Predictors and Real-World Use of Prostate-Specific Radioligand Therapy: PSMA and Beyond

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overview

PSMA is a transmembrane protein that is markedly overexpressed in prostate cancer, making it an excellent target for imaging and treating patients with prostate cancer. Several small molecule inhibitors and antibodies of PSMA have been radiolabeled for use as therapeutic agents and are currently under clinical investigation. PSMA-based radionuclide therapy is a promising therapeutic option for men with metastatic prostate cancer. The phase II TheraP study demonstrated superior efficacy, lower side effects, and improved patient-reported outcomes compared with cabazitaxel. The phase III VISION study demonstrated that radionuclide therapy with β-emitter ^{177}Lu-PSMA-617 can prolong survival and improve quality of life when offered in addition to standard-of-care therapy in men with PSMA-positive metastatic castration-resistant prostate cancer whose disease had progressed with conventional treatments. Nevertheless, up to 30% of patients have inherent resistance to PSMA-based radionuclide therapy, and acquired resistance is inevitable. Hence, strategies to increase the efficacy of PSMA-based radionuclide therapy have been under clinical investigation. These include better patient selection; increased radiation damage delivery via dosimetry-based administered dose or use of α-emitters instead of β-emitters; or using combinatorial approaches to overcome radioresistance mechanisms (innate or acquired), such as with novel hormonal agents, PARP inhibitors, or immunotherapy.

PSMA is a type 2 membrane glycoprotein that is expressed selectively by prostate cells, with expression level increasing dramatically in malignant prostatic tissue.[1] Because of its properties, PSMA has emerged as an attractive target for theranostics in prostate cancer.[2] In the past decade, numerous imaging and therapeutic radiopharmaceuticals targeting PSMA have been developed and investigated in clinical trials.[3–8] PSMA-based radionuclide therapy (RNT) is a promising therapeutic option for men with metastatic prostate cancer.[5] PSMA radioligands are internalized after binding to the target, enabling delivery of radiation directly into the malignant cells.

The β-emitting radioisotope ^{177}Lu conjugated with small molecule PSMA-617 (^{177}Lu-PSMA-617) is the PSMA-based RNT currently furthest along in clinical development. The VISION study, an international, open-label, randomized phase III trial, demonstrated that ^{177}Lu-PSMA-617 can prolong survival and improve quality of life when offered in addition to standard care in men with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed with taxanes and novel antiandrogens.[5] In this trial, 831 patients were randomly assigned in a 2:1 ratio to ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks for six cycles; 551 patients) plus best standard of care or standard of care alone (280 patients). The trial met both primary endpoints of overall survival (OS) and radiographic progression-free survival (PFS). The median OS was 15.3 months in the ^{177}Lu-PSMA-617 arm versus 11.3 months in the standard of care–alone arm, resulting in a 38% reduction in the risk of death. The median radiographic PFS was 8.7 versus 3.4 months, respectively. Another randomized trial (TheraP) showed that ^{177}Lu PSMA-617 led to higher prostate-specific antigen (PSA) response rates (66% vs. 37%), superior PFS (HR, 0.63), and fewer grade 3 or 4 adverse effects compared with cabazitaxel in men with mCRPC whose disease progressed after docetaxel.[9]

The U.S. Food and Drug Administration recently approved ^{177}Lu-PSMA-617 for men with PSMA-positive mCRPC previously treated with androgen receptor–targeted agents and taxane-based chemotherapy.[10] Nevertheless, a subset of patients has inherent resistance to PSMA-based RNT (approximately 30% in VISION[5] and 17% in TheraP[9]), and acquired resistance is inevitable. Hence, strategies to increase the efficacy of PSMA-based RNT have been under clinical investigation. These include better patient selection; increased

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PRACTICAL APPLICATIONS

- Standardized criteria in PSMA PET/CT for patient selection for ^{177}Lu-PSMA radionuclide therapy (RNT) have been established, but further refinement to enhance therapeutic responses is warranted.
- Prognostic factors for outcome after ^{177}Lu-PSMA RNT were identified and included in nomograms to assist during the patient selection process.
- Contributing factors of resistance to PSMA-based RNT include heterogeneity of tumor PSMA expression, failure to deliver a lethal dose of radiation to metastatic sites, tumor microenvironment, and tumor biological radioresistance.
- Combining PSMA-based RNT with potentially synergistic agents (e.g., immune checkpoint inhibitors, PARP inhibitors, antiandrogens, CDK-4/6 inhibitor) or RNT with α-emitters may improve therapeutic responses.
- Biological targets other than PSMA showed potential for theranostic applications in prostate cancer and are currently being investigated.

radiation damage delivery via dosimetry-based administered dose or use of α-emitters instead of β-emitters; or use of combinatorial approaches to overcome radioresistance mechanisms (innate or acquired), such as with novel hormonal agents, PARP inhibitors, or immunotherapy. In this article, we provide an overview of the currently available and forthcoming PSMA-based RNT and discuss approaches aimed at improving the efficacy and safety of PSMA-based RNT.

