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Clinical Trials of Prostate-Specific Membrane Antigen Radiopharmaceutical Therapy

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Abstract

Prostate-specific membrane antigen (PSMA) theranostics has been a momentous triumph for nuclear medicine. The recent approvals of PSMA-targeted imaging agents (68Ga-PSMA-11, 18F-DCFPyL) and radiopharmaceutical therapy (177Lu-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 radiopharnaecutical therapy clinical trials with the beta emitter, 177Lu-PSMA-617, and the alpha emitter, 225Ac-PSMA-617, in prostate cancer.

Radiopharmaceutical therapy (RPT) with radiolabeled agents targeted to the prostatespecific 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 (FDA) approved Gallium-68 (68Ga)-PSMA-11 on December 1, 2020, based on two comparable new drug applications submitted by the University of California, Los Angeles, and the University of California, San Francisco. The first commercial fluorine 18 (18F)-labeled PSMA radiotracer, 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine 3-carbonyl)- amino]- pentyl}-ureido)-pentanedioic acid (18F-DCFPyL; also known as 18F-piflufolastat or Pylarify, Lantheus) was approved on May 27, 2021. Two kits (Illuccix, Telix Pharmaceuticals; and Locametz, Novartis) for the preparation of 68Ga-Gozetotide (68Ga-PSMA-11) were also approved on December 20, 2021, and March 23, 2022, respectively. The approved indications are for, 1) for the imaging evaluation of men with suspected metastasis who are candidates for initial definitive therapy, and 2) suspected recurrence on the basis of 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 lutetium-177 (177Lu)- vipivotide tetraxetan (Pluvicto, Novartis) PSMA RPT is indicated. Moreover, the recent National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer, version 4-2022, indicated that both 68Ga-PSMA-11 or 18F-piflufolastat PSMA PET imaging can be used to determine eligibility of patients for receiving 177Lu-PSMA-617 RPT (1).

Similar opinions have been expressed in the joint European Association of Urology (EAU) and the European Association of Nuclear Medicine (EANM) consensus statement (2). Over the past several years, the growing interest in PSMA RPT has ensued an increasing number of clinical trials in this clinical space utilizing beta emitting radiolabels 177Lu-PSMA-617, and 177Lu-PSMA-I&T (I&T stands for Imaging and Therapy), and more recently alpha emitting 225Ac-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 men had received chemotherapy (80% docetaxel, 47% cabazitaxel) and 25 men had received second-generation anti-androgens (enzalutamide, abiraterone acetate, or both) (7). The men were screened with 68Ga-PSMA-11 PET/CT to confirm high PSMA expression (lesion maximum standardize uptake value [SUVmax] of at least 1.5 times hepatic SUVmean), and no 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, neutrophil > 1.5x10^9/L, platelet >75x10^9/L) functions. The primary endpoint of the trial was PSA response rate according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria defined as a 50% or more PSA decline from baseline (PSA50) with confirmation 3–4 weeks apart. Treatment toxicity was assessed according to the Common Terminology

Criteria for Adverse Events version 4.03. The men received a mean administration of 7.5 GBq per cycle (range 4.4-8.7 GBq) of 177Lu-PSMA-617 for up to 4 cycles at 6 weekly intervals. The number of therapy cycles received by men were 1 cycle (100%), 2 cycles (93%), 3 cycles (80%), and 4 cycles (47%). 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 elated deaths. The encouraging results of the LuPSMA trial paved the way for subsequent randomized controlled trials.

