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

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Summary

Background The TheraP study reported improved prostate-specific antigen responses with lutetium-177 [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in men with metastatic castration-resistant prostate cancer progressing after docetaxel. In this Article, we report the secondary outcome of overall survival with mature follow-up, and an updated imaging biomarker analysis. We also report the outcomes of participants excluded due to ineligibility on gallium-68 [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) PET-CT.

Methods TheraP was an open-label, randomised phase 2 trial at 11 centres in Australia. Eligible participants had metastatic castration-resistant prostate cancer progressing after docetaxel, and PET imaging with [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG that showed prostate-specific membrane antigen (PSMA)-positive disease and no sites of metastatic disease with discordant 2-[^{18}F]FDG-positive and PSMA-negative findings. Participants were randomly assigned (1:1) to treatment with [^{177}Lu]Lu-PSMA-617 (every 6 weeks for a maximum of six cycles; starting at 8·5 GBq, decreasing by 0·5 GBq to 6·0 GBq for the sixth cycle) versus cabazitaxel (20 mg/m^2 every 3 weeks, maximum of ten cycles). Overall survival was analysed by intention-to-treat and summarised as restricted mean survival time (RMST) to account for non-proportional hazards, with a 36-month restriction time corresponding to median follow-up. This trial is registered with ClinicalTrials.gov, NCT03392428, and is complete.

Findings 291 men were registered from Feb 6, 2018, to Sept 3, 2019; after study imaging, 200 were eligible and randomly assigned to treatment with [^{177}Lu]Lu-PSMA-617 (n=99) or cabazitaxel (n=101). After completing study treatment, 20 (20%) participants assigned to cabazitaxel and 32 (32%) assigned to [^{177}Lu]Lu-PSMA-617 were subsequently treated with the alternative regimen. After a median follow-up of 35·7 months (IQR 31·1 to 39·2), 77 (78%) participants had died in the [^{177}Lu]Lu-PSMA-617 group and 70 (69%) participants had died in the cabazitaxel group. Overall survival was similar among those assigned to [^{177}Lu]Lu-PSMA-617 versus those assigned to cabazitaxel (RMST 19·1 months [95% CI 16·9 to 21·4] *vs* 19·6 months [17·4 to 21·8]; difference –0·5 months [95% CI –3·7 to 2·7]; p=0·77). No additional safety signals were identified with the longer follow-up in this analysis. 80 (27%) of 291 men who were registered after initial eligibility screening were excluded after [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET. In the 61 of these men with follow-up available, RMST was 11·0 months (95% CI 9·0 to 13·1).

Interpretation These results support the use of [^{177}Lu]Lu-PSMA-617 as an alternative to cabazitaxel for PSMA-positive metastatic castration-resistant prostate cancer progressing after docetaxel. We did not find evidence that overall survival differed between the randomised groups. Median overall survival was shorter for men who were excluded because of low PSMA expression or 2-[^{18}F]FDG-discordant disease.

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Introduction

Lutetium-177 [^{177}Lu]Lu-PSMA-617, also known as prostate-specific membrane antigen (PSMA) radioligand therapy, is a small molecule with a radioactive payload enabling targeted treatment of prostate cancer.[1] In the first analysis of the TheraP trial,[2] we reported that in patients with progressive metastatic castration-resistant prostate cancer following both docetaxel and an androgen

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Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies available from study inception on Oct 31, 2017, up to the finalisation of the updated statistical analysis plan on Feb 1, 2022, 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 uncontrolled and retrospective designs. No randomised data were available. Therefore, we designed a phase 2 trial to compare the activity and safety of [^{177}Lu]Lu-PSMA-617 versus cabazitaxel. After this trial began, a phase 3 trial (VISION) reported improved overall survival with the addition of [^{177}Lu]Lu-PSMA-617 to a range of protocol-defined options.