MODELS TO PROGNOSTICATE OUTCOME AFTER PSMA-BASED RNT IN PROSTATE CANCER

Clinical Parameters Prognostic for Outcome After PSMA-Based RNT

Information gained from initial diagnosis of prostate cancer, treatment history, baseline clinical status, and laboratory values are evaluated during the screening process for PSMA-based RNT. The prognostic value of clinical parameters for outcome after PSMA-based RNT has been assessed in multiple retrospective studies.[11] Longer time from diagnosis of prostate cancer to initiation of ^{177}Lu-PSMA RNT was found to have a positive impact on OS and PFS.[12–14] The impact of exposure to previous systemic treatments on outcome after PSMA-based RNT has been addressed in several studies. Prior treatment with radium-223 and androgen receptor signaling inhibitors was found not to be associated with short- or long-term outcome after ^{177}Lu-PSMA RNT.[11,15–20] In contrast, two studies reported that prior treatment with second-line taxane-based chemotherapy is associated with worse OS.[15,16] These data, however, are subject to substantial lead-time bias. The clinical status of the patient is of importance during the screening process for PSMA-based RNT. Commonly, those with acceptable performance status are eligible for the treatment.[5] A higher Eastern Cooperative Oncology Group score (≥2) and need for pain medication at treatment initiation were found to be associated with worse outcome after ^{177}Lu-PSMA RNT.[13,16,17,21,22] Furthermore, sufficient bone marrow reserve is an important inclusion criterion among candidates for PSMA-based RNT.[5] Bone marrow impairment may be caused by bone marrow replacement with tumor cells or exposure to prior treatments, such as chemotherapy or radiation. Patients with diffuse bone marrow involvement or "superscan" appearance on a screening bone scan were excluded from the VISION study because of lack of safety data in such patients at the time of study design.[5] However, a report found later that ^{177}Lu-PSMA RNT is efficacious at acceptable toxicity levels in patients with diffuse bone marrow involvement, suggesting that these patients could still benefit from PSMA-based RNT.[23] Lower concentrations of hemoglobin at treatment initiation were found to be associated with shorter OS after ^{177}Lu-PSMA RNT.[12,14,22,24] The impact of baseline tumor markers was evaluated in multiple retrospective analyses. Higher concentrations of serum PSA were prognostic of worse OS but were not associated with PFS or PSA responses.[13,14,25,26] Higher concentrations of lactate dehydrogenase and alkaline phosphatase were also found to have a negative impact on patient prognosis.[22,25–27] The prognostic value of neuroendocrine tumor markers such as chromogranin A and pro–gastrin-releasing peptide was also investigated; however, no correlation with OS or tumor response was found.[25,28] Like with other mCRPC treatments, serum markers mirroring liver involvement have been found to be correlated with OS after ^{177}Lu-PSMA RNT,[21,22,29] and visualization of liver metastases on imaging (M1c) is associated with worse outcome after ^{177}Lu-PSMA RNT.[12–16,22,24,26] The impact of other image-derived features on treatment outcome are discussed in the following sections.

PSMA-PET as a Gatekeeper for PSMA-Targeted RNT

As part of the theranostic approach, candidates for PSMA-based RNT are routinely screened with PSMA-targeted PET/CT to evaluate the presence of PSMA-positive lesions. The VISION trial used PSMA PET/CT to select patients for inclusion. Patients eligible on the basis of PET had PSMA-positive metastatic lesions (defined as tumor maximum standardized uptake value greater than liver standardized uptake

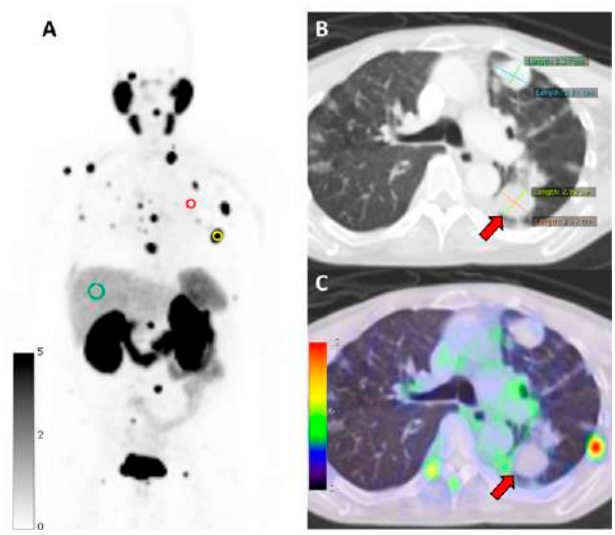

FIGURE 1. Patient Selection for PSMA-Based Radionuclide Therapy Using ^{68}Ga-PSMA-11 PET/CT

Left rib lesion (yellow circle) with PSMA uptake higher than liver uptake (green circle) (tumor maximum standardized uptake value [SUV_{max}], 17.4; greater than liver SUV_{max}, 4.2) and on PSMA PET imaging **(A)**. This lesion is classified as "PSMA-positive" by VISION PET criteria. Left lung mass measurable by CT images according to RECIST 1.1 criteria (2.93 × 2.97 cm) (red arrows) **(B,C)** with PSMA uptake (red circle) lower than liver uptake (tumor SUV_{max}, 1.6; less than liver SUV_{max}, 4.2). This lesion is classified as "PSMA-negative" by VISION PET criteria.

Images courtesy of Masatoshi Hotta, University of California, Los Angeles.

value) and no PSMA-negative lesion measurable by CT (Fig. 1). The rationale of the VISION criteria for PSMA PET images was presented recently.[30] The liver was chosen as a reference organ to assess tumor PSMA positivity based on Deauville criteria from fluorodeoxyglucose (FDG)-PET for lymphoma,[31] whereas the definition of PSMA-negative lesions was based on RECIST 1.1 criteria.[32] The screen failure rate was "only" 13% (126 of 1,003), and some have argued that the trial could have been positive even in an unselected population.[33] A retrospective study analyzed a multicenter dataset of 301 patients treated with ^{177}Lu-PSMA to identify patients who would have been screen failures by the VISION PET criteria and were nevertheless treated on the basis of local assessment.[34] Twenty-nine (10%) of 301 patients with VISION PET screen failure criteria were identified, among whom 8 (3%) of 301 had low PSMA expression and 21 (7%) of 301 had PSMA-negative lesions. These patients had notably lower PSA response rates (21% vs. 50%) and shorter PSA PFS (median, 2.1 vs. 4.1 months) than patients who met the VISION PET criteria (272 [90.4%] of 301).[34] Similarly, several phase I/II trials of PSMA-based radioimmunotherapy (J591 Ab) performed PSMA-targeted imaging at baseline but did not use images for patient selection.[7,35–38] A post hoc analysis of these studies demonstrated that high PSMA uptake on baseline imaging was associated with higher rates of PSA response ≥50%.[39]

Quantitative Parameters Versus Visual Criteria for Patient Selection for PSMA-Based RNT

