[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

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Summary

Background Lutetium-177 [^{177}Lu]Lu-PSMA-617 is a radiolabelled small molecule that delivers β radiation to cells expressing prostate-specific membrane antigen (PSMA), with activity and safety in patients with metastatic castration-resistant prostate cancer. We aimed to compare [^{177}Lu]Lu-PSMA-617 with cabazitaxel in patients with metastatic castration-resistant prostate cancer.

Methods We did this multicentre, unblinded, randomised phase 2 trial at 11 centres in Australia. We recruited men with metastatic castration-resistant prostate cancer for whom cabazitaxel was considered the next appropriate standard treatment. Participants were required to have adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group performance status of 0–2. Previous treatment with androgen receptor-directed therapy was allowed. Men underwent gallium-68 [^{68}Ga]Ga-PSMA-11 and 2-flourine-18[^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET-CT scans. PET eligibility criteria for the trial were PSMA-positive disease, and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings. Men were randomly assigned (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/m² intravenously every 3 weeks for up to ten cycles). The primary endpoint was prostate-specific antigen (PSA) response defined by a reduction of at least 50% from baseline. This trial is registered with ClinicalTrials.gov, NCT03392428.

Findings Between Feb 6, 2018, and Sept 3, 2019, we screened 291 men, of whom 200 were eligible on PET imaging. Study treatment was received by 98 (99%) of 99 men randomly assigned to [^{177}Lu]Lu-PSMA-617 versus 85 (84%) of 101 randomly assigned to cabazitaxel. 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% (95% CI 16–42; p<0·0001; and 66% *vs* 44% by treatment received; difference 23% [9–37]; p=0·0016). Grade 3–4 adverse events occurred in 32 (33%) of 98 men in the [^{177}Lu]Lu-PSMA-617 group versus 45 (53%) of 85 men in the cabazitaxel group. No deaths were attributed to [^{177}Lu]Lu-PSMA-617.

Interpretation [^{177}Lu]Lu-PSMA-617 compared with cabazitaxel in men with metastatic castration-resistant prostate cancer led to a higher PSA response and fewer grade 3 or 4 adverse events. [^{177}Lu]Lu-PSMA-617 is a new effective class of therapy and a potential alternative to cabazitaxel.

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Introduction

Metastatic castration-resistant prostate cancer is incurable. Treatments that are proven to prolong overall survival include docetaxel,[1] androgen receptor-directed therapies such as abiraterone,[2] and enzalutamide.[3] Cabazitaxel improves survival in men with metastatic castration-resistant prostate cancer[4,5] progressing after previous treatment with docetaxel.

Radiolabelled small molecules that bind to prostate-specific membrane antigen (PSMA), such as lutetium-177 [^{177}Lu]Lu-PSMA-617, are promising treatments for patients with advanced prostate cancer.[6] [^{177}Lu]Lu-PSMA-617 delivers high doses of radiation to prostate cancer cells via β-particulate emission with a 0·7 mm mean path length. This short range results in highly specific tumour targeting while limiting damage to normal tissues. Encouraging activity and safety has been reported in several non-randomised studies in men with metastatic castration-resistant prostate cancer that progressed after standard therapies.[7–10] We reported a decrease in prostate-specific antigen (PSA) of 50% or more in 64% of men and a favourable toxicity profile in a

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Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies up to the finalisation of protocol on Oct 31, 2017, using the search terms "Lutetium-177", "Lu-177", "PSMA" or "Prostate Specific Membrane Antigen". We also reviewed key journals and congress abstracts in the fields of urological oncology and nuclear medicine. We found studies of compassionate access treatment with lutetium-177 [^{177}Lu]Lu-PSMA in men with metastatic castration-resistant prostate cancer, showing promising efficacy and safety. Data were limited by retrospective design without comparison with a control group. No randomised data were available. Therefore, we designed a phase 2 trial to compare activity and safety of [^{177}Lu]Lu-PSMA-617 versus cabazitaxel. Since commencement of this trial, a prospective single-centre study in 50 patients showed a prostate-specific antigen decline of 50% or more in 64% of men, with a favourable toxicity profile.

