THERAPEUTIC ADVANCES in
Medical Oncology

Review

Novel radionuclide therapy combinations in prostate cancer

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Ther Adv Med Oncol

2023, Vol. 15: 1–18

DOI: 10.1177/17588359231187202

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***Abstract*:** Prostate cancer remains the commonest cancer diagnosed in males and a leading cause of cancer-related death. Men with metastatic castration-resistant prostate cancer (mCRPC) who have progressed on chemotherapy and androgen receptor pathway inhibitors (ARPI) have limited treatment options, significant morbidity, and poor outcomes. Prostate-specific membrane antigen (PSMA)-directed radionuclide therapy (RNT) is emerging as an efficacious and well-tolerated therapy; however, disease progression is universal. Several ongoing RNT trials focus on combination strategies to improve efficacy and durability of treatment response, including combinations with ARPIs, chemotherapy, immunotherapy, and targeted therapies. Further, efforts are underway to expand the role of PSMA-directed RNT to earlier stages of disease including hormone-sensitive and localized prostate cancer. In this review, we discuss the rationale and ongoing RNT combination therapeutic trials in prostate cancer and summarize the efficacy and toxicity associated with RNT.

Keywords: radionuclide therapy, radioligand therapy, radiation, theranostics, prostate cancer

Received: 27 February 2023; revised manuscript accepted: 21 June 2023.

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Introduction

Prostate cancer is the second-commonest cancer diagnosed in men worldwide and the fifth leading cause of cancer death for males annually.[1–3] There has been significant therapeutic advances in the last two decades, including the introduction of sipuleucel-T, docetaxel, cabazitaxel, androgen receptor pathway inhibitors (ARPIs), poly(ADP-ribose) polymerase (PARP) inhibitors, radium-223 (^{223}Ra), and most recently lutetium-177 labeled PSMA 617 (^{177}Lu-PSMA-617), all of which have improved disease control, overall survival (OS), and quality of life for men with metastatic prostate cancer. Despite this, prostate cancer inevitably develops castration resistance that marks the lethal phase of this condition. Treatment options for metastatic castration-resistant prostate cancer (mCRPC) after exhausting standard therapies remain limited, and there is a critical need to develop novel therapeutic options.

Prostate-specific membrane antigen (PSMA) has emerged as an important imaging and therapeutic target in prostate cancer due to the low level of expression in normal tissue compared to prostate cancer.[4] In March 2022, ^{177}Lu-PSMA-617, a radionuclide therapy (RNT) delivering beta radiation to PSMA-expressing prostate cancer cells was approved by the Food and Drug Administration (FDA) for mCRPC based on improved radiological progression-free survival (rPFS) and OS seen in the phase III VISION trial.[5] However, primary resistance occurs in approximately 17–30% of patients treated with single agent ^{177}Lu-PSMA-617, despite strict participant selection based on PSMA positron emission tomography (PET) scans, and disease progression following a response is universal.[5,6]

Research is underway to evaluate PSMA-directed RNT combinations to overcome tumor heterogeneity and improve the depth and durability of responses. Potential strategies include ^{177}Lu-PSMA-617 administered with ARPIs, chemotherapy, immunotherapy, and targeted therapies. The rationale for these varied approaches includes radiosensitization, immune modulation, upregulation of tumor PSMA expression and enhancement of DNA damage, all

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Table 1. Radionuclides with different class of radiation emission with potential application in prostate cancer.

Radiation emission	Beta	Alpha	Auger electron
Nuclides	^{177}Lu, ^{161}Tb, ^{67}Cu, ^{199}Y	^{227}Th, ^{225}Ac, ^{223}Ra, ^{212}Pb	^{161}Tb
Range	0.1–10 mm (100–600 cells)	<80 µm (2–10 cells)	<1 µm (<1 cell)
LET	<1 KeV/µm	50–230 KeV/µm	1–23 KeV/µm

Actinium, ^{225}Ac; Copper, ^{67}Cu; Lead, ^{212}Pb; LET, linear energy transfer; Lutetium, ^{177}Lu; Radium, ^{223}Ra; Terbium, ^{161}Tb; Terbium, ^{166}Tb; Thorium, ^{227}Th; Yttrium, ^{199}Y.

with the ultimate goal of improving tumoral death. The growing efficacy and safety data of ^{177}Lu-PSMA-617 in mCRPC have paved the way to further the trials of ^{177}Lu-PSMA-617 and other novel radioligand-isotope combinations as earlier lines of therapy and in earlier stages of prostate cancer. These studies have significant heterogeneity in trial inclusion criteria, PSMA expression thresholds on imaging for enrollment, and prior treatment exposure. In this review, we summarize the rationale and ongoing results of combination RNT clinical trials in prostate cancer and discuss some of the newer RNT targets that are in development.

Development of radionuclide therapy

RNT is a rapidly growing treatment modality wherein radionuclides deliver highly targeted radiation to tumor cells throughout the body while sparing healthy normal tissues. The RNT, iodine-131 (^{131}I), was first recognized as an effective treatment for thyroid disease in the 1940s by exploiting the physiology of thyroid cells that take up iodine.[7] The last decade has witnessed a rapid expansion of clinical applications of RNT and regulatory approvals of multiple agents, including lutetium-177 (^{177}Lu)-Dotatate for advanced somatostatin receptor-2 expressing neuroendocrine tumors, iodine-131 meta-iodobenzylguanidine entering tumor cells through norepinephrine transporters in advanced pheochromocytoma and paraganglioma, ^{223}Ra a calcimimetic targeting osteoblastic bone metastases, and most recently ^{177}Lu-PSMA-617 targeting PSMA in mCRPC.[5,6,8–10]

Radioisotopes used in RNT have different radiation properties. While the most established agents use beta particles, there is growing research interest in highly potent, short path length alpha particles, ultra-short path length Auger electrons, or combinations thereof. The higher linear energy transfer (LET) of the alpha-emitting radioisotopes leads to much higher cytotoxic activity compared to beta emitters, potentially overcoming cellular mechanisms for radioresistance.[11] Furthermore, shorter path length of alpha particles with an approximate range of 2–10 cells, makes them more suitable for resistant micrometastatic disease when less cross-fire radiation occurs (Table 1). Auger electron emitters have high LET with even shorter range than alpha particles, leading to cytotoxic effect within a single cell range.[12]

In most cases, suitability for RNT is determined by the presence and intensity of the biological target using whole-body diagnostic companion molecular imaging. After treatment, the imaging properties of some radionuclides, especially gamma emission from beta emitters such as ^{177}Lu, ^{67}Copper (^{67}Cu), or ^{161}Terbium (^{161}Tb) allow verification of delivery of the radiation payload to tumor sites. Apart from qualitative assessment of RNT distribution, quantitative measures derived from these techniques can be used for the assessment of target binding and pharmacodynamics of the radiopharmaceuticals, as well as dosimetry estimates in normal organs and tumor sites. These unique properties of RNT that enable firstly the precise identification of the therapeutic target and then the delivery of tumor-directed radiation therapy are coined ‘Theranostics’ and facilitate precision oncology.[13]

