[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

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Summary

Background Progressive metastatic castration-resistant prostate cancer is a highly lethal disorder and new effective therapeutic agents that improve patient outcomes are urgently needed. Lutetium-177 [^{177}Lu]-PSMA-617, a radiolabelled small molecule, binds with high affinity to prostate-specific membrane antigen (PSMA) enabling beta particle therapy targeted to metastatic castration-resistant prostate cancer. We aimed to investigate the safety, efficacy, and effect on quality of life of [^{177}Lu]-PSMA-617 in men with metastatic castration-resistant prostate cancer who progressed after standard treatments.

Methods In this single-arm, single-centre, phase 2 trial, we recruited men (aged 18 years and older) with metastatic castration-resistant prostate cancer and progressive disease after standard treatments, including taxane-based chemotherapy and second-generation anti-androgens, from the Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. Patients underwent a screening PSMA and FDG-PET/CT to confirm high PSMA-expression. Eligible patients had progressive disease defined by imaging (according to Response Evaluation Criteria In Solid Tumours [RECIST] or bone scan) or new pain in an area of radiographically evident disease, and were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or lower. Eligible patients received up to four cycles of intravenous [^{177}Lu]-PSMA-617, at six weekly intervals. The primary endpoint was PSA response according to Prostate Cancer Clinical Trial Working Group criteria defined as a greater than 50% PSA decline from baseline and toxicity according to CTCAE. Additional primary endpoints were imaging responses (as measured by bone scan, CT, PSMA, and FDG PET/CT) and quality of life (assessed with the EORTC-Q30 and Brief Pain Inventory-Short Form questionnaires), all measured up to 3 months post completion of treatment. This trial is registered with the Australian New Zealand Clinical Trials Registry, number 12615000912583.

Findings Between Aug 26, 2015, and Dec 8, 2016, 43 men were screened to identify 30 patients eligible for treatment. 26 (87%) had received at least one line of previous chemotherapy (80% docetaxel and 47% cabazitaxel) and 25 (83%) received prior abiraterone acetate, enzalutamide, or both. 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. There were no treatment-related deaths. The most common toxic effects related to [^{177}Lu]-PSMA-617 were grade 1 dry mouth recorded in 26 (87%) patients, grade 1 and 2 transient nausea in 15 (50%), and G1–2 fatigue in 15 (50%). Grade 3 or 4 thrombocytopenia possibly attributed to [^{177}Lu]-PSMA-617 occurred in four (13%) patients. Objective response in nodal or visceral disease was reported in 14 (82%) of 17 patients with measurable disease. Clinically meaningful improvements in pain severity and interference scores were recorded at all timepoints. 11 (37%) patients experienced a ten point or more improvement in global health score by the second cycle of treatment.

Interpretation Our findings show that radionuclide treatment with [^{177}Lu]-PSMA-617 has high response rates, low toxic effects, and reduction of pain in men with metastatic castration-resistant prostate cancer who have progressed after conventional treatments. This evidence supports the need for randomised controlled trials to further assess efficacy compared with current standards of care.

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Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of death from cancer worldwide.[1] Since the approval of docetaxel as first-line chemotherapy in 2004, several new life-prolonging systemic treatments have been introduced for metastatic, castration-resistant prostate cancer including abiraterone, enzalutamide, cabazitaxel, and radium-223.[2–5] However, all patients subsequently progress and there is an urgent need for effective therapeutic agents that can improve patient outcome including ameliorating disease-related symptoms and improving quality of life in the terminal stages of disease.[6]

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published in English up to the commencement of our trial design in July, 2015, with the search terms "Lu-177-PSMA", "Lutetium", "radioligand treatment", and "PSMA". We also reviewed key journals and congress abstracts in the fields of nuclear medicine and urological oncology. We found small retrospective case reports or series suggesting high activity in patients given treatment on a compassionate basis after failing conventional treatments. No prospective data for radionuclide treatment with [^{177}Lu]-labelled PSMA were available. Therefore, we designed a phase 2 prospective trial to investigate the efficacy, safety, and effect on quality of life of this treatment. Several retrospective studies have been published since, but high-quality, prospectively collected data on outcomes and safety are still unavailable.

Added value of this study

This is the first prospective phase 2 study to provide compelling evidence that radionuclide treatment with [^{177}Lu]-PSMA-617 has promising anti-tumour activity, a favourable toxicity profile, and improves quality of life in men with metastatic castration-resistant prostate cancer who have progressed after standard treatments including chemotherapy and second-generation anti-androgens.

Implications of all the available evidence

Collective data from this phase 2 study and several retrospective series, provides proof of concept that [^{177}Lu]-PSMA-617 has promising anti-tumour activity, low toxicity, and improves quality of life in patients with metastatic castration-resistant prostate cancer who have not responded to most conventional treatments and exhibit high PSMA expression on PSMA PET/CT. In view of the almost ubiquitous nature of PSMA expression in most metastatic castration-resistant prostate cancers, [^{177}Lu]-PSMA-617 offers a potential additional treatment option for men with metastatic castration-resistant prostate cancer. Studies comparing [^{177}Lu]-PSMA-617 to existing standards of care, or in combination with other treatments are now required. The evidence from this study formed the basis of a recently commenced Australian multicentre randomised phase 2 trial comparing [^{177}Lu]-PSMA-617 to cabazitaxel (NCT03392428), and several early phase trials combining [^{177}Lu]-PSMA-617 with other new treatments.

