Radionuclide Therapy in Prostate Cancer: From Standalone to Combination PSMA Theranostics

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Despite significant advances in therapeutic developments for prostate cancer over the last 2 decades, metastatic prostate cancer remains a lethal disease. Prostate-specific membrane antigen (PSMA), which is markedly overexpressed in prostate cancer cells and metastatic sites but has low normal-tissue expression, has emerged as an important theranostic target for this disease. Both β-emitting and α-emitting PSMA-targeted radionuclide therapy (RNT) are in clinical development. Several of these agents have already shown promising activity; however, a subset of patients have primary resistant disease, and secondary resistance invariably occurs. Further, the effect of these therapies on healthy organs limits their therapeutic window. Elucidating the biology of PSMA and characterizing the pharmacokinetic and pharmacodynamic properties of PSMA-targeted RNT and mechanisms of resistance will facilitate therapeutic approaches aimed at improving efficacy and safety. In this review, we provide an overview of existing PSMA-targeting RNT and novel RNT combinatorial approaches, such as those with novel hormonal agents, poly-[adenosine diphosphate-ribose]-polymerase inhibitors and immunotherapy, currently under investigation.

Key Words: PSMA; radionuclide therapy; theranostics; Lu-PSMA; prostate cancer

Prostate cancer is one of the most common causes of male cancer mortality globally (*1*). Although localized disease is curable with surgery or radiotherapy, a third of patients presents with or develops lethal metastatic disease, which is invariably fatal (*2,3*). Prostate-specific membrane antigen (PSMA) has emerged as a promising theranostic target for prostate cancer, and PSMA-targeted therapies are rapidly changing the therapeutic landscape. Clinical trials of PSMA-targeted therapies have demonstrated antitumor activity in patients with advanced disease; clinical evaluation in earlier stages of disease and larger randomized studies are ongoing (*4*). To date, several clinical trials have shown that PSMA-targeting radionuclide therapy (RNT) is tolerable and effective; however, a subset of patients have primary resistant disease, and secondary resistance is inevitable. In this review, we

provide an overview of existing PSMA-targeting RNT and an update on therapeutic strategies aimed at minimizing toxicity and improving the efficacy of PSMA-targeting RNT both as monotherapy and in combination with other agents.

BIOLOGY OF PSMA

PSMA, also known as hydrolase 1 (FOLH1), is a cell-surface, transmembrane aminopeptidase. It consists of a large extracellular domain, a small transmembrane domain, and a cytoplasmic tail (*5*). PSMA is overexpressed on most prostate cancer cells, compared with normal prostatic epithelium, and is further increased in metastatic, castrate resistant and high-Gleason-score disease (*6*). However, PSMA expression is also observed on proximal renal tubules, duodenum, salivary and lacrimal glands, and nonmyelinated ganglia (*7*). On-target, off-tumor effects at these sites account for some of the treatment-related toxicities of PSMA-targeted RNT.

The function of PSMA on prostate cancer cells remains incompletely understood. PSMA has multiple established physiologic functions. In the duodenum, PSMA is involved in the processing and uptake of dietary folates; it cleaves γ-linked glutamates from polyglutamated folates (known as folate hydrolase activity) (*8*). Prostate cancer cells also demonstrate increased glutamine use and, therefore, may in part depend on PSMA for nucleotide biosynthesis and metabolism, which in turn impacts cell proliferation and invasiveness (*9*).

PSMA-TARGETING RADIONUCLIDE (RNT)

PSMA-targeting tracers can be labeled with different radionuclides for diagnostic or therapeutic purposes. These consist of a PSMA-binding domain, a linker, and a chelator labeled with various radionuclides. The PSMA-targeting small molecules are divided into 3 types—urea-based, phosphorus-based, and thiol-based—with the urea-based compounds preferentially used for their superior PSMA binding affinity (*10*). Changing the linker or chelator structure can influence PSMA binding efficacy and pharmacokinetics. In addition, adding an albumin-binding domain, which effectively increases the agent's size, has been explored to increase circulation time within the tumor vasculature and reduce healthy-organ circulation time, with the goal of mitigating on-target, off-tumor toxicities (*11*). Different approaches to modifying components of PSMA RNT have been extensively reviewed elsewhere (*12*).

On accumulation of the PSMA-targeting tracer at the tumor site, radioactive decay of the α- or β-emitting radionuclides induces DNA strand breaks and causes cell death. α-radiation reaches a shorter range (40–100 μm) than β-particles (50–12,000 μm) but

has a linear energy transfer significantly higher than that of β-particles (5–9 vs. 0.1–2.2 MeV) ([12]). α-emitting radionuclides therefore lead to several ionizing events, resulting in DNA double-strand breaks (DSBs) in a short range ([13]). The result is a more effective tumor kill that is largely independent of cell cycle or oxygenation and potentially has less off-target toxicity ([14]). However, these properties also mean that α-emitting RNT are associated with greater on-target damage to healthy tissue, including irreversible damage to lacrimal and salivary glands ([15]). The effectiveness of α-particles was demonstrated by the bone-targeting α-emitter ^{223}Ra chloride, which in a phase 3 randomized trial was shown to improve overall survival (OS) and delay the time to the first symptomatic skeletal event in patients with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases ([16]). Both PSMA-targeted α-emitting RNT and PSMA-targeted β-emitting RNT are now in clinical development ([17–22]).