Unlike chemotherapy, responses with RNT agents are typically observed within a limited number of administrations provided the biological target is present. It is important that the workflow enables serial assessment of the presence of the target prior to repeated administration. Single-photon emission computerized tomography/computed tomography (CT) post-administration allows visualization of the residual tumor mass and target and therefore planning for the subsequent administration.[14]

RNT development remains a multidisciplinary effort, requiring expertise in radiochemistry, radiopharmacy, radiobiology, medical physics, and medical oncology, which provides opportunities for cross-collaboration to realize the true potential of this treatment modality. Despite promising results from RNT in prostate cancer so far, the quality of treatment response is heterogenous, and most patients will progress after the initial response. Therefore, there remains an unmet need for optimizing RNT through improved patient selection and rational combination therapies to improve efficacy and durability of responses.

RNT in prostate cancer

While ^{89}strontium, ^{153}samarium, and ^{186}rhenium were early RNT assessed in mCRPC with bone-only disease, none of these agents demonstrated a survival benefit.[15] 223Ra was the first RNT approved for use in mCRPC with a demonstrated improvement in OS. The phase III ALSYMPICA trial randomized ^{223}Ra *versus* placebo in 921 participants with mCRPC with two or more bone metastases and no visceral disease and demonstrated an OS benefit (median 14.9 *versus* 11.3 months, hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.58–0.83; $p < 0.001$), fewer grade 3–4 adverse events (56% *versus* 62%), and improvement in quality of life measures (25% *versus* 16% ; $p = 0.02$).[10]

PSMA as an imaging and therapeutic target for prostate cancer

Folate hydrolase 1 is a gene encoding PSMA, a type II transmembrane glycoprotein that is over expressed in prostate cancer with highest PSMA expression observed in aggressive and castration-resistant disease.[4] PSMA has low levels of expression in normal tissue sites including the small intestine, proximal renal tubules, and nonmyelinated ganglia;[4,16–18] however, the salivary and lacrimal glands have high level of PSMA expression, accounting for the on-target toxicity from PSMA-directed RNT.[16] PSMA has a role in folate and glutamate metabolism within the duodenum and likely in malignant prostatic diseases as well.[19] The relatively low extra-prostatic PSMA expression outside of these sites contributes to the favorable toxicity profile with restricted and predictable on-target and off-tumor effects.

PSMA-targeted imaging, such as ^{68}Gallium PSMA-11 PET/CT, has demonstrated superior sensitivity and specificity compared to conventional imaging (CT and bone scan), revolutionizing imaging of prostate cancer.[20] Several phase III trials of PSMA-directed imaging have demonstrated improved sensitivity and specificity for detection of locoregional and distant metastatic disease leading to FDA approval for use of ^{68}Ga PSMA-11 and ^{18}F-DCFPyLL for use in different stages of disease.[20–23] The ProPSMA ($n = 302$) and OSPREY ($n = 385$) phase III trials demonstrated superior preoperative staging with ^{68}Ga PSMA PET/CT and ^{18}F-DCFPyL-PET/CT for high-risk localized prostate cancer compared with conventional imaging, whereas CONDOR (NCT03739684) enrolled 208 patients with negative or equivocal findings on conventional imaging and demonstrated that ^{18}F-DCFPyL-PET/CT resulted in a change of management for 72.5% (103/144) of their cohort.[20–22] 68Ga-PSMA-11 PET/CT was also prospectively validated in a phase III trial of 764 patients with intermediate or high-risk prostate cancer planned for surgery; those without pelvic nodal or distant metastatic disease on PSMA imaging demonstrated higher biochemical recurrence free survival (33 *versus* 7.3 months; $p < 0.0001$).[23] Furthermore, two systematic reviews confirmed that PSMA-directed radiotracer imaging improved detection of prostate cancer metastases in biochemical recurrence, even at low PSA levels of <2 ng/ml.[24,25]

PSMA as a radionuclide target for prostate cancer

^{177}Lu-PSMA-617, consisting of the therapeutic radioisotope ^{177}Lu and targeting ligand PSMA 617 with high affinity for PSMA, delivers beta particle radiation to prostate cancer cells. Multiple retrospective studies demonstrated promising efficacy from ^{177}Lu-PSMA-617 and manageable toxicity in heavily pretreated mCRPC.[26–36] The first prospective phase II study of ^{177}Lu-PSMA-617 in mCRPC enrolled 50 people with mCRPC who had progressed on ARPIs and one to two lines of taxane chemotherapy. Participants were required to have PSMA expression of a maximum standardized uptake value (SUVmax) $\geqslant 1.5$ times that of normal liver on ^{177}Ga-PSMA-11 PET/CT scan at one tumor site, with no discordance seen on fluorodeoxyglucose (FDG) PET/CT (FDG PET positive and PSMA PET negative sites of disease).[37] Participants received up to four cycles of ^{177}Lu-PSMA-617, six-weekly. The primary endpoint, a reduction in PSA $\geqslant 50\%$ from baseline (PSA_{50}), was seen in 64% (32/50, 95% CI

50–77%). More than half (15/27, 56%) of those with measurable disease demonstrated an objective response (OR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[38] Median PSA progression-free survival (PSA-PFS) was 7.6 months (95% CI 10.4–22.7), and median OS was 13.3 months (95% CI 10.5–18.7).[38] The commonest treatment-related adverse event (TRAE) was grade 1 dry mouth (87%) and grade 3 TRAEs reported in ⩾10% included lymphocytopenia (37%), thrombocytopenia (10%), and anemia (13%).[37] Fifteen participants who had previously had a response and subsequently developed disease progression went on to receive additional ^{177}Lu-PSMA-617 cycles (median 2, range 1–5).[38] The PSA_{50} in this group was 73% (11/15), however, responses were shorter than on the first exposure. The median OS in the subset of patients who received re-treatment with ^{177}Lu-PSMA-617 at the time of first or second relapse (after initial PSA_{50} response) was 26.6 months.[38]