Lutetium-177 [^{177}Lu]-PSMA-617 (LuPSMA), is a small molecule inhibitor that binds with high affinity to prostate-specific membrane antigen (PSMA). The short-range 1 mm path length of the beta-particle emitted by ^{177}Lu enables effective delivery of radiation to tumours while minimising damage to surrounding normal tissues. PSMA, also known as folate hydrolase I, is a transmembrane glycoprotein overexpressed 100 to 1000 times in prostate cancers, with expression further increased in metastatic and castration-resistant carcinomas.[7] LuPSMA is a variant of [^{68}Ga]-PSMA-11 used for PET imaging that has been optimised for therapeutic use. LuPSMA was developed by the German Cancer Research Center (DKFZ, Deutsches Krebsforschungszentrum) in collaboration with University Hospital Heidelberg.[8] LuPSMA is distinct from antibodies such as J591[9] showing more rapid plasma clearance and higher affinity binding to PSMA. Several retrospective studies[10–17] of LuPSMA have reported favourable biochemical and imaging responses as well as significant pain relief in the patients treated.

See Online for appendix

In this prospective, phase 2 trial, we aimed to investigate the efficacy, safety, and effect on quality of life of LuPSMA in men with progressive metastatic castration-resistant prostate cancer who had failed standard therapies.

Methods

Study design and participants

For this investigator-initiated, single-institution phase 2 trial, eligibility criteria included pathologically (adenocarcinoma) confirmed metastatic castration-resistant prostate cancer with progressive disease after standard treatments, including taxane-based chemotherapy and second-generation anti-androgen treatment (abiraterone, enzalutamide, or both), unless patients were medically unsuitable for or refused these standard treatments. Progressive disease for trial entry was defined by imaging progression (according to Response Evaluation Criteria In Solid Tumours [RECIST] or bone scan) or new pain in an area of radiographically evident disease. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status[18] score of 2 or lower and a life expectancy greater than 12 weeks. Patients were not eligible if they had clinically significant impaired bone marrow, liver, or kidney function defined by glomerular filtration rate (GFR) lower than 40 mL/min, platelet count lower than 75×10^9/L, neutrophil count lower than $1{\cdot}5\times10^9$/L, haemoglobin concentration lower than 90 g/L, or albumin concentration of 25 g/L or lower. Patients were also excluded if they were using concomitant nephrotoxic drugs, had recent radiotherapy (within 6 weeks) to a sole site of assessable disease, or uncontrolled intercurrent illness (appendix p 1).

All patients underwent imaging with [^{68}Ga]-PSMA-11 as part of the screening assessments to confirm high PSMA expression, which was defined as a site of metastatic disease with intensity significantly greater than normal liver (standardised uptake value $[SUV]_{max}$ of tumour involvement at least 1·5 times SUV of liver). Additionally, patients underwent ^{18}F-fluorodeoxyglucose (FDG) PET/CT and were excluded if sites of FDG-positive disease without high PSMA expression were identified.

The study protocol was approved by the institutional ethics board (appendix p 15), and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and all patients gave written informed consent before study entry.

Procedures

All patients underwent the following investigations within 8 weeks of treatment: [^{68}Ga]-PSMA-11 PET/CT; ^{18}F-FDG PET/CT; radionuclide bone scan; contrast-enhanced CT of the chest, abdomen, and pelvis; ^{51}Cr-EDTA GFR; thyroid function; and testosterone. Within 2 weeks before treatment, full blood count, urea and electrolytes, liver function tests, lactate dehydrogenase, calcium, and PSA concentrations were measured.

DKFZ-PSMA-617 precursor (ABX, Radeberg, Germany) was radiolabelled to no-carrier-added lutetium-177 chloride ([^{177}Lu]-Cl_3; Australian Nuclear Science and Technology Organisation [ANSTO], Sydney, Australia) in our hospital radiopharmacy according to manufacturer's instructions. 100 µg of the precursor was diluted with 500 µl of 0·04 M sodium acetate buffer pH 5·0 (Merck) containing 1 mg diethylenetriaminepentaacetic acid (DTPA), and added to 10 GBq of [^{177}Lu]-Cl_3 in 0·05 mol/L HCl. 25 µl of sterile 20% L-ascorbic acid was added and the solution heated to 95°C for 15 min with intermittent gentle agitation. After cooling down of the reaction, the volume was adjusted to 2 mL using normal saline and filtered. Radiochemical purity was established by thin layer chromatography.

LuPSMA was administered by slow intravenous injection over 2–10 min. Patients were encouraged to be well hydrated by consuming 1·5 L of oral fluids on the day of LuPSMA administration. No specific measures to minimise dry mouth were used. Radiation emission was measured with a hand-held gamma counter and patients were discharged when below 9 µSv per h at 2 m as per local regulations; this generally occurred within 2–4 h and after first void. After the first cycle, quantitative single photon emission CT/CT (qSPECT/CT) scans were acquired at 4, 24, and 96 h from the vertex to the thighs using a previously validated technique[19] enabling quantitation of LuPSMA retention within tumour and normal tissues. For subsequent cycles, a single time-point 24 h qSPECT/CT was acquired.

