Clinical Trials of Prostate-Specific Membrane Antigen Radiopharmaceutical Therapy

Hossein Jadvar and Patrick M. Colletti

Division of Nuclear Medicine, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, California

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Prostate-specific membrane antigen (PSMA) theranostics has been a momentous triumph for nuclear medicine. The recent approvals of PSMA-targeted imaging agents (^{68}Ga-PSMA-11, ^{18}F-DCFPyL) and radiopharmaceutical therapy (^{177}Lu-PSMA-617) have paved the way for theranostics as a viable care strategy for men with metastatic castration-resistant prostate cancer. The imaging clinical trials OSPREY, CONDOR, and those conducted at the University of California (Los Angeles and San Francisco), as well as the randomized phase 3 therapy trial VISION, have been the fruitful beginnings for PSMA theranostics. There are currently several ongoing clinical trials to expand the reach of PSMA theranostics to the earlier phases of prostate cancer and to optimize its utility in combination therapeutic regimens. We provide a brief narrative review of the many PSMA-directed radiopharmaceutical therapy clinical trials with the β-emitter ^{177}Lu-PSMA-617 and the α-emitter ^{225}Ac-PSMA-617 in prostate cancer.

Key Words: prostate; cancer; PET; radiopharmaceutical; therapy; VISION

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Radiopharmaceutical therapy (RPT) with radiolabeled agents targeted to the prostate-specific membrane antigen (PSMA) has provided an effective treatment strategy with manageable adverse events in men with metastatic castration-resistant prostate cancer (mCRPC). PSMA RPT is the therapeutic arm of the theranostics algorithm in which sufficient PSMA expression is first documented with imaging in accordance with the concept of precision oncology. The U.S. Food and Drug Administration approval of ^{68}Ga-PSMA-11 on December 1, 2020, was based on 2 comparable new-drug applications submitted by the University of California, Los Angeles, and the University of California, San Francisco. The first commercial ^{18}F-labeled PSMA radiotracer, 2-(3-{1-carboxy-5-[(6-^{18}F-fluoro-pyridine 3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPyL, also known as ^{18}F-piflufolastat or Pylarify [Lantheus]) was approved on May 27, 2021. Two kits (Illuccix [Telix Pharmaceuticals] and Locametz [Novartis]) for the preparation of ^{68}Ga-gozetotide (^{68}Ga-PSMA-11) were also approved—on December 20, 2021, and March 23, 2022, respectively. The approved indications are, first, for the imaging evaluation of men with suspected metastasis who are candidates for initial definitive therapy and, second, for suspected recurrence based on elevated serum prostate-specific antigen (PSA) levels. The Locametz kit is also approved for the selection of patients with mCRPC for whom the recently approved ^{177}Lu-vipivotide tetraxetan (Pluvicto [Novartis]) PSMA RPT is indicated. Moreover, the recent National Comprehensive Cancer Network guidelines for prostate cancer, version 4-2022, indicated that both ^{68}Ga-PSMA-11 and ^{18}F-piflufolastat PSMA PET imaging can be used to determine whether patients are eligible to receive ^{177}Lu-PSMA-617 RPT (*1*). Similar opinions have been expressed in a joint consensus statement by the European Association of Urology and the European Association of Nuclear Medicine (*2*). Over the past several years, the growing interest in PSMA RPT has ensured an increasing number of clinical trials in this clinical space using the β-emitting radiolabels ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T (I&T stands for imaging and therapy) and, more recently, the α-emitting ^{225}Ac-PSMA-617 (*3–6*). The aim of this narrative review is to summarize some of the major PSMA-directed RPT clinical trials.