The TheraP phase II trial randomized 200 participants with mCRPC to either ^{177}Lu-PSMA-617 (8.5 GBq decreasing by 0.5 GBq per cycle, for up to six cycles) or cabazitaxel chemotherapy (20 mg/m^2 every 3 weeks for up to 10 cycles) in the third-line setting following disease progression on an ARPI and docetaxel.[6] Study inclusion is required for PSMA-positive disease with a SUVmax of ⩾20 at one site and ⩾10 at all other measurable sites with no discordance on FDG PET/CT.[6] The primary endpoint of PSA_{50} response was achieved in 66% (65/99; 95% CI 56–75) of those receiving ^{177}Lu-PSMA-617 compared with 37% (37/101; 95% CI 27–46) receiving cabazitaxel ($p < 0.001$).[6] The OR rate (ORR) in participants with RECIST1.1 measurable disease was 48% (18/37; 95% CI 33–65) *versus* 24% (10/41; 95% CI 11–38) favoring ^{177}Lu-PSMA-617 (Relative Risk [RR] 2.12; 95% CI 1.10–4.08; $p = 0.019$).[6] ^{177}Lu-PSMA-617 was better tolerated with less grade 3–4 AEs compared to cabazitaxel (33% *versus* 53%) and demonstrated numerically higher pain responses (60% (29/48) *versus* 43% (18/42); RR 1.4; 95% CI 0.9–2.2, $p = 0.10$).[6] The rates of grade 3–4 anemia, thrombocytopenia, and neutropenia were 8% *versus* 8%, 11% *versus* 0%, and 4% *versus* 13% in the ^{177}Lu-PSMA-617 and cabazitaxel cohorts, respectively. Other common toxicities included dysgeusia in 12% *versus* 27%, and dry eyes in 30% *versus* 4% in the ^{177}Lu-PSMA-617 and cabazitaxel groups. Those receiving ^{177}Lu-PSMA-617 had superior present pain intensity progression-free survival (HR 0.72; 95% CI 0.53–0.97; $p = 0.033$) and deterioration-free survival for global health status (29%, 95% CI 21–38 *versus* 14%, 95% CI 7–12; $p = 0.0002$) than those receiving cabazitaxel.[6] Despite superior responses, there was no difference in OS in the ^{177}Lu-PSMA-617 arm compared to cabazitaxel (19.1 *versus* 19.6 months; 95% CI −3.7–2.7). This trial was not adequately powered for OS. Furthermore, a number of participants in both arms went on to receive post-protocol therapy, including cabazitaxel ($n = 21$) and ^{177}Lu-PSMA-617 ($n = 20$) for those randomized to cabazitaxel, and ^{177}Lu-PSMA-617 ($n = 5$) and cabazitaxel ($n = 32$) for those randomized to ^{177}Lu-PSMA-617.[39]

The VISION phase III trial randomized 831 mCRPC participants with prior exposure to ARPI and taxane chemotherapy 2:1 to receive up to 6 cycles of ^{177}Lu-PSMA-617 in conjunction with protocol specified standard of care (SOC) *versus* SOC alone.[5] In this trial, SOC excluded chemotherapy, RNT, immunotherapy, or investigational agents and was largely composed of ARPIs, glucocorticoids, gonadotrophin-releasing hormone (GnRH) analogs, and/or palliative radiation.[5] Key eligibility criteria included ^{68}Ga-PSMA 11 uptake within tumor greater than that of liver parenchyma, which contrasts with the higher SUVmax required for TheraP. The co-primary endpoints for VISION, rPFS, and OS, were superior in the ^{177}Lu-PSMA-617 cohort with a median rPFS of 8.7 months *versus* 3.4 months (HR 0.40; 99.2% CI 0.29–0.57; $p < 0.001$) and median OS of 15.3 months *versus* 11.3 months (HR 0.62; 95% CI 0.52–0.74; $p < 0.001$).[5] Therapy after discontinuation of trial treatment included taxane chemotherapy (18.0% ^{177}Lu-PSMA-617 arm *versus* 21.8% SOC), radiopharmaceuticals (2.9% ^{177}Lu-PSMA-617 *versus* 8.2% SOC), immunotherapy (2.5% ^{177}Lu-PSMA-617 *versus* 6.6% SOC), and ARPI (4.2% ^{177}Lu-PSMA-617 *versus* 4.6% SOC). Common grade ⩾3 AEs in the ^{177}Lu-PSMA-617 arm were anemia (12.9%), thombocytopenia (7.9%), lymphopenia (7.8%), and fatigue (5.9%), with dry mouth of any grade reported in 39.3% patients (all ⩽grade 2).

PSMAfore is a phase III randomized study comparing six cycles of ^{177}Lu-PSMA-617 to a change in ARPI.[40] This trial enrolled 450 people with taxane-naïve mCRPC to evaluate rPFS and OS

with this strategy. A preliminary media release revealed that the study met the primary endpoint, demonstrating superior rPFS.[41]

Alternative RNT strategies targeting PSMA are also being investigated. Lu-PSMA imaging and therapy (I&T) shares the same PSMA-binding motif as ^{177}Lu-PSMA-617, and several small trials in mCRPC comparing their kinetics have demonstrated comparable efficacy with PSA_{50} responses ranging from 33% to 50%.[28,42–44] In a study of 100 participants treated with ^{177}Lu-PSMA-I&T, few grade 3–4 toxicities occurred, all of which were hematological (anemia 9%, thrombocytopenia 4%, neutropenia 6%).[44] Xerostomia occurred in 24% (24/100)of patients (all grade ⩽2) and no dry eye symptoms were reported. The European association of nuclear medicine guidelines for ^{177}Lu-labeled PSMA RNT provided consensus that Lu-PSMA-617 and PSMA-I&T are equivalent based on published data.[45]

J591 is a radiolabeled monoclonal antibody binding to the extracellular domain of PSMA. Phase I and II monotherapy studies demonstrated efficacy in heavily pretreated mCRPC patients with 59.6% (28/32)of patients demonstrating any PSA decline with a tolerable toxicity profile.[46,47] Hematological toxicity was higher compared to ^{177}Lu-PSMA-617 monotherapy, with grade ⩾3 anemia in 10.6%, thrombocytopenia in 68.1%, and neutropenia in 61.7%. While common, hematological toxicity was largely self-limiting with no haemorrhagic episodes and complete platelet recovery in the majority (82.9%). One individual (2.1%) experienced febrile neutropenia.

PROSTACT (NCT04876651) is a planned phase III trial comparing two doses of the PSMA-targeted antibody ^{177}Lu DOTA-rosopatamab administered with physician choice of the best standard of care (BSC) compared with BSC alone. The trial aims to enroll 387 patients with mCRPC after the failure of ARPI to assess rPFS.

Bullseye (NCT04443062) is an ongoing phase II trial examining ^{177}Lu-PSMA-617 as first-line metastasis-directed therapy for oligometastatic hormone-sensitive prostate cancer (HSPC).[48] Fifty-eight individuals with ⩽5 metastases on PSMA-PET/CT who have not commenced androgen deprivation therapy (ADT) will be randomized 1:1 to either watchful waiting or ⩾2 cycles of ^{177}Lu-PSMA-617. The primary endpoint is 6-month biochemical or clinical progression-free survival.[48]

Combination RNT studies

Several RNT combination strategies are being explored to improve treatment efficacy through potential synergistic or combinatory effects. The mechanistic basis of these approaches includes upregulation of PSMA expression to enhance radiation activity delivered to cancer cells, leveraging radiosensitization to improve tumor cell killing, modulating the immune microenvironment to generate anticancer responses, and combinations with agents that have established anticancer activity in prostate cancer (See Table 2). The favorable toxicity profile of RNT monotherapy in prostate cancer makes combination therapeutics possible with a broad range of drug classes.