Safety reviews and repeated blood tests (full blood count, urea and electrolytes, liver function tests and PSA) were undertaken at 2 and 4 weeks after each cycle. Additionally, all patients were reviewed 24 h after LuPSMA administration. In the event of significant toxic effects, blood tests were repeated weekly until resolution. Adverse events were graded and causality assigned according to Common Terminology Criteria for Adverse Events (version 4.03) at each clinical review up to the 12-week follow-up visit after the last administration of LuPSMA. Beyond the 12-week follow-up visit, only adverse events deemed to be related to treatment were reported. Participants completed health-related quality-of-life questionnaires within 7 days before each cycle, and at the 12-week follow-up visit. At this time, ^{51}Cr-EDTA GFR, [^{68}Ga]-PSMA-11, and ^{18}F-FDG PET/CT, bone-scan, and CT chest-abdomen-pelvis were repeated. Thereafter, patients were followed up with data collection including PSA, further treatments, and date of death.

Up to four cycles of treatment were administered at 6 weekly intervals. The administered radioactivity was adjusted from 6 GBq according to tumour burden, patient weight and renal function, adapted from our [^{177}Lu]-DOTATATE experience.[20] Activity was increased by 1 GBq if there were more than 20 sites of disease, or decreased by 1 GBq if fewer than ten sites. Activity was increased by 0·5 GBq per factor if weight was more than 90 kg or GFR was more than 90 mL per min, and decreased by 0·5 GBq if weight was lower than 70 kg or GFR was less than 60 mL per min. Standard supportive care including blood transfusions, bisphosphonates, or palliative radiotherapy were permitted as clinically indicated. Patients were not permitted to have concurrent chemotherapy but were allowed to continue on second-generation anti-androgens. In patients who responded to LuPSMA, but subsequently progressed after trial completion, further treatment with LuPSMA using a compassionate access programme was permitted provided eligibility criteria were still met.

Treatment omissions for toxic effect management and exceptional responses were prespecified in the protocol. If retreatment criteria with regards to adequate organ function (haemoglobin concentration ≥90 g/L, platelet count $\geq 75\,000 \times 10^9$/L, neutrophil count $\geq 1{\cdot}5 \times 10^9$/L) were not met, bloods were repeated weekly and treatment delayed until recovery to acceptable levels. If post-treatment imaging showed no or minimal uptake of radionuclide at sites of tumour, indicative of an exceptional response to previous cycles, no further cycles were administered. Treatment was also stopped in patients who were deemed to be no longer clinically benefiting after discussion within a multidisciplinary panel.

Outcomes

The primary endpoint of the trial was PSA response rate according to Prostate Cancer Clinical Trials Working Group 2 (PCWG)[21] criteria defined as a 50% or more PSA decline from baseline with confirmation 3–4 weeks apart and toxicity according to CTCAE (version 4.03). Additional primary endpoints were radiological response up to 3 months after completion of therapy assessed by CT (modified Response Evaluation Criteria in Solid Tumors [mRECIST 1.1], according to recommendations by PCWG[21]) for soft tissue response, bone scan, PSMA, and FDG PET/CT. PSMA PET/CT and FDG PET/CT responses were evaluated using Hicks qualitative criteria.[22] Patient-reported quality-of-life evaluations included the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)[23] and

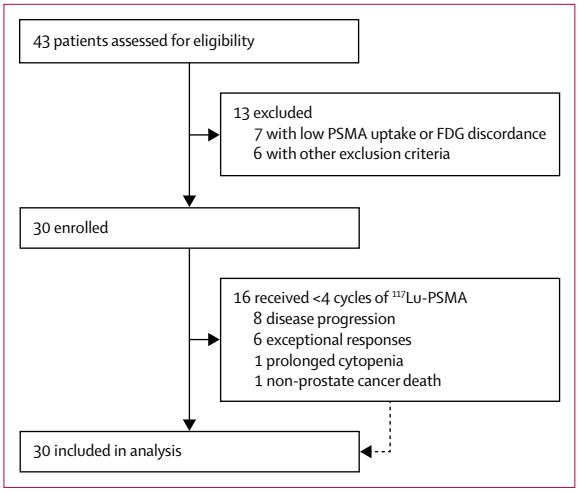

Figure 1: **Trial profile**
FDG=^{18}F-fluorodeoxyglucose. PSMA=prostate-specific membrane antigen.

Brief Pain Inventory (BPI).[24] Primary endpoints were assessed by the study investigators and not centrally reviewed. Secondary endpoints were overall survival and progression-free survival defined by time to PSA progression as per PCWG2; both endpoints measured from the date of patient enrolment. A further secondary objective was the dosimetry analysis from serial quantitative SPECT/CT enabling estimation of dose to tumours as well as normal tissues; this will be reported separately.