TheraP

TheraP was the first randomized study of 177Lu-PSMA-617 RPT. It was an Australian multicenter, unblinded, randomized phase 2 trial in the clinical setting of progressive mCRPC (prior docetaxel therapy with rising serum PSA level according to the PCWG3 criteria) that compared the safety and efficacy of Lu-PSMA-617 therapy in 98 men with cabazitaxel chemotherapy in 85 men (NCT03392428) (8). PET imaging eligibility criteria were PSMA-positive disease with a maximum SUVmax of at least 20 at a site of disease and greater than 10 at all other measurable sites of metastatic disease, and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings. Based on these imaging criteria, 10% and 18% of men were ineligible due to low metastasis PSMA uptake and discordant 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 PCWG3 criteria), and radiographic progression (RECIST 1.1 criteria for CT and PCWG3 criteria for bone

lesions). 177Lu-PSMA-617 RPT was more effective than cabazitaxel in terms of PSA50 which was observed in 66% of men in the 177Lu-PSMA-617 group vs. 44% in the cabazitaxel group. There were also fewer grade 3-4 toxicity in the 177Lu-PSMA-617 group than in the cabazitaxel group (33% vs. 53%, respectively). Grade 1-2 xerostomia was observed in 61% of the patients in the 177Lu-PSMA-617 RPT group only. No deaths occurred attributable to 177Lu-PSMA-617 RPT. The trial concluded that 177Lu-PSMA-617 may be a viable alternative to cabazitaxel in view of the 177Lu-PSMA-617 enhanced efficacy and less toxicity compared to cabazitaxel.

VISION

The multi-national, randomized phase 3 VISION trial was a pivotal milestone for nuclear medicine. The study design was similar to that of the ALSYMPCA phase 3 randomized trial that led to the approval of 223Ra dichloride (Xofigo, Bayer) for men with bonedominant mCRPC. Men with mCRPC were randomized 2:1 to receive either, 177Lu- PSMA-11 (7.4 GBq [200 mCi] every 6 weeks for 4 cycles, with additional 2 cycles for total of 6 cycles at the discretion of treating physicians in responding patients, plus best supportive care / best standard of care, SOC) vs 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 skeletal related events (SREs). 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 contrastenhanced diagnostic CT of the chest, abdomen, and pelvis, total body bone scintigraphy, and 68Ga-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 cut-off threshold) and no PSMAnegative lesions (defined as uptake equal to or lower 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 superscan pattern on bone scintigraphy were excluded. With these imaging selection criteria, 12.6% of patients were excluded after PSMA PET/CT imaging. FDG PET/CT was not performed. The imaging eligibility criteria that excluded FDG PET/CT was an operational decision for reducing complexity, basic needs for regulatory approval, avoidance of potential issues with reimbursement of 2 PET/CT scans, requirement for devising a scheme for combined scan interpretation, and reasonable accommodations for patient and physician acceptance. The trial showed a 4.0-month OS benefit, a 5.3-month rPFS benefit, and a 4.3-month time to first SREs benefit with the experimental arm of 177Lu-PSMA-617 plus best SOC over 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 177Lu-PSMA-617 plus SOC was at par with those previously reported with other non-radioactive drug regimens in the mCRPC clinical space. The favorable results of the VISION trial led to the FDA approval of Pluvicto on March 23, 2022. Despite the approval, the debate on the most optimal imaging selection criteria and issue of the potential need for individualized dosimetry for improved outcome continues (10-16). Nevertheless, reports indicate poor outcome in patients with low PSMA expression or discordant FDG-avid disease who are considered ineligible for 177Lu-PSMA-617 treatment (17-19).

EnzaP

The goal of this ongoing open label, randomized, stratified, 2-arm, multicenter phase 2 clinical trial is to investigate the safety and activity of adding 177Lu-PSMA-617 RPT to enzalutamide (androgen receptor antagonist) in patients with mCRPC not previously treated with chemotherapy (NCT04419402)(20). The trial recruits 160 participants over 12 months and are followed until 150 events occur (approximately another 18 months). The randomization is 1:1 to either enzalutamide alone or enzalutamide plus 177Lu-PSMA-617 RPT. The enzalutamide dose will be 160 mg per day orally (until there is no benefit or there is unacceptable toxicity). The 177Lu-PSMA-617 will be given as intravenous dose of 7.5 GBq (+10%) each for 4 doses on days 15, 57, 113, and 169. 68Ga-PSMA-11 PET/CT is performed mid cycle on day 92. Stratification factors will be study site, volume of disease (>20 vs. <20 disease sites on 68Ga-PSMA-11 PET/CT),