RNT and ARPI

ERA 223 was a phase III study randomizing 806 mCRPC participants with bone-only disease to abiraterone acetate and prednisolone with or without ^{223}Ra (up to six doses).[49] The primary endpoint was symptomatic skeletal event-free survival. The trial was unblinded prematurely after an unplanned analysis revealed increased rates of deaths and fractures in the ^{223}Ra group.[49] At the time of unblinding, ^{223}Ra or placebo had been administered to all enrollees at least 9 months prior to the announcement.[49] Symptomatic skeletal events or death were reported in 49% (196/401)of patients in the ^{223}Ra group compared with 47% (190/405) placebo.[49] The ^{223}Ra cohort demonstrated worse median symptomatic skeletal event-free survival at 22.3 months compared with 26 months with placebo (HR 1.122, 95% CI 0.92–1.37; $p = 0.26$), and twice as many symptomatic pathological bone fractures as the first event (18% *versus* 9%).[49] At the time of primary analysis, median OS was worse in the ^{223}Ra group at 30.7 months (95% CI 25.8- not estimable NE) *versus* 33.3 months (95% CI 30.2–41.1) (HR 1.95; 95% CI 0.95–1.51: $p = 0.13$). It has been postulated that simultaneous activation of osteoclasts with radiotherapy and prednisolone, with inhibitory effects on osteoblasts from modulation of androgen signaling, may account for the increased fracture rates seen with ^{223}Ra, abiraterone, and prednisolone.[50]

In hormone-sensitive disease, targeting androgen receptor (AR) signaling with ADT and ARPIs

Table 2. Combination RNT trials in prostate cancer.

Combination RNT trials in prostate cancer							
Trial Name/NCT	**Phase**	**Enrolled or target enrollment (*n* = number of patients)**	**RNT**	**Combination**	**Primary endpoint**	**Results if available**	**Patient demographics including prior treatment**
RNT and hormonal therapy							
Vision[5]	III	831	LuPSMA	SOC (ARPI in 52.6% combination arm)	Radiological PFS and OS	PFS 8.7 months LuPSMA *versus* 3.4 months (HR0.62); median OS 15.3 months *versus* 11.3 months (HR 0.62)	mCRPC with prior ARPI and taxane
Enza P[61]	II	160	LuPSMA	Enzalutamide	PSA-PFS		mCRPC after ADT
PSMAddition[65]	III	1126	LuPSMA	ADT + ARPI	rPFS		Treatment naïve or minimally treated
ERA 223[49]	III	806	^{223}Ra	Abiraterone and prednisolone	Symptomatic skeletal event-free survival	EFS 22.3 months *versus* 26 months placebo (HR 1.122)	mCRPC, bone-only disease
NCT03724747	I	63	PSMA-targeted thorium 227 conjugate	Darolutamide	MTD		mCRPC prior ARPI and ⩽1 taxane
NCT00859781	II	55	^{177}Lu-J591	Ketoconazole and hydrocortisone	18-month-metastasis-free survival (MFS)	18-month MFS 50% *versus* 24% matched placebo ($p = 0.0066$) and PSA_{50} 82% *versus* 71%	PSA only progression after local treatment
RNT and chemotherapy							
LuCAB (NCT05340374)	I/II	38	LuPSMA	Cabazitaxel	MTD, DLT, and RP2D		mCRPC prior docetaxel and ARPI
Upfront PSMA (NCT04343885)	II	140	LuPSMA	Docetaxel	Undetectable PSA at 12 months		mHSPC newly diagnosed
NCT00916123	I	15	^{177}Lu-J591	Docetaxel	DLT and RP2D	No DLT identified. PSA_{50} response 73%	mCRPC allowed prior docetaxel
ARROW (NCT03939689)	II	120	I-^{131}-1095	Enzalutamide	PSA_{50} response		mCRPC
RNT and immunotherapy							
NCT03805594	I	18	LuPSMA	Pembrolizumab	RP2D and ORR	ORR 44%	mCRPC prior ARPI
PRINCE[74]	I	37	LuPSMA	Pembrolizumab	Safety/tolerability and PSA_{50} RR	PSA_{50}RR 76%	mCRPC prior ARPI and chemotherapy
EVOLUTION (NCT05150236)	II	110	LuPSMA	Ipilimumab and Nivolumab	PSA-PFS at 1 year		mCRPC ARPI and chemotherapy
NCT04946370	I/II	76	^{225}Ac-J591	Pembrolizumab (and ARPI)	DLT, RP2D of 225Ac-J591 composite response rate (PSA_{50}, radiological and conversion of circulating tumor cell count)		mCRPC

(Continued)

Table 2. (Continued)

Combination RNT trials in prostate cancer							
Trial Name/NCT	**Phase**	**Enrolled or target enrollment (*n* = number of patients)**	**RNT**	**Combination**	**Primary endpoint**	**Results if available**	**Patient demographics including prior treatment**
RNT and targeted therapy							
COMRADE[78]	I/II	133	^{223}Ra	Olaparib	RP2D and safety profile	RP2D 200 mg BD	mCRPC, bone only
LuPARP (NCT03874884)	I	52	LuPSMA	Olaparib	DLT, MTD, and RP2D		mCRPC
LuPIN[82]	I/II	56	LuPSMA	Idronoxil (NOX66)	Safety and tolerability	PSA_{50} all cohorts 61% (34/56; 95% CI 47–74), median PSA-PFS 7.5 months (95% CI 5.9–9.0) median OS 19.7 months (95% CI 9.5–30 months)	mCRPC chemotherapy and ARPI
RNT and surgery							
LuTectomy[84]	I/II	20	LuPSMA	Radical prostatectomy	Radiation-absorbed dose	No grade 2–5 adverse events no Clavien-Dindo grade 3–5 surgical complications	High-risk localized prostate cancer
NCT04297410	I	14	LuPSMA	robot-assisted radical prostatectomy (RARP) and lymph node dissection	Surgical safety and early oncological outcomes	No grade ⩾3 adverse events during treatment. Postoperative and continence recoveries similar to RARP alone	High-risk localized prostate cancer
Combination RNT and/or external beam radiation							
AlphaBet (NCT05383079)	I/II	36	LuPSMA I&T	^{223}Ra	DLT, MTD, RP2D, PSA_{50}		mCRPC prior ARPI and chemotherapy
VIOLET (NCT05521412)	I/II	36	LuPSMA I&T	[161 Tb]Tb PSMA-I&T	MTD, Adverse events, DLT, RP2D		mCRPC ⩾1 line of chemotherapy and ARPI
POPSTAR I[89]	I	39	LuPSMA	SABR	Feasibility	Feasibility rate 97%	Oligometastatic prostate cancer
POPSTAR II (NCT05560659)	II	92	SABR	SABR and 177-Lu-PSMA	bPFS		Oligometastatic prostate cancer
ROADSTER (NCT05230251)	II	12	LuPSMA	HDR brachytherapy	Safety and feasibility		Local disease recurrence
NCT04886986	I/II	33	225Ac-J591	^{177}Lu-PSMA-I&T	DLT, MTD, and PSA decline		Progressive mCRPC