Added value of this study

This is the first randomised study of [^{177}Lu]Lu-PSMA-617, a radiolabelled small molecule that enables delivery of β-particle therapy that is targeted to metastatic castration-resistant prostate cancer. This phase 2 study provides evidence that [^{177}Lu]Lu-PSMA-617 is a potential alternative to cabazitaxel in men with metastatic castration-resistant prostate cancer, with greater activity but less severe side-effects and improvements in patient-reported outcomes.

Implications of all the available evidence

Collective data from this randomised study and other series provide compelling evidence that [^{177}Lu]Lu-PSMA-617 is an active treatment for men with castration-resistant prostate cancer who have progressed after docetaxel chemotherapy and androgen receptor-directed therapy. This theranostic approach uses a paired diagnostic test, gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT, to select men for whom [^{177}Lu]Lu-PSMA-617 might not be suitable. The side-effect profile and patient reported outcomes favour [^{177}Lu]Lu-PSMA-617 and this treatment might be a particularly useful option in men for whom cabazitaxel is not suitable. No benefit in overall survival has been shown. Further health economic analyses are required to enable widespread access for prostate-specific membrane antigen theranostics.

single-arm, phase 2 trial in 50 men with metastatic castration-resistant prostate cancer progressing after docetaxel and a novel anti-androgen.[11,12]

In the TheraP trial, we aimed to compare the activity and safety of [^{177}Lu]Lu-PSMA-617 with cabazitaxel, in men for whom cabazitaxel was considered the next appropriate standard treatment.

Methods

Study design and participants

TheraP (ANZUP 1603) was a multicentre, unblinded, randomised phase 2 trial done at 11 centres in Australia (appendix p 3).

We registered men with metastatic castration-resistant prostate cancer who had been previously treated with docetaxel, and with progressive disease defined by a rising PSA as per Prostate Cancer Working Group 3 (PCWG3) criteria.[13] Eligible participants were men with metastatic castration-resistant prostate cancer for whom cabazitaxel was considered the next appropriate standard treatment. Participants were required to have adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group performance status of 0–2 (appendix p 14). Previous treatment with androgen receptor-directed therapy was allowed. Men underwent gallium-68 [^{68}Ga]Ga-PSMA-11 and 2-flourine-18 [^{18}F] fluoro-2-deoxy-D-gluycose (FDG) PET-CT scans. PET eligibility criteria for the trial were PSMA-positive disease with a maximum standardised uptake value (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 2-[^{18}F]FDG-positive and PSMA-negative findings.

The study had ethics approval at participating sites and all participants provided signed, written, informed consent.

The trial protocol has been previously published (appendix p 32).[14]

Randomisation and masking

Participants were randomly assigned to cabazitaxel or [^{177}Lu]Lu-PSMA-617. Participants were randomly assigned (1:1) via a centralised web-based system that stratified by disease burden (>20 sites *vs* ≤20 sites by PSMA PET-CT), previous treatment with enzalutamide or abiraterone, and study site using minimisation with a random component. Neither participants nor investigators were masked to group assignment.

Procedures

Patients in the control group were treated with cabazitaxel 20 mg/m² intravenously, every 3 weeks for a maximum of ten cycles. Patients in the experimental group were treated with [^{177}Lu]Lu-PSMA-617 intravenously, every 6 weeks for a maximum of six cycles. The administered starting dose of radioactivity was 8·5 GBq, and was decreased by 0·5 GBq per cycle. 1·5 L oral hydration was encouraged on the day of [^{177}Lu]Lu-PSMA-617 administration. No intervention to protect salivary glands was done. Planar and single-photon emission CT with CT (SPECT-CT) was done 24 h following each [^{177}Lu]Lu-PSMA-617 administration to assess ^{177}Lu retention in target and off-target tissues. Treatment was suspended if the SPECT-CT showed very

low or no PSMA uptake at sites of metastatic disease (intensity less than physiological liver activity) on central review. Treatment could be recommenced with [^{177}Lu]Lu-PSMA-617 at symptomatic progression, PSA progression, or radiological progression if patients had received fewer than six cycles and repeat imaging with [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET-CT met the criteria for PET scan eligibility. Dose modifications and delays for toxicity were specified in the trial protocol.