Added value of this study

Mature follow-up of TheraP provides evidence that [^{177}Lu]Lu-PSMA-617 is a suitable alternative to cabazitaxel in patients with metastatic castration-resistant prostate cancer. Collectively, the trial findings indicate that [^{177}Lu]Lu-PSMA-617 has less severe side-effects, better patient-reported outcomes, higher PSA response and objective tumour response rates, longer progression-free survival, and similar overall survival to cabazitaxel. Metabolic tumour volume on 2-[^{18}F]fluoro-2-deoxy-D-glucose PET-CT was prognostic for overall survival. SUVmean on gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT was prognostic for overall survival independent of treatment, but not predictive of a treatment effect of [^{177}Lu]Lu-PSMA-617 versus cabazitaxel.

Implications of all the available evidence

Data from the TheraP and VISION trials support the use of [^{177}Lu]Lu-PSMA-617 in patients with PSMA-positive, metastatic castration-resistant prostate cancer progressing after docetaxel and an androgen-receptor pathway inhibitor. Molecular imaging represents a novel prognostic biomarker for overall survival.

receptor-pathway inhibitor (abiraterone or enzalutamide), those randomly assigned to treatment with [^{177}Lu]Lu-PSMA-617 versus cabazitaxel had a higher prostate-specific antigen (PSA) response rate (66% *vs* 37%), higher objective response rate (per the Response Evaluation Criteria In Solid Tumours [RECIST] version 1.1; 49% *vs* 24%), longer progression-free survival (hazard ratio [HR] 0·63 [95% CI 0·46–0·86]), fewer grade 3–4 adverse events (33% *vs* 53%), and better patient-reported outcomes. We also reported that high mean standardised uptake value (SUVmean) on gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT was predictive of a greater likelihood of favourable response to [^{177}Lu]Lu-PSMA-617 versus cabazitaxel, and high metabolic tumour volume (MTV) on 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) PET-CT was associated with a lower response rate regardless of randomly assigned treatment.[3]

In a population of patients in whom disease had progressed after androgen receptor pathway inhibitors and either one or two taxane regimens, the phase 3 VISION trial reported improved overall survival and quality of life with [^{177}Lu]Lu-PSMA-617 when added to a protocol-defined option.[4,5] However, VISION did not compare [^{177}Lu]Lu-PSMA-617 with an active treatment, and did not allow cabazitaxel, or any other life-prolonging option, among its protocol-defined options.

TheraP was designed to compare the activity and safety of [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients for whom cabazitaxel was considered to be the next appropriate standard treatment.[2,6] Cabazitaxel was selected as the control treatment as it had been reported to lead to improvements in overall survival in patients with metastatic castration-resistant prostate cancer progressing after previous treatment with docetaxel.[7,8] In this Article, we report on the TheraP trial secondary outcome of overall survival with mature follow-up. We also report on the outcomes of patients who were excluded because of low PSMA expression or discordant disease on imaging with [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET; and on the utility of PET as a biomarker.

Methods

Study design and participants

TheraP (Australian and New Zealand Urogenital and Prostate Cancer Trials Group [ANZUP] protocol 1603) was an open-label, randomised, phase 2 trial done at 11 centres in Australia (appendix p 2). The protocol,[6] primary outcome, and key secondary outcomes up to a median follow-up of 18·4 months were previously described (data cutoff July 20, 2020).[2] This updated analysis with a data cutoff of Dec 31, 2021, focuses on overall survival (a secondary outcome) and the survival of patients excluded from the trial on the basis of their PET imaging with [^{68}Ga]Ga-PSMA-11 or 2-[^{18}F]FDG (prespecified exploratory analysis). We also report exploratory analyses of associations between overall survival and previously described predictive or prognostic biomarkers on [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET.[3]

We registered patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and with progressive disease, defined by increasing PSA as per Prostate Cancer Working Group 3 (PCWG3) criteria.[9] Eligible participants were patients for whom cabazitaxel was considered the next appropriate standard

treatment. They were required to have adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 (appendix pp 14–15). Previous treatment with an androgen receptor pathway inhibitor was allowed. Participants underwent [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET scans. PET eligibility criteria for the trial were PSMA-positive disease with a [^{68}Ga]Ga-PSMA-11 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.

All participants provided signed, written, informed consent. The protocol was approved at each participating institution, and the trial was done in accordance with the principles of the Good Clinical Practice guidelines and the Declaration of Helsinki.