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; bPFS, biochemical PFS; DLT, dose-limiting toxicity; EFS, event-free survival; HDR, high-dose radiation; HR, hazard ratio; LuPSMA ^{177}Lu-PSMA-617; mCRPC, metastatic castrate-resistant prostate cancer; MTD, maximum-tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PSA_{50} PSA decline ⩾50% from baseline; RNT, radionuclide therapy; RP2D, recommended phase II dosage; RR, response rate; SABR, stereotactic ablative body radiotherapy; SOC, standard of care.

can cause a marked reduction of tumor volume and correspondingly reduced PSMA expression, however, some sites may also exhibit increased PSMA expression.[51] In contrast, ARPIs increase PSMA expression in the setting of castration resistance, including in low PSMA-expressing prostate cancer.[52–56] Manipulation of the interplay between AR signaling and PSMA expression provides an opportunity for enhanced antitumoral effects from PSMA-directed RNT in prostate cancer. Furthermore, androgen blockade with an ARPI offers synergistic effects and may confer some level of radiosensitization through effects on DNA repair and altered transcription of genes implicated in DNA repair.[57,58]

An observational study involving 58 patients with mCRPC demonstrated improved OS from ^{177}Lu-PSMA-617 administered in combination with abiraterone acetate (median OS 16 months) compared with ^{177}Lu-PSMA-617 alone (median 8 months).[59] In the VISION phase III trial 52.6% (278/529) in the ^{177}Lu-PSMA-617 plus SOC arm received an ARPI as the SOC (enzalutamide [157/278], abiraterone acetate [132/278], apalutamide [10/278], or darolutamide [2/278]).[5] Although the rPFS and OS benefits with ^{177}Lu-PSMA-617 were observed regardless of the SOC therapy, the magnitude of benefit for survival was numerically larger in the subset of patients receiving concurrent ARPI (HR for OS 0.55; 95% CI 0.43–0.70 *versus* HR 0.70; 95% CI 0.53–0.93).[60] One possible explanation for this difference is upregulation of PSMA expression with concurrent use of an ARPI in the setting of castration resistance resulting in enhanced cellular uptake of ^{177}Lu-PSMA-617 and higher absorbed radiation doses within the tumor.

The phase II EnzaP (NCT04419402) trial randomized 160 men with mCRPC to up to four doses of ^{177}Lu-PSMA-617 in combination with enzalutamide or enzalutamide alone.[61] Participants were eligible if they had no prior treatment with ARPI (allowing abiraterone in HSPC) or docetaxel chemotherapy for castration-resistant disease (permitted in HSPC setting), and $\geq$2 poor prognostic features (lactate dehydrogenase $\geq$ upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq$ ULN, albumin $<$35 g/L, AJCC stage M1 disease at diagnosis, $<$3 years from initial diagnosis to randomization, $>$5 bone metastases, visceral metastases, PSA doubling time $<$84 days, and pain requiring opiates $>$ 14 days).[61] The primary endpoint, PSA-PFS, is anticipated to be read out in the next 12 months[61] EnzaP is also prospectively evaluating the modulatory impact of enzalutamide on PSMA expression using serial PET/CT scans and circulating tumor cells (CTCs) obtained on days 15, 92, and at disease progression. These imaging and circulating biomarkers will shed light on the complex interplay between targeting AR signaling with ARPI and PSMA expression in mCRPC.

The ARROW (NCT03939689) phase II trial is examining I-131-1095, a radiolabeled monoclonal antibody that binds to the extracellular domain of PSMA with favorable drug distribution and clearance.[62] The ARROW trial will randomize 120 mCRPC patients 2:1 to receive enzalutamide and I-131-1095 or enzalutamide monotherapy to assess the PSA_{50} response, ORR, and PFS.

PSMA-targeted thorium-277 conjugate (PSMA-TTC), an immunoglobulin G monoclonal antibody alpha therapy is currently being evaluated in combination with darolutamide in an ongoing phase I study (NCT03724747) to ascertain the maximum-tolerated dose (MTD) of this therapeutic strategy in mCRPC.[63]

A phase II trial (NCT00859781) examining ^{177}Lu HuJ591 (^{177}Lu-J591), a PSMA-targeted monoclonal antibody, in combination with ketoconazole, a nonspecific steroid biosynthesis inhibitor, in 55 patients with PSA only progression after local treatment is underway. Participants received ^{177}Lu-J591 with ketoconazole and hydrocortisone or matched placebo comparator. This combination demonstrated superior metastasis-free survival (MFS) at 18 months, 50% (^{177}Lu-J591) *versus* 24% ($p = 0.066$) and a median MFS of 23.8 *versus* 20.8 months.[64] The PSA_{50} response rate was 82% *versus* 71% and PSA-PFS was 18.67 *versus* 8.87 months compared to matched placebo. Grade $\geq$3 hematological toxicity was common in the combination arm with neutropenia in 57% *versus* 11% and thrombocytopenia in 77% *versus* 11% of the participants.[64]

PSMAddition (NCT04720157) is a phase III study comparing ^{177}Lu-PSMA-617 with SOC (ADT and ARPI) *versus* SOC alone in 1126 mHSPC patients who are either treatment naïve or 'minimally treated' with ADT or ARPI, who do not require upfront chemotherapy.[65] The primary endpoint is rPFS with key secondary endpoints including OS.[65] This trial is examining the

role of ^{177}Lu-PSMA in earlier stages of disease and allows for a cross over from ARPI monotherapy arm to concurrent treatment with ^{177}Lu-PSMA-617 at the time of confirmed disease progression.[65]

RNT and chemotherapy combination trials

The commonest site of disease progression following ^{177}Lu-PSMA-617 is bone, possibly owing to limited radiation delivery to micrometastatic disease at this site.[38] Combination chemotherapy and RNT may potentially improve efficacy in bone sites of disease by sensitizing cells to radiation-induced DNA damage, thereby increasing tumor death and possibly the durability of responses. This approach may also overcome resistance due to cellular tumor heterogeneity in PSMA expression that is not discernible on molecular imaging. Given the significant proportion of participants excluded from TheraP, VISION, and LuPSMA trials owing to 'unfavorable' imaging phenotypes, an approach combining ^{177}Lu-PSMA-617 with chemotherapy could broaden the efficacy among patients with lower PSMA expression, FDG discordant disease, or dedifferentiated disease thus, potentially overcoming prostate cancer tumor heterogeneity and expanding the target population.