LUPSMA

LuPSMA was a prospective single-center, single-arm, phase 2 clinical trial conducted in Australia that enrolled 30 men with mCRPC and progressive disease, of whom 28 had received chemotherapy (80% docetaxel, 47% cabazitaxel) and 25 had received second-generation antiandrogens (enzalutamide, abiraterone acetate, or both) (*7*). The men

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For correspondence or reprints, contact Hossein Jadvar (jadvar@med.usc.edu).
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were screened with ^{68}Ga-PSMA-11 PET/CT to confirm high PSMA expression (a lesion SUV_{max} of at least 1.5 times the hepatic SUV_{mean}), and no ^{18}F-FDG–positive disease without sufficient PSMA expression. With these dual imaging criteria, 16% of the patients were excluded. The patients were also required to have sufficient renal (glomerular filtration rate $>$ 40 mL/min), hepatic (albumin $>$ 25 g/L), and bone marrow (hemoglobin $>$ 90 g/L, neutrophils $> 1.5 \times 10^9$/L, platelets $> 75 \times 10^9$/L) function. The primary endpoint of the trial was PSA response rate according to the Prostate Cancer Clinical Trials Working Group (PCWG) 2 criteria, defined as a 50% or more PSA decline from baseline (PSA50) with confirmation 3–4 wk apart. Treatment toxicity was assessed according to the Common Terminology Criteria for Adverse Events, version 4.03. A mean ^{177}Lu-PSMA-617 dose of 7.5 GBq was administered per cycle (range, 4.4–8.7 GBq) for up to 4 cycles at 6-week intervals. The men received 1 (100%), 2 (93%), 3 (80%), or 4 (47%) therapy cycles. PSA50 was achieved in 57% of patients. The most common adverse event was grade 1 xerostomia, in 87% of patients, and grade 3–4 thrombocytopenia, in 13% of patients. There were no treatment-related deaths. The encouraging results of the LuPSMA trial paved the way for subsequent randomized controlled trials.

THERAP

TheraP was the first randomized study of ^{177}Lu-PSMA-617 RPT. It was an Australian multicenter, unmasked, randomized, phase 2 trial in the clinical setting of progressive mCRPC (prior docetaxel therapy with a rising serum PSA level according to the PCWG 3 criteria) that compared the safety and efficacy of Lu-PSMA-617 therapy in 98 men with the safety and efficacy of cabazitaxel chemotherapy in 85 men (NCT03392428) (*8*). The eligibility criteria for PET imaging were PSMA-positive disease with an SUV_{max} of at least 20 at a site of disease, an SUV_{max} of greater than 10 at all other measurable sites of metastatic disease, and no sites of metastatic disease with discordant ^{18}F-FDG–positive and PSMA-negative findings. On the basis of these imaging criteria, 10% and 18% of men were ineligible because of low metastasis PSMA uptake and discordant ^{18}F-FDG–positive disease, respectively. The primary endpoint was PSA50. The secondary endpoints were progression-free survival (interval from randomization to first evidence of PSA progression per the PCWG 3 criteria) and radiographic progression (RECIST 1.1 for CT and PCWG 3 criteria for bone lesions). ^{177}Lu-PSMA-617 RPT was more effective than cabazitaxel in terms of PSA50, which was observed in 66% of men in the ^{177}Lu-PSMA-617 group versus 44% in the cabazitaxel group. There was also less grade 3–4 toxicity in the ^{177}Lu-PSMA-617 group than in the cabazitaxel group (33% vs. 53%, respectively). Grade 1 or 2 xerostomia was observed in 61% of the patients in the ^{177}Lu-PSMA-617 RPT group only. No deaths were attributable to ^{177}Lu-PSMA-617 RPT. The trial concluded that ^{177}Lu-PSMA-617 may be a viable alternative to cabazitaxel in view of the enhanced efficacy and decreased toxicity of ^{177}Lu-PSMA-617 compared with cabazitaxel.