Randomisation and masking

Participants were randomly assigned (1:1) to [^{177}Lu]Lu-PSMA-617 or cabazitaxel with a centralised, web-based system that stratified for disease burden (>20 sites *vs* ≤20 sites by [^{68}Ga]Ga-PSMA-11 PET), 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

Participants in the the control group were treated with cabazitaxel 20 mg/m² intravenously, every 3 weeks for a maximum of ten cycles. The experimental group was 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 down to 6·0 GBq for the sixth cycle. Planar and single-photon emission CT with CT (SPECT-CT) was done 24 h after each [^{177}Lu]Lu-PSMA-617 administration. Treatment was suspended if the [^{177}Lu]Lu SPECT-CT showed low uptake, defined by [^{177}Lu]Lu intensity less than physiological liver activity on central review. Treatment could be recommenced with [^{177}Lu]Lu-PSMA-617 at progression.[2]

During study treatment, participants were reviewed every 3 weeks, which included routine haematology, biochemistry, and serum PSA. CT of the chest, abdomen and pelvis, and technetium-99m bone scans were done every 12 weeks until radiological progression. Follow-up continued every 12 weeks thereafter. Treatment after completion or discontinuation of study treatment was at the discretion of the treating clinicians. Subsequent anticancer therapy after study treatment was recorded as part of follow-up.

Patients who were registered as meeting study criteria but who were found to be ineligible for random assignment on central review of pre-treatment PET scans, owing to either low [^{68}Ga]Ga-PSMA-11 uptake or discordant 2-[^{18}F]FDG-positive disease on the [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET screening, had been asked to provide consent when registered for collection of data on overall survival and their next line of therapy for prostate cancer.

We prospectively collected the quantitative parameters on the pre-treatment [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET in a central database using the WIDEN system.[10] Three central reviewers (AI, LE, and MSH) used a semi-automated procedure with MIM software (Cleveland, OH, USA) to measure the whole-body MTV (mL), SUVmax, and SUVmean. According to a previously defined method,[11] the whole-body MTV was delineated automatically with an SUV threshold of at least 3 for [^{68}Ga]Ga-PSMA-11 PET and an SUV threshold equal to or greater than the liver SUVmean plus 2 SDs for 2-[^{18}F]FDG PET. Physiological uptake was thereafter removed. This occurred before randomisation. All participating sites were certified for PET scanner validation[12] and radiopharmaceutical production.

Outcomes

The primary outcome was PSA response, defined as a PSA reduction of at least 50% from baseline. The present updated analysis focuses on the secondary outcome of overall survival, defined as the interval from the date of randomisation to the date of death from any cause or the date of last follow-up alive. We also report updated progression-free survival as a secondary outcome, defined as the interval from randomisation to first evidence of PSA progression (increase of ≥25% and ≥2 ng/mL after 12 weeks, as per PCWG3[9]), radiographic progression (per locally reported CT and bone scans using RECIST version 1.1 for CT and PCWG3 for bone lesions), commencement of non-protocol anticancer treatment, or death from any cause.

We previously showed [^{68}Ga]Ga-PSMA-11 PET SUVmean to be a predictive biomarker for PSA response, and 2-[^{18}F]FDG PET MTV to be a prognostic biomarker for PSA response, using PSA response and progression-free survival as outcomes.[3] These PET indices were evaluated against overall survival in the present report as a prespecified exploratory analysis.

Statistical analysis

The statistical analysis plan was prespecified before unblinded analysis (appendix p 20). 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, as previously detailed.[6]

The study was not powered to detect improvements in the secondary outcome of overall survival. Initially we planned to assess overall survival after 170 deaths. In an

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See **Online** for appendix

updated statistical analysis plan, the cutoff for survival analysis was amended to Dec 31, 2021 (statistical analysis plan addendum 1; appendix p 20). The statistical analysis plan was also updated to include the calculation of restricted mean survival time (RMST), with 95% CIs, for time-to-event outcomes in this extended follow-up analysis, to provide an estimate of the treatment effect without reliance on the assumption of proportional hazards (statistical analysis plan addendum 2; appendix p 20). A 36-month restriction time was applied for overall survival, approximately corresponding to the median duration of follow-up. The primary analysis was by intention-to-treat, and participants who withdrew after randomisation were not replaced. Sensitivity analyses according to treatment received (per protocol) were also done. The per-protocol population comprised all randomly assigned participants who received at least one dose of assigned treatment. Additionally, time-to-event outcomes were analysed with Kaplan-Meier curves and stratified log-rank tests with the stratification factors at randomisation. Cox proportional hazards regression was used to estimate HRs and 95% CIs, adjusted for stratification factors. RMST statistics were derived with the R package survRM2 (version 1.0-4).

