Prostate Cancer Foundation of Australia

RESEARCH AWARENESS SUPPORT

25 October 2021

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Lu-PSMA Imaging & Therapy for men with end-stage prostate cancer

Improving Australian access to safe, affordable, quality cancer care

Dear Professor Ward,

I write on behalf of Prostate Cancer Foundation of Australia (PCFA) to unreservedly support application 1686 to the Medical Services Advisory Committee for Medicare Benefit Schedule listing of the therapeutic technology ^{177}Lutetium PSMA i&t for metastatic castrate resistant prostate cancer.

^{177}Lutetium PSMA therapy, or lutetium-177 prostate specific membrane antigen therapy, is a treatment for men with advanced prostate cancer. It is used when the disease has spread and other treatments have failed. PSMA is a type of protein found on the surface of cells on the prostate gland. It also appears in other parts of the body where prostate cancer has metastasised. ^{177}Lutetium PSMA therapy uses a molecule which attaches itself to the PSMA receptors on the cancer cells and emits beta radiation to destroys the cancer cells. The PSMA molecule targets the tumour site, preventing radiation exposure to other parts of the body.

With findings published recently from the Australian TheraP study, co-funded by PCFA, and from the VISION clinical trial, we expect other comparable international jurisdictions to approve and regulate Lu-PSMA treatment as a safe and effective therapy with benefits for overall survival. We also expect Novartis to apply for US registration of the ligand labelled chemically to ^{177}Lutetium, PSMA 617, at a cost of around $45,000 per dose and $270,000 per course.

To maintain Australia's reputation as a leading international jurisdiction for prostate cancer research and treatment, and ensure Australian men get access to life-saving care, we support the call for provision of affordable access via the Medicare Benefit Schedule to ^{177}Lutetium PSMA i&t for Australian men with end-stage metastatic castration resistant prostate cancer.

We further support the application's recommendation to provide for up to six doses of LuPSMA therapy at six-weekly intervals – until the clinical benefits to the patient have been exhausted or the patient is relieved of significant persistent disease which can be targeted with LuPSMA therapy.

On cessation of LuPSMA therapy and when the patient is no longer clinically benefiting, the patient's health care team will determine the next appropriate treatment options based on disease volume and phenotype, patient age, co-morbidities and consultation with the patient.

A full summary of available evidence and evidence yet-to-be published has been provided on the pages 3-9 of this submission for the Committee's information.

PCFA will provide its full support to patients, their families, and their health care teams throughout this treatment process and in the days, weeks, and years afterwards. We plan to do this via the ongoing expansion of our Prostate Cancer Specialist Nursing and Telenursing Service and other specialised supportive care programs, working jointly with multi-disciplinary teams.

Should you require additional information in support of this submission, please don't hesitate to contact PCFA's Chief Operating Officer, Anne Savage, via email to Anne.Savage@pcfa.org.au or by calling 0417 709 869.

We note with concern that 33,000 Australian men are certain to die over the next 10 years if no action is taken. We respectfully call on MSAC to respond in their favour.

Yours sincerely,

Professor Jeff Dunn AO
Chief Executive Officer
Prostate Cancer Foundation of Australia

Summary of published evidence

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Lu PSMA i&t evidence					
1	Retrospective	Factors affecting overall survival and progression -free survival in patients with metastatic castration resistant prostate cancer received 177Lu PSMA i&t Ogen Bulbul et al Hell J Nucl Med 2020;23(3):229-239	**45 men** with mCRPC treated with 164 cycles Lu PSMA i&t at 6-8 weekly intervals. PSA response rate (>50% decline) was 33%. Median OS and PFS 17.1 months and 7.4 months[2]	10.1967/s002449912201	2020
2.	Retrospective	Treatment Outcome, Toxicity, and Predictive Factors for Radioligand Therapy with ^{177}Lu-PSMA-I&T in Metastatic Castration-resistant Prostate Cancer[3] Heck et al; European Urology Volume 75 Issue 6 June 2019 920-926	Clinical experience with RLT using 177-lutetium–labeled PSMA-I&T in **100 patients** were treated under a compassionate use protocol with 319 cycles (median two cycles, range 1–6). Eligibility criteria were abiraterone or enzalutamide, previous taxane-based chemotherapy or chemoineligibility, and positive PSMA-ligand uptake at positron-emission tomography scan. The **^{177}Lu-PSMA-I&T** was given 6–8 weekly with an activity of 7.4 GBq up to six cycles. Prostate-specific antigen decline of ≥50% was achieved in 38 patients (38%), median clinical progression-free survival (cPFS) was 4.1 mo, and median overall survival (OS) was 12.9 mo. Treatment-emergent hematologic grade 3/4 toxicities were anemia (9%), thrombocytopenia (4%), and neutropenia (6%). Grade 3/4 nonhematologic toxicities were not observed. RLT with ^{177}Lu-PSMA-I&T showed good activity in more than one-third of patients with late-stage mCRPC at low toxicity.	https://www.sciencedirect.com/science/article/abs/pii/S030228381830873X?via%3Dihub	June 2019