The impact of whole-body tumor burden parameters derived from baseline PET images on outcome after PSMA-based RNT has been investigated in multiple retrospective studies and prospectively in the TheraP trial.[12,27,40–43] The predictive value of PSMA-PET whole-body tumor parameters as a quantitative imaging biomarker for treatment response to ^{177}Lu-PSMA-617 was further established in a planned analysis of the randomized TheraP trial.[44] Higher PSMA tumor uptake (whole-body tumor mean standardized uptake value ≥ 10) on screening ^{68}Ga-PSMA-11 PET/CT was associated with higher odds of achieving a PSA response ≥ 50% in the ^{177}Lu-PSMA-617 group compared with the cabazitaxel group (odds ratio, 12.2 vs. 2.2). Patients with very high PSMA expression randomly assigned to ^{177}Lu-PSMA-617 had a 91% response rate. The TheraP trial only included patients with high PSMA expression, and, accordingly, the group with lower PSMA expression still had a high response rate (52%). Nevertheless, calculation of whole-body tumor burden parameters requires tumor segmentation of patients with heavily metastasized disease, which is manually laborious. To enable quantitative assessment of total disease burden during treatment, different vendors are currently developing software tools, but none has been clinically validated.[40,45–47] Hence, the quantification of whole-body tumor volume is not performed in clinical routine outside of research-focused academic centers. Given the recent U.S. Food and Drug Administration approval of ^{177}Lu-PSMA-617, optimal standardized criteria for patient selection for PSMA-targeted RNT represents an urgent clinical need. Visual criteria and standardized uptake value measurement of individual lesions seem feasible for clinical use in the near future. PROMISE criteria proposed a visual score for grading PSMA tumor expression on PET images relative to liver and parotid glands as reference organs.[48] Currently, only the liver PSMA uptake has been used as an organ of reference for screening patients for PSMA-targeted RNT.[5,49] The feasibility of using parotid glands as an organ of reference for patient selection for PSMA-targeted RNT was investigated in a multicenter retrospective study.[34] Patients with higher whole-body tumor PSMA uptake than salivary gland uptake assessed visually achieved higher rates of PSA response (63% vs. 33% vs. 17%) and longer median PSA PFS (6.7 vs. 3.8 vs. 1.9 months) than those with intermediate and lower uptake. Overall, PSMA PET is a predictive whole-body imaging biomarker for response to

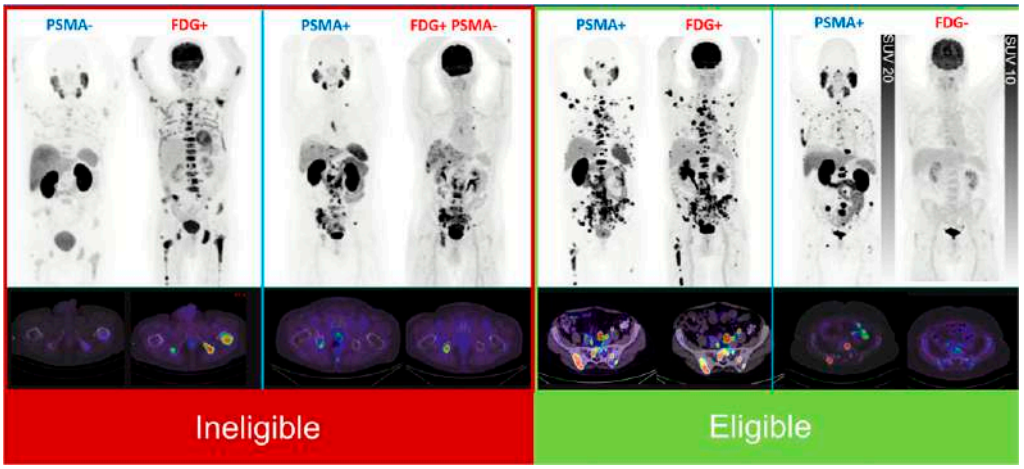

FIGURE 2. Patient Selection for PSMA-Based Radionuclide Therapy Using Dual-Tracer ^{18}F-Fluorodeoxyglucose and ^{68}Ga-PSMA-11 PET/CT Screening Procedure

Images courtesy of Prof. Michael S. Hofman, Peter MacCallum Cancer Center, Australia.

PSMA-targeted therapies in prostate cancer. Inclusion versus exclusion criteria based on baseline PSMA PET/CT imaging may be further refined.[50]

Statistical Prognostic Models for Outcome After PSMA-Based RNT

An international multicenter study centralized retrospectively collected data of 270 patients treated with ^{177}Lu-PSMA RNT at six centers to develop predictive models (nomograms) for treatment outcome.[12] A penalized Cox proportional hazards model using the adaptive least absolute shrinkage and selection operator was used to develop three models to predict three outcomes: OS, PSA PFS, and PSA response. Baseline PSMA PET/CT parameters were analyzed in combination with clinical and laboratory parameters, and 18 variables were tested for associations with outcome data. Shorter time since diagnosis, previous treatment with taxanes, lower hemoglobin concentrations, lower whole-body tumor PSMA expression assessed by mean standardized uptake value, lower number of PSMA-positive tumor lesions (<20), and absence of bone (M1b) and liver (M1c) metastases were associated with longer OS (model C-index = 0.72). Similarly, shorter time since diagnosis, previous treatment with taxanes, higher whole-body tumor PSMA expression assessed by mean standardized uptake value, pelvic nodal disease (N1), and absence of bone (M1b) and liver (M1c) metastases were associated with longer PSA PFS (model C-index = 0.71). Previous treatment with taxanes, lower whole-body tumor PSMA expression assessed by mean standardized uptake value, no pelvic nodal involvement (N0), and presence of liver metastases (M1c) were associated with lower PSA response rates (model area under the curve = 0.78). Based on these nomograms, an online risk calculator was developed and is available online at https://uclahealth.org/nuc/nomograms. Importantly, these prognostic nomograms were developed on the basis of data from a single-arm retrospective study. Their predictive value is yet to be evaluated using data from randomized clinical trials.

Promising Biomarkers for PSMA-Based RNT

^{18}F-FDG-PET/CT Absent or low target expression limits the response to PSMA-targeted therapies. However, one key driving parameter of patient outcome seems to be the presence of PSMA-negative lesions that can be identified with ^{18}F-FDG-PET. Two Australian landmark studies of PSMA-targeted RNT with ^{177}Lu-PSMA-617 screened patients with dual-tracer ^{68}Ga-PSMA-11 and ^{18}F-FDG-PET/CT.[9,49] Eligibility criteria included high PSMA tumor uptake at metastatic site(s) and no discordant disease (FDG-positive lesion with no or low PSMA uptake; Fig. 2). The screen failure rates based on these combined FDG/PSMA PET images were 21% in the LuPSMA trial and 28% in the TheraP trial, which is higher than the PSMA PET-only screen failure rate of the VISION trial (13%). The PSA response rates of the LuPSMA and TheraP trials were higher than in the VISION trial (64% vs. 66% vs. 46%), likely attributed to superior patient selection by FDG-PET/CT. The prognostic value of FDG-positive tumor volume as a quantitative imaging biomarker for outcome after ^{177}Lu-PSMA-617 was established in further analyses of these trials: High FDG-positive whole-body tumor volume is prognostic of worse outcome independent of treatment (cabazitaxel or ^{177}Lu-PSMA-617).[27,44] Previous studies demonstrated that patients with FDG^{+}/PSMA^{-} discordant disease who were excluded from receiving ^{177}Lu-PSMA-617 had a notably worse OS than patients who were deemed eligible by dual FDG/PSMA PET/CT.[51,52] One