prior treatment with early docetaxel for castrate-sensitive disease, and prior treatment with early abiraterone acetate (androgen biosynthesis inhibitor) for castrate-sensitive disease. Imaging exclusion criteria entails measurable metastatic lesions (>10 mm) that display SUVmax <10 on 68Ga-PSMA-11 PET/CT. The primary outcome measure is PSA PFS. PSA progression is defined as a rise in PSA by more than or equal 25% and more than or equal 2 ng/mL above nadir, which needs to be confirmed by a repeat PSA measurement performed 3 weeks later. There are also a number of secondary outcome measures including rPFS, PSA response rate, etc.

PSMAFore

The purpose of this ongoing phase 3, open-label, multi-center, 1:1 randomized clinical trial (NCT04689828) is to compare 177Lu-PSMA-617 (7.4 GBq i.v. every 6 weeks for 6 cycles) vs. a change in androgen **r**eceptor-directed therapy in taxane-naïve patients with progressive mCRPC (21). Best supportive care is allowed in both study arms. The primary outcome measure is rPFS according to the PCWG3-modified RECIST 1.1 criteria. OS is a key secondary endpoint. PSMA expression is confirmed with 68Ga-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 177Lu-PSMA-617 (7.4 GBq i.v. every 6 weeks for up to 6 cycles) plus SOC vs. SOC alone in men with metastatic castrate sensitive prostate cancer (mCSPC) (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 candidates for hormonal therapy with PSMA positive disease on 68Ga-PSMA-11 PET/CT. Patients with rapidly progressing tumors who require chemotherapy are excluded. The approximate cohort will be 1126 patients. rPFS is the primary endpoint.

UPFrontPSMA

This ongoing phase 2 open-label, multicenter Australian, 1:1 randomized clinical trial compares the efficacy of 177Lu-PSMA-617 (7.5 GBq i.v. every 6 weeks for 2 cycles) followed 6 weeks later by docetaxel chemotherapy (75 mg/m_2 every 3 weeks for 6 cycles) vs. docetaxel chemotherapy in patients with newly diagnosed high-volume (4 or more bone metastases with 1 or more bone lesion outside axial skeleton, and/or visceral metastases) mCSPC (NCT04343885) (23). All patients also receive continuous ADT and up to 4 weeks of ADT are permitted prior to commencement of screening. PSMA expression is confirmed with 68Ga-PSMA-11 PET/CT with no major discordance on FDG PET/CT (defined as 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 months. There are also a number of secondary and exploratory endpoints. The planned cohort is 140 participants.

SPLASH

This ongoing multicenter, open-label, phase 3 clinical trial evaluates the efficacy of 177Lu-PNT2002 (177Lu-PSMA I&T; I&T stands for Imaging and Therapy) 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 177Lu-PNT2002 6.8 GBq i.v. every 8 weeks. In the randomization phase, about 390 patients will be randomized 2:1 to receive either 177Lu-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 PCWG3 criteria. Cross over of patients progressing on the androgen receptor pathway inhibitor therapy arm to the 177Lu-PNT2002 therapy arm is allowed. Sufficient PSMA expression is confirmed with PSMA PET/CT. Exclusion criteria include patients with prior cytotoxic chemotherapy for mCRPC, hepatic metastases 1 cm or greater, central nervous system metastases, and superscan on bone scintigraphy.