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	Retrospective	177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy Richard P. Baum*1, Harshad R. Kulkarni*1, Christiane Schuchardt1, Aviral Singh1, Martina Wirtz2, Stefan Wiessalla1, Margret Schottelius2, Dirk Mueller1, Ingo Klette1, and Hans-Jürgen Wester. The journal of nuclear medicine. Vol. 57 No.7 July 2016[1]	56 mCRPC patients underwent PSMA radioligand therapy (RLT) with 177Lu-PSMA. 68Ga-PSMA PET/CT was used for patient selection and follow-up after PSMA RLT. Dosimetry was performed in 30 patients. Results: 177Lu-PSMA demonstrated high absorbed tumor doses (median, 3.3 mGy/MBq). All patients tolerated the therapy without any acute adverse effectsThe severity of pain was significantly reduced in 2 of 6 patients (33.3%). A decrease in prostate-specific antigen levels was noted in 45 of 56 patients (80.4%).The median progression-free survival was 13.7 mo, and the median overall survival was not reached during follow-up for 28 mo.	10.2967/jnumed.115.168443	2016
4.	Retrospective	Clinical Outcomes of ^{177} Lu-PSMA Radioligand Therapy in Earlier and Later Phases of Metastatic Castration-Resistant Prostate Cancer Grouped by Previous Taxane Chemotherapy. Thomas W Barber , Aviral Singh , Harshad R Kulkarni , Karin Niepsch , Baki Billah , Richard P Baum · J Nucl Med2019 Jul;60(7):955-962[4]	**167 patients** with mCRPC who underwent ^{177}Lu-PRLT. Clinical outcome for taxan-pre-treated and taxane-naïve patients was assessed by overall survival (OS), radiographic progression-free survival, and prostate-specific antigen (PSA) response rate. Of the 167 patients treated with ^{177}Lu-PRLT, 83 were Taxane-pretreated and 84 were Taxane-naïve. Median OS was 10.7 mo for T-pretreated patients and 27.1 mo for T-naïve patients. Median radiographic progression-free survival was 6.0 mo for T-pretreated patients and 8.8 mo for T-naïve patients. PSA response assessment was evaluable in 132 patients and seen in 25 of 62 (40%) Taxane-pretreated patients and 40 of 70 (57%) Taxane-naïve patients.	10.2967/jnumed.118.216820	2019

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	Meta-analysis of Lu PSMA i&t and Lu PSMA-617	Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review and meta-analysis. R J S Calopedos , V Chalasani , R Asher , L Emmett, H Woo. Prostate Cancer Prostatic Dis 2017 Sep;20(3):352-360[5]	A systematic review was conducted using electronic databases up to December 2016. The main outcome of interest was anti-tumour biochemical response of ^{177}Lu-PSMA, analysing two measures: 'any PSA decline' and '>50% decline' from baseline. Abstracts and proportions were summarised by chemical type (^{177}Lu-J591/DKZ/I&T). The pooled proportion of patients with any PSA decline was 68% (95% confidence interval (CI): 61-74). The pooled proportion of patients with >50% PSA decline was 37% (95% CI: 22-52).	10.1038/pcan.2017.23	2017
Lu PSMA-617 Evidence					
5.	Randomised Phase III	Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. Oliver Sartor , Johann de Bono , Bernd J Krause , VISION Investigators.[6] N Engl J Med. 2021 Jun 23. doi: 10.1056/NEJMoa2107322. PMID: 34161051	International, open-label, phase 3 trial evaluating ^{177}Lu-PSMA-617 in patients with mCRPC previously treated with a positive (^{68}Ga)-labeled PSMA-11 PET scans. Patients were randomly assigned in a 2:1 ratio to **^{177}Lu-PSMA-617** (7.4 GBq every 6 weeks for four to six cycles) or standard care. Primary end points were imaging-based progression-free survival and 831 patients randomized. ^{177}Lu-PSMA-617 significantly prolonged progression-free survival (median, 8.7 vs. 3.4 months; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; P<0.001).	https://pubmed.ncbi.nlm.nih.gov/34161051/	June 2021