CLINICAL DEVELOPMENT OF PSMA-TARGETED RNT

Clinical Development of β-Emitting PSMA-Targeting RNT

The ^{177}Lu-conjugated small-molecule peptide ^{177}Lu-PSMA-617 is the PSMA-targeted RNT currently furthest in clinical development. ^{177}Lu has favorable physical characteristics, with a short-range medium-energy β-particle for crossfire to surrounding tumor cells, a relatively long half-life of 6.7 days, and a low-energy γ emission that enables RNT administration in an ambulatory setting as well as posttreatment dosimetry. Promising antitumor activity and modest toxicity were first reported in retrospective case series ([18]). A metaanalysis of 10 PSMA RNT trials in patients with mCRPC treated with prior enzalutamide or abiraterone showed a greater than 50% prostate-specific antigen (PSA) decline in 51% (123/238) of patients (Table 1) ([23]).

A prospective phase 2 trial conducted in Australia evaluated up to 4 cycles of ^{177}Lu-PSMA-617 (mean radioactivity, 7.5 GBq per cycle) delivered every 6 weeks to mCRPC patients who had progressed after most conventional therapies. Thirty-two (64%) of 50 patients achieved a PSA response defined as a decline in PSA of greater or equal to 50%. Importantly, treatment with ^{177}Lu-PSMA-617 improved the quality of life ([17,24]). Fifteen patients (30%) for whom there was an initial PSA response but subsequent disease progression received further cycles of ^{177}Lu-PSMA-617 therapy on confirmation of the presence of adequate PSMA-expressing metastatic disease and adequate organ function prior to retreatment. Eleven (73%) of these patients had PSA responses of at least 50%, although the duration of response with retreatment was shorter and disease progression eventually occurred in all patients ([24]). Expectedly, a PSA decline of at least 50% predicted

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NOTEWORTHY

■ Numerous PSMA-targeting RNTs, which include α- and β-emitters, are currently under clinical development.

■ The ^{177}Lu-conjugated small-molecule peptide ^{177}Lu-PSMA-617 is the most developed PSMA-targeted RNT, with phase 3 outcome data.

■ Elucidating the biology of PSMA expression, regulation, and function will facilitate the development of novel sequential, combinatorial approaches aimed at improving response and safety.

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improved OS. Given that the OS on this study was 13.3 months, data on longer-term effects of lutetium-PSMA on marrow and renal function are required, especially if this treatment is to be implemented in earlier stages of disease.

The randomized phase II TheraP trial compared ^{177}Lu-PSMA-617 (8.5 GBq decreasing by 0.5 GBq per cycle, for up to 6 cycles) versus cabazitaxel (20 mg/m^2 every 3 weeks) in 200 mCRPC patients with PSMA-positive scans who had prior treatment with docetaxel. Ninety-one percent also had prior treatment with an androgen receptor (AR)–targeted inhibitor ([25]). Patients were selected using PSMA and ^{18}F-FDG PET/CT, requiring an SUV_{max} of at least 20 at one site of disease, an SUV_{max} of at least 10 at sites of measurable soft-tissue metastasis, and no site with ^{18}F-FDG–positive, PSMA-negative disease. Notably, 28% of patients were ineligible on the basis of these stringent imaging criteria ([25,26]). ^{177}Lu-PSMA-617 led to a significant improvement in PSA responses of at least 50%, compared with cabazitaxel (66% vs. 37%). ^{177}Lu-PSMA-617 had a higher rate of thrombocytopenia (grade 1–2, 18% vs 5%; grade 3–4, 11% vs. 0%), xerostomia (grade 1–2 only, 60% vs. 21%), and dry eyes (grade 1–2, 30% vs. 4%), although the rate of grade 3–4 toxicity was overall higher with cabazitaxel (54% vs. 35%). ^{177}Lu-PSMA-617 delayed radiographic and PSA progression compared with cabazitaxel (hazard ratio, 0.63). At 12 months, 19% had not progressed with ^{177}Lu-PSMA-617, compared with 3% with cabazitaxel, although the median progression-free survival (PFS) was similar at 5.1 months, with a greater benefit for ^{177}Lu-PSMA-617 emerging after 6 months. The objective response rate defined by RECIST 1.1 was higher with ^{177}Lu-PSMA-617 (49% vs. 24%). Patient-reported outcomes favored ^{177}Lu-PSMA-617, with significantly less diarrhea, fatigue, hair loss, skin rash, sore hands or feet, dizziness, insomnia, and urinary symptoms reported in the patients receiving ^{177}Lu-PSMA-617 than in those receiving cabazitaxel ([25,26]).