VISION

The multinational, randomized, phase 3 VISION trial was a pivotal milestone for nuclear medicine. The study design was similar to that of the ALSYMPCA randomized, phase 3 trial that led to the approval of ^{223}Ra-dichloride (Xofigo [Bayer]) for men with bone-dominant mCRPC. Men with mCRPC were randomized 2:1 to receive either ^{177}Lu-PSMA-11 (7.4 GBq [200 mCi] every 6 wk for 4 cycles, with an additional 2 cycles for total of 6 cycles at the discretion of treating physicians in responding patients, plus the best supportive care or the best standard of care [SOC]) or SOC only (NCT03511664) (*9*). The primary outcome measure was overall survival (OS). The secondary outcome measures were radiographic progression-free survival (rPFS) and time to first skeleton-related events. Eligible patients were those who had progressed on at least one taxane-based chemotherapy (41% were previously treated with 2 taxane regimens) and one or more androgen pathway inhibitors (abiraterone acetate, enzalutamide, darolutamide, or apalutamide). The best SOC did not permit additional chemotherapy (e.g., cabazitaxel), immunotherapy (e.g., pembrolizumab), or use of investigational drugs (e.g., olaparib). This decision was reasoned in view of lack of safety data on combination therapies and potential imbalance that may occur with variable additional treatments between the 2 study arms. However, additional androgen deprivation therapy, bone-health–directed therapy, or palliative radiation therapy were allowed at the discretion of the treating physician. The screening included imaging with contrast-enhanced diagnostic CT of the chest, abdomen, and pelvis; total-body bone scintigraphy; and ^{68}Ga-PSMA-11 PET/CT to confirm sufficient PSMA expression of at least 1 metastatic lesion (defined as uptake greater than that of liver parenchyma in lesions of any size in any organ system; no SUV cutoff threshold) and no PSMA-negative lesions (defined as uptake no higher than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any solid-organ lesion with a short axis of at least 1.0 cm, or in any bone lesion with a soft-tissue component of at least 1.0 cm in the short axis). Patients with a superscan pattern on bone scintigraphy were excluded. With these imaging selection criteria, 12.6% of patients were excluded after PSMA PET/CT imaging. ^{18}F-FDG PET/CT was not performed. The imaging eligibility criteria that excluded ^{18}F-FDG PET/CT were an operational decision to reduce complexity, meet the basic needs for regulatory approval, avoid potential issues with reimbursement of 2 PET/CT scans, meet the requirement for devising a scheme for combined scan interpretation, and provide reasonable accommodations for patient and physician acceptance. The trial showed a 4.0-mo OS benefit, a 5.3-mo rPFS benefit, and a 4.3-mo benefit regarding the time to the first skeleton-related event with the experimental arm of

^{177}Lu-PSMA-617 plus best SOC over the best-SOC-only arm. The incidence of grade 3 or higher adverse events was higher in the experimental arm than in the control arm (52.7% vs. 38%, respectively), but quality of life was not adversely affected. No grade 3 or higher xerostomia was observed in the experimental arm. The OS benefit with ^{177}Lu-PSMA-617 plus SOC was at par with those previously reported with other nonradioactive drug regimens in the mCRPC clinical space. The favorable results of the VISION trial led to the Food and Drug Administration approval of Pluvicto on March 23, 2022. Despite the approval, the debate on the most optimal imaging selection criteria continues, as does the issue of the potential need for individualized dosimetry for improved outcome (*10–16*). Nevertheless, reports indicate a poor outcome in patients with low PSMA expression or discordant ^{18}F-FDG–avid disease who are considered ineligible for ^{177}Lu-PSMA-617 treatment (*17–19*).

ENZAP

The goal of the ongoing open-label, randomized, stratified, 2-arm, multicenter, phase 2 EnzaP clinical trial is to investigate the safety and activity of adding ^{177}Lu-PSMA-617 RPT to enzalutamide (an androgen receptor antagonist) in patients with mCRPC not previously treated with chemotherapy (NCT04419402) (*20*). The trial is recruiting 160 participants over 12 mo and following them until 150 events occur (approximately another 18 mo). The randomization is 1:1 to either enzalutamide alone or enzalutamide plus ^{177}Lu-PSMA-617 RPT. The enzalutamide dose will be 160 mg per day orally (until there is no benefit or there is unacceptable toxicity). The ^{177}Lu-PSMA-617 will be given as an intravenous dose of 7.5 GBq (±10%) each for 4 doses on days 15, 57, 113, and 169. ^{68}Ga-PSMA-11 PET/CT is performed at mid cycle on day 92. Stratification factors will be study site, volume of disease (>20 vs. <20 disease sites on ^{68}Ga-PSMA-11 PET/CT), prior treatment with early docetaxel for castration-sensitive disease, and prior treatment with early abiraterone acetate (an androgen biosynthesis inhibitor) for castration-sensitive disease. Imaging exclusion criteria entail measurable metastatic lesions (>10 mm) that display an SUV_{max} of less than 10 on ^{68}Ga-PSMA-11 PET/CT. The primary outcome measure is PSA PFS. PSA progression is defined as a rise in PSA by at least 25% and at least 2 ng/mL above the nadir, which needs to be confirmed by a repeat PSA measurement 3 wk later. There are also several secondary outcome measures, including rPFS, PSA response rate, and others.