Statistical analysis

The selected sample size of 30 patients was pragmatic, as the study aimed to be a descriptive, proof-of-concept study. This sample size was prespecified and based on available departmental resources and supply agreement for ^{177}Lu. A two-sided exact binomial 95% CI was calculated for the PSA response. Percentage change in PSA concentrations was recorded and represented in a waterfall plot. Imaging outcomes are presented as absolute numbers of patients and percentage of the cohort. All patients who had received at least one dose of LuPSMA were included in the primary and secondary outcome analyses. The proportions of patients who had any grade of toxic effect were recorded. We analysed time-to-event outcomes including PSA progression-free survival and overall survival were analysed using Kaplan-Meier statistics. We used linear mixed models to assess the EORTC-QLQ-C30 and brief pain inventory endpoints; no imputation for missing values was used. We estimated mean differences from baseline and 95% CIs from the linear mixed models contrasts. The proportion of patients with at least a ten point improvement[25] in global health score after the first cycle of treatment was recorded. Patients were included in the pain analysis if this was present at baseline and at least one post-baseline datapoint was available. Statistical analyses were done in R Statistics (version 3.4.0) with ggplot2 package. We collected and managed study data using REDCap electronic data capture tools.[26]

This trial is registered with the Australian New Zealand Clinical Trials Registry, number 12615000912583.

	All patients (n=30)
Age (years)	71 (67–75)
Time since diagnosis of prostate cancer (years)	9 (5–13)
Gleason score at diagnosis	8 (7–9)
Alkaline phosphatase (U/L)	117·5 (80·8–184·5)
Haemoglobin (g/L)	118 (103–127)
Lactate dehydrogenase (U/L)*	247 (209–304)
PSA (µg/L)	189·8 (80·1–372·0)
PSA doubling time (µg/L per month)	2·4 (1·4–3·5)
ECOG performance status	
0	11 (37%)
1	14 (47%)
2	5 (17%)
Number of previous chemotherapy regimens	
1	12 (40%)
2	12 (40%)
≥3	2 (7%)
Previous treatments	
Abiraterone or enzalutamide or both	25 (83%)
Docetaxel	24 (80%)
Cabazitaxel	14 (47%)
Palliative-intent radiotherapy	14 (47%)
Bisphosphonate or denosumab	22 (73%)
Sites of disease on PSMA-PET	
Bone	29 (97%)
Nodal	24 (80%)
Visceral†	4 (13%)
Extent of disease on PSMA-PET	
≤20 metastases	2 (7%)
>20 metastases	28 (93%)
On opiate analgesia for pain	15 (50%)
Pain at baseline (BPI score‡)	
No pain (<1)	5 (17%)
Mild (1–4)	18 (60%)
Moderate to severe (5–10)	7 (23%)

Data are median (IQR) or n (%). PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. PSMA=prostate-specific membrane antigen. BPI=Brief Pain Inventory. *Data missing for four patients. †Visceral includes adrenal, lung, liver, and spleen. ‡As per Chow et al.[27]

Table 1: **Baseline characteristics**

Role of the funding source

There was no direct funding source for the study. ^{177}Lu (no carrier added) was supplied by the Australian Nuclear Science and Technology Organisation (ANSTO, Sydney, Australia) and PSMA-617 by Advanced Biochemical Compounds (ABX, Radeberg, Germany). Neither had any role in study design, data collection, data analysis and interpretation, or writing of the report. The

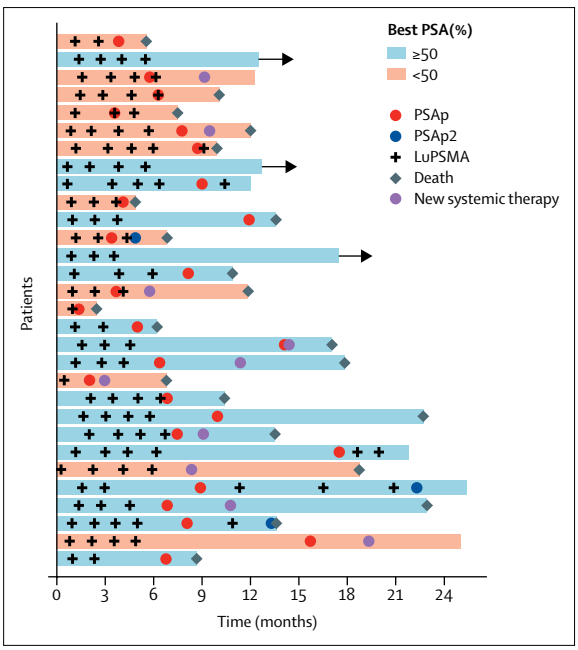

Figure 2: **Patient events**
Arrow indicates patients without PSA progression up to cut-off date. PSA=prostate-specific antigen. LuPSMA=lutetium-prostate-specific membrane antigen. PSAp2=second-PSA progression in patients with initial response who progressed after trial completion and responded to further LuPSMA.