Summary of published evidence

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
	Randomised Phase II	[^{177} Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial Michael S Hofman , Louise Emmett , Ian D Davis Lancet 2021 Feb [7] 27;397(10276):797-804.	Multicentre, unblinded, randomised phase 2 trial at 11 centres in Australia. Men with mCRPC for whom cabazitaxel was considered the standard treatment. Men underwent [^{68}Ga]Ga-PSMA-11 and 2-flourine-18[^{18}F]FDG) PET with PET eligibility criteria for the trial PSMA-positive disease, and no discordant FDG-sites. 160 men randomised(1:1) to [^{177}Lu]Lu-PSMA-617 (6·0-8·5 GBq intravenously every 6 weeks for up to six cycles) or cabazitaxel (20 mg/m^2) Primary endpoint was prostate-specific antigen (PSA) response. PSA responses were more frequent among men in the **[^{177}Lu]Lu-PSMA-617** group than in the cabazitaxel group (65 vs 37 PSA responses; 66% vs 37% by intention to treat; difference 29% p=0·0016). Grade 3-4 adverse events occurred in 33% with [^{177}Lu]Lu-PSMA-617 53% with cabazitaxel. Lu-PSMA-617 is a new effective class of therapy and a potential alternative to cabazitaxel.	NCT03392428. https://pubmed.ncbi.nlm.nih.gov/33581798/	February 2021
	Prospective single centre	[^{177} Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study [8].Michael S Hofman John Violet , Shahneen Sandhu Lancet Oncol 2018 Jun;19(6):825-833	Single-arm, single-centre, phase 2 trial, men with progressive mCRPC. Patients underwent screening with PSMA and FDG-PET/CT to confirm high PSMA-expression. Eligible patients received up to four cycles of intravenous **[^{177}Lu]-PSMA-617**, at six weekly intervals. The primary endpoint was PSA response. 43 men were screened to identify 30 patients eligible for treatment. The mean administered radioactivity was 7·5 GBq per cycle. 17 (57%) of 30 patients (95% CI 37-75) achieved a PSA decline of 50% or more. No treatment-related deaths. The most common toxic effects were grade 1 dry mouth 87%, grade 1 transient nausea 50%, and G1-2 fatigue in(50%). Objective response in nodal or visceral disease was reported in 82%).	https://www.ncbi.nlm.nih.gov/pubmed/29752180	Australian New Zealand Clinical Trials Registry, number 12615000912583.

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	Prospective single centre phase I/II	Phase I/II Trial of the Combination of ^{177} Lutetium Prostate specific Membrane Antigen 617 and Idronoxil (NOX66) in Men with End-stage Metastatic Castration-resistant Prostate Cancer (LuPIN)[9] Megan Crumbaker Sarennya Pathmanandavel, Louise Emmett Eur Urol Oncol 2020 Aug 2; S2588-9311(20)30093-6	32 men with progressive mCRPC previously treated with taxane-based chemotherapy (91% treated with both docetaxel and cabazitaxel) and abiraterone. Screening with ^{68}Ga PSMA and ^{18}FDG PET. Men received up to six cycles of **LuPSMA-617** (7.5 GBq) on day 1, with escalating doses of NOX66 on days 1-10 of a 6-wk cycle. Common AEs included xerostomia, fatigue, and anaemia. Anal irritation attributable to NOX66 occurred in 28%. PSA responses: 91% (29/32) had any PSA response and 62.5% (20/32) had a PSA fall of >50% (95% CI 45-77). Median PSA progression-free survival 6.1 mo (95% CI 2.8-9.2) and median overall survival 17.1 mo (95% CI 6.5-27.1).	https://www.ncbi.nlm.nih.gov/pubmed/32758400	