The LuCAB trial (NCT05340374) is phase I/II study evaluating the combination ^{177}Lu-PSMA-617 and cabazitaxel in up to 38 mCRPC patients who have previously been treated with docetaxel and progressed on prior ARPI. Key eligibility includes PSMA avid disease with minimum SUVmax of 15 at least one site of disease. This combination is aiming to leverage potential synergistic effects from radiosensitization with taxane chemotherapy and DNA damage with ^{177}Lu-PSMA-617. The primary objective is to determine the MTD, dose-limiting toxicities (DLT), and recommended phase II dose (RP2D) of the combination.

UpFront PSMA (NCT04343885) is a phase II trial of 140 men with denovo mHSPC, randomizing 1:1 to sequential delivery of two cycles of ^{177}Lu-PSMA-617 to debulk tumor followed by six cycles of docetaxel or alternatively six cycles of docetaxel. The primary endpoint is undetectable PSA ($\leqslant$0.2 ng/L) at 12 months.[66]

^{177}Lu-J591 was combined with docetaxel in a phase I dose escalation study of 15 individuals with mCRPC (NCT00916123 trial).[67] Patients were eligible after prior treatment with docetaxel only if disease had not progressed during chemotherapy. There were no PSMA imaging selection criteria for enrolment. Patients received two upfront cycles of docetaxel followed by two fractionated doses of ^{177}Lu-J591 concurrent with the third cycle of docetaxel and then ongoing docetaxel every 3 weeks. The primary endpoint was DLT and RP2D with several secondary response outcomes.[67] Overall, 73% (11/15) of participants demonstrated a PSA_{50} response, 60% (3/5) with measurable disease had a partial response by RECIST 1.1 and 85.7% (12/14) had decline in CTC count $>$ 30%.[67] The combination approach was well-tolerated with no DLT identified, providing some early support for this approach.[67]

RNT and immunotherapy combinations

Immune checkpoint inhibitor (ICI) therapy such as anti-cytotoxic T-lymphocyte-associated protein-4, anti-programmed death-1 (PD1), and anti-PD ligand-1 (PDL-1) enhances T-cell activation and has dramatically improved survival in many cancers, including microsatellite (MSI) unstable prostate cancer. However, it has been underwhelming for unselected mCRPC patients, possibly due to prostate cancer being an 'immune-cold' disease.[68–70]

Radiation at different doses and schedules has direct antitumoral effects and can additionally generate immunomodulatory effects on the tumor microenvironment including activating the stimulator of interferon genes pathway, enhancing tumor antigen presentation, recruitment of tumor-infiltrating lymphocytes, and enhanced T-cell function, all of which are essential for immunotherapy efficacy.[71,72] Several early phase studies aiming to leverage the PSMA RNT-induced immune modulation by concurrent treatment with ICIs are currently underway or in follow-up.

A phase 1b trial (NCT03805594) of mCRPC after progression on ARPI and without prior chemotherapy, enrolled across three cohorts of six participants, explored schedules of ^{177}Lu-PSMA-617 and pembrolizumab (either one cycle of ^{177}Lu-PSMA-617 before, after or concurrently with pembrolizumab). The sequential schedule of ^{177}Lu-PSMA-617 followed by pembrolizumab is being explored in the expansion phase of the trial. Preliminary results reported that the ORR was

44% (8/18) with the median duration of response not reached (1.9–15.9 months). All patients were MSI stable and did not have evidence of homologous recombination repair (HRR) deficiencies.[73]

PRINCE (NCT03658447) is a phase I trial combining up to six cycles of ^{177}Lu-PSMA-617 with pembrolizumab 3 weekly for up to 2 years in patients with mCRPC after progression on prior ARPI and one line of chemotherapy. Participants were required to have a PSMA SUVmax of ⩾20 at least one site of disease and > 10 at all sites. After a median follow-up of 16 months the PSA_{50} response was demonstrated in 76% (28/37; 95% CI 59–88) and the ORR 70% (7/10) in those with RECIST1.1 measurable disease. The median rPFS was 11.2 months (95% CI 5.1–14.1) and OS was 17.8 months (95% CI 13.4- not estimable NE). The safety profile of the combination was in keeping with that expected of both treatments.[74]

EVOLUTION (NCT05150236) is a phase II trial randomizing 100 mCRPC participants 2:1 to receive up to six cycles of ^{177}Lu-PSMA-617 in conjunction with ipilimumab (anti-CTLA4) at 3 mg/kg every 6 weeks for four doses and nivolumab (anti-PD1) at1mg/kg every 3 weeks for eight doses, followed by maintenance nivolumab at 480 mg every 4 weeks, or alternatively, six cycles of ^{177}Lu-PSMA-617 monotherapy. Participants are required to have progressed on an ARPI and can have had one prior line of chemotherapy with PSMA avid disease (SUVmax > 15 at least one site and > 10 all sites). The primary outcome is PSA-PFS at 1 year, with key secondary endpoints of PSA_{50}, ORR, PFS, and OS.

A phase I/II trial (NCT04946370) is recruiting 76 individuals with mCRPC to assess the combination of 225Ac-J591 at either 65 or 90 KBq/kg with 6-weekly pembrolizumab (anti-PD-1) and an ARPI to determine the DLT, RP2D of 225Ac-J591, and composite response rate (PSA_{50}, radiological and conversion of circulating tumor cell count).

RNT and targeted therapy combinations

^{177}Lu-PSMA-617 induces proportionally greater single strand breaks (SSB) than DNA double strand breaks (DSB) in tumor cells. Poly-(ADP)-ribose polymerase (PARP) enzymes play a central role in repairing radiotherapy-induced DNA SSBs, minimizing potentially lethal radiation-induced damage and conferring resistance.[75] PARP inhibitors block base excision repair and results in conversion of SSBs to lethal DSBs. Multiple preclinical and clinical studies have shown enhanced antitumor activity from the combination of PARP inhibitors and radiotherapy including RNT, suggesting possible expansion of the indication for PARP inhibitors beyond those with HRR deficient tumors.[76,77]

COMRADE (NCT03317392) is a combined phase I/II trial of olaparib and ^{223}Ra in 133 patients with mCRPC and ⩾2 bone-only metastases.[78] Four-weekly doses of ^{223} Ra (55 kBq/kg IV) for six doses was administered with escalating doses of olaparib (3 + 3 design) to assess the primary endpoint RP2D and safety. Three out of twelve patients enrolled in the phase 1 study demonstrated grade 3–4 TRAE and the RP2D of olaparib was 200mg twice daily with ^{223}Ra. PSA_{50} was 16.7% (one patient at each dose levels 1 and 2) and a 6-month radiological PFS was 57% (95% CI 25–80).[78]

LuPARP (NCT03874884) is an ongoing phase I dose trial of olaparib and ^{177}Lu-PSMA-617 in mCRPC. Patients must have had one prior line of taxane chemotherapy and progressed on an ARPI with a minimum PSMA SUVmax of 15 at one site and > 10 other sites without FDG discordant disease analogous to the LuCAB trial. Patients receive 4–6 cycles of ^{177}Lu-PSMA-617 in conjunction with an escalating dose schedule of olaparib. The primary endpoint is to define the RP2D and MTD for subsequent clinical development.