The phase 3 VISION study (NCT03511664) randomized patients who had progressed on at least 1 novel antiandrogen therapy and 1 or 2 taxanes to receive ^{177}Lu-PSMA-617 (7.4 GBq) (every 6 weeks for up to 6 cycles) plus the standard of care or to receive the standard of care alone (1:1 randomization). The study reported an improvement in its 2 alternate primary endpoints, OS (median, 11.3 to 15.3 months; hazard ratio, 0.62) and radiologic PFS (median, 3.4 to 8.7 months; hazard ratio, 0.4), in the ^{177}Lu-PSMA-617 arm. Cabazitaxel and ^{223}Ra were not permitted in the standard-of-care arm, and the study initially reported the control arm to have a high dropout rate that was subsequently improved after site education. The side effect profile of ^{177}Lu-PSMA-617 was as expected, with a common serious side effect being bone marrow suppression (all grades, 47%; grades 3–5, 23%); common low-grade toxicities being xerostomia (grade 1 or 2 only, 39%), nausea, and vomiting (all grades, 39%; grades 3–5, 1.5%); and 5 deaths (1%) occurring during the study ([27]). The study will likely see ^{177}Lu-PSMA-617 become part of the mCRPC treatment paradigm, initially to be sequenced following chemotherapy and novel antiandrogen therapy.

Since a dose-escalation study was never performed for ^{177}Lu-PSMA-617, a 44-patient phase 1/2 study exploring the benefit of a fractionated (2 doses 2 weeks apart) higher cumulative dose of ^{177}Lu-PSMA-617 (3.75–11.1 GBq per fractionated dose) is ongoing. Preliminary results show no dose-limiting toxicity, and 61% had a PSA decline of 50% or more ([28]). A ^{177}Lu-labeled DOTAGA–based PSMA ligand, PSMA-I&T, has demonstrated a

TABLE 1
Key Prospective Clinical Trials of PSMA-Targeting Radionuclides in Prostate Cancer

Parameter	Trial	Setting	Treatment	Phase	Primary endpoint	Outcome
Neoadjuvant	NCT04430192 (Lutectomy) (66)	High-risk localized or locoregional advanced prostate cancer with high PSMA uptake	^{177}Lu-PSMA-617 (1–2 cycles)	Phase 1/2 single arm	Absorbed radiation dose in prostate and involved lymph nodes	Recruiting
	NCT04297410	Locally advanced prostate cancer with PSMA uptake	^{177}Lu-PSMA-I&T	Feasibility	Surgical safety; surgical histology; postoperative PSA	Recruiting
Metastatic hormone-sensitive prostate cancer	NCT04443062 (Bullseye)	Oligometastatic hormone-sensitive prostate cancer with high PSMA uptake	^{177}Lu-PSMA-I&T vs SOC	Phase 2 randomized	Disease progression at 6 months	Recruiting (SOC = deferred androgen deprivation therapy)
	NCT04343885 (UpFrontPSMA) (67)	Newly diagnosed high-volume metastatic hormone-naive prostate cancer	^{177}Lu-PSMA-617 followed by docetaxel vs. docetaxel	Phase 2 randomized	Undetectable PSA rate at 12 months	Recruiting
	NCT04720157 (PSMAddition)	Metastatic hormone-sensitive prostate cancer	^{177}Lu-PSMA-617 + NAAT vs. NAAT	Phase 3	rPFS	Recruiting
mCRPC	NCT03042468 (68)	mCRPC ($n = 44$); prior taxane chemotherapy and at least 1 line of prior NAAT	^{177}Lu-PSMA-617 2 weeks apart	Phase 1/2 single arm	DLT, MTD, R2PD	No DLT at any preplanned dose; RP2D: 22.2 GBq per cycle
	ANZCTR 12615000912583 (published) (17,61)	mCRPC ($n = 50$; 30 in initial; 20 in expansion); at least 1 line of prior taxane chemotherapy	^{177}Lu-PSMA-617	Phase 2 single arm	% patients with ≥50% PSA decline	≥50% PSA decline: 64%
	NCT03392428 (TheraP)	mCRPC ($n = 200$) for which cabazitaxel was considered appropriate next line of treatment; previous treatment with NAAT permitted	^{177}Lu-PSMA-617 vs. cabazitaxel	Phase 2 randomized	% patients with ≥50% PSA decline	PSA decrease of ≥50% from baseline: 66% vs. 37%, favoring ^{177}Lu-PSMA-617, $P < 0.0001$
	NCT03511664 (VISION)	mCRPC ($n = 831$); prior taxane chemotherapy and NAAT	^{177}Lu-PSMA-617 + SOC vs. SOC (2:1)	Phase 3 randomized	OS, rPFS	OS: 15.3 vs. 11.3 months favoring ^{177}Lu-PSMA-617; HR: 0.62, $P < 0.001$.
	NCT04689828 (PSMAfore)	mCRP ($n = 495$); prior NAAT	^{177}Lu-PSMA-617 vs. abiraterone or enzalutamide (2:1)	Phase 3 randomized	rPFS	Recruiting
	NCT04647526 (SPLASH)	mCRPC with PSMA PET–positive disease; no prior NAAT or chemotherapy, except in HSPC setting	^{177}Lu-PSMA-I&T vs abiraterone or enzalutamide (2:1)	Phase 3 randomized	rPFS	Recruiting

SOC = standard of care; rPFS = radiologic progression-free survival; NAAT = novel antiandrogen; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose; HR = hazard ratio; HSPC = hormone-sensitive prostate cancer; PET = positron emission tomography.

biodistribution similar to that of ^{177}Lu-PSMA-617, with a comparable response and safety profile in a retrospective case series of 100 patients who had received prior novel antiandrogen therapy and taxane chemotherapy and had PSMA-avid disease. A PSA decline of at least 50% was achieved in 38 patients, and the median OS was 12.9 months (29). Likewise, a PSA response of at least 50% was associated with improved OS (median, 16.7 vs. 7.4 months) (29). Prospective studies in earlier disease settings, including as neoadjuvant treatment in high risk primaries and as an earlier line of treatment for mCRPC and metastatic hormone-sensitive prostate cancer, are ongoing (NCT04297410, NCT04647526, NCT04689828, and NCT04720157).