PSMAFORE

The purpose of the ongoing open-label, multicenter, 1:1 randomized, phase 3 PSMAFore clinical trial (NCT04689828) is to compare ^{177}Lu-PSMA-617 (7.4 GBq intravenously every 6 wk for 6 cycles) versus a change in androgen receptor–directed therapy in taxane-naïve patients with progressive mCRPC (*21*). The best supportive care is allowed in both study arms. The primary outcome measure is rPFS according to the PCWG 3–modified RECIST 1.1. OS is a key secondary endpoint. PSMA expression is confirmed with ^{68}Ga-PSMA-11 PET/CT. The estimated enrollment is 450 participants.

PSMADDITION

PSMAddition (NCT04720157) is an ongoing international, prospective, open-label, 1:1 randomized, phase 3 trial comparing the safety and efficacy of ^{177}Lu-PSMA-617 (7.4 GBq intravenously every 6 wk for up to 6 cycles) plus SOC versus SOC alone in men with metastatic castration-sensitive prostate cancer (*22*). SOC is defined as androgen receptor pathway inhibitors and androgen deprivation therapy. Docetaxel is not allowed. Eligible patients are treatment-naïve or minimally treated hormonal therapy candidates with PSMA-positive disease on ^{68}Ga-PSMA-11 PET/CT. Patients with rapidly progressing tumors who require chemotherapy are excluded. The approximate cohort will be 1,126 patients. rPFS is the primary endpoint.

UPFRONTPSMA

UPFrontPSMA is an ongoing open-label, multicenter Australian, 1:1 randomized, phase 2 clinical trial comparing the efficacy of ^{177}Lu-PSMA-617 (7.5 GBq intravenously every 6 wk for 2 cycles) followed 6 wk later by docetaxel chemotherapy (75 mg/m^2 every 3 wk for 6 cycles) versus docetaxel chemotherapy in patients with newly diagnosed high-volume (4 or more bone metastases with 1 or more bone lesion outside the axial skeleton, or visceral metastases) metastatic castration-sensitive prostate cancer (NCT04343885) (*23*). All patients also receive continuous androgen-deprivation therapy, and up to 4 wk of androgen-deprivation therapy are permitted before commencement of screening. PSMA expression is confirmed with ^{68}Ga-PSMA-11 PET/CT with no major discordance on ^{18}F-FDG PET/CT (defined as ^{18}F-FDG–positive disease with minimal PSMA expression in more than 5 sites or more than 50% of total disease volume). The primary endpoint is undetectable PSA (<0.2 ng/mL) at 12 mo. There are also several secondary and exploratory endpoints. The planned cohort is 140 participants.

SPLASH

SPLASH is an ongoing multicenter, open-label, phase 3 clinical trial evaluating the efficacy of ^{177}Lu-PNT2002 (^{177}Lu-PSMA I&T) in men with progressive mCRPC after androgen receptor pathway inhibitor therapy (NCT04647526) (*24*). In the dosimetry phase, 25 patients will receive up to 4 cycles of ^{177}Lu-PNT2002, 6.8 GBq intravenously, every 8 wk. In the randomization phase, about 390 patients will be randomized 2:1 to receive either ^{177}Lu-PNT2002 (n = 260) or androgen receptor pathway inhibitor therapy (enzalutamide or abiraterone acetate, with prednisone or dexamethasone; n = 130). The primary endpoint is rPFS as assessed by RECIST 1.1. and PCWG 3 criteria. Crossover of patients progressing on the androgen receptor pathway inhibitor therapy arm to the ^{177}Lu-PNT2002 therapy arm is allowed. Sufficient