During study treatment, participants were reviewed every 3 weeks and had blood tests for routine haematology, biochemistry, and serum PSA. CT of the chest, abdomen and pelvis, and technetium-^{99m}-phosphonate bone scans were done every 12 weeks until radiological progression. Patient-reported outcome measures included the McGill-Melzack scale for present pain intensity (PPI), European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), and the Patient Disease and Treatment Assessment Form (DATA) every 3 weeks until the end of study treatment, and subsequently every 4 weeks until radiographic progression. A safety assessment was done at 30 days and 12 weeks after the last dose of study treatment, and follow-up continued every 12 weeks thereafter. Treatment after completion or discontinuation of study treatment was at the discretion of the treating clinicians.

All participating sites were certified for PET scanner validation[13] and radiopharmaceutical production for both ^{68}Ga and ^{177}Lu radiopharmaceuticals (appendix p 15) before site activation. PET-CT images that were obtained as part of the eligibility assessment were centrally reviewed by three expert nuclear medicine physicians (AI, LE, MSH) using the WIDEN system[15] and MIM software (Cleveland, OH, USA).

Outcomes

The primary endpoint was PSA response rate, defined as the proportion of participants with a PSA reduction of 50% or more from baseline. Progression-free survival was defined as the interval from randomisation to first evidence of PSA progression defined by an increase of at least 25% and at least 2 ng/mL after 12 weeks (as per PCWG3[16]), radiographic progression using locally reported CT and bone scanning (Response Evaluation Criteria In Solid Tumors [RECIST] 1.1[17] and PCWG3 criteria for bone lesions), commencement of non-protocol anticancer treatment, or death from any cause. Objective response rate was defined according to RECIST 1.1. Adverse events were reported according to the Common Terminology Criteria for Adverse Events version 4.03. Pain response was restricted to men with a PPI score at baseline of 2 or more, and defined as a reduction from baseline of 2 or more points. PPI-progression-free survival was defined as the interval from randomisation to first evidence of an increase of 1 point or greater from the nadir PPI score, commencement of non-protocol anticancer treatment, or death from any cause. Exploratory endpoints related to prognostic and predictive biomarkers await analysis and results will be published separately.

Statistical analysis

The sample size of 200 participants was designed to provide 80% power to detect an absolute improvement of 20% in the PSA response rate (from 40% with cabazitaxel to 60% with [^{177}Lu]Lu-PSMA-617), with a two-sided type 1 error of 5% and allowance of 3% for missing data. This prespecified analysis after 170 progression-free survival events additionally provided 80% power to detect a true hazard for progression-free survival of 0·65, assuming a median progression-free survival of 3 months in those allocated cabazitaxel, 24 months for accrual, and an additional 6 months for follow-up. The primary analysis was by intention to treat and patients who withdrew following randomisation were not replaced. Sensitivity analyses according to treatment received (per protocol) were also done. The per-protocol population comprised all randomised participants who received at least one dose of assigned treatment. Safety per-protocol analyses included participants who received at least one dose of study treatment.

The primary endpoint was a comparison of PSA response rate in the two treatment groups using a Cochran-Mantel-Haenszel χ^2 test accounting for the stratification factors at randomisation. Multivariable logistic regression was used to estimate odds ratios and CIs for assigned treatment adjusted for stratification factors. Other binary endpoints were analysed similarly. Time-to-event endpoints were analysed with Kaplan-Meier curves and stratified log-rank tests, with hazard ratios (HRs) and their CIs calculated with Cox proportional hazards regression. QLQ-C30 scales were analysed using a repeated measures model with a compound symmetry covariance structure. Groups were compared on the predicted means from the models. Deterioration-free survival was defined by a 10-point or more deterioration in health status from baseline (without subsequent 10-point or more improvement compared with baseline, or an improvement to ≥90 if the baseline score was ≥90), progression, death, or treatment discontinuation; two deterioration-free survival endpoints were derived from the EORTC QLQ-C30 physical function scale and global health scale. Comparisons between treatment groups for the prevalence of troublesome symptoms, or troublesome effects on other aspects of patient-reported outcomes assessed with the DATA form, were done with logistic regression adjusting for baseline score. Analyses were done with SAS (version 9.4) and R (version 4.0.1).