Summary of yet-to-be published evidence

	Type of study design	Title of research	Short description ofresearch	Website link to research	Date
1.	Randomised phase 3 treatment trial	SPLASH trial A Phase 3, Open-Label, Randomized Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using PSMA **[Lu-177]-i&t** Therapy After Second-line Hormonal Treatment.	The primary objective of the study is to determine the efficacy of [Lu-177]-PNT2002 ([Lu-177]-PSMA-I&T) versus abiraterone or enzalutamide in delaying radiographic progression in patients with mCRPC. The study will randomize treatment in 390 patients in a 2:1 ratio to receive either [Lu-177]-PSMA i&t (Arm A), or enzalutamide or abiraterone (Arm B). Patients in Arm B who experience radiographic progression per central review and meet protocol defined eligibility, may crossover to receive [Lu-177]-PNT2002. All patients will be followed in long-term follow-up for at least 5 years from the first therapeutic dose, death, or loss to follow up (Part 3).	https://www.clinicaltrials.gov/ct2/show/NCT04647526	Commenced February 2021 Expected to finalise results 2029.
2.	Prospective Phase II Randomised trial	ENZA-p trial protocol: a randomized phase II trial using prostate-specific membrane antigen as a therapeutic target and prognostic indicator in men with metastatic castration-resistant prostate cancer treated with enzalutamide (ANZUP 1901)[10] Louise Emmett Shalini Subramaniam , Ian D Davis BJU Int 2021 May 24.doi: 10.1111/bju.15491	ENZA-p (ANZUP 1901) is an open-label, randomized, two-arm, multicentre, phase 2 trial. Participants are randomly assigned (1:1) to treatment with enzalutamide 160 mg daily alone or enzalutamide plus ^{177} Lu-PSMA-617 7.5 GBq on Days 15 and 57. Two additional **^{177} Lu-PSMA-617** doses are allowed, informed by Day-92 Gallium-68 (^{68} Ga)-PSMA positron emission tomography (PET; up to four doses in total). The primary endpoint is prostate-specific antigen (PSA) progression-free survival (PFS). Other major endpoints include radiological PFS, PSA response rate, overall survival, health-related quality of life, adverse events and cost-effectiveness.	https://www.ncbi.nlm.nih.gov/pubmed/34028967	Commenced August 2020

Summary of yet-to-be published evidence

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3.	Prospective Phase II randomised trial	UpFrontPSMA: a randomized phase 2 study of sequential ^{177} Lu-PSMA-617 and docetaxel vs docetaxel in metastatic hormone-naïve prostate cancer (clinical trial protocol)[11] Nattakorn Dhiantravan, Louise Emmett , Michael S Hofman , Arun A Azad BJU Int 2021 Mar 7.doi: 10.1111/bju.15384	UpFront PSMA is an open-label, randomized, multicentre, phase 2 trial, recruiting 140 patients at 12 Australian centres. Key eligibility criteria include: prostate cancer with a histological diagnosis within 12 weeks of screening commencement; PSA >10 ng/mL at diagnosis; ≤4 weeks on ADT; high-volume prostate-specific membrane antigen (PSMA)-avid disease with a maximum standardized uptake value >15; Patients are randomized 1:1 to experimental treatment, Arm A (**^{177} Lu-PSMA-617** 7.5GBq q6w × 2 cycles followed by docetaxel 75 mg/m^2 q3w × 6 cycles), or standard-of-care treatment, Arm B (docetaxel 75 mg/m^2 q3w × 6 cycles).	(NCT04343885)	Commenced April 2020

^{177}LuPSMA i&t for metastatic castrate resistant prostate cancer: The case for support

Recommendation

Medical Services Advisory Committee support for Medicare Benefit Schedule listing of ^{177}Lutetium PSMA i&t for metastatic castrate resistant prostate cancer, providing equitable access to men around Australia with symptomatic metastatic prostate cancer to a new class of drugs that improve survival and quality of life and delay treatment progression.

Key Points

- LuPSMA therapy is significantly superior to second line chemotherapy for treatment response, pain control and quality of life in men with metastatic prostate cancer in an Australia wide randomised trial (Lancet publication February 2021).
- LuPSMA therapy improves overall survival in men with metastatic prostate cancer (VISION trial June 2021).
- Evidence for LuPSMA therapy is all using a patented ligand (PSMA 617) which is unlikely to be registered in Australia within the next 5 years (cost and market causes). LuPSMA i&t is an off-patent ligand used for clinical purposes in Australia with equivocal efficacy that does not have high level evidence to submit for funding, and no pharma support.
- There is currently marked inequity of access to LuPSMA therapy across Australia for men with symptomatic metastatic prostate cancer (available in Victoria (philanthropic funding) – not elsewhere). This is leading Australian men to pay up to $60,000 to access LuPSMA therapy privately, causing financial toxicity and stress in a highly vulnerable population.
- Around 3,300 men die from prostate cancer every year in Australia with 80% likely to gain extra benefit from this life prolonging, well tolerated additional treatment option.
- LuPSMA i&t is likely a very cost-effective solution to treatment of metastatic prostate cancer – while providing immediate access to men with symptomatic disease.