TABLE 1
Clinical Trials of PSMA RPT

Trial	Year	Subjects (*n*)	Location	Description	Diagnostic agent	Therapeutic agent	Clinical phase	Outcome	Comments
LuPSMA (*7*)	2018	30	Australia	Prospective phase 2, single-center, single-arm trial	^{68}Ga, no ^{18}F-FDG+	^{177}Lu	mCRPC	PSA50 achieved by 57%	Grade 1 xerostomia in 87% and grade 3–4 thrombocytopenia in 13%
TheraP (*8*), NCT03392428	2021	35	Australia	Randomized phase 2 trial	^{68}Ga, no ^{18}F-FDG+	^{177}Lu	mCRPC	^{177}Lu-PSMA more effective than cabazitaxel	RPT with less grade 3–4 toxicity (33%) than cabazitaxel (53%); RPT with 61% grade 1–2 xerostomia
VISION (*9*), NCT03511664	2022	831	International	Open-label, 2:1 randomized, phase 3 trial of ^{177}Lu-PSMA + SOC vs. SOC; previously treated with at least 1 ARPI and taxane	^{68}Ga	^{177}Lu	mCRPC	PFS (median, 8.7 vs. 3.4 mo); OS (median, 15.3 vs. 11.3 mo)	Adverse events of grade ≥ 3 higher with ^{177}Lu-PSMA than without (52.7% vs. 38.0%)
EnzaP (*20*), NCT04419402	2020	160	Australia	Open-label, 1:1 randomized, phase 2 trial of ENZ alone or ENZ + ^{177}Lu-PSMA	^{68}Ga	^{177}Lu	mCRPC	PSA PFS	Ongoing prospective trial
PSMAFore (*21*), NCT04689828	2022	Estimation: 450	International	Open-label, phase 3, multicenter trial	^{68}Ga	^{177}Lu	mCRPC	rPFS	Ongoing prospective trial
PSMAddition (*22*), NCT04720157	2022	Estimation: 1,126	International	Open-label, phase 3, 1:1 randomized trial of RPT + SOC vs. SOC	^{68}Ga	^{177}Lu	mCSPC	rPFS	Ongoing prospective trial
UPFrontPSMA (*23*), NCT04343885	2021	Estimation: 140	Australia	Open-label, multicenter, phase 2, 1:1 randomized trial of RPT + DTX vs. DTX	^{68}Ga	^{177}Lu	mCSPC	Undetectable PSA at 1 y	Ongoing prospective trial
SPLASH (*24*), NCT04647526	2021	Estimation: 260	International	Open-label, multicenter, phase 3 trial	^{68}Ga or ^{18}F	^{177}Lu	mCRPC	rPFS	Ongoing prospective trial
ECLIPSE (*25*), NCT05204927	2022	Estimation: 400	United States	Open-label, multicenter, phase 3 trial	^{68}Ga or ^{18}F	^{177}Lu	mCRPC	rPFS	Ongoing prospective trial
LuTectomy (*26*), NCT04430192	2021	20	Australia	Open-label, phase 1/2, nonrandomized trial of dosimetry, efficacy, safety of ^{177}Lu-PSMA	^{68}Ga	^{177}Lu	High-risk prostate cancer	Absorbed radiation dose of prostate and metastatic lymph nodes	Ongoing prospective trial
PRINCE (*27*), NCT03658447	2022	37	Australia	Phase 1/2, safety and efficacy trial of RPT and programmed death 1 inhibitor	^{68}Ga	^{177}Lu	mCRPC	PSA50	Ongoing prospective trial
LuPARP (*28*), NCT03874884	2022	52	Australia	Phase 1 dose-escalation and dose-expansion trial	^{68}Ga	^{177}Lu	mCRPC	Primary outcomes: DLT, MTD, and RP2D	Ongoing prospective trial
TATCIST (*29*), NCT05219500	2022	Estimation: 100	Texas	^{225}Ac-PSMA I&T	^{68}Ga	^{225}Ac	mCRPC	PSA50	Ongoing prospective trial

^{177}Lu-PSMA = ^{177}Lu-PSMA-617; ARPI = androgen receptor pathway inhibitor; PFS = progression-free survival; ENZ = enzalutamide; DTX = docetaxel; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose.