An independent data and safety monitoring committee reviewed the progress and results of the trial. The protocol was approved at each participating institution and the trial was done in accordance with the principles of Good Clinical Practice guidelines and the Declaration of Helsinki.

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See Online for appendix

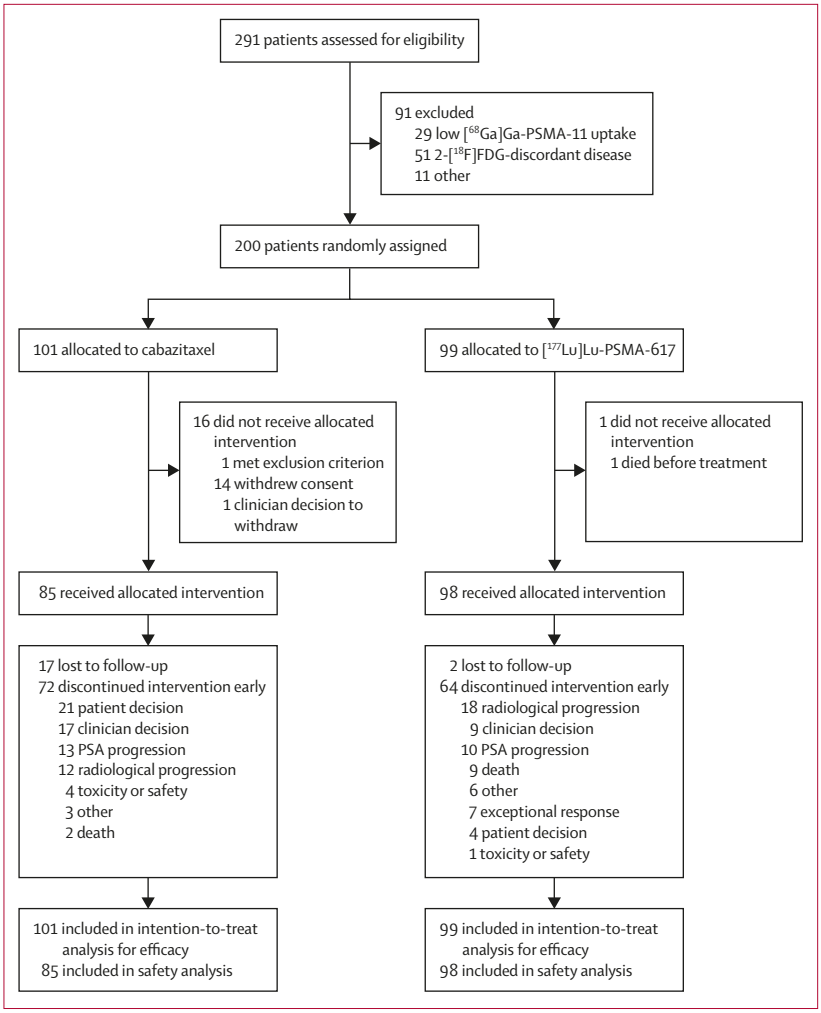

Figure 1: **Trial profile**
[68]Ga=gallium-68. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. [177]Lu=lutetium-177. [18]F=fluorine-18.

	[177Lu]Lu-PSMA-617 (n=99)	Cabazitaxel (n=101)
Age, years		
Mean (SD)	71·7 (7·9)	71·5 (7·0)
Median (IQR)	72·1 (66·9–76·7)	71·8 (66·7–77·3)
>20 metastases*	77 (78%)	79 (78%)
ECOG performance status		
0	42 (42%)	44 (44%)
1	53 (54%)	52 (52%)
2	4 (4%)	4 (4%)
Missing data	0	1 (1%)
PSA, ng/mL	93·5 (44–219)	110 (64–245)
Alkaline phosphatase, U/L	111 (83–199)	130 (79–187)
Gleason score at diagnosis		
≤7	25 (25%)	35 (35%)
≥8	53 (53%)	50 (50%)
Missing data	21 (21%)	16 (16%)
Disease stage		
Lymph node only	7 (7%)	9 (9%)
Bone metastases	90 (91%)	90 (89%)
Visceral metastases	7 (7%)	13 (13%)
Previous treatment		
Abiraterone only	21 (21%)	24 (24%)
Enzalutamide only	49 (50%)	58 (57%)
Both	21 (21%)	9 (9%)

Data are n (%), mean (SD), or median (IQR). [177]Lu=lutetium-177. PSMA=prostate-specific membrane antigen. ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. *Assessed using gallium-68 [68GA]Ga-PSMA-11 PET-CT by central review.