retrospective study showed that patients with discordant FDG^{+}/PSMA^{-} lesions who were still treated with ^{177}Lu-PSMA-617 had shorter OS than those without discordant disease (median OS, 6 vs. 16 months).[53] However, there are many unresolved issues that surround whether adding ^{18}F-FDG-PET in the clinical setting as a screening procedure for candidates with mCRPC for PSMA-based RNT is advantageous (two different imaging procedures on two separate days, dual-reading standardized results format, insurance coverage).[54]

RESISTANCE MECHANISMS AND COMBINATORIAL APPROACHES TO ENHANCE PSMA-BASED RADIONUCLIDE RESPONSES

RNT Principles

RNT requires radionuclides to be conjugated to carrier molecules for targeted delivery to tumor cells. Some RNT agents, such as radium-223-dichloride or ^{131}I are directly delivered to the targets without a carrier molecule.[55] Prostate cancer RNT can be achieved with different radionuclides emitting decay products.

β-Particles (50-2300 keV) have the lowest linear energy transfer (0.2 keV/mm) and cause mainly single-strand DNA breaks. Because of their longer range (0.05–12 mm), β-particles travel to nearby cells (crossfire). This can be an advantage in large heterogeneous tumors but may also harm adjacent normal tissue. α-Particles (two-proton and two-neutron naked helium nucleus) have high energy (5–9 MeV) with shorter range (40–100 μm) and the highest linear energy transfer (80 keV/mm), causing double-stranded DNA breaks and chromosomal damage independent of cell cycle and oxygenation status. This is best for small tumors or micrometastases because adjacent normal cells are spared as long as the cells themselves are not targeted by the radionuclide.[56–58] Compared with β-particles, the equivalent radiation dose deposited in both microscopic and measurable disease is much higher when administered at a much lower administered dose.[58] Auger electrons emitted during electron capture of certain radiotracers have very low energy and moderate linear energy transfer (4–26 keV/mm) with the shortest range (2–500 nm) and must be delivered at or near the nucleus, limiting their effect to single cells.[59]

Tumoricidal effects of RNT are also attributed to radiation-induced bystander effect, which is an off-target therapeutic effect on neighboring tumor cells that are not directly exposed to ionizing radiation, possibly because of complex cell signaling. An abscopal effect also may occur in distant tumor cells through a systemic immunologic response, which may also be associated with α-therapy.[60]

Mechanisms of Resistance

The durability of responses for PSMA-based RNT is often short-lived, even in patients with initial responses. The mechanisms of how tumors develop resistance to PSMA-based RNT are currently not well understood. A summary of the potential mechanisms of resistance to PSMA-based RNT is provided in Fig. 3.

Insufficient radiation dose delivery The mean whole-body tumor-absorbed radiation dose was reported to be substantially higher in responders to ^{177}Lu-PSMA than in nonresponders (median, 14.1 Gy vs. 9.6 Gy).[61] The PSMA-targeting radiopharmaceutical accumulates at the tumor sites and delivers radiation that induces DNA strand breaks and causes cell death. ^{177}Lu is a β-particle emitter with a maximum soft-tissue penetration of 1.5 mm. β-Particulate emission leads mainly to single-stranded DNA breaks, and higher absorbed doses are often needed to induce double-stranded DNA breaks.[62,63] A lack of tumor PSMA expression leads to insufficient radiopharmaceutical delivery and therefore insufficient radiation dose delivery. This is directly visualizable on PET imaging in the form of low PSMA uptake at all sites or tumor heterogeneity with areas of PSMA-negative and -positive disease.[64,65] Neuroendocrine differentiation, which can occur in advanced prostate cancer, particularly after prolonged androgen deprivation, also suppresses PSMA expression.[66–68] The failure to deliver a lethal dose of radiation to micrometastatic sites may also contribute to treatment resistance. Because of their travel path length, β-particles deliver high absorbed radiation to macrotumors but a lower absorbed dose to small metastatic cell clusters.[69,70] The most frequent progression pattern after treatment with ^{177}Lu-PSMA is diffuse marrow infiltration, which may be due to small-volume disease receiving an inadequate radiation dose.[9]

Given that the therapeutic failure of ^{177}Lu-PSMA appears to be linked in many cases to the progression of micrometastatic disease, the shorter path length of other radionuclides may overcome this.[58,71,72] α-Particles or Auger electrons differ from β-particles in terms of energy, tissue range, linear energy transfer, and the number of DNA hits required to exert a cytotoxic effect.[73,74] In contrast to β-particles, the traversal of a single α-particle or Auger electron (if close enough to the nucleus) is enough to induce cytotoxic double-stranded DNA breaks.[58,62,75]

Tumor microenvironment The distribution of metastatic disease also impacts response to treatment. Nodal metastases have demonstrated more significant responses than have osseous metastases to PSMA-based RNT.[76] Hepatic metastases are associated with poor response to ^{177}Lu-PSMA and inferior survival outcomes, regardless of PSMA expression.[77] Liver metastases that develop after PSMA-based RNT frequently have low PSMA expression and high metabolic activity.[27,78] Pulmonary metastases, however, have reasonable response rates to ^{177}Lu-PSMA and do not confer a negative survival outcome.[15,79] These differential responses based on metastatic site may be related to

