing scheme was used relative to the VISION trial. Prostate-specific antigen (PSA) response (defined by a reduction of over 50% from baseline) was more frequent in the ^{177}Lu-PSMA-617 group compared to the cabazitaxel group (66% *versus* 37% in the intention-to-treat group, $p < 0.0001$). The radiographic or PSA PFS favored the ^{177}Lu-PSMA-617 group (HR, 0.63; 95% CI, 0.46–0.86; $p = 0.0028$). Grade 3/4 adverse events were lower in the ^{177}Lu-PSMA-617 group (33% *versus* 53%), although grade 3/4 thrombocytopenia was more common in the ^{177}Lu-PSMA-617 group. HRQoL overall favored the ^{177}Lu-PSMA-617 group. OS was similar between the two treatment groups (19.1 *versus* 19.6 months; HR, 0.97; 95% CI, 0.70–1.4; $p = 0.99$), although there was possible confounding due to post-protocol crossover and post-randomization withdrawal from the cabazitaxel cohort, as reported at the 2022 ASCO Annual Meeting.[18] Notably, of the patients screened who were not eligible for the study because of discordant FDG/PSMA PET scans, their mOS (11.0 months) was significantly worse compared to the trial patients.

PSMAfore (NCT04689828) is an open-label phase III trial randomizing 450 patients with taxane-naïve mCRPC and ARPI treatment failure in a 1:1 ratio to receive either six cycles of 7.4 GBq of ^{177}Lu-PSMA-617 every 6 weeks or a change of ARPI to either abiraterone or enzalutamide.[19] The primary endpoint will be rPFS, and important secondary endpoints include OS, safety and tolerability, and HRQoL. Crossover will be allowed for those reaching rPFS in the control group. The study is expected to report initial data in 2023.

UpFrontPSMA (NCT04343885) is an open-label phase II trial randomizing 140 patients with newly diagnosed metastatic prostate cancer from 12 centers in Australia in a 1:1 fashion to either sequential ^{177}Lu-PSMA-617 (7.5 GBq every 6 weeks for two cycles) followed by six cycles of docetaxel compared to six cycles of docetaxel, with both groups receiving continuous ADT.[20] The primary endpoint will be the proportion of patients with undetectable PSA 1 year after starting therapy, while important secondary endpoints include OS, PSA and radiographic PFS, time to castration resistance, early PSMA PET response, HRQoL, and adverse events. The study is expected to be complete by April 2024.

Another phase I/II trial that brings ^{177}Lu-PSMA-617 into an even earlier setting is LuTectomy (NCT04430192), enrolling 20 patients with high PSMA-expressing high-risk localized or locoregional advanced prostate cancer evaluating dosimetry, safety, and possible benefit of ^{177}Lu-PSMA-617 prior to radical prostatectomy and pelvic lymph node dissection.[21] This study is expected to be completed by June 2023.

^{177}Lu-PSMA-I&T monotherapy

^{177}Lu-PSMA-I&T (also known as ^{177}Lu-PTN2002) is another lutetium-labeled PSMA-targeting tracer that is being used in clinical trials. Although both urea-based small molecules have similar tumor uptake, ^{177}Lu-PSMA-I&T was shown to have increased kidney uptake compared to ^{177}Lu-PSMA-617 resulting in a less favorable tumor-to-kidney ratio; however, absorption in the lacrimal glands may be diminished.[22,23] 177Lu-PSMA-I&T has been used in the compassionate setting with good treatment response in a subset of patients.[24]

Two phase III trials are in process with ^{177}Lu-PSMA-I&T against an ARPI in the pre-chemotherapy mCRPC space: SPLASH and ECLIPSE. SPLASH (NCT04647526) is a phase III open-label trial randomizing 415 patients with mCRPC who have progressed despite one ARPI therapy.[25] It involves two parts: the first part involves a safety and dosimetry arm with 25 patients receiving up to four cycles of ^{177}Lu-PSMA-I&T at 6.8 GBq every 8 weeks, and the second part aims to randomize 390 patients in a 2:1 ratio to either ^{177}Lu-PSMA-I&T or abiraterone/enzalutamide with the option of crossover from the control arm to the experimental arm after rPFS. The primary endpoint is rPFS, and important secondary endpoints include ORR, PSA response, duration of response, and OS. The estimated primary study completion date is March 2023.