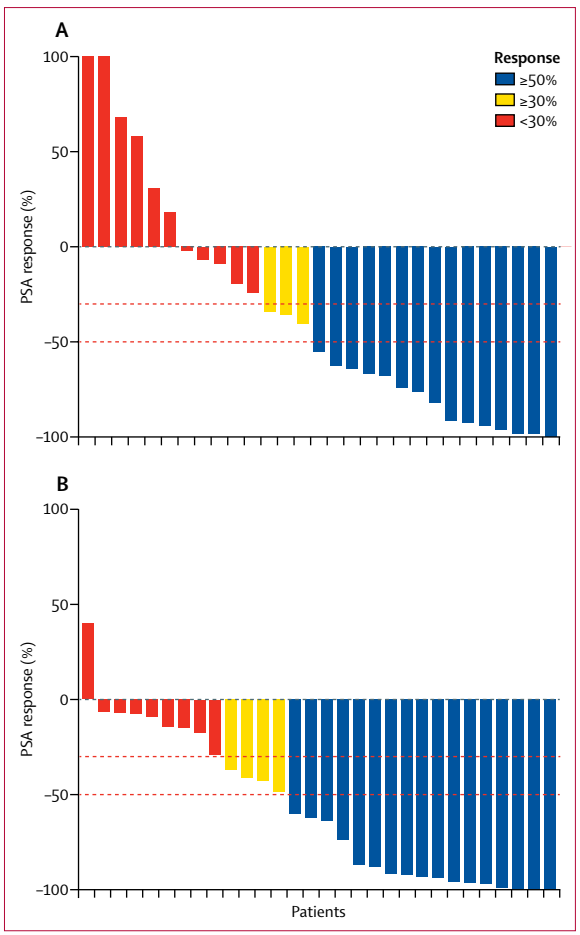

Figure 3: **(A) PSA response after 12 weeks* and (B) best PSA response from baseline**
Two dashed lines represent PSA response greater than 30 and 50%. PSA=prostate-specific antigen. *One patient deceased by 12 weeks (non-prostate related).

study was sponsored by the Peter MacCallum Cancer Centre (Melbourne, Australia). All authors had full access to all of the data. The corresponding author takes final responsibility for the analysis and decision to submit for publication.

Results

Between Aug 26, 2015, and Dec 8, 2016, 43 patients were screened to identify 30 patients who met the eligibility criteria (figure 1). The first LuPSMA treatment was administered on Oct 22, 2015, and the last cycle administered on May 18, 2017. The data cutoff for follow-up was Nov 9, 2017. Seven (16%) patients were excluded as PET/CT showed either low PSMA-avidity or FDG-discordant disease (appendix p 1). Baseline characteristics of the cohort are summarised in table 1 and individual patient data are in the appendix (p 2). 26 (87%) patients had received previous chemotherapy, 14 (47%) had received second-line cabazitaxel, and 25 (83%) patients prior enzalutamide or abiraterone.

All 30 patients received cycle 1 of LuPSMA, and 28 (93%), 24 (80%), and 14 (47%) patients received cycles two, three, and four, respectively. The reasons for not completing all four cycles were disease progression in eight (27%) patients, exceptional response in six (20%), prolonged cytopenia in one (3%), and non-prostate-related death in one (3%). The mean administered radioactivity was 7·5 GBq per cycle (range 4·4–8·7, SD 1·0; appendix p 3). The median time between treatment cycles was 6·1 weeks (range 5·3–12·1). We created a swimmers plot to visualise individual events and outcomes (figure 2). The median follow-up was 25·0 months (IQR 12·7–25·2).

The primary endpoint of PSA decline of 50% or more was achieved in 17 (57%) patients (95% CI 37–75). 21 (70%) patients (95% CI 51–85) achieved a PSA decline of at least 30%, 13 (43%) patients (20–56) of at least 80%, and six (20%) patients (8–39) of 96% or higher. Notably, 29 (97%) of 30 patients experienced a PSA decline. Figure 3 shows waterfall plots for percentage change in PSA response at 12 weeks and best PSA response, compared with baseline. Two (7%) patients achieved a PSA nadir of 0·2 µg/L or lower from 94 µg/L and 15 µg/L, which have been durable at 530 and 379 days of follow-up.

Table 2 summarises imaging response at 3 months after the last cycle of LuPSMA. Non-progressive disease (complete response, partial response, and stable disease) was seen on [^{68}Ga]-PSMA-11, FDG, and bone scanning in 40%, 37%, and 37% of patients, respectively. 17 (57%) patients had PCWG2 RECIST 1.1 evaluable nodal or visceral target lesions on CT at baseline. 14 (82%) of these

	Bone scintigraphy	Soft-tissue lesions (nodal and visceral;* n=17)	PSMA PET	FDG PET
Complete response	n/a	5 (29%)	3 (10%)	6 (20%)
Partial response	n/a	9 (53%)	9 (30%)	4 (13%)
Stable disease	11 (37%)†	0	0	1 (3%)
Progressive disease	9 (30%)	2 (12%)	8 (27%)	8 (27%)
Not performed (clinical progression or death)	9 (30%)	0	9 (30%)	10 (33%)
Not performed (death from other cause)	1 (3%)	1 (6%)	1 (3%)	1 (3%)

Data are n (%). The FDG PET refers to metabolic responses. PSMA=prostate-specific membrane antigen. *As assessed by Response Evaluation Criteria in Solid Tumors (version 1.1) with Prostate Cancer Clinical Trials Working Group 2 caveats. †Non-progressive disease on bone scintigraphy incudes patients with complete or partial response or stable disease.