ECLIPSE

This ongoing trial is a prospective, multi-center, open-label, randomized phase 3 study to compare the safety and efficacy of 177Lu-PSMA I&T vs. hormone therapy in mCRPC patients (NCT05204927) (25). Approximately 400 patients will be randomized on a 2:1 ratio to either receive 177Lu-PSMA I&T or SOC hormone therapy (abiraterone acetate with prednisone, or enzalutamide). PSMA expression is confirmed with either 68Ga-PSMA 11 PET/CT or 18F-DCFPyL PET/CT as determined by central readers. Exclusion criteria includes prior treatment with radioligand therapy, 223Ra dichloride therapy within the past 12 weeks, prior chemotherapy, or any other concurrent therapy. The primary outcome measure is rPFS as assessed by RECIST 1.1 and PCWG3 criteria.

There are also a number of secondary outcomes including OS and PSA50 response rate, and others.

LuTectomy

This ongoing Australian study is an open-label phase 1/2 non-randomized trial to assess the dosimetry, efficacy, and safety of 177Lu-PSMA-617 in men with high-risk (defined as PSA>20 ng/mL, ISUP grade group 3-5, clinical stage T2c or higher) localized or locoregional (N1) prostate cancer prior to undergoing radical prostatectomy and pelvic lymph node dissection (NCT04430192) (26). The first 10 patients will receive 5 GBq of 177Lu-PSMA-617 i.v. for the dosimetry study. The subsequent 10 patients will receive 2 cycles of 5 GBq 177Lu-PSMA-617 i.v. separated by 6 weeks. The primary outcome measure is to determine the radiation absorbed dose in the prostate and metastatic lymph nodes. PSMA PET/CT will be performed to confirm high PSMA expression defined as SUVmax >20. Patients with prior prostate radiotherapy and/or ADT, and evidence of metastatic disease involving the bone, viscera, and lymph nodes above the common iliac bifurcation are excluded.

PRINCE

This ongoing Australian phase 1/2 study will assess the safety and efficacy of the combination of 177Lu-PSMA-617 (up to 6 weekly cycles with initial dose of 8.5 GBq i.v. reduced by 0.5 GBq i.v. for each subsequent 5 cycles) and programmed death 1 (PD-1) protein inhibitor, pembrolizumab (200 mg every 3 weeks 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 177Lu-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

This Australian phase 1 dose-escalation and dose-expansion trial evaluates the safety and tolerability of the poly-ADP ribose polymerase (PARP) inhibitor, olaparib in combination with 177Lu-PSMA-617 in 52 mCRPC patients (NCT03874884)(28). Patients will be administered 177Lu-PSMA-617 (7.4 GBq i.v. every 6 weeks) together with olaparib on days 2-15 of each cycle for total of 4 cycles; a cycle is 42 days. The recommended phase 2 dose of olaparib will be used during the dose expansion part of the trial. Exclusion criteria include patients with superscan pattern on bone scintigraphy, FDG positive disease with low PSMA expression (SUVmax < 10), history of brain or leptomeningeal metastases, and prior exposure to 177Lu-PSMA-617, cabazitaxel, platinums, PARP inhibitors, mitoxantrone, or cyclophosphamide. The primary outcome measures are determination of the dose limiting toxicity (DLT), maximum tolerate dose (MDT), and the recommended phase 2 dose (RP2D). PSA50 and rPFS are among a number of secondary outcome measures.

TATCIST

This trial is an oncoming prospective, open-label, single-arm study to assess the efficacy of PSMA-targeted alpha particle therapy with 225Ac-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 177Lu-PSMA-617 or 177Lu-PSMAI&T. All patients will receive 225Ac-PSMA I&T at 8+1-week interval, with the initial activity of 100 kBq/kg (+/-10%), followed by de-escalation 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 reviewed several major clinical trials that employ 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 onto the proper sequencing and combination with other treatments to optimize overall therapeutic efficacy and patient outcome at acceptable biological and financial toxicities.