In a similar trial, ECLIPSE (NCT05204927) is a phase III open-label trial randomizing 400 patients with mCRPC in a 2:1 ratio to either up to four doses of ^{177}Lu-PSMA-I&T at 7.4 GBq every 6 weeks or a limited SoC (abiraterone or enzalutamide). Crossover from the control arm to the experimental arm is allowed. The primary endpoint is rPFS, and important secondary endpoints include OS, time to first symptomatic skeletal event, and HRQoL. The estimated study primary completion date is January 2024.

Additional PSMA-RLT agents used as monotherapy

Because a significant number of prostate cancer patients (up to one in three) do not respond to lutetium-177 therapy, there is interest in using other radionuclides, notably actinium-225, that deliver higher energy particles compared to the beta-particles emitted by lutetium-177.[26] A pilot experience for mCRPC patients with progressive disease despite ^{177}Lu-PSMA-617 therapy and then subsequently received ^{225}Ac-PSMA-617 suggests that targeted alpha therapy may be effective for patients who have failed ^{177}Lu-PSMA-617 therapy.[27,28] Prospective trials using PSMA-RLT involving actinium-225 are still in initial phases. AcTION (NCT04597411) is a phase I trial enrolling 60 patients with PSMA-positive prostate cancer either naïve to or previously treated with lutetium therapy to evaluate dosimetry and safety for a maximum of six cycles of ^{225}Ac-PSMA-617, with estimated primary completion by October 2023. TATCIST (NCT05219500) is a phase II trial enrolling 100 patients with mCRPC to four doses of ^{225}Ac-PSMA-I&T in 8-week intervals and evaluating the efficacy and safety. This study allows for patients with prior exposure to lutetium, and the estimated primary completion is December 2022.

Monoclonal antibodies to target PSMA have been known for a few decades and even prior to the development of PSMA small molecule binders.[29] Monoclonal antibodies have generally been considered inferior to the PSMA small molecule binders because of their larger size, slower tumor uptake, and longer half-lives which lead to more systemic radiation exposure and hematotoxicity. However, the larger size of monoclonal antibodies means less penetration into other tissue such as salivary glands and kidneys compared to the small molecule binders which may decrease the adverse events (such as dry mouth) seen in the clinical trials that use PSMA small molecule binders.[30] The J591 antibody, which binds to the extracellular PSMA domain,[31] has been extensively studied and conjugated to different radionuclides and is the monoclonal antibody used most often in anti-PSMA radioimmunotherapy clinical trials.[32] Both lutetium-177 and actinium-225 have been conjugated to J591 in phase I/II clinical trials. To better mitigate hematotoxicity and increase tolerability, fractionated administration of ^{177}Lu-J591 allowed for higher cumulative radiation dosing and therefore a better PSA decrease and OS for patients with mCRPC.[33] Phase III trials are planned with a ^{177}Lu labeled monoclonal antibody termed TLX-591 (NCT04876651). ^{225}Ac-J591 is being evaluated in a dose-escalation phase I/II trial (NCT04506567) in patients with mCRPC. Once dose-finding studies are complete, a phase III trial of ^{225}Ac-J591 is anticipated.