For imaging biomarker analysis, we tested whether a pre-treatment [^{68}Ga]Ga-PSMA-11 PET SUVmean of at least 10 modified the effect of [^{177}Lu]Lu-PSMA-617 on overall survival using a Cox proportional hazards regression model, both as a predictive and prognostic biomarker. We also tested whether a pre-treatment 2-[^{18}F]FDG PET MTV of at least 200 mL was prognostic for overall survival in the cabizitaxel group, the [^{177}Lu]Lu-PSMA-617 group, and in the total population. These cutoffs were prespecified before biomarker analysis on the basis of previous work.[9] Wald tests were used to obtain p values for the main effect and interaction terms in the Cox proportional hazard models. We adjusted for randomised treatment when evaluating the prognostic value of imaging biomarkers. For both [^{68}Ga]Ga-PSMA-11 PET SUVmean and 2-[^{18}F]FDG PET MTV, we also explored whether conclusions were sensitive to the choice of cutoff point by re-running the analyses using quartile values of the [^{68}Ga]Ga-PSMA-11 PET SUVmean to split the cohort into subsets. The prognostic value of 2-[^{18}F]FDG PET MTV was further explored after adjustment for the established prognostic factors of ECOG performance status (≥1), alkaline phosphatase (continuous), haemoglobin (continuous), bone involvement (binary), and liver involvement (binary). In a post-hoc analysis, overall survival in the [^{177}Lu]Lu-PSMA-617 group was analysed by extent of PSA response up to 12 weeks. PSA response status was categorised as less