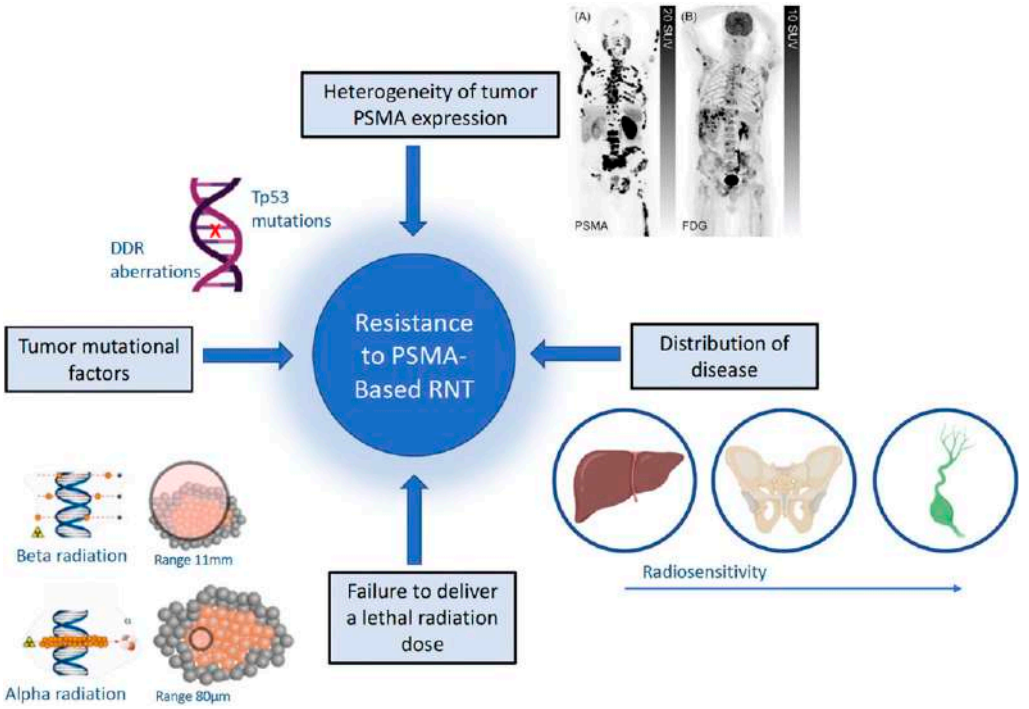

FIGURE 3. Mechanisms of Resistance to PSMA-Based Radionuclide Therapy
Abbreviations: DDR, DNA damage response; RNT, radionuclide therapy.

changes in the tumor microenvironment, with intertumor molecular heterogeneity common in advanced disease.[80] Tumor metastatic site appears to be a prognostic factor in men with mCRPC and hence is disease-specific rather than treatment-related.[81] Strategies to increase the response of specific metastatic sites to ^{177}Lu-PSMA or other mCRPC systemic treatments are yet to be established.

Radioresistance Tumor mutational factors can also impact response to PSMA-based RNT. TP53 mutations, present in up to 43% of prostate cancer tumors, have been associated with radioresistance in several in vivo studies.[82,83] The DNA damage response pathway is also implicated in radioresistance, with some DNA damage response aberrations being associated with poor responses to PSMA-based RNT.[84] DNA damage response alterations are present in up to 28% of prostate cancers.[85] Importantly, however, some DNA damage response alterations, such as BRCA2, increase responses to radiotherapy and possibly to RNT. To overcome radioresistance, combinatorial approaches of ^{177}Lu-PSMA with agents known to have radiosensitizing properties are currently under clinical investigation. These combinatorial approaches are discussed in the next section.

Combination Approaches

Combining PSMA-based RNT with potentially synergistic agents may improve responses. Mechanisms for this include upregulating PSMA expression through androgen receptor–targeted agents, increasing tumor radiosensitivity through DNA repair inhibitors or agents causing additional DNA damage, targeting different PSMA-binding sites, and combining with immune checkpoint inhibitors (Fig. 4).[86] Several potential combinations are being evaluated in ongoing clinical studies (Table 1).

RNT may potentiate an immunogenic response leading to improved clinical outcomes when combined with immune checkpoint therapy. Prostate cancer is considered immunogenically "cold" with minimal T-cell infiltrates, leading to peripheral immune tolerance of the developing tumor.[87–89] Several trials have evaluated PD-1/PD-L1 or CTLA-4 checkpoint inhibitors in patients with mCRPC, with limited clinical benefit.[90–94] There is a need to convert the tumors from "cold" to "hot," whereby tumor-infiltrating T cells increase to generate an antitumor response. Radiotherapy increases DNA damage and neoantigen load through its direct cytotoxic effect, leading to increased immunogenicity.[95–97] Some clinical studies support the hypothesis that radiotherapy combined with immune checkpoint therapy may improve outcomes in mCRPC.[98,99] The phase I/II PRINCE trial (NCT03658447) evaluates the combination of pembrolizumab with ^{177}Lu-PSMA-617 in patients with mCRPC whose disease has progressed with a novel antiandrogen. An interim analysis found that this combination did not lead to increased toxic-

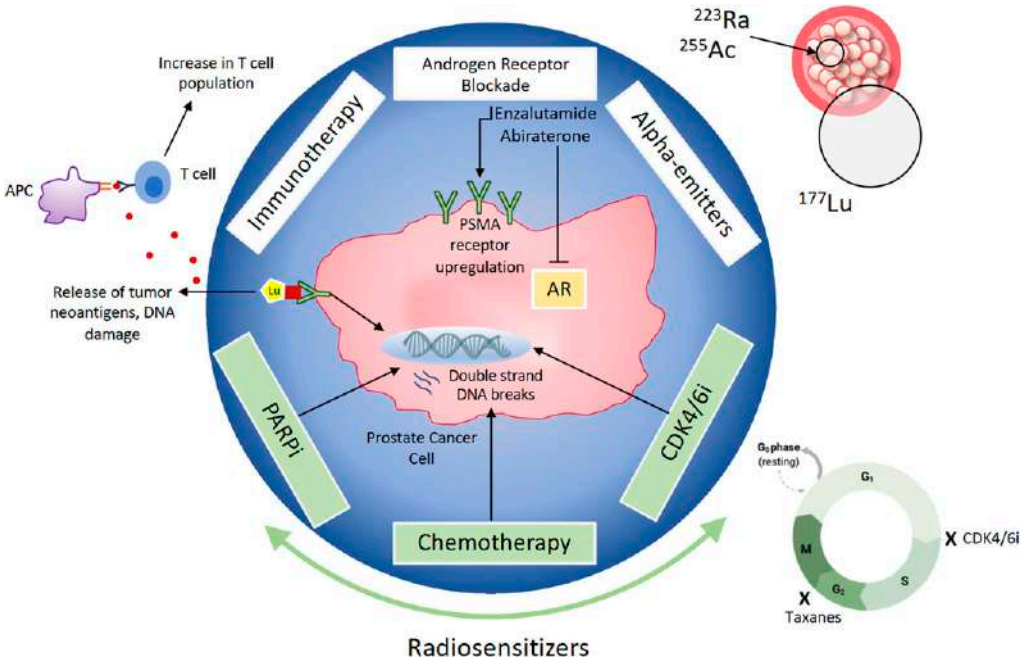

FIGURE 4. Mechanistic Rationale of PSMA-Targeting Radionuclide Therapy Combination Approaches
Abbreviation: PARPi, PARP inhibitor.