Table 1: **Baseline characteristics of the intention-to-treat population**

This trial was registered with ClinicalTrials.gov, NCT03392428.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 6, 2018, and Sept 3, 2019, 291 participants were registered and underwent study imaging with [68Ga]Ga-PSMA-11 and 2-[18F]FDG PET-CT (figure 1; appendix p 5). 91 men were ineligible, including 29 (10%) with low uptake on [68Ga]Ga-PSMA-11 PET-CT and 51 (18%) with discordant 2-[18F]FDG-avid disease. 200 men were randomly assigned, 101 (50%) to cabazitaxel and 99 (50%) to [177Lu]Lu-PSMA-617. The characteristics of participants at baseline were similar in the two groups (table 1; appendix p 17). 91 (91%) men in each group had previous treatment with enzalutamide or abiraterone. One man who was randomly assigned to [177]Lu-PSMA-617 died before receiving study treatment. Among men who were randomly assigned to cabazitaxel, 14 (14%) withdrew from the study before commencing treatment, one (1%) withdrew owing to clinician preference, and one (1%) man met an exclusion criterion (thrombocytopenia) after initial eligibility.

Among 98 men randomly assigned and treated with [177Lu]Lu-PSMA-617, 45 (46%) completed protocol therapy. The median number of cycles was five (IQR 3–6). Among 85 men randomly assigned and treated with cabazitaxel, 31 (36%) received all ten planned cycles of cabazitaxel (median eight [5–10]). The data cutoff of July 20, 2020, was triggered on reaching the prespecified target of 170 PSA progression-free survival events after a median follow-up of 18·4 months.

A PSA reduction of 50% or more from baseline was more frequent in men randomly assigned to [177Lu]Lu-PSMA-617 than to cabazitaxel, occurring in 65 (66%) of 99 men (95% CI 56–75), compared with 37 (37%) of 101 men (27–46), by intention to treat (difference 29% [16–42]; p<0·0001; figure 2). In the pre-specified sensitivity analysis by treatment received, a PSA reduction of 50% or more

from baseline occurred in 65 (66%) of 98 men (57–76) who received [177Lu]Lu-PSMA-617, compared with 37 (44%) of 85 (33–54) who received cabazitaxel (difference 23% [9–37]; p=0·0016).

Seven (7%) men randomly assigned to [177Lu]Lu-PSMA-617 suspended treatment because of a protocol-defined exceptional PSMA response on post-therapy SPECT-CT. Six (86%) of those seven men recommenced study treatment at progression (appendix p 20): three completed six cycles, two stopped because of radiological progression, and one response is ongoing.

Progression events were documented in 173 men (90 in the [177Lu]Lu-PSMA-617 group and 83 in the cabazitaxel group). [177Lu]Lu-PSMA-617 delayed progression, as compared with cabazitaxel (HR 0·63 [95% CI 0·46–0·86; p=0·0028; figure 3). Similar benefits were seen for radiographic progression (0·64 [0·46–0·88]; p=0·0070) and PSA progression-free survival (0·60 [0·44–0·83]; p=0·0017; appendix p 6). Results and conclusions were similar in the per-protocol sensitivity analyses (appendix p 20). The effect of treatment on progression-free survival, radiographic progression, and PSA progression-free survival was not constant with respect to time, with progression-free survival benefits with [177Lu]Lu-PSMA-617 more apparent after 6 months compared with cabazitaxel. Progression-free survival at 12 months was 19% (95% CI 12–27) in the [177Lu]Lu-PSMA-617 group compared with 3% (1–9) in the cabazitaxel group. Median progression-free survival was 5·1 months (3·4–5·7) in men randomly assigned to [177Lu]Lu-PSMA-617 and 5·1 months (2·8–6·0) for men randomly assigned to cabazitaxel.