PSMA expression is confirmed with PSMA PET/CT. Exclusion criteria include patients with prior cytotoxic chemotherapy for mCRPC, hepatic metastases 1 cm or larger, central nervous system metastases, and a superscan on bone scintigraphy.

ECLIPSE

ECLIPSE is an ongoing prospective, multicenter, open-label, randomized, phase 3 study to compare the safety and efficacy of ^{177}Lu-PSMA I&T versus hormone therapy in mCRPC patients (NCT05204927) (*25*). Approximately 400 patients will be randomized at a 2:1 ratio to receive either ^{177}Lu-PSMA I&T or SOC hormone therapy (abiraterone acetate with prednisone, or enzalutamide). PSMA expression is confirmed with either ^{68}Ga-PSMA 11 PET/CT or ^{18}F-DCFPyL PET/CT as determined by central readers. Exclusion criteria include prior treatment with radioligand therapy, ^{223}Ra-dichloride therapy within the past 12 wk, prior chemotherapy, or any other concurrent therapy. The primary outcome measure is rPFS as assessed by RECIST 1.1 and PCWG 3 criteria. There are also several secondary outcomes, including OS and PSA50 response rate, among others.

LUTECTOMY

LuTectomy is an ongoing Australian open-label, nonrandomized, phase 1/2 trial to assess the dosimetry, efficacy, and safety of ^{177}Lu-PSMA-617 in men with high-risk (defined as PSA $>$ 20 ng/mL, International Society of Urological Pathology grade group 3–5, clinical stage T2c or higher) localized or locoregional (N1) prostate cancer before undergoing radical prostatectomy and pelvic lymph node dissection (NCT04430192) (*26*). The first 10 patients will receive 5 GBq of ^{177}Lu-PSMA-617 intravenously for the dosimetry study. The subsequent 10 patients will receive 2 cycles of 5 GBq of ^{177}Lu-PSMA-617 intravenously, separated by 6 wk. The primary outcome measure is to determine the absorbed radiation dose in the prostate and metastatic lymph nodes. PSMA PET/CT will be performed to confirm high PSMA expression defined as an SUV_{max} of more than 20. Patients with prior prostate radiotherapy or androgen-deprivation therapy, and evidence of metastatic disease involving the bone, viscera, and lymph nodes above the common iliac bifurcation, are excluded.

PRINCE

PRINCE is an ongoing Australian phase 1/2 study assessing the safety and efficacy of the combination of ^{177}Lu-PSMA-617 (up to 6-week cycles with an initial intravenous dose of 8.5 GBq reduced by 0.5 GBq for each of the subsequent 5 cycles) and the programmed death 1 protein inhibitor pembrolizumab (200 mg every 3 wk for up to 35 doses) in 37 mCRPC patients (NCT03658447) (*27*). Major exclusion criteria include any prior exposure to immunotherapy drug regimens, cabazitaxel chemotherapy, and ^{177}Lu-PSMA-617 RPT. The primary outcome measures are PSA50, incidence of adverse events, and tolerability (defined as time from treatment commencement to treatment discontinuation due to toxicity).

LUPARP

LuPARP is an Australian dose-escalation and dose-expansion phase 1 trial evaluating the safety and tolerability of the poly(adenosine diphosphate ribose) polymerase (PARP) inhibitor olaparib in combination with ^{177}Lu-PSMA-617 in 52 mCRPC patients (NCT03874884) (*28*). Patients will be administered ^{177}Lu-PSMA-617 (7.4 GBq intravenously every 6 wk) together with olaparib on days 2–15 of each cycle for total of 4 cycles; a cycle is 42 d. The recommended phase 2 dose of olaparib will be used during the dose expansion part of the trial. Exclusion criteria include patients with a superscan pattern on bone scintigraphy, ^{18}F-FDG–positive disease with low PSMA expression (SUV_{max} $<$ 10), a history of brain or leptomeningeal metastases, and prior exposure to ^{177}Lu-PSMA-617, cabazitaxel, platinum, PARP inhibitors, mitoxantrone, or cyclophosphamide. The primary outcome measures are determination of the dose-limiting toxicity, maximum tolerated dose, and recommended phase 2 dose. PSA50 and rPFS are among several secondary outcome measures.