Table 2: **Imaging response at 3 months after last cycle of LuPSMA received**

	Grade 1–2	Grade 3	Grade 4	Grade 1–2, attributed to LuPSMA*	Grade 3 attributed to LuPSMA*	Grade 4 attributed to LuPSMA*
Dry mouth	26 (87%)	0	0	26 (87%)	0	0
Lymphocytopenia	12 (40%)	13 (43%)	0	11 (37%)	11 (37%)	0
Thrombocytopenia	12 (40%)	5 (17%)	3 (10%)	8 (27%)	3 (10%)	1 (3%)
Fatigue	16 (53%)	1 (3%)	0	15 (50%)	0	0
Nausea	15 (50%)	0	0	15 (50%)	0	0
Anaemia	7 (23%)	7 (23%)	0	4 (13%)	4 (13%)	0
Neutropenia	12 (40%)	2 (7%)	0	8 (27%)	2 (7%)	0
Pain	8 (27%)	3 (10%)	0	5 (17%)	1 (3%)	0
Vomiting	10 (33%)	0	0	10 (33%)	0	0
Anorexia	8 (27%)	0	0	7 (23%)	0	0
Dry eyes	5 (17%)	0	0	5 (17%)	0	0
Weight loss	3 (10%)	0	0	3 (10%)	0	0
Disseminated intravascular coagulation	0	1 (3%)	0	0	0	0
Oculomotor nerve disorder	1 (3%)	0	0	1 (3%)	0	0
Spinal fracture	0	1 (3%)	0	0	0	0
Hip fracture	0	1 (3%)	0	0	0	0

Data are n (%). Grade 1–2 adverse events occurring in ≥10% of the cohort and all grade ≥3 adverse events are presented. There were two grade 5 adverse events not attributed to LuPSMA: pneumonia (n=1), hepatic failure (n=1). LuPSMA=lutetium-177 prostate-specific membrane antigen-617. *Possibly, probably, or definitely according to Common Terminology Criteria for Adverse Events.

Table 3: **Treatment-emergent adverse events**

17 patients had a confirmed objective response, including a complete and partial response of 29% and 53%, respectively (appendix p 7). At 3 months after the last cycle of LuPSMA, seven (41%) of these 17 patients had PSA progression in conjunction with non-measurable osseous or marrow disease on PSMA-PET imaging.

Administration of Lu-PSMA was well tolerated, with no immediate adverse effects recorded during injection and no treatment-related deaths. The most common treatment-related toxic effect was dry mouth, recorded in 26 (87%) patients (table 3). This adverse event was exclusively grade 1 and usually did not require intervention; several patients used salivary substitute gels to relieve symptoms. Dry eyes occurred in five (17%) patients, similarly all grade 1, except for one patient with grade 2, which required the transient use of artificial tears with recovery over time. Grade 3–4 thrombocytopenia occurred in eight (27%) patients with four (13%) possibly attributed to LuPSMA and the remaining 14% occurring in patients with unequivocal marrow progression (appendix p 6). In these patients, the mean time to platelet nadir was 35 days. Grade 3 anaemia and neutropenia possibly attributable to LuPSMA occurred in four (13%) and two (7%), respectively. Grade 1–2 nausea was limited to the first 24–48 h after treatment and easily managed with anti-emetics. Grade 3 bone pain flare attributed to LuPSMA occurred in one patient, which improved after commencement of dexamethasone. Three patients had symptomatic disease-related skeletal events (spinal cord compression, traumatic hip fracture, and base of skull disease causing ophthalmoplegia) treated with radiotherapy or surgery resulting in delay but not cessation of further LuPSMA treatment. No renal toxic effects occurred.

Mean changes from baseline scores of quality-of-life and pain domains at each post-baseline assessment are shown in table 4 (appendix p 8 shows the baseline scores). 27 (90%) of 30 patients had pain at baseline on brief pain inventory questionnaires. In these patients, pain improved at all timepoints, both in severity and interference (appendix p 9). 11 (37%) patients experienced a ten point or more improvement in global health score by the second cycle treatment, and eight (73%) of these 11 patients achieved a 50% or higher PSA response during the course of treatment. Ten (37%) of 27 patients with baseline pain experienced a 1 point or more improvement in pain severity score by the second cycle of treatment. Compared with baseline, cognitive functioning, insomnia, and pain improved during the course of treatment (appendix pp 10, 11).

PSA progression occurred in 27 (90%) patients with median PSA progression-free survival of 7·6 months (95% CI 6·3–9·0). Median overall survival was 13·5 months (95% CI 10·4–22·7; appendix p 4). 22 (73%) of 30 patients are deceased at time of data cut-off. One death occurred within 60 days of LuPSMA commencement and was attributed to pneumonia. The remaining deaths were attributed to prostate cancer progression (appendix p 5), although causation was certain in two patients who died of traumatic subdural haematomas with platelet counts of 98 and 38, respectively. The most common pattern of disease progression was bone marrow replacement with progressive thrombocytopenia and anaemia in 13 patients. Bone marrow biopsy samples were taken in three patients in the setting of thrombocytopenia and showed extensive prostate cancer infiltration.