Idronoxil (NOX66) is a derivative of the flavonoid genistein which inhibits tumor turnover through promoting apoptosis and G2/M cell cycle arrest.[79] When administered in combination with radiation, NOX66 results in inhibition of NF-κB, increased radiosensitivity, and enhanced tumor apoptosis.[79] Lupin was a phase I/II dose escalation trial of ^{177}Lu-PSMA-617and NOX66 enrolling 56 mCRPC patients after disease progression on chemotherapy and ARPI to receive up to six cycles of ^{177}Lu-PSMA-617 in combination with NOX66 (across three different dose cohorts).[80,81] PSA_{50} responses across all cohorts were 61% (34/56; 95% CI 47–74), median PSA-PFS was 7.5 months (95% CI 5.9–9.0), and median OS was 19.7 months (95% CI 9.5–30 months).[82] Of 34 patients with pain scores ⩾3 at baseline, 53% (18/34) demonstrated significant improvement in pain indicators.[82] The only grade 3 toxicity reported was anemia in 5% and fatigue in 2%.

RNT studies in combination with surgery

A phase I trial demonstrated safety of two or three doses of ^{177}Lu-PSMA-617 prior to RARP and lymph node dissection for high-risk localized disease.[83] None of the 14 patients treated with ^{177}Lu-PSMA-617 demonstrated grade ⩾3 AEs during treatment and the postoperative and continence recoveries were similar to RARP alone.[83]

LuTectomy (NCT04430192) is an ongoing phase II non-randomized trial of 20 patients with high-risk localized prostate cancer, to assess the radiation-absorbed dose in the prostate and lymph nodes after either one or two cycles of ^{177}Lu-PSMA-617 prior to prostatectomy.[84] Preliminary results reported ^{177}Lu-PSMA-617 was safe prior to surgery and well-tolerated with no grade 2–5 AEs and no Clavien-Dindo grade 3–5 surgical complications.[85] Dosimetry analysis showed clinically meaningful doses of radiation delivered to tumor with a median of 48 Gy and 50 Gy to the prostate and lymph nodes, respectively, with further results awaited.[85]

Combination of radiopharmaceuticals, external beam radiation, or brachytherapy

The commonest site of ^{177}Lu-PSMA-617 progression is the bone marrow, which may occur due to failure to treat resistant cells or small cell clusters with lower energy beta radiation, and less cross-fire radiation from neighboring cells compared to larger tumors.[38] Furthermore, the density of bone leads to high attenuation of beta particles, and more pronounced spatial nonuniformity of dose distribution in bone metastases.[86]

Of relevance, ^{223}Ra, is an alpha emitter with short path length but with a much higher LET compared to beta emitters, which leads to highly targeted radiation deposition within a few cell ranges. The combination of beta and alpha-emitting radioisotopes may leverage synergistic effects of treating a wider range of metastatic lesion sizes and optimize the treatment of resistant clones.

AlphaBet (NCT05383079) is a phase I/II trial of ^{177}Lu-PSMA-I&T (7.4 GBq) fixed dose combination with escalating activity of ^{223}Ra (28 kBq/kg–55 kBq/kg) to assess the co-primary endpoints of safety and antitumoral activity. The dose escalation component will define the MTD, DLT, and RP2D of ^{223}Ra in combination with ^{177}Lu-PSMA-I&T and will be followed by a phase II assessment of treatment efficacy (PSA_{50}). Thirty-six participants will be recruited with bone-only mCRPC and PSMA avid disease SUVmax ⩾20 at least one site and ⩾10 all sites of measurable disease after progression on ARPI and ⩽1 line of chemotherapy.

^{161}Tb delivers higher doses of radiation than ^{177}Lu-PSMA-617 through delivery of substantially higher numbers of conversion and Auger electrons. The doses delivered by ^{161}Tb or ^{177}Lu to 10 m-diameter spheres were demonstrated to be comparable, however, for 100 µm-diameter and 10 µm-diameter spheres, ^{161}Tb could deliver 1.8 and 3.6 times higher doses compared to ^{177}Lu and may be better suited for treating micrometastatic disease.[87] The VIOLET trial (NCT05521412) is assessing if ^{161}Tb can target single tumor cells and micrometastatic disease usually resistant to ^{177}Lu-PSMA-617 and will investigate ^{161}Tb PSMA-I&T in a single-arm phase I trial. This study will recruit 36 participants with mCRPC who have progressed on ⩾1 line of prior chemotherapy and ARPI to establish the MTD, DLT, and RP2D in the phase I component.

A dose escalation phase I/II trial of 225Ac-J591 plus ^{177}Lu-PSMA-I&T (NCT04886986) is currently recruiting 33 progressive mCRPC patients to assess DLT, MTD, and PSA decline. The monoclonal antibody J591 has low uptake in the salivary glands and kidneys, therefore, circumventing the DLT of xerostomia observed with small molecule alpha emitters targeting PSMA. By combining ^{177}Lu-PSMA-I&T with 225Ac-J591, alpha and beta concurrent emission could potentially treat a range of tumor lesions with variable geometry.[88]

Following on the POPSTAR I trial in oligometastatic prostate cancer demonstrating feasibility, tolerability, and preliminary efficacy, POPSTAR II (NCT05560659) is a recruiting phase II trial planned to assess biochemical PFS from SABR compared to combination SABR and two cycles of ^{177}Lu-PSMA-617 in 92 individuals with oligometastatic prostate cancer.[89]

ROADSTER (NCT05230251) is a two-part phase II trial currently recruiting to assess the safety and feasibility of one cycle ^{177}Lu-PSMA-617 followed by high-dose radiation (HDR) brachytherapy to the entire prostate, or two brachytherapy treatments alone. Twelve participants will be recruited with local disease recurrence after prior

primary radiation within the last 2 years to ascertain safety, efficacy, and PSA_{50} response rate.