PSMA-Targeting α-Emitting Radionuclides

The antitumor activity of α-emitting RNT was first demonstrated by [223]Ra-dichloride, an α-emitting RNT that binds areas of increased bone turnover. [223]Ra-dichloride showed an OS benefit and a reduced time to the first symptomatic skeletal event in patients with mCRPC involving bone (16). Several α-emitting PSMA-targeted RNTs, including an antibody-based RNT, [225]Ac-J591, and the small molecules [225]Ac-PSMA-617 and PSMA-targeted [227]Th conjugate (BAY2315497) are in clinical development. The high-energy, short-range α-emissions enable pinpoint tumor targeting, which has advantages in patients with marrow infiltration due to the limited crossfire effect on surrounding bone marrow reserve but also has limitations in the setting of heterogeneous cellular PSMA expression within tumor deposits (30,31).

Antibody-based RNTs have pharmacokinetics different from those of small molecules and have been shown to have less uptake in glandular tissue and kidneys but may also have less tumor uptake (32). In a phase 1 clinical trial, 22 men (55% had previously received ^{177}Lu-PSMA) received a single dose of [225]AC-J591 across 7 dose levels (13.3–93.3 kBq/kg). One patient receiving 80 kBq/kg had dose-limiting toxicities, with grade 4 thrombocytopenia and anemia in the context of prior treatment with ^{177}Lu-PSMA. Thirty-five percent of patients to date have had a PSA decline of more than 50%, and although PSMA uptake was not a selection criterion, most patients had PSMA uptake with an SUV-$_{max}$ greater than that seen in the liver (33). This trial has recently begun the phase 2a expansion.

Retrospective case series of patients treated with [225]Ac-PSMA-617 showed antitumor activity in 60%–70%, including in some patients who had progressed on ^{177}Lu-PSMA. Xerostomia and weight loss were clinically significant (34). A recent study evaluating [225]Ac-PSMA-617 in mCRPC patients who had progressed on abiraterone or enzalutamide, taxane-based chemotherapy, and ^{177}Lu-PSMA and demonstrated PSMA-ligand uptake on imaging reported a PSA decline of at least 50% in 17 of 26 (65%) patients. Median OS was 7.7 months. Grade 3 or 4 myelosuppression was seen in 35% of patients, grade 1 or 2 renal impairment in 19%, and grade 1 or 2 xerostomia in 100% (35). The clinical context in which α-emitting RNT will be used is yet to be defined. Given the differences in physical properties between α-particle and β-particle emitters, these therapies may have specific indications based on disease pattern and biology and should be compared prospectively. Moreover, given their distinct properties and emerging evidence of antitumor activity when α- and β-emitting PSMA-targeted therapies are given sequentially, rational combination of these radioisotopes may serve a complementary role when delivered concurrently or sequentially.

COMBINATION STRATEGIES WITH PSMA-TARGETING RNT

Despite antitumor activity being observed in patients treated with PSMA-targeted RNT, all patients invariably develop recurrence (Fig. 1). In the phase II TheraP trial, in which patients were selected on the basis of PSMA expression on PSMA PET and the absence of discordant ^{18}F-FDG PET–avid disease, 17 of 99 (17%) patients had primary resistance with no decline in PSA (25). Purported acquired resistance mechanisms include heterogeneity or loss of PSMA expression or a failure to deliver a sustained lethal dose to the target. Potential strategies to improve PSMA-targeted therapies include combining PSMA-targeted therapies with agents that upregulate PSMA expression, increase tumor radiosensitivity, target different PSMA-binding sites, or exhibit complementary antitumor effects (36). To this end, several potential combinations are being explored in ongoing clinical studies. These include the combination of PSMA-targeting RNT with AR-targeted agents, DNA repair inhibitors, immunotherapies, chemotherapy, or a combination of different PSMA-targeting RNTs (Table 2).

Combining AR Blockade and RNT

There are several mechanisms through which AR blockade may synergize with PSMA RNT. First, AR blockade has been reported to sensitize to radiotherapy by delaying DNA repair through temporal prolongation of repair factor complexes and halting the cell cycle (37). Second, AR blockade has been shown to modulate the expression of PSMA, although the exact effect of AR blockade on PSMA expression likely hinges on the state of castration. In a study of 20 paired prostate tumor samples collected before and after castration, the expression of PSMA increased in 55% of posttreatment primary tissues and 100% of posttreatment metastatic specimens (38). A recent study indicated that AR blockade appears to have dichotomous effects on PSMA expression in patients at different disease states (39); in patients with hormone-sensitive prostate cancer, a significant reduction in ^{68}Ga-PSMA intensity occurred in 86% of men as early as 9 days after starting androgen blockade, whereas in patients with CRPC, AR blockade caused an increase in PSMA expression (39). The duration of AR blockade may also play a role in PSMA expression although this has not been systematically studied. Third, treatment with enzalutamide, dutasteride, and rapamycin has been shown to increase the uptake and internalization of ^{177}Lu-PSMA in prostate cancer cell lines (40). These studies provide a rationale for combining PSMA-targeted RNT and drugs that block AR signaling in the castration-resistant setting. They also highlight the need to carefully consider the differential impact of AR blockade on PSMA at different disease stages when designing combinatorial approaches.