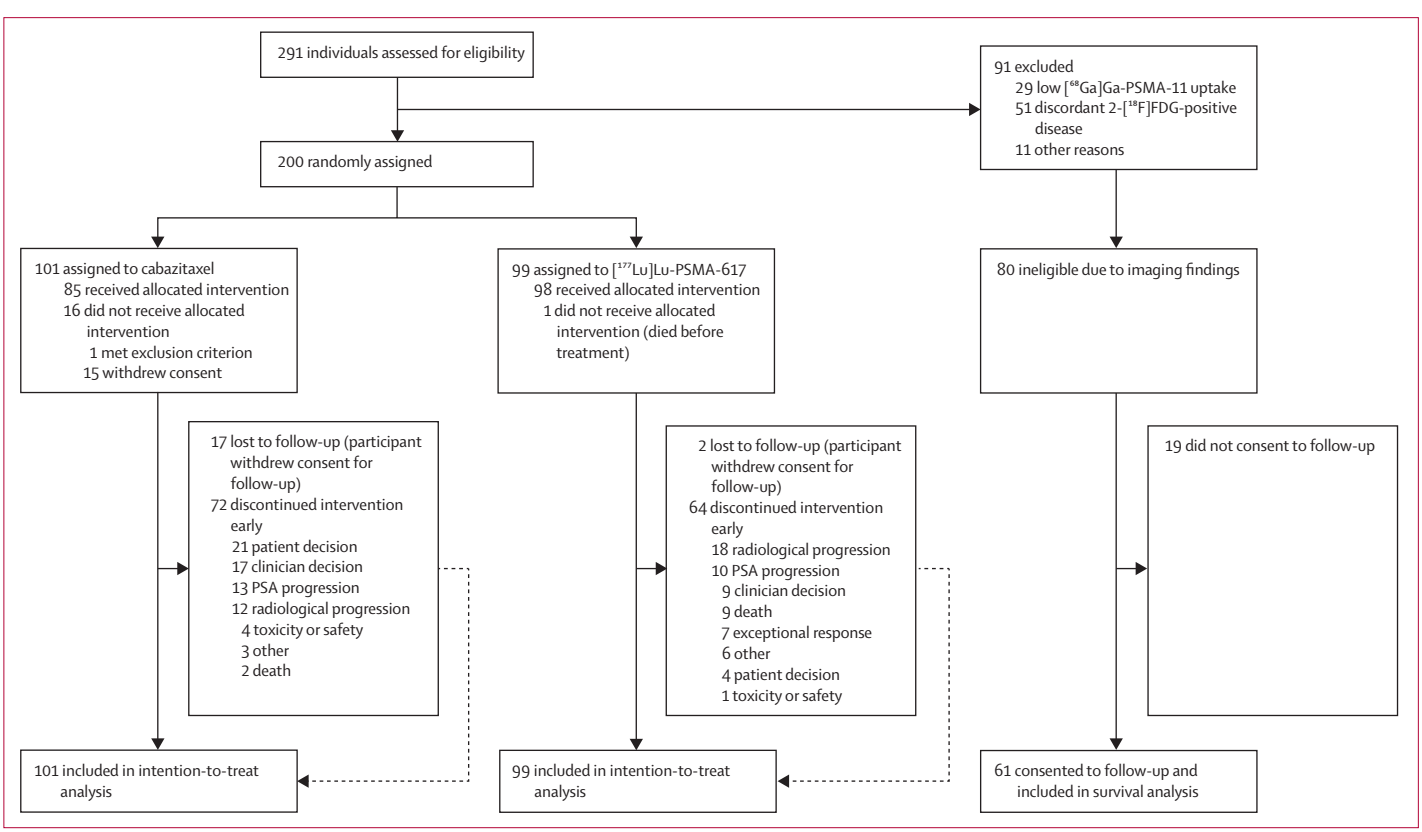

Figure 1: **Trial profile**
2-[^{18}F]FDG=2-[^{18}F]fluoro-2-deoxy-D-glucose. ^{18}F=fluorine-18. ^{68}Ga=gallium-68. ^{177}Lu=lutetium-177. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.

than 50%, 50% to less than 90%, and 90% or greater, and fitted as a time-dependent covariate in a Cox proportional hazards regression, and Simon-Makuch plots were constructed.

p values of less than 0·05 were considered to indicate statistical significance. Analyses were done with SAS (version 9.4) and R (version 4.3.0).

An independent data and safety monitoring committee reviewed the progress and results of the trial. The trial was registered on 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

From Feb 6, 2018, to Sept 3, 2019, 291 men were registered and underwent study imaging with [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG PET-CT (figure 1). 91 (31%) of 291 individuals were ineligible: 29 (10%) with low [^{68}Ga]Ga-PSMA-11 uptake, 51 (18%) with discordant 2-[^{18}F]FDG-positive disease, and 11 (4%) for other reasons. 200 men were randomly assigned, 101 to treatment with cabazitaxel and 99 to treatment with [^{177}Lu]Lu-PSMA-617. The characteristics of participants at baseline were similar in the two groups (table; appendix pp 16–18). All participants had been treated previously with docetaxel (part of the eligibility criteria), and 91 (91%) in each group had previously received enzalutamide or abiraterone (or both). One participant randomly assigned to the [^{177}Lu]Lu-PSMA-617 group died before receiving study treatment. Among participants randomly assigned to the cabazitaxel group, 14 (14%) withdrew from the study before starting study treatment due to patient preference not to proceed with chemotherapy, one (1%) withdrew due to clinician preference, and one (1%) met an exclusion criterion (thrombocytopenia) after randomisation (figure 1). Patient experiences related to decision making in the TheraP trial have been described elsewhere.[13]

The next line of therapy as a post-protocol treatment for participants randomly assigned to cabazitaxel was further cabazitaxel in 21 (21%) of 101 participants, [^{177}Lu]Lu-PSMA-617 in 20 (20%), enzalutamide in nine (9%), and abiraterone in seven (7%). Further treatment was not recorded for the remaining 44 participants. For participants randomly assigned to [^{177}Lu]Lu-PSMA-617, the next line of therapy post-protocol was cabazitaxel in 32 (32%) of 99 participants, [^{177}Lu]Lu-PSMA-617 in five (5%), abiraterone in five (5%), and enzalutamide in two (2%). Next-line therapy was not recorded for the remaining 55 participants. Subsequent lines of treatment were not recorded.