Combinations involving RLT

Several trials are using combination therapy with ^{177}Lu-PSMA-617 to increase the efficacy of already approved agents, including ARPIs, chemotherapy, PARP inhibitors, and immune checkpoint inhibitors. Primary endpoints for these studies are generally focused on efficacy and safety. PSMAddition (NCT04720157) is an open-label phase III study randomizing 1126 patients with mHSPC in a 1:1 ratio to either ^{177}Lu-PSMA-617 with SoC (ARPI with ADT) or SoC alone, with estimated primary completion in August 2024.[34] ENZA-p (NCT04419402) is an open-label phase II study randomizing 160 patients with mCRPC in a 1:1 ratio to either ^{177}Lu-PSMA-617 (up to four doses) with enzalutamide *versus* enzalutamide alone, with estimated study completion in June 2023.[35] This study also aims to identify possible predictive and prognostic biomarkers using circulating tumor cells (CTCs) and circulating tumor DNA. LuCAB (NCT05340374) is a phase I/II trial involving 44 patients with mCRPC to evaluate the combination of up to six cycles of 7.4 GBq of ^{177}Lu-PSMA-617 with cabazitaxel. A phase I trial, LuPARP (NCT03874884), has enrolled 52 patients with mCRPC with progression on ARPI to evaluate safety and tolerability of olaparib with 7.4 GBq of ^{177}Lu-PSMA-617 every 6 weeks for up to four cycles. Similarly, a phase I/II trial, PRINCE (NCT03658447), has enrolled 37 patients with mCRPC with progression on ARPI to evaluate safety and tolerability of

pembrolizumab every 3 weeks with ^{177}Lu-PSMA-617 every 6 weeks for up to six cycles starting at 8.5 GBq and dose-reducing by 0.5 GBq each cycle. Another phase II trial, EVOLUTION (NCT05150236), is evaluating 7.4 GBq of ^{177}Lu-PSMA-617 every 6 weeks for six cycles in combination with ipilimumab and nivolumab for patients with mCRPC, with primary endpoint measuring PSA PFS at 1 year.

RLT themselves have been combined, especially with the different radioisotopes, small molecules, and antibodies available. The co-administration of ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617 in tandem is also of potential interest as lower doses of alphas can be employed, thus possibly mitigating toxicities.[36] Interestingly, there is a phase I/II clinical trial (NCT04886986) combining the small molecule ^{177}Lu-PSMA-I&T and the monoclonal ^{225}Ac-J591 enrolling 33 patients with progressive mCRPC, with the primary objectives of assessing dose-limiting toxicity and the proportion of patients with >50% PSA decline.[37] The combination of monoclonal antibody and small molecule ligand with alpha- and beta-emitters may be synergistic in treatment effect while mitigating adverse effects, and the estimated primary completion study date is December 2024.

Management of small-volume oligometastatic disease with PSMA-RLT

There has been a growing interest in metastases-directed therapy (e.g. EBRT) mainly to postpone ADT-related adverse effects or even cure selected patients with mainly limited number of metastases (five or less), considered oligometastatic prostate cancer.[38] The use of PSMA-RLT appears to be quite effective in this setting, as was shown in a phase I/II trial (NCT03828838).[39] There is an ongoing prospective randomized multicenter phase II trial, BULLSEYE, to assess the efficacy of ^{177}Lu-PSMA-617 in oligometastatic hormone-sensitive prostate cancer (defined by five or fewer metastases on PSMA PET) to postpone disease progression and to avoid ADT.[40] A phase I study (NCT05079698) is currently recruiting patients to assess the role of therapy of oligometastatic disease (up to three lesions that are detectable with PSMA PET) with two cycles of ^{177}Lu-PSMA-617, followed with SBRT. Another currently active phase I study, PROQURE-1 (NCT05162573), combines EBRT with ^{177}Lu-PSMA-617 to treat N1M0 prostate cancer. Additional studies are planned in this space.