Given that the existing reported trials of PSMA-targeting RNT were conducted in the castration-resistant setting, the effect of hormone sensitivity and androgen deprivation on the response to PSMA-targeting therapy is unclear. Enza-P (NCT04419402) is a phase II randomized control trial of the combination of enzalutamide and ^{177}Lu-PSMA versus enzalutamide alone in patients with mCRPC who have previously progressed on docetaxel in the setting of hormone-sensitive disease but are naive to a novel antiandrogen inhibitor. This trial is recruiting 160 mCRPC patients with risk factors that predict for early treatment failure with single-agent enzalutamide. Patients will be randomized 1:1 to receive either concurrent enzalutamide with up to 4 cycles of ^{177}Lu-PSMA or enzalutamide alone. This study embeds multiple-time-point PSMA PET/CT and
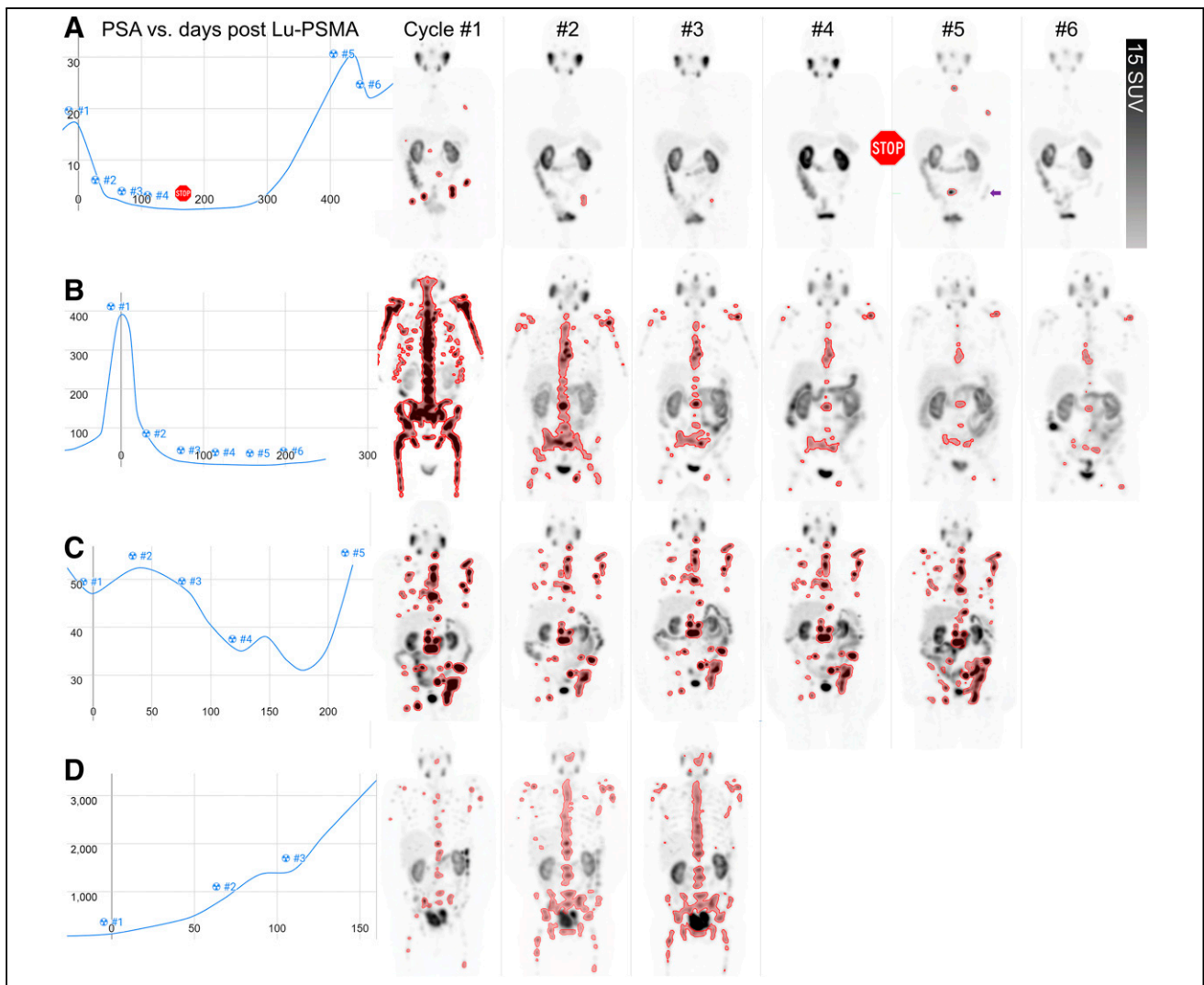
FIGURE 1. Examples of patterns of progression in men with mCRPC undergoing ^{177}Lu-PSMA-617 therapy. Shown are PSA over time and posttherapy quantitative SPECT/CT imaging after each cycle of treatment. (A) Patient with relatively small-volume disease with complete response. At time of progression, some disease has low PSMA expression in left pelvis (arrow), and response to further cycles is limited. (B) Patient with PSMA superscan and exceptional response to treatment. Disease eventually recurred (not shown) with diffuse marrow involvement. (C) Rise in PSA after cycle 1 but subsequent response at cycles 2–4, with subsequent progressive PSMA-avid disease but limited response. (D) Primary progression. After cycle 3, patient was switched to cabazitaxel with good response (not shown).

translational biomarkers to investigate the longitudinal effects of enzalutamide on PSMA receptor expression on PET scans and circulating tumor cells.