In 78 men with measurable disease by RECIST criteria at baseline, the objective response rate was greater in men in the [177Lu]Lu-PSMA-617 group (49% [95% CI 33–65] *vs* 24% [11–38]; relative risk [RR] 2·12 [95% CI 1·10–4·08]; p=0·019; appendix p 7).

90 deaths were documented at the time of this analysis. Analysis of overall survival is planned to occur after 170 deaths and results will be published when ready.

183 participants who received at least one dose of [177Lu]Lu-PSMA-617 or cabazitaxel were included in the safety analyses. Grade 3 or 4 adverse events occurred in 32 (33%) of 98 men treated with [177Lu]Lu-PSMA-617 versus 45 (53%) of 85 men treated with cabazitaxel (table 2; appendix p 21). Grade 3–4 thrombocytopenia was more common with [177Lu]Lu-PSMA-617 than with cabazitaxel (11% *vs* 0%; table 2). Grade 3–4 neutropenia was less common with [177Lu]Lu-PSMA-617 (4% *vs* 13%), with no episodes of febrile neutropenia (0% *vs* 8%).

Study treatment was discontinued because of toxicity in one (1%) of 98 men treated with [177Lu]Lu-PSMA-617 and three (4%) of 85 men treated with cabazitaxel (appendix p 28). Dose reductions were documented in 12 men treated with [177Lu]Lu-PSMA-617, compared with 21 men treated with cabazitaxel (appendix p 28). From time of randomisation to 12 weeks after last administration

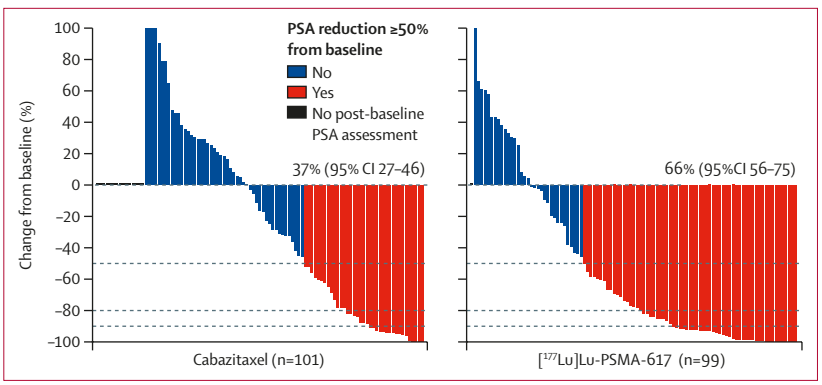

Figure 2: **PSA response**
PSA=prostate-specific antigen. 177Lu=lutetium-177.

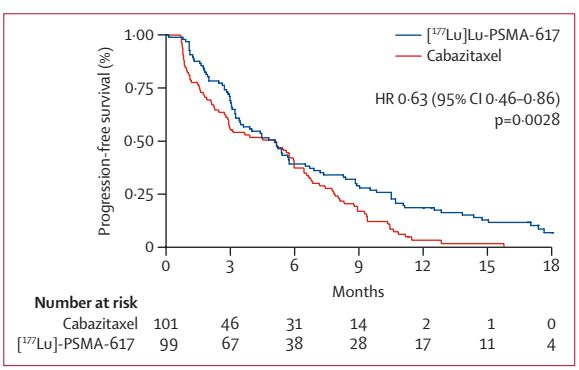

Figure 3: **Radiographic or PSA progression-free survival**
HR=hazard ratio. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. 177Lu=lutetium-177.

of study treatment, 19 deaths occurred: 13 among men assigned to [177Lu]Lu-PSMA-617 and six among those assigned to cabazitaxel. 12 deaths were attributed to prostate cancer, five to infection, one to subdural haematoma, one to pulmonary embolism, and none attributed to study treatment.