ity compared with either agent alone, though the results were not striking compared with ^{177}Lu-PSMA monotherapy, suggesting a need for additional checkpoint blockade to achieve synergy.[100] The EVOLUTION trial (NCT05150236), evaluating the triplet combination of nivolumab, ipilimumab, and ^{177}Lu-PSMA-617 in patients with mCRPC, will begin recruitment in 2022.

Inhibitors of DNA repair or DNA-damaging agents combined with PSMA-targeting RNT are likely to be synergistic. Radiation from PSMA-based RNT induces single-stranded DNA breaks and double-stranded DNA breaks by generating oxidative free radicals, activating DNA damage repair mediators such as PARP. Unrepaired double-stranded DNA breaks lead to mutagenic events and are highly cytotoxic. PARP enzyme inhibition has a radiosensitizing effect by preventing the repair of single-stranded DNA breaks and promoting cancer cell death through the accumulation of double-stranded DNA breaks.[101] Several preclinical studies have demonstrated enhanced antitumor activity from the combination of PARP inhibitors and RNT.[102–104] An ongoing phase I study is currently evaluating the safety and antitumor activity of olaparib in combination with ^{177}Lu-PSMA-617 in patients with mCRPC whose disease has previously progressed with novel antiandrogen therapy and docetaxel (NCT03874884).

Other agents with known radiosensitizing properties are currently being evaluated with β-emitting PSMA-based RNT. A phase I/II study is currently underway investigating the safety and preliminary efficacy of the CDK-4/6 inhibitor abemaciclib, administered for 2 weeks before each dose of ^{177}Lu-PSMA-617 (NCT05113537). Preclinical studies have demonstrated that CDK-4/6 inhibitors sensitize cells to radiotherapy through inhibiting DNA damage repair and thereby enhancing apoptosis and blockade of cell cycle progression.[105] In addition, a phase I/II trial in men with mCRPC found that ^{177}Lu-PSMA-617 plus the radiosensitizer idronoxil (NOX66) is safe, although it remains unclear if this combination confers an additional antitumor effect.[106]

Chemotherapy may improve the efficacy of RNT through treating non–PSMA-expressing sites of disease and by creating additional DNA damage.[107,108] Taxanes, as microtubule-stabilizing agents, cause cell cycle arrest in the most radiosensitive part of the cell cycle (G_2-M phase) and lead to tumor reoxygenation and apoptosis, thereby resulting in increased treatment potency when combined with radiotherapy.[109,110] Previous studies have demonstrated that combining docetaxel with β-emitting PSMA-based RNT is safe and efficacious.[111,112] A study is currently underway in Australia evaluating whether treatment with ^{177}Lu-PSMA-617 followed by docetaxel in de novo high-volume metastatic hormone-naive prostate cancer is superior to docetaxel alone (NCT04343885). In the mCRPC setting, a phase I/II trial is planned to open in 2022 in Australia, evaluating the combination of cabazitaxel chemotherapy and ^{177}Lu-PSMA-617.

Androgen receptor blockade may result in upregulation of PSMA receptor expression in castration-resistant disease, and therefore the combination with PSMA-targeted therapy

TABLE 1. Current PSMA-Targeting Radionuclide Therapy Combination Studies

Trial	Setting	Phase	Combination Strategy	Treatment
Immunotherapy				
NCT03658447	mCRPC	I/II	RNT + immune checkpoint inhibitor	^{177}LuPSMA-617 + pembrolizumab
NCT03805594	mCRPC	I	RNT + immune checkpoint inhibitor	^{177}LuPSMA-617 + pembrolizumab
NCT05150236	mCRPC	II	RNT + immune checkpoint inhibitor	^{177}Lu-PSMA-617 + ipilimumab + nivolumab
NCT04946370	mCRPC	I/II	RNT + immune checkpoint inhibitor + antiandrogen therapy	^{225}Ac-J591 + pembrolizumab + AR pathway inhibitor (e.g., enzalutamide)
Radiosensitizers				
NCT03874884	mCRPC	I/II	RNT + PARP inhibitor	Olaparib + ^{177}Lu-PSMA-617
NCT05113537	mCRPC	I/II	RNT + CDK-4/6 inhibitor	Abemaciclib + ^{177}Lu-PSMA-617
NCT05340374	mCRPC	I/II	RNT + chemotherapy	Cabazitaxel + ^{177}Lu-PSMA-617
NCT00916123	mCRPC	I	RNT + chemotherapy	Docetaxel + ^{177}Lu-J591
NCT04343885	mHSPC	II	RNT + chemotherapy	^{177}Lu-PSMA-617 followed by upfront docetaxel
PSMA Upregulation				
NCT04419402	mCRPC	II	RNT + antiandrogen	Enzalutamide + ^{177}Lu-PSMA-617
Radionuclides				
NCT04886986	mCRPC	I/II	α- + β-RNT	^{225}Ac-J591 + ^{177}Lu-PSMA-I&T
AlphaBet (planned)	mCRPC	I/II	α- + β-RNT	^{233}Ra + ^{177}Lu-PSMA-I&T

Abbreviations: AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer; RNT, radionuclide therapy.

may be synergistic.[113–117] A retrospective analysis of patients with mCRPC comparing those who received ^{177}Lu-PSMA alone versus in combination with abiraterone acetate found that survival outcomes were superior in the combination group.[118] Androgen receptor pathway inhibitors were administered in combination with ^{177}LuPSMA-617 in 52.6% of patients in the VISION trial, and responses were most pronounced in this subgroup. The ENZA-p trial is currently recruiting and is evaluating the combination of enzalutamide with ^{177}Lu-PSMA-617 versus enzalutamide alone.[119]

RNT with α-particles targets micrometastatic disease more efficiently than β-particles and hence may improve the therapeutic effect of RNT. ^{255}Ac-J591, a PSMA-directed monoclonal antibody radiolabeled with an α-emitter, is currently being studied with ^{177}Lu-PSMA-I&T (NCT04886986). The different binding sites of J591 and PSMA-I&T mean that theoretically additive radiation to PSMA-positive cells should occur when administered concurrently. A phase I/II study, the AlphaBet trial, evaluating the combination of ^{177}Lu-PSMA with ^{223}Ra to target both the PSMA-expressing cancer cells and the bone microenvironment around the osseous metastasis, will start recruitment in 2022 in Australia.

Combining potentially synergistic agents with RNT has the potential for increased toxicity, and it is yet to be determined whether a combination or sequential approach is more efficacious. There is an ongoing need for randomized controlled trials to assess this. The additional antiproliferative effect of some agents may also reduce cellular sensitivity to radiation; however, this is yet to be observed.[84]

Clinical trials of RNT with ^{177}Lu-PSMA earlier in the prostate cancer disease course are ongoing. The LuTectomy trial[120] is evaluating the use of ^{177}Lu-PSMA-617 in the neoadjuvant setting in men with high-risk PSMA-positive prostate cancer who are undergoing surgery. The UpfrontPSMA[121] and PSMAddition[122] trials are evaluating ^{177}Lu-PSMA-617 in the metastatic hormone-sensitive space, whereas the ENZA-p,[119] PSMAfore,[123] and NCT04663997 trials are evaluating RNT in early-stage mCRPC. These trials may provide guidance for the optimal sequencing of ^{177}Lu-PSMA in prostate cancer. The impact on resistance mechanisms of applying PSMA-based RNT in these earlier stages is yet to be determined.

BEYOND LUTETIUM: NEXT-GENERATION RADIONUCLIDE THERAPEUTICS IN PROSTATE CANCER

^{177}Lu-PSMA-617 has shown promise in the theranostic approach to the treatment of prostate cancers but has its own limitations.[9,124–127] As described above, α-emitters have advantages in their mechanisms of cell damage.[58] This

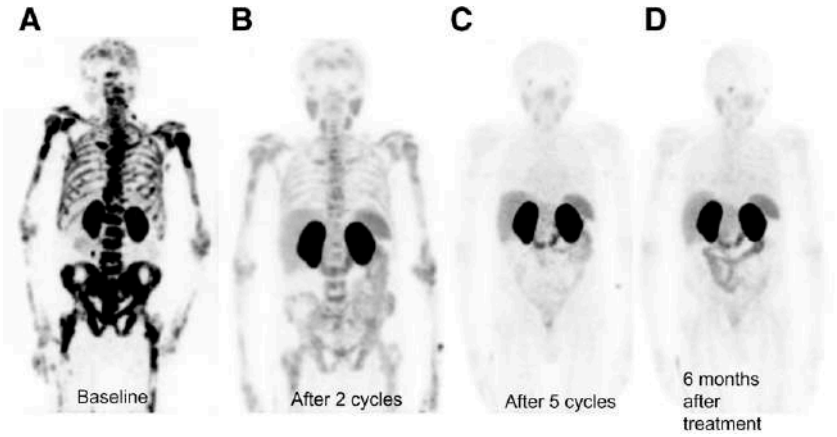

FIGURE 5. Case Example of PSMA-Targeted α-Radionuclide Therapy

A 69-year-old male with metastatic castration-resistant prostate cancer progressing after docetaxel was treated with five cycles of ^{225}Ac-PSMA-617. The patient experienced a remarkable response to targeted α-therapy by serum prostate-specific antigen (declining from 4,495 ng/mL at baseline to 18.51 ng/mL [−99%] after five cycles and 4.75 ng/mL [−99%] at 6 months after completion of treatment) and by PSMA PET [baseline ^{68}Ga-PSMA-11 PET/CT coronal maximum intensity projection (A) after two cycles of 225Ac-PSMA-617, (B) after five cycles of 225Ac-PSMA-617, (C) and at 6 months after completion of treatment (D)] without additional treatment.

Images courtesy of Mike Sathekge's laboratory and Ishmaheel Lawal, University of Pretoria, South Africa.

may be advantageous in diffuse bone marrow tumor infiltration and when prior RNT has failed owing to fewer off-target adverse effects. However, there is limited availability of α-emitters,[128] radiochemistry is more challenging, and the α-particles can have toxic effects if a healthy organ expresses the molecular targets (e.g., salivary gland toxicity with PSMA radioligands labeled with ^{225}Ac). Although they do not pose any external radiation hazard, α-particles can be dangerous if internalized, so proper radionuclide handling is important.[129] Most of the current limited sources of ^{225}Ac are obtained from thorium-229 generators derived from stockpiles of uranium-233.[128] Other potential production methods are currently being explored, with growing interest in targeted α-therapy.[130]

Radium-223 Dichloride The first clinically approved α-emitter agent for mCRPC was ^{223}Ra-dichloride, offering a large improvement in quality of life and reduction in alkaline phosphatase and skeleton-related events, with some advantage in OS.[55] However, this bone-specific radionuclide has no effect on soft-tissue or circulating components of the tumor.

^{225}Ac-based targeted α-therapy The most studied targeted α-therapy in prostate cancer is ^{225}Ac-PSMA-617, a urea-based anti-PSMA small molecule using a DOTA chelator with good tumor cell internalization and low renal uptake. ^{225}Ac has a physical half-life of 9.9 days. Early studies indicate a good safety profile with low bone marrow toxicity even in patients with extensive osseous metastases.[131] Among patients most often selected for ^{225}Ac targeted α-therapy, multiple lines of therapies have often failed, including chemotherapy, androgen deprivation therapy, and/or ^{177}Lu-PSMA RNT, with PSMA PET/CT demonstrating radiotracer uptake within metastatic lesions. Treatment regimens vary from a standard fixed dose of 100 kBq/kg each cycle[131,132] to a de-escalation approach starting at 8 MBq,[133] ranging from one to eight cycles approximately 8 weeks apart.