PSMA RNT Plus Inhibitors of DNA Damage Repair and Radioresistance Mechanisms

Since RNTs cause cell damage through DNA strand breaks, combinations of PSMA-targeting RNT with inhibitors of DNA repair or DNA-damaging agents are likely to be synergistic (41). RNT induces both DNA single-strand breaks (SSBs) and DSBs. Depending on the type of DNA damage incurred, different DNA damage-sensing and repair mediators such as poly-[adenosine diphosphate-ribose]-polymerase (PARP), ataxia telangiectasia mutated (ATM), and ATM and RAD3-related (ATR) are triggered. Specifically, PARP-1 and PARP-2 are involved in the detection and repair of SSBs. DSBs are repaired either by homologous recombination (key mediators include BRCA1/2, PALB2,

ATM, ATR, RAD51, CHEK2, MRE11, and XRCC2/3) or by error-prone nonhomologous end-joining. PARP-1 inhibitors, such as olaparib, impair DNA SSB repair; this leads to replication fork arrest and conversion to DSBs, which require homologous recombination for repair and continued replication (42). Suboptimal repair of DSBs in the setting of defective homologous recombination in mCRPC tumors with germline (~12%) or somatic DNA repair gene defects (~20%–25%) leads to vulnerability to PARP inhibition (43). Drugs targeting ATR have also shown activity in tumors with ATM loss in preclinical models and are synergistic with PARP inhibition in these models (44). Other likely targets that could sensitize RNT include ATM and DNA-dependent protein kinase (DNA-PK) inhibitors (45). As such, targeting the various mediators of these repair mechanisms in combination in PSMA-targeting RNT can impair repair of DNA strand breaks and mediate radiosensitization and improved cell death. Targeting other mechanisms of radioresistance, such as AKT (protein

TABLE 2
Key PSMA-Targeting RNT Combination Studies

Combination strategy	Trial	Setting	Treatment	Phase
RNT plus immune checkpoint inhibitor	NCT03805594	mCRPC; PSMA PET–positive at 3 or more metastatic sites; prior treatment with NAAT; no prior chemotherapy, except in HSPC setting	^{177}Lu-PSMA-617 and pembrolizumab	1
	NCT03658447 (PRINCE)	mCRPC; prior treatment with NAAT; prior docetaxel permitted	^{177}Lu-PSMA-617 and pembrolizumab	1/2
RNT plus radiosensitizer	NCT03511664 (LuPIN)	mCRPC; prior treatment with taxane and NAAT	^{177}Lu-PSMA-617 and idronoxil	1/2
RNT plus PARP inhibitor	NCT03874884 (LuPARP)	mCRPC; prior treatment with NAAT and taxane chemotherapy	^{177}Lu-PSMA-617 plus olaparib	1
RNT plus novel antiandrogen therapy	NCT04419402 (ENZA-p)	mCRPC with PSMA-positive disease; no prior chemotherapy, except in HSPC setting	^{177}Lu-PSMA-617 plus enzalutamide vs. enzalutamide	2

NAAT = novel antiandrogen; HSPC = hormone-sensitive prostate cancer.

kinase B) activation, should also be considered (46). Since a key mechanism of radiotherapy-induced cell death is apoptosis, pro- and antiapoptotic pathways may also be targeted to overcome radioresistance. As such, potential synergy between PSMA-targeting RNT and drugs targeting potential radioresistance mechanisms warrants further evaluation.

The first clinical evidence for combining agents that impair DNA repair and RNT comes from studies of [223]Ra-dichloride, an α-emitter. A retrospective analysis showed that the presence of defective DNR repair (somatic or germline) was associated with improved OS and a prolonged reduction in alkaline phosphatase (47). Synergy between an ATR inhibitor and [223]Ra has also been demonstrated (48). A phase 1 dose-escalation study is currently evaluating the safety and antitumor activity of ^{177}Lu-PSMA-617 plus olaparib in mCRPC patients who have previously progressed on novel antiandrogen therapy and docetaxel (NCT03874884). Other DNA repair inhibitors (e.g., targeting ATR kinase, DNA-PK, or polymerase 1) may also enhance the antitumor activity of ^{177}Lu-PSMA-617. Strategies to overcome mechanisms of radioresistance have also been explored. A nonrandomized phase II study combined idronoxil (a synthetic flavonoid derivative with radiosensitizing properties mediated through the inhibition of nicotinamide adenine dinucleotide oxidase 2 to induce apoptosis and cell cycle arrest) with ^{177}Lu-PSMA-617 in mCRPC patients with PSMA-PET–avid metastatic disease and no discordant ^{18}F-FDG–avid disease. This study showed that 63% of patients had a PSA response of more than 50%. Twenty-eight percent of patients experienced anal inflammation attributable to the mode of delivery of idronoxil, and other side effects were as expected with ^{177}Lu-PSMA-617 (49). Although the aforementioned strategies appear overall tolerable when combined with PSMA-targeting RNT, determining whether they truly improve efficacy would require randomized clinical evaluation.