In a post-hoc analysis, patients with PSA decline of 50% or higher had a significantly longer PSA progression-free survival and overall survival compared with those

	Cycle 2, baseline	Cycle 3, baseline	Cycle 4, baseline	3-month follow-up *vs* baseline
Global health status	3 (–4 to 11)	4 (–4 to 12)	4 (–4 to 13)	0 (–9 to 8)
Functional scales				
Physical functioning	0 (–6 to 7)	2 (–5 to 9)	3 (–5 to 10)	0 (–8 to 7)
Role functioning	–6 (–15 to 3)	2 (–8 to 11)	–8 (–19 to 3)	–10 (–20 to 1)
Emotional functioning	9 (4 to 14)	6 (0 to 12)	8 (2 to 15)	6 (0 to 12)
Cognitive functioning	11 (4 to 18)	10 (2 to 17)	9 (1 to 18)	10 (1 to 18)
Social functioning	6 (–3 to 15)	–4 (–14 to 6)	–2 (–13 to 9)	–2 (–13 to 9)
Symptom scales and items				
Fatigue	–3 (–10 to 4)	–5 (–12 to 2)	–4 (–13 to 4)	–8 (–16 to 0)
Nausea and vomiting	3 (–6 to 11)	3 (–6 to 12)	3 (–7 to 14)	–2 (–12 to 7)
Pain	–13 (–23 to –3)	–11 (–21 to 0)	–11 (–23 to 1)	–4 (–15 to 8)
Dyspnoea	–3 (–11 to 5)	2 (–7 to 10)	–4 (–14 to 5)	–1 (–10 to 8)
Insomnia	–12 (–21 to –3)	–6 (–15 to 4)	–16 (–26 to –5)	–15 (–25 to –5)
Appetite loss	–5 (–17 to 6)	–3 (–15 to 9)	–3 (–17 to 10)	–5 (–18 to 8)
Constipation	–10 (–22 to 1)	–5 (–17 to 7)	4 (–10 to 18)	–1 (–14 to 13)
Diarrhoea	1 (–4 to 6)	–3 (–9 to 2)	–2 (–8 to 4)	4 (–2 to 10)
Brief pain inventory				
Pain severity	–1·0 (–1·7 to –0·4)	–1·1 (–1·9 to –0·4)	–0·9 (–1·7 to –0·1)	–1·1 (–1·9 to –0·4)
Pain interference	–0·8 (–1·5 to 0·0)	–1·2 (–2·0 to –0·4)	–1·1 (–2·0 to –0·2)	–1·0 (–1·9 to –0·1)

Data are mean (95% CI). EORTC=European Organisation for Research and Treatment of Cancer. QLQ-C30=Quality of Life Questionnaire-Core 30.

Table 4: **EORTC QLQ-C30 and brief pain inventory mean difference in scores from baseline**

with a decline less than 50% (progression-free survival 9·9 months [95% CI 7·4–NA] *vs* 4·1 months [3·6–NA], overall survival 17·0 months [13·5–NA] *vs* 9·9 months [6·8–NA], respectively; appendix p 12).

Five patients who responded to LuPSMA received one to three further cycles of LuPSMA upon progression as part of a compassionate access programme. Two of these patients had received only two of the four planned cycles of LuPSMA, ceasing treatment after an exceptional response. Upon re-treatment, four of these five patients had further responses with PSA reductions of 80%, 64%, 53%, and 20%, compared with the new baseline PSA prior to re-treatment. One patient died of disease progression shortly after. 11 patients received further lines of systemic treatment with a PSA response reported in four of these patients; however, only one patient had a more than 50% reduction.

Discussion

In this phase 2 study using PSMA theranostics to deliver personalised LuPSMA treatment in a poor prognostic cohort of men with metastatic castration-resistant prostate cancer who progressed after standard treatments, we recorded a 50% or higher PSA response of 57%. Additionally, we recorded rapid and clinically meaningful improvements in quality of life. Overall, LuPSMA treatment was well tolerated with predominantly G1 treatment-related toxicities that were largely self-limiting and easily managed. Our results are broadly consistent with retrospective reports published to date.[10–17] Collectively, these data suggest that LuPSMA is a useful therapeutic option for patients with metastatic castration-resistant prostate cancer and additional studies are warranted to understand how to position this new treatment in the evolving treatment paradigm for metastatic castration-resistant prostate cancer.