Predictive and prognostic biomarkers of ^{177}Lu-PSMA-617 RNT

While many patients respond to ^{177}Lu-PSMA-617, intrinsic resistance occurs in up to a third of mCRPC individuals, and acquired resistance is universal thus underpinning the importance of biomarkers of response and resistance. Despite strict trial criteria and a 'favorable' imaging phenotype defined as having an SUVmax of ⩾10, a proportion of patients do not respond to ^{177}Lu-PSMA-617 in clinical trials. There are several proposed mechanisms of ^{177}Lu-PSMA-617 resistance, including heterogeneity of PSMA expression, failure to deliver a lethal radiation dose to the tumor, tumor mutational and microenvironment factors, as well as emergence of neuroendocrine or dedifferentiated disease.[90]

Clinical studies have identified prognostic markers associated with worse outcomes on ^{177}Lu-PSMA-617, including poor performance status, lower cumulative dose, lower baseline hemoglobin, higher alkaline phosphatase, liver metastases, and lower serum albumin.[38,90–95] In terms of predictive markers, a larger PSA reduction has consistently demonstrated to be predictive of improved survival with ^{177}Lu-PSMA-617.[91]

Several studies have reported predictive imaging biomarkers of response to ^{177}Lu-PSMA-617. In the TheraP trial, quantitative PET/CT parameters such as whole-body SUVmean ⩾10 was predictive of PSA_{50} response. A total of 91% (32/35) of individuals with SUVmean ⩾10 receiving ^{177}Lu-PSMA-617 achieved a PSA_{50} compared with 52% (33/64) when PSMA SUVmean was <10.[96] TheraP reported responses to ^{177}Lu-PSMA-617 for cohorts based on SUVmean by quartile range; patients in the lowest quartile (Q1) with SUVmean <6.9 consistently demonstrated lower response rates with PSA_{50} 29% (95% CI 12–52), median rPFS 5.6 months (95% CI 3.8–10.8) and median PSA-PFS 2.0 months (95% CI 1.3–5.5) compared to higher SUV mean scores by quartile subsets (Q2–Q4).[97] Likewise, imaging analysis from the VISION trial demonstrated longer PFS and OS in patients in the highest quartile compared to those in the lowest quartile of PSMA SUVmean.[98] Higher SUVmean was strongly correlated with improved clinical outcomes including rPFS (HR 0.86; 95% CI 0.82–0.90; $p < 0.001$) and OS (HR 0.88; 95% CI 0.84–0.91; $p < 0.001$).[98] The correlation between PSMA SUVmean and outcome is intuitive as dosimetry analysis of the LuPSMA study showed mean whole-body tumor absorbed activity of ^{177}Lu-PSMA-617 after the first cycle appears to correlate with whole-body PSMA SUVmean on pretreatment ^{68}Ga-PSMA 11 and PSA response at 12 weeks.[99]

FDG avid metabolic tumor volume (MTV) may also be a prognostic marker in mCRPC. A MTV ⩾200mL was associated with lower PSA_{50} responses after ^{177}Lu-PSMA-617 compared to a MTV < 200 mL (23/60 [38%; 95% CI 26–52] *versus* 79/140 [56%; 48–65]; odds ratio [OR] 0.44; 95% CI 0.23–0.84; $p = 0.014$).[96,97] Although molecular imaging biomarkers appear to be important in predicting likely response to ^{177}Lu-PSMA-617, a significant subset of patients will exhibit primary resistance despite having favorable imaging features and further investigation is needed.

Strict imaging inclusion criteria in landmark prospective trials has resulted in many potential participants being excluded with imaging screen fail rate was reported to be 12.6% in VISION, 16% in the LuPSMA study, and 28% in TheraP.[5,6,37] PSA_{50} responses were higher in the LuPSMA study (17/30; 57%) and TheraP (65/99; 66%) trial with stricter PET/CT criteria and patient selection compared to the VISION trial (PSA_{50} response 177/385; 46%).[5,6,37] It is possible that imaging criteria should become less strict when combining ^{177}Lu-PSMA-617 with other systemic agents with established activity in PSMA negative disease, thereby broadening the clinical utility in a wider subset of participants with more heterogeneous PSMA expression.

While most clinical studies have adhered to standard activity of ^{177}Lu-PSMA-617 administered on a 6-weekly schedule, another potential strategy includes personalization of treatment administered radioactivity and scheduling of RNT based on tumor burden. Further research is also needed into the longe-term outcomes of patients retreated with PSMA-targeted RNT on progression after an initial response.[38] Combination therapeutics is an expanding field demonstrating great promise for the future of RNT in personalized therapeutics for prostate cancer.[90,100]

Novel RNT targets

Human kallikrein2 (KLK2), a kallikrein-related serine protease highly and specifically expressed in prostatic tissues, is currently under active investigation as a useful theranostic target in prostate cancer. KLK2 provides a novel target for RNT against metastatic prostate cancer with less off-tumor toxicity.[101,102] Three KLK2-based phase I clinical trials are ongoing in mCRPC: JNJ-75229414 a chimeric antigen receptor T-cell (CAR-T) therapy directed against KLK2 (NCT05022849), JNJ-78278343 a bispecific anti-KLK2/CD3 antibody (NCT NCT04898634), and JNJ-69086420 an actinium-225-labeled antibody targeting human KLK2 (NCT04644770). It is anticipated that these agents will be combined with other systemic therapies in mCRPC.

Conclusion

RNT is rapidly evolving as an effective and well-tolerated treatment for mCRPC. The toxicity profile of PSMA-directed RNT lends itself to rational combination approaches with agents such as hormonal therapies, chemotherapy, immunotherapy, targeted therapies, and other RNT. Collectively, these combination approaches aim to increase the depth and durability of responses as well as circumvent resistance. Further, combination RNT strategies have the potential to broaden the therapeutic reach of RNT to patients with modest or heterogeneous PSMA expression. However, there are data gaps in relation to defining the optimal treatment sequencing, patient selection for PSMA-directed RNT, and mechanisms of resistance. While high expression of PSMA on PSMA PET/CT appears to be a very useful predictive biomarker, further molecular biomarkers are needed to characterize primary and acquired resistance. Combination RNT strategies have the potential to expand the role of RNT to different phenotypes and earlier stages of disease and may be able to bridge the gap to improve patient outcomes.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consented by all authors.

Author contributions

Andrisha–Jade Inderjeeth: Writing – original draft; Writing – review & editing.

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Shahneen Sandhu: Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

AJ Inderjeeth: Honoraria for educational events from Pfizer and BMS.

A Iravani: Consultant for Curium Pharma.

S Subramaniam: Nil.

C Conduit: Honoraria for speaker fees from AstraZeneca.

S Sandhu: SS is consultant advisor for AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Advanced Accelerators Applications (a Novartis company) funds to the institution. Grant funding to the institution from Advanced Accelerators Applications (a Novartis company), Amgen, Merck Sharp & Dohme, Senwha, Genentech, and AstraZeneca to undertake investigator-initiated research.

Availability of data and materials

Not applicable.

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