Combining ^{177}Lu-PSMA-617 with Immune Checkpoint Inhibitors

Although prostate cancer outcomes have not been significantly impacted by recent advances in cancer immunotherapy, there is substantial preclinical and clinical evidence that radiotherapy is immunostimulatory. The abscopal effect, in which nonirradiated tumors have been observed to shrink in some patients after radiation therapy targeted to other tumor sites, is hypothesized to be mediated by the generation of systemic antitumor immune responses after immune recognition at the irradiated site (50). Mechanistically, genomic instability in the context of DNA damage and suboptimal repair is associated with increased neoantigen formation, antigen presentation, immune recognition, and immunogenic cell death (51). DNA damage and the release of cytosolic DNA also causes activation of cyclic GMP–AMP synthase (cGAS) and signalling effector stimulator of interferon genes (STING), an innate immune signaling pathway, thereby facilitating an adaptive immune response (52). Moreover, immunogenic cell death accompanied by the release of danger-associated molecular signals can induce further immune cell recruitment (53). Finally, in a mouse model, programmed death ligand 1 in the tumor microenvironment was upregulated after treatment with ionizing radiation (54). Specifically, α-emitters have been shown to elicit an immunogenic response (55), although there is no published study directly comparing the relative immunogenicity of different RNTs in prostate cancer. Taken together, these findings suggest that PSMA-targeted RNT may have the potential to synergize with immune checkpoint inhibitors.

The phase Ib/II PRINCE trial (NCT03658447) is testing the combination of pembrolizumab with ^{177}Lu-PSMA-617 in mCRPC patients who have progressed on a novel antiandrogen. Patients will receive continuous dosing with pembrolizumab for up to 2 years (35 cycles given every 3 weeks) and up to 6 cycles of

^{177}Lu-PSMA-617 (6 weeks apart). The 2 primary objectives of this study are to determine the PSA response rate and the safety and tolerability of the treatment combination. The hypothesis that pembrolizumab may enhance the systemic immune response to ^{177}Lu-PSMA-617 is currently being evaluated in another phase 1 study in a similar patient population (NCT03805594). This trial evaluates 3 different sequences, a single cycle of ^{177}Lu-PSMA-617 followed by pembrolizumab, both drugs given on the same day, and pembrolizumab given 21 days before ^{177}Lu-PSMA-617. Early results showed a PSA decline of ≥50% in 28% and an objective response rate of 44% (ASCO GU, 2021).

Combining RNT and Chemotherapy

Taxane chemotherapy can radiosensitize tumors to the effect of radiation by impairing DNA damage repair, improving tumor reoxygenation (which, in turn, sensitizes cells to the effects of radiation), and preventing accelerated repopulation during radiotherapy (56). Theoretically, chemotherapy can target areas of non–PSMA-avid disease to prevent their outgrowth after selective killing of PSMA-expressing tumors by PSMA-targeting RNT. However, the antiproliferative effect of chemotherapy may also reduce cellular sensitivity to radiation, although this is less likely to be an issue with α-emitting RNT (34).

The UpFrontPSMA study (NCT04343885) is a phase II randomized study comparing 2 sequential doses of ^{177}Lu-PSMA-617 delivered 6 weeks apart followed by 6 cycles of docetaxel versus docetaxel alone in patients with newly diagnosed high-volume metastatic castration-sensitive prostate cancer (i.e., within 12 weeks of diagnosis and within 4 weeks of commencing ADT) based on PSMA-PET scans. This study will shed light on the impact of castration sensitivity and ^{177}Lu-PSMA-617 in addition to the docetaxel standard of care. In this study, PSMA PET/CT will be performed at baseline, within 4 weeks of commencing ADT, and 12 weeks after commencing treatment. The study will enable evaluation of the effect of ADT on PSMA expression by comparing the PSMA PET/CT performed before ADT commencement and that performed at study entry. Separately, a phase 1 trial is evaluating the combination of standard docetaxel (75 mg/m^2 every 3 weeks) administered with 2 fractionated doses of ^{177}Lu-J591 (initial dose, 740 MBq [20 mCi]/m^2 × 2 up to maximum of 1,480 MBq [40 mCi]/m^2 × 2), with cycle 3 of docetaxel being given to patients with mCRPC. Among the 15 patients enrolled, 11 (73.3%) patients had a PSA decline of more than 50% and no dose-limiting toxicity was seen, although 3 (20%) patients experienced grade 4 neutropenia and 2 patients experienced grade 4 thrombocytopenia (57).

Combining Different RNTs

Since different PSMA-targeting antibodies and small molecules may have different extracellular PSMA binding sites, cotargeting with multiple agents could result in additive benefit (58). Additionally, given that different PSMA RNTs have different biodistributions and different toxicity profiles, a combination of different agents at lower doses may improve their collective therapeutic window.