The highly targeted nature of ^{177}Lu with a short-range beta particle limits effects on normal tissue, except for sites of physiological PSMA expression including salivary and lacrimal glands. LuPSMA was well tolerated with no dose-limiting toxicities seen. We observed grade 1 xerostomia in most patients, which is higher than previously reported, possibly attributed to specific questioning of this potential toxicity within a prospective trial setting. The occurrence of treatment-related grade 3–4 haematological toxicity was low and comparable to the largest retrospective cohort published to date.[11] Notably, all patients with grade 3–4 treatment-related toxicity had baseline thrombocytopenia or anaemia due to a combination of reduced marrow reserve after previous chemotherapy or marrow infiltration. Given the lack of PSMA-expression in normal bone marrow,[28] the haematoxicity arising from LuPSMA is probably the result of damage to adjacent marrow in patients with extensive osseous disease. Overall, however, owing to the rapid plasma clearance of the small-molecule ligand, haematoxicity appears substantially lower than with the [^{177}Lu]-J591 antibody.[9]

LuPSMA theranostics enable a highly personalised approach using PSMA PET/CT to non-invasively image and quantitate PSMA expression to select patients most likely to benefit from treatment. In this study, we additionally excluded patients if they had sites of low or absent PSMA expression demonstrating high

FDG-avidity. We also ceased administering further cycles of treatment if there was no or low uptake on post-treatment imaging indicative of an exceptional response. This treatment paradigm applied in our protocol has evolved from our experience using peptide receptor radionuclide therapy for the treatment of metastatic neuroendocrine tumours (NETs). The principals and expertise required here broadly parallel those using [^{68}Ga]-DOTATATE PET/CT and [^{177}Lu]-DOTATATE in NET.[29] The optimal number of LuPSMA cycles was, however, not determined in this study and administration of additional cycles could be clinically beneficial, especially given the low toxicity observed. Further research is also needed to define the proportion of patients who progress with PSMA-positive or PSMA-negative disease.

Improving quality of life and avoiding detrimental effects of treatment are important considerations for patients with metastatic castration-resistant prostate cancer, many of whom are already symptomatic from their disease. LuPSMA appears particularly effective for pain palliation with rapid relief of pain observed in many patients. For 27 patients with pain at baseline, this improved in 37% after the first cycle of treatment. This effect appears to be better than other agents such as cabazitaxel, with only 9% of patients experiencing pain relief in the TROPIC trial.[4]

The greater than 50% PSA response of 57% in this study is encouraging, particularly when compared with established agents (eg, a response of 39% was observed after treatment with cabazitaxel).[4] 76% of patients had a PSA response greater than 30% compared to 16% in the Ra-223 ALSYMPCA study[3] highlighting the advantage of a tumour-targeted compound compared with an exclusively bone-seeking agent.

The PSA progression-free survival of 7 months noted in this study is similar to that noted in the cabazitaxel TROPIC trial[4] and longer than the 3·6 months recorded with Ra-223.[3] Our results must be interpreted in the context of a heavily pre-treated patient cohort who had exhausted most standard therapies, including cabazitaxel in almost 50%, and had a declining performance status. Indeed, any sustained response to further treatment in this setting is promising, especially if the treatment improves quality of life without significant toxic effects. Nevertheless, without a control group, our results must be interpreted with caution. Additionally, we selected patients based on a predefined imaging phenotype that might have excluded patients with an especially unfavourable prognosis. Our data suggest that LuPSMA could represent a new life-prolonging treatment for men with metastatic castration-resistant prostate cancer, and randomised trials comparing LuPSMA with existing standards of care are now needed.

The results of multi-modality imaging can be summarised as demonstrating remarkable responses in nodal and visceral disease, but a pattern of ultimate progression in new sites of osseous disease or marrow infiltration. We postulate that ^{177}Lu is less effective in targeting microscopic deposits of marrow disease, below the limits of detection on baseline PSMA PET imaging, but that subsequently progress. Future analysis of the voxel-based dosimetric data collected in this cohort to quantify radiation delivered to tumour and normal lesions could enable optimisation of ^{177}Lu administered activities and establish the safety of administering more than four cycles of LuPSMA. PSMA-617 radiolabelled to alpha-emitters such as actinium-225,[30] or combining LuPSMA with other treatments, such as chemotherapy, poly(ADP-ribose) polymerase inhibitors, or anti-programmed death ligand might also be feasible and warrant investigation. Although the current study focuses on a heavily pre-treated population of metastatic castration-resistant prostate cancer patients with terminal disease, the safety and efficacy of this treatment earlier in the therapeutic paradigm might also be worth assessing, perhaps even before the emergence of castration-resistance.

In conclusion, we show in a prospective study that in men with metastatic castration-resistant prostate cancer who have progressed after standard treatments with PSMA-avid disease, LuPSMA resulted in high responses, a low toxicity profile, and improves quality-of-life parameters especially in men with pain. Based on this promising data, we have commenced a multicentre randomised trial comparing LuPSMA with cabazitaxel chemotherapy (NCT03392428).

Contributors

MSH, JV, RJH, SGW, and SS designed the study. MSH, JV, SS, SPT, and JF collected data. MSH, JV, and JF analysed data. MSH, JV, SS, SGW, and RJH interpreted data. MSH, JV, SGW, TA, AI, GK, ARK, DGM, RJH, and SS were responsible for the accrual of patients. PE had oversight of radiopharmaceutical protocol and manufacture, MS was the co-ordinating nuclear medicine technologist, and PJ performed dosimetry analysis. MSH presented interim study findings at a major congress (2017 ESMO congress, abstract 785O); and all authors contributed to the writing and approval of this report.

Declaration of interests

MSH reports personal fees for honoraria from Ipsen Australia, Sanofi Genzyme, and Endocyte, all outside of the submitted work. JV reports personal fees for Honoraria from Janssen Australia, outside of the submitted work. All other authors declare no competing interests.

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