Among the 90 men with a PPI score of 2 or more at baseline, a pain response occurred in 29 60% of 48 men in the [177Lu]Lu-PSMA-617 group versus 18 (43%) of 42 for cabazitaxel (RR 1·4 [95% CI 0·9–2·2]; p=0·10). PPI-progression-free survival favoured the [177Lu]Lu-PSMA-617 group (HR 0·72 [95% CI 0·53–0·97]; p=0·033; appendix p 8).

176 (88%) men completed a baseline questionnaire for health-related quality of life. Mean global health status was similar in the randomly assigned treatment groups (63 in the [177Lu]Lu-PSMA-617 group [95% CI 60–67] *vs* 60 in the cabazitaxel group [57–64]; p=0·20). Patient-reported outcomes showed clinical meaningful improvements in quality of life and symptoms with [177Lu]Lu-PSMA-617 compared with cabazitaxel in the following domains: diarrhoea (9 [95% CI 6–11] *vs* 16 [13–19]; p<0·0001), fatigue (34 [31–38] *vs* 40 [36–43]; p=0·027), social functioning (79 [75–82] *vs* 73 [69–77]; p=0·030), and insomnia (23 [20–27] *vs* 29 [25–33]; p=0·023; appendix

	[^{177}Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. ^{177}Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

Table 2: **Adverse events**

pp 9, 29). Additionally, troublesome symptoms, as per DATA, reported less frequently with [^{177}Lu]Lu-PSMA-617 than with cabazitaxel included diarrhoea (31% *vs* 55%; p=0·0014), urinary symptoms (38% *vs* 62%; p=0·0019), feeling dizzy or lightheaded (38% *vs* 53%; p=0·0091), altered sense of taste (54% *vs* 69%; p=0·042), hair loss (10% *vs* 42%; p<0·0001), skin rash (14% *vs* 32%; p=0·0029), and sore hands or feet (35% *vs* 43%; p=0·024). No patient-reported outcomes were better for cabazitaxel than for [^{177}Lu]Lu-PSMA-617 (appendix pp 9–12, 29–31). Deterioration-free survival for global health status at 6 months was better for men randomly assigned to [^{177}Lu]Lu-PSMA-617 (29% [95% CI 21–38] *vs* 13% [7–21]; p=0·0002; appendix p 13).

Discussion

TheraP is the first reported randomised trial comparing [^{177}Lu]Lu-PSMA-617 with a standard-of-care therapy. We found that in men with metastatic castration-resistant prostate cancer [^{177}Lu]Lu-PSMA-617 was more active than cabazitaxel. Furthermore, the frequencies of objective tumour responses, grade 3–4 adverse events, and scores for several patient-reported outcomes also favoured [^{177}Lu]Lu-PSMA-617.

We chose cabazitaxel, a life-prolonging therapy that is standard of care in this setting, as the optimal treatment for our control group. This choice is supported by subsequent data from the CARD trial,[5] showing improved overall survival with cabazitaxel compared with a second-line, novel anti-androgen in a similar population of men.[5] This choice differs from that of the ongoing phase 3 VISION trial (NCT03511664), which uses best supportive care without active anticancer treatment in the control group.

Our trial has three important limitations. First, 15 men who were assigned to cabazitaxel withdrew from the trial before receiving study treatment, presumably because they sought treatment with ^{177}Lu-PSMA or did not want chemotherapy, and provided no further data. Prespecified sensitivity analysis by treatment received corroborated the evidence of activity from our primary analysis by intention to treat. Second, we used a randomised phase 2 design, and sample size was focused on biological activity (PSA response and progression-free survival), rather than on direct measures of patient benefit (overall survival or quality of life). Our data provide strong evidence that [^{177}Lu]Lu-PSMA-617 is more active than cabazitaxel, but longer follow-up of TheraP, and results from VISION, are needed to understand the effects on overall survival. Third, we selected participants with concordant disease on imaging using [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET-CT. Our findings might not be applicable to men selected less carefully.