Background

Metastatic prostate cancer is a lethal condition for which there remain limited treatment options. More than 3,300 men die from prostate cancer every year, many of whom would benefit with improved quality of life and prolonged survival from a new class of treatment (LuPSMA therapy) that involves targeted radiation directly to the cancer cell, avoiding other tissues and minimising side effects.

Targeting of the PSMA receptor to both diagnose and treat prostate cancer arose from high quality radiochemistry and molecular biological work in Germany around 10 years ago. A small molecule peptide was developed that bound tightly to the PSMA receptor

and that linked to multiple radionuclide agents (68Ga, 177 Lu, 18 F). PSMA targeted PET imaging is now in the recommended guidelines for management of men with biochemical recurrence of prostate cancer following radical prostatectomy with evidence demonstrating both high diagnostic accuracy, changes in management, and improved patient outcomes.

^{177}LuPSMA therapy trials followed shortly after the PSMA targeted imaging trials. This targeted treatment has few significant side effects, and significantly reduced pain levels in the majority of men. An Australian multi-site randomised prospective trial comparing LuPSMA 617 to cabazitaxel chemotherapy in mCRPC post docetaxel (TheraP) was developed and run by ANZUP and funded by PCFA, ANSTO, AAA and others. It demonstrated a higher PSA response rate with ^{177}LuPSMA 617 vs cabazitaxel chemotherapy (66% vs 37%) with an improvement in PSA progression free survival, radiographic progression free survival and quality of life parameters in the LuPSMA 617 arm compared to chemotherapy.

Further, it demonstrated that the treatment was safe, and well tolerated. The multinational VISION trial has shown an overall survival benefit for ^{177}LuPSMA 617 vs best supportive care. The TheraP and VISION trials have jointly established LuPSMA 617 as a new standard of care in metastatic prostate cancer.

PSMA Ligands

The therapy trials in Australia have been using the PSMA 617 ligand labelled chemically to Lutetium-177 as the therapeutic beta emitter. PSMA 617 ligand is owned by Novartis and has been the subject of most prospective clinical trials to date, including TheraP and VISION. It is expected that Novartis will apply for registration for PSMA 617 in Europe and the USA after the results from VISION are released. Based on the costings of ^{177}Lu DOTATATE (Lutathera) also owned by Novartis, the cost of this will be around $45,000/dose. Novartis have no current plans to register PSMA 617 in Australia.

PSMA Imaging and Therapy (PSMA i&t) is an almost identical peptide to PSMA 617 – with slightly different chemistry linking the PSMA peptide to the Beta emitter radionuclide ^{177}Lutetium. There are retrospective studies published in Germany using PSMA I&T for the treatment of men with end stage metastatic castrate resistant prostate cancer. ^{177}LuPSMA i&t is used for clinical compassionate use in Australia to treat men with end-stage symptomatic prostate cancer who do not qualify for trials.

While PSMA 617 is under IP, this is not the case for PSMA i&t, which is available to buy from chemical company ABX. This allows cost effective manufacture and ready availability of PSMA i&t.

Evidence

^{177}LuPSMA is currently being used clinically in Australia with equivalent effect to that achieved with LuPSMA 617. Due to the lack of IP on PSMA i&t, there is no pharma support to develop evidence. The advantage of this to Australia is that cost of

production and delivery is significantly lower, with treatment currently being delivered for $5000 per dose, or $30,000 for a six-dose course of treatment.

The evidence is clear that MBS listing of ^{177}LuPSMA i&t will improve outcomes for eligible men with metastatic prostate cancer and provide equitable access across Australia.

This approach is feasible and achievable because of the strong multi-disciplinary clinical trial network established across Australia as part of the TheraP and other trials.

Currently, there are 13 centres across Australia capable of manufacturing and delivering ^{177}LuPSMA i&t. A key aim of this initiative would be to develop capability in more rural and regional centres to ensure ongoing equitable access to treatment for Australian men irrespective of geographical location.

This achieves the multiple aims of:

1. Providing immediate equitable access to treatment for a vulnerable group.
2. Education and facilitation of this new technology across Australia to allow safe administration and widespread high-quality care.

Summary

Australia has been leading the way in undertaking high quality clinical trials providing evidence for the use of ^{177}LuPSMA therapy in men with metastatic prostate cancer. These have demonstrated impressive efficacy and safety of this new class of treatment – particularly improving pain control and quality of life. Developing evidence for ^{177}LuPSMA i&t through MBS listing will help to further improve clinical efficacy, safety and cost effectiveness while also giving equitable access around Australia to men with symptomatic metastatic prostate cancer.