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Table 1. Clinical Trials of Prostate-Specific Membrane Antigen Radiopharmaceutical Therapy

Trial (reference)	Year	Participants (location)	Description (Dx/Rx agents)	Clinical Phase	Outcome	Comments
LuPSMA (7)	2018	30 (Australia)	Prospective phase 2, single-center, single-arm (68Ga, no FDG+/177Lu)	mCRPC	57% achieved PSA50	Grade 1 xerostomia in 87% and grade 3-4 thrombocytopenia in 13%
TheraP (8) NCT03392428	2021	35 (Australia)	Randomized phase 2 (68Ga, no FDG+/177Lu)	mCRPC	LuPSMA-617 more effective than cabazitaxel	RPT had less grade 3-4 toxicity (33%) v. cabazitaxel (53%). RPT had 61% grade 1-2 xerostomia
VISION (9) NCT03511664	2022	831 (international)	Open-label, 2:1 randomized, phase 3, LuPSMA+SOC v. SOC; previously treated with at least 1 ARPI & taxane (68Ga/177Lu)	mCRPC	PFS (median, 8.7 vs. 3.4 months; OS (median, 15.3 vs. 11.3 months)	AE of grade $\geq$3 higher with LuPSMA than without (52.7% vs. 38.0%)
EnzaP (20) NCT04419402	2020	160 (Australia)	Open-label, 1:1 randomized, phase 2, ENZ alone or ENZ+Lu-PSMA (68Ga/177Lu)	mCRPC	PSA PFS	Ongoing prospective trial
PSMAFore (21) NCT04689828	2022	Est 450 (international)	Open-label, phase 3, multicenter (68Ga/177Lu)	mCRPC	rPFS	Ongoing prospective trial
PSMAddition (22) NCT04720157	2022	Est 1126 (international)	Open-label, phase 3, 1:1 randomized, RPT+SOC v. SOC (68Ga/177Lu)	mCSPC	rPFS	Ongoing prospective trial
UPFrontPSMA (23) NCT04343885	2021	Est 140 (Australia)	Open-label, multicenter, phase2, 1:1 randomized, RPT+DTX v. DTX (68Ga/177Lu)	mCSPC	Undetectable PSA at 1y	Ongoing prospective trial
SPLASH (24) NCT04647526	2021	Est 260 (international)	Open-label, multicenter, phase 3 (68Ga or 18F/177Lu)	mCRPC	rPFS.	Ongoing prospective trial
ECLIPSE (25) NCT05204927	2022	Est 400 (USA)	Open-label, multicenter, phase 3 (68Ga or 18F/177Lu)	mCRPC	rPFS	Ongoing prospective trial
LuTectomy (26) NCT04430192	2021	20 (Australia)	Open-label phase 1/2 non-randomized trial of dosimetry, efficacy, safety of LuPSMA (68Ga/177Lu)	high-risk prostate cancer	RAD of prostate and metastatic lymph nodes	Ongoing prospective trial
PRINCE (27) NCT03658447	2022	37 (Australia)	Phase 1/2, safety & efficacy of RPT & PD-1 inhibitor (68Ga/177Lu)	mCRPC	PSA50	Ongoing prospective trial
LuPARP (28) NCT03874884	2022	52 (Australia)	Phase 1 dose-escalation and dose-expansion (68Ga/177Lu)	mCRPC	Primary outcomes are DLT, MDT, & RP2D	Ongoing prospective trial
TATCIST (29) NCT05219500	2022	Est 100 (Texas)	225Ac-PSMA I&T (68Ga/225Ac)	mCRPC	PSA50	Ongoing prospective trial

AE = adverse event; ARPI = androgen receptor inhibitor pathway; DLT = dose limiting toxicity; DTX = docetaxel; ENZ = enzalutamide; LuPSMA =177Lu-PSMA-617; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; MDT = maximum tolerated dose; OS = overall survival; PSA = prostate specific antigen; PSA50 = PSA decline of 50% or more; PFS = progression-free survival; PSMA = prostate specific membrane antigen; RAD = radiation absorbed dose; RP2D = recommended phase 2 dose; rPFS = radiographic progression-free survival; RPT = radiopharmaceutical therapy; SOC = standard of care