Predicting outcomes with PSMA-RLT

With the increasing use of PSMA-RLT, there is a need to determine which patients with mCRPC are candidates for ^{177}Lu-PSMA-617 to predict treatment outcomes to improve candidate selection and assist with clinical decision-making. Many predictive biomarkers based on laboratory and imaging findings are being investigated.[41,42] In a multicenter retrospective study, Gafita and colleagues developed nomograms to predict OS, PSA PFS, and PSA50 (PSA decline of at least 50% from baseline).[43] The authors took data from two prior phase II clinical trials (NCT03042312 and ACTRN12615000912583) and compassionate use at participating sites with patients who had received either 6.0–8.5 GBq of ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T every 6–8 weeks for a maximum of six cycles. They had a study population of 196 patients for nomogram development and then independently validated the nomograms in 74 patients. The selected predictors included time since diagnosis of prostate cancer, chemotherapy status, baseline hemoglobin concentration, bone involvement status, liver involvement status, number of metastatic lesions, and tumor SUVmean, as the nomograms successfully incorporated both traditional and novel prognostic variables. In the study, high levels of tumor PSMA expression were required for a favorable outcome following therapy, and bone metastases were not very well controlled with therapy. These nomograms may be useful in assisting with the design of clinical trials and decision-making for individual patients, but they need to be validated using data from phase III trials.

The importance of the PSMA PET scan before treatment initiation was again emphasized as a likely predictive biomarker on further analysis of the TheraP trial. Buteau and colleagues[44] assessed the use of SUV on ^{68}Ga-PSMA-11 PET as a predictive biomarker for ^{177}Lu-PSMA-617 from the patients enrolled in TheraP. The authors defined a cutoff of SUVmean $\geq$ 10 as high PSMA expression, which included 35/99 men assigned to the ^{177}Lu-PSMA-617 cohort and 30/101 men assigned to the cabazitaxel cohort. Patients with high PSMA expression had a higher PSA response rate for ^{177}Lu-PSMA-617 compared to cabazitaxel (91% *versus* 47%), while patients with low PSMA expression still responded to ^{177}Lu-PSMA-617 compared to cabazitaxel but was less robust (52% *versus* 32%). More data are needed to assess the importance of this observation using survival as an endpoint.

Liquid biopsy, which involves collecting biological fluid from patients to analyze tumor characteristics

such as cell-free DNA and CTCs, has rapidly advanced in the field of prostate cancer for guiding diagnosis and treatment plans due to the ease of collection compared to tissue biopsies.[45] Studies with liquid biopsies and RLT are underway. Gorges *et al.*[46] studied the detection of PSMA expression on CTCs; according to this study, PSMA expression mostly showed intra-patient heterogeneity in metastatic prostate cancer, which may explain the lack of response to PSMA-RLT in a subgroup of patients. Kessel *et al.*[47] studied gene expression analysis of CTCs [expression of AR full length [AR-FL], AR splice variant [AR-V7], PSA, and PSMA). This study showed that CTC mRNA expression of AR-FL and its splice variant AR-V7 may serve as prognostic biomarkers displaying high tumor burden in mCRPC patients before PSMA-RLT. Widjaja *et al.*[48] evaluated DNA damage repair (DDR) markers in peripheral blood lymphocytes (PBLs) to assess if these markers could predict outcome of ^{177}Lu-PSMA-RLT; this preliminary study showed that low baseline DDR markers in PBLs trended toward poor treatment outcomes. Future studies ideally will be embedded into phase III trials with clinically meaningful endpoints.

Conclusion

PSMA-RLT is a field that has made significant progress in the past few years, culminating in United States FDA and European Commission approval of ^{177}Lu-PSMA-617 for patients with PSMA-positive mCRPC that have progressed despite ARPI and taxane chemotherapy in 2022 (based on the VISION trial results). Although this is currently the only regulatory approval, multiple other clinical trials with different radioisotopes and conjugates are underway to determine other optimal settings for PSMA-RLT. Both monoclonal antibodies and small molecules are of interest. Both beta- and alpha-emitters are of interest. There remain several unknowns to PSMA-RLT, such as the optimal dosing, optimal selection criteria for therapy, and further development of predictive biomarkers, but the rate of current progress suggests that many of these questions will find answers soon.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Albert Jang: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Ayse T. Kendi: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Oliver Sartor: Conceptualization; Formal analysis; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

Not applicable.

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