The toxicity of [^{177}Lu]Lu-PSMA-617 observed in this study was similar to that of previous single-arm studies.[7–9,11,12] This study showed that [^{177}Lu]Lu-PSMA-617 resulted in fewer grade 3–4 toxicities compared with cabazitaxel, except thrombocytopenia. The low toxicity profile of [^{177}Lu]Lu-PSMA-617 is attributed to the high binding affinity to the PSMA receptor and rapid renal excretion, limiting toxicity to non-target organs. Additionally, we showed that patient-reported outcomes were similar or better with [^{177}Lu]Lu-PSMA-617 than with cabazitaxel. The time to pain progression also favoured [^{177}Lu]Lu-PSMA-617 over cabazitaxel. We also observed greater improvements in fatigue, social functioning, and insomnia with [^{177}Lu]Lu-PSMA-617 than with cabazitaxel. [^{177}Lu]Lu-PSMA-617 might be of benefit to men for whom cabazitaxel might be unsuitable because of their age or comorbidities.

Patients were selected on the basis of molecular imaging phenotype using the combination of PSMA and 2-[^{18}F]FDG PET-CT, to maximise the probability of observing benefit. These stringent imaging criteria resulted in 28% of men who were screened for TheraP not meeting the eligibility criteria, mainly due to [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET-CT discordance. We have previously shown poor outcomes in these patients.[18] This ability to select patients who are most likely to benefit from [^{177}Lu]Lu-PSMA-617 therapy is a key advantage of the theranostic approach of combining imaging and therapy modalities. Our study does not inform whether patients with lower PSMA expression or discordant 2-[^{18}F]FDG-avid disease would also benefit from [^{177}Lu]Lu-PSMA-617.

We await the results of the VISION trial, a phase 3 randomised trial comparing [^{177}Lu]Lu-PSMA-617 to best

standard of care or best supportive care. TheraP will provide complementary data because cabazitaxel was not included in the standard-of-care group in the VISION trial. Both trials used [^{68}Ga]Ga-PSMA-11 for patient selection, although TheraP used a quantitative PET parameter (ie, SUVmax) and 2-[^{18}F]FDG to assist identifying patients with discordant 2-[^{18}F]FDG-positive, PSMA-negative disease.

The promising efficacy and safety profile of [^{177}Lu]Lu-PSMA-617 seen in men with metastatic castration-resistant prostate cancer who have progressed after multiple lines of therapy has generated interest in exploring rational treatment combinations and use of [^{177}Lu]Lu-PSMA-617 earlier in the course of prostate cancer. Multiple trials are underway including [^{177}Lu]Lu-PSMA-617 combined with immune checkpoint inhibitors (NCT03658447 and NCT03805594), a poly(ADP-ribose) polymerase inhibitor inhibitor (NCT03874884), or enzalutamide (NCT04419402). Use of [^{177}Lu]Lu-PSMA-617 up-front in men with newly diagnosed metastatic hormone-sensitive prostate cancer is also being explored (NCT04343885).

In conclusion, TheraP showed better activity, safety, and patient-reported outcomes with [^{177}Lu]Lu-PSMA-617 than with cabazitaxel in men with metastatic castration-resistant prostate cancer progressing after docetaxel.

Contributors

MSH, LE, AJM, MRS, JAV, and IDD were members of the protocol development working party contributing to conceptualisation and writing the first version of the protocol. MSH, LE, SS, AI, AMJ, JCG, DAP, THT, IDK, SN, RJF, CG, NKR, AW, AMS, S-TL, EMK, AAA, SR, ADR, WM, AG, EH, WC, PL, JAV, and SGW accrued patients and collected data. MSH, LE, and AI performed imaging central review. MSH, MRS, AJM, and IDD contributed to the statistical analysis plan. AJM led the statistical analysis and verified underlying data. AYZ and MMM provided project administration via the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP). MSH was the coordinating principal investigator and wrote the first draft of the manuscript with major input from LE, MRS, and IDD. MSH, AJM, and IDD accessed the verified data. All authors contributed to the writing and approval of this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

De-identified participant data will be made available to bona fide researchers registered with an appropriate institution following publication. Methodologically sound proposals for any purpose will be considered by the trial executive committee who will have the right to review and comment on any draft manuscripts before publication. Proposals should be directed to michael.hofman@petermac.org. To gain access, data requesters will sign a data access agreement.

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