Median duration of follow-up for overall survival was 35·7 months (IQR 31·1 to 39·2). Death was documented in 147 participants (77 [78%] in the [^{177}Lu]Lu-PSMA-617 group and 70 [69%] in the cabazitaxel group). RMST was similar between those assigned to [^{177}Lu]Lu-PSMA-617 and those assigned to cabazitaxel (19·1 months [95% CI 16·9 to 21·4] *vs* 19·6 months [17·4 to 21·8], difference –0·5 months [95% CI –3·7 to 2·7], p=0·77; figure 2A). Median overall survival was also similar between those assigned to [^{177}Lu]Lu-PSMA-617 versus those assigned to cabazitaxel (16·4 months [95% CI 13·7 to 19·4] *vs* 19·4 months [14·0 to 21·7]), with a HR of 0·97 (95% CI 0·70 to 1·35); p=0·99; figure 2B). Effects of treatment on overall survival differed between the groups over time, with the survival curves crossing at approximately 24 months. Results and conclusions were similar in the per-protocol sensitivity analysis (appendix p 5).

Disease burden was a prognostic factor, with improved overall survival for participants who had 20 or fewer metastatic sites on [^{68}Ga]Ga-PSMA-11 PET-CT regardless of treatment group (HR 0·42 [95% CI 0·27–0·65], p<0·0001; data not shown). Regarding previous treatment, given that 91% of participants in each group had been treated with enzalutamide or abiraterone, an association with overall survival could not be analysed. Stratification by study site is not shown.

	[^{177}Lu]Lu-PSMA-617 group (n=99)	Cabazitaxel group (n=101)	Ineligible individuals with follow-up (n=61)
Age, years	72 (67–77)	72 (67–77)	72 (65–77)
>20 metastases*	77 (78%)	79 (78%)	NA
ECOG performance status			
0	42 (42%)	44 (44%)	21 (34%)
1	53 (54%)	52 (51%)	26 (43%)
2	4 (4%)	4 (4%)	6 (10%)
Missing	0	1 (1%)	8 (13%)
PSA, ng/mL	94 (44–219)	110 (64–245)	NA
Alkaline phosphatase, U/L	111 (83–199)	130 (79–187)	145 (90–344)
Gleason score at diagnosis			
≤7	25 (25%)	35 (35%)	16 (26%)
≥8	53 (54%)	50 (50%)	29 (48%)
Missing	21 (21%)	16 (16%)	16 (26%)
Disease stage			
Lymph node only	7 (7%)	9 (9%)	5 (8%)
Bone metastases	90 (91%)	90 (89%)	52 (90%)†
Visceral metastases	7 (7%)	13 (13%)	10 (16%)
Previous treatment			
Abiraterone only	21 (21%)	24 (24%)	10 (23%)‡
Enzalutamide only	49 (49%)	58 (57%)	21 (48%)‡
Both	21 (21%)	9 (9%)	11 (25%)‡
[^{68}Ga]Ga-PSMA-11 SUVmean*	9·7 (4·0)	9·3 (3·8)	5·9 (1·9)
2-[^{18}F]FDG MTV*	187 (264)	219 (373)	586 (816)

Data are n (%), mean (SD), or median (IQR). ECOG=Eastern Cooperative Oncology Group. 2-[^{18}F]FDG=2-[^{18}F]fluoro-2-deoxy-D-glucose. ^{18}F=fluorine-18. ^{68}Ga=gallium-68. ^{177}Lu=lutetium-177. MTV=metabolic tumour volume. NA=not available. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. SUV=standardised uptake value. SUVmean=mean SUV. *Determined by central imaging review; metastases and SUV measured on [^{68}Ga]Ga-PSMA-11 PET-CT and MTV measured on 2-[^{18}F]FDG PET-CT. †Missing data in three patients. ‡Missing data in 17 patients.

Table: **Baseline characteristics of randomly assigned individuals and those deemed ineligible after central review of [^{68}Ga]Ga-PSMA-11 or 2-[^{18}F]FDG PET-CT**