TATCIST

TATCIST is an oncoming prospective, open-label, single-arm study to assess the efficacy of PSMA-targeted α-particle therapy with ^{225}Ac-PSMA I&T in approximately 100 patients with mCRPC (NCT05219500) (*29*). Eligible patients include those with progressive disease on taxane chemotherapy or those who are naïve to or have been treated previously and progressed with ^{177}Lu-PSMA-617 or ^{177}Lu-PSMAI& T. All patients will receive ^{225}Ac-PSMA I&T at an interval of 8 ± 1 wk, with the initial activity of 100 kBq/kg (±10%), followed by deescalation to 87 kBq/kg (±10%), 75 kBq/kg (±10%), or 50 kBq/kg (±10%) in cases of good response at the discretion of the investigator. The primary outcome measure is PSA50.

SUMMARY

We have reviewed several major clinical trials that use PSMA-directed RPT (Table 1). The VISION trial established PSMA-directed therapy as a viable treatment strategy option in men with mCRPC. The other ongoing trials will hopefully expand the applicability of PSMA-targeted RPT to earlier phases of prostate cancer and shed light on the proper sequencing and combination with other treatments to optimize overall therapeutic efficacy and patient outcome at acceptable biologic and financial toxicities.

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REFERENCES

1. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): prostate cancer—version 1.2023. National Comprehensive Cancer Network website. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Published September 16, 2022. Accessed January 17, 2023.
2. Fanti S, Brigatti A, Emmett L, et al. EAU-EANM consensus statements on the role of the prostate-specific membrane antigen positron emission tomography/computed tomography in patients with prostate cancer and with respect to [^{177}Lu]Lu-PSMA radioligand therapy. *Eur Urol Oncol.* 2022;5:530–536.
3. Sadaghiani MS, Sheikhbahaei S, Werner RA, et al. ^{177}Lu-PSMA radioligand therapy in metastatic castration-resistant prostate cancer: an updated systematic review and meta-analysis. *Prostate.* 2022;82:826–835.
4. Kim YJ, Kim YI. Therapeutic responses and survival effects of ^{177}Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer: a meta-analysis. *Clin Nucl Med.* 2018;43:728–734.
5. Satapathy S, Sood A, Das CK, Mittal BR. Evolving role of ^{225}Ac-PSMA radioligand therapy in metastatic castration-resistant prostate cancer-a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis.* 2021;24:880–890.
6. Ballal S, Yadav MP, Sahoo RK, et al. ^{225}Ac-PSMA-617-targeted alpha therapy for the treatment of metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. *Prostate.* 2021;81:580–591.
7. Hofman MS, Violet J, Hicks RJ, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration resistant prostate cancer (LuPSMA trial): a single-center, single-arm, phase 2 study. *Lancet Oncol.* 2018;19:825–833.
8. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-167 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomized, open-label, phase 2 trial. *Lancet.* 2021;397:797–804.
9. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385:1091–1103.
10. Calais J, Czernin J. PSMA expression assessed by PET imaging is a required biomarker for selecting patients for any PSMA-targeted therapy. *J Nucl Med.* 2021;62:1489–1491.
11. Srinivas S, Iagaru A. To scan or not to scan: an unnecessary dilemma for PSMA radioligand therapy. *J Nucl Med.* 2021;62:1487–1488.
12. Jadvar H. The VISION forward: recognition and implication of PSMA−/^{18}F-FDG+ mCRPC. *J Nucl Med.* 2022;63:812–815.
13. Jackson P, Hofman M, McIntosh L, et al. Radiation dosimetry in ^{177}LuPSMA-617 therapy. *Semin Nucl Med.* 2022;52:243–254.