In a retrospective analysis of tandem PSMA-targeting RNT combining a single lower dose of ^{225}Ac-PSMA-617 (median, 5.3 MBq) with ^{177}Lu-PSMA-617 (median, 6.9 GBq) in 20 mCRPC patients with inadequate responses to ^{177}Lu-PSMA-617, 13 of 20 (65%) patients had a PSA decline of more than 50%. Xerostomia was generally mild (grade 1–2), although formal studies

comparing this approach with RNT monotherapy are required (59). In another retrospective case series, 15 patients with confirmed PSMA expression on PSMA PET received ^{225}Ac-PSMA-617 after disease progression on ^{177}Lu-PSMA. Five had a PSA decline of more than 50%. The treatment was poorly tolerated, with 5 patients discontinuing treatment because of xerostomia, 2 patients developing grade 2 renal impairment, 4 patients developing grade 3–4 anemia, and 2 patients developing grade 3 thrombocytopenia (60). Currently, there are no published results from prospective studies of a combination of different PSMA-targeting RNTs.

BIOMARKER SELECTION IN THE ERA OF COMBINATORIAL THERAPIES

Evaluating the intensity of PSMA expression across metastatic sites with PSMA PET offers the advantage of selecting patients most likely to respond to PSMA-targeting RNT. Several studies selected patients on the basis of PSMA expression on PSMA PET and the absence of discordant ^{18}F-FDG PET–avid disease (25,61). The relationship between PSMA uptake on imaging and immunohistochemical analysis is also of interest since imaging does not capture the heterogeneity of PSMA expression at a cellular level. For example, a study showed that the lack of PSMA protein expression on immunohistochemistry predicted a lack of avidity on PSMA PET, although it is unclear whether a subset of patients who have PSMA-PET–negative disease may have some level of PSMA expression at a cellular level (62). At the same time, given the heterogeneity of PSMA expression at different metastatic sites and the discordance between primary and metastatic disease, it would be difficult to predict response based on PSMA immunohistochemistry using tissue from a single metastatic site (30,62). Moreover, PSMA expression evolves with treatments, thereby limiting the utility of archival, diagnostic tumor samples for assessing PSMA expression. It is notable that approximately 20% of patients who meet the stringent patient selection criteria based on PSMA expression and absence of discordant FDG-PET avid disease do not respond, highlighting the importance of other inherent tumor biology factors that likely determine absorbed dose, genomic DNA repair mechanism and radiosensitivity. Finally, the clinical utility of patient selection based on PSMA expression in the setting of combination therapies with other efficacious systemic therapies is yet to be defined.

Low-energy γ-irradiation from ^{177}Lu allows for posttreatment scintigraphic imaging that provides information such as whether residual targetable disease is present, allowing response to be monitored and dosimetry to be ascertained. Dosimetry analysis from our phase II study established that a mean whole-body tumor dose of 14.7 Gy was associated with a PSA response of at least 50% at 12 weeks, compared with doses of 10.4 Gy ($P < 0.01$), as well as a strong correlation between the SUV$_{mean}$ of PSMA expression and at least a 50% PSA reduction, although the SUV threshold for optimal PSMA avidity remains to be defined (63).

As expected, a PSA response of at least 50% has been shown in several studies to be associated with improved OS in a median range of 16.7–18 months, compared with 7.4–8.7 months in patients with PSA declines of less than 50% (29). Beyond PSA response, ^{18}F-FDG–positive molecular tumor volume and PSMA intensity (SUV$_{mean}$) in patients receiving ^{177}Lu-PSMA-617 were most prognostic of OS, followed by lactate dehydrogenase, alkaline phosphatase, and the bone scan index (64). Patients who were

18F-FDG–positive and PSMA-negative and were excluded from the phase 2 trial of ^{177}Lu-PSMA-617 had a poor prognosis, with a median OS of 2.5 months (65).

Combinatorial therapies add further to the complexity. If treatments such as AR blockade can induce PSMA expression, then combinatorial studies may be effective in patients with PSMA-negative disease, and on-treatment evaluation of PSMA expression, such as after AR inhibition alone, may dictate the sequential use of PSMA-targeted treatment. Additionally, it is unclear whether treatments such as the combination of DNA damage repair inhibitors and PSMA-targeting RNT are effective only in tumors with defective DNA repair or are more broadly applicable as a radiosensitization strategy. Finally, the patient's disease profile may also impact the modality chosen, with, for example, a preference for treatments with less marrow toxicity in patients who have a heavy burden of bone disease. In summary, clinical, molecular, and imaging biomarkers should be incorporated into future studies of PSMA RNT combinations.

CONCLUSION

The field of PSMA-targeting RNT has seen rapid progress, with promising antitumor activity being observed across several agents. However, developing strategies to achieve a more durable response and a better understanding of optimal patient selection and therapeutic resistance remains a key ongoing challenge. Refinement of the PSMA RNT molecules to achieve even better targeting is ongoing. Multiple biologically rational combinations, including the combination of PSMA-targeting RNT with immunotherapy, DNA damaging agents, AR-targeted therapy, and radiosensitizers, are at various stages of clinical development and will require careful consideration about patient selection and dose schedules. The overall aim is to be able to use these combinations in a biomarker-driven manner to overcome resistance and to improve disease control, quality of life, and OS in patients with lethal prostate cancers.

DISCLOSURE

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