A systemic review and meta-analysis of ^{225}Ac-PSMA-617 targeted α-therapy in mCRPC including 141 patients showed advantages in PSA response and patient outcome with a low toxicity profile. Any PSA decline was reported in 83% of patients and ≥ 50% PSA decline in 59% of patients. Molecular response was reported in 17% (Fig. 5). Advantages in survival (median PFS, 12 months) were observed. The most often encountered side effect was xerostomia (63%), followed by anemia (54%), fatigue (45%), grade 3 nephrotoxicity (5%), and grade 3 leukopenia/thrombocytopenia (0.9%).[134] Outcome appears to vary with treatment-resistant disease and prior treatment modalities.[131,133,135–137] 225Ac-PSMA-617/^{177}Lu-PSMA-617 tandem therapy methods in patients for whom ^{177}Lu-PSMA-617 RNT has failed are being explored with stable to partial treatment response in up to two-thirds of the patients, with authors reporting less severe xerostomia and hematotoxicity.[138,139]

Other targeted α-therapy options ^{211}At has favorable characteristics with a 7.2-hour half-life, and a urea-based small PSMA molecule is being studied. Preclinical studies have shown improved results in micrometastatic models.[140] Other agents being evaluated for PSMA-targeted targeted α-therapy include lead-212–labeled small peptides,

^{213}Bi-labeled small molecules/nanoparticles, and PSMA-targeted thorium-227 conjugates.[141–143]

Auger Electron-Based Therapy

Terbium-161 is a dual β/Auger emitter, with higher radiation-absorbed doses in modeling suggesting superior responses for micrometastatic disease in single-cell or cell cluster models.[144] These have been confirmed in survival viability, survival, and in vivo experiments in tumor-bearing mice.[145] Auger electron emitters such as ^{125}I are being explored when complexed to PSMA targets. In vivo studies evaluating a highly specific small-molecule ^{125}I-DCIBzL have shown antitumor effects with the potential for fewer off-target and on-target adverse consequences.[146,147]

Radionuclide Vectors

The therapeutic and adverse effects of RNT are also dependent on the carrier molecule (i.e., vector), including the binding molecule and the chelator, especially with α-emitters such as ^{225}Ac, which has multiple decays and may dissociate from the chelator.[57] PSMA-targeting carriers include antibodies to PSMA, as well as urea-, phosphorous-, or thiol-based small molecules that interact with the PSMA transmembrane glycoprotein.[148] Antibody-based ligands such as J591 may have a more controlled biodistribution, thereby reducing radiation damage to normal tissues such as salivary glands because of relatively lower concentration in salivary tissue, but they can have hematotoxic effects due to longer circulation time in comparison with small molecules because of their size.[57,149] Small molecules are cleared faster, demonstrate increased tumor penetration, and can overcome barriers to tumor drug delivery compared with larger molecules or antibodies, and they have advantages of better tumor penetration and faster clearance with lower bone marrow dose, especially in patients with bone marrow infiltration. However, strategies to decrease salivary gland damage from these molecules must be explored.[59,149] These radiopharmaceuticals have a wide range of pharmacokinetics, and matching the physical half-life with the biologic half-life is crucial to balancing the therapeutic effects with potential toxicity.[59,150] Using chelators such as albumin-based chelators can increase the biologic circulating half-life and tissue distribution of the RNT agents, resulting in increased and longer uptake in the tumor cells with reduced renal retention.[151] Studies using radiopharmaceuticals other than the carrier PSMA-617 targeting small molecules/antibodies for RNTs include ^{177}Lu-PSMA-I&T,[26,152,153] ^{177}Lu-rhPSMA,[154] Glu-urea-Lys target moieties such as ^{177}Lu-L1/^{225}Ac-L1,[155] ^{177}Lu-CTT1403, a peptidomimetic inhibitor of PSMA,[156] PSMA-targeted thorium-227 conjugate,[142] ^{177}Lu-Ludodiapep (FC705),[157] ^{177}Lu-PSMA-R2,[158] and ^{177}Lu-EB-PSMA-617,[159] among others. Also underway are studies evaluating ^{225}Ac-PSMA-J591, a human monoclonal antibody targeting the extracellular PSMA domain (see Table 1).[160–162]

Potential Other Biologic Targets (Non-PSMA)

Potential non-PSMA targets are also being explored for prostate cancer RNT. Mitochondrial hexokinase-2 activity in prostate cancer cells has been seen in androgen-deprived cancer cells. Inhibiting hexokinase-2 may make these cells respond to androgen deprivation therapy and may be the basis of a new targeted RNT approach.[163]

RNT targeting a serine protease enzyme, human kallikrein 2, is being studied with ^{177}Lu and ^{225}Ac-hu11B6 in prostate xenografts[164,165] and in a phase I trial (NCT04644770). STEAP and DMT1 are overexpressed in many malignant tumor cells.[166] ^{89}Zr DFO-MSTP2109A, an antibody against STEAP1, is currently being studied.[167]

Prostate cancer cells with neuroendocrine differentiation after treatment pose treatment challenges.[168] These cells preferentially express the inhibitory cell surface ligand δ-like ligand 3, which may be a potential biomarker target for non–PSMA-based PET detection using radiotracers such as ^{89}Zr-SC16.[169] Similarly, CEACAM5, a prostate neuroendocrine tumor-specific target, is being evaluated.[68] Somatostatin receptor–targeting theranostics approaches may be exploited in these patients if there is sufficient somatostatin receptor expression by these cells.[170–172]

CONCLUSION

PSMA-based RNT is a novel therapeutic option and a new third-line treatment option for patients with mCRPC. As part of the theranostic approach, patients are being screened with PSMA PET/CT to confirm PSMA-positive disease. Standardized criteria for PSMA PET/CT–based patient selection have been developed. Addition of FDG-PET/CT as a screening procedure may increase therapeutic responses in more selectively treated patients, but its added value in the clinical setting requires further investigation. Predictive factors for outcome after ^{177}Lu-PSMA RNT were identified and incorporated in nomograms to assist during the patient selection process. Resistance mechanisms to PSMA-based RNT include low or heterogeneous tumor PSMA receptor expression, failure to deliver a lethal dose of radiation to metastatic sites, tumor microenvironment, and tumor biologic radioresistance. Combining PSMA-based RNT with potentially synergistic agents (e.g., immune checkpoint inhibitors, PARP inhibitors, antiandrogens, CDK-4/6 inhibitor, taxanes) or using PSMA-based RNT with α-emitters may improve therapeutic responses. Biologic targets other than PSMA are currently being investigated for potential theranostic applications in prostate cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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