14. Kuo PH, Benson T, Messmann R, Groaning M. Why we did what we did: PSMA PET/CT selection criteria for the VISION trial. *J Nucl Med.* 2022;63:816–818.
15. Eshghi A, Covington MF, Eshgi N, Kuo PH. Utility of PET to appropriately select patients for PSMA-targeted theranostics. *Clin Nucl Med.* 2022;47:488–495.
16. Chandran E, Figg WD, Madan R. Leutetium-177-PSMA-617: a vision of the future. *Cancer Biol Ther.* 2022;23:186–190.
17. Thang SP, Violet J, Sandhu S, et al. Poor outcomes for patients with metastatic castration-resistant prostate cancer with low prostate-specific membrane antigen (PSMA) expression deemed ineligible for ^{177}Lu-labelled PSMA radioligand therapy. *Eur Urol Oncol.* 2019;2:670–676.
18. Sartor O, Herrmann K. Prostate cancer treatment: ^{177}Lu-PSMa-617 considerations, concepts, and limitations. *J Nucl Med.* 2022;63:823–829.
19. Hotta M, Gafita A, Czernin J, Calais J. Outcome of patients with PSMA PET/CT screen failure by VISION criteria and treated with ^{177}Lu-PSMA therapy: a multicenter retrospective analysis. *J Nucl Med.* 2022;63:1484–1488.
20. Enzalutamide with Lu PSMA-617 versus enzalutamide alone in men with metastatic castration-resistant prostate cancer (ENZA-p). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT04419402. Published June 5, 2020. Updated February 16, 2022. Accessed January 17, 2023.
21. Sartor O, Morris MJ, Chi KN, et al. PSMAFore: a phase 3 study to compare ^{177}Lu-PSMA-617 treatment with a change in androgen receptor pathway inhibitor in taxane-naïve patients with metastatic castration-resistant prostate cancer [abstract]. *J Clin Oncol.* 2022;40(suppl):TPS211.
22. Sartor O, Tagawa ST, Saad F, et al. PSMAddition: a phase 3 trial to compare treatment with ^{177}Lu-PSMA-617 plus standard of care (SOC) versus SOC alone in patients with metastatic hormone-sensitive prostate cancer [abstract]. *J Clin Oncol.* 2022;40(suppl):TP210.
23. Azad A, Dhiantravan N, Emmett L, et al. UpfrontPSMA: a randomized phase II study of sequential ^{177}Lu-PSMA-617 and docetaxel in metastatic hormone-naïve prostate cancer (mHNPC) [abstract]. *J Clin Oncol.* 2021;39(suppl):TPS180.
24. Chi KN, Metser U, Czernin J, et al. Study evaluating metastatic castrate resistant prostate cancer (mCRPC) treatment using ^{177}Lu-PNT2002 PSMA therapy after second-line hormonal treatment (SPLASH) [abstract]. *J Clin Oncol.* 2021;39(suppl):TPS5087.
25. Lu-177-PSMA-I&T for metastatic castration-resistant prostate cancer. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT05204927?term=eclipse&cond=Prostate+Cancer&draw=2&rank=3. Published January 24, 2022. Updated December 20, 2022. Accessed January 17, 2023.
26. Dhiantravan N, Violet J, Eapen R, et al. Clinical trial protocol for LuTectomy: a single-arm study of the dosimetry, safety, and potential benefit of ^{177}Lu-PSMA-617 prior to prostatectomy. *Eur Urol Focus.* 2021;7:234–237.
27. PRINCE (PSMA-lutetium radionuclide therapy and immunotherapy in prostate cancer. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03658447?term=prince&cond=prostate+cancer&draw=2&rank=1. Published September 5, 2018. Updated May 25, 2022. Accessed January 17, 2023.
28. ^{177}Lu-PSMA-617 therapy and olaparib in patients with metastatic castration resistant prostate cancer (LuPARP). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03874884. Published March 14, 2019. Updated November 17, 2022. Accessed January 17, 2023.
29. Targeted alpha therapy with ^{225}actinium-PSMA-I&T of castration-resistant prostate cancer (TATCIST). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT05219500?term=225ac-psma&cond=Prostate+Cancer&draw=2&rank=1. Published February 2, 2022. Accessed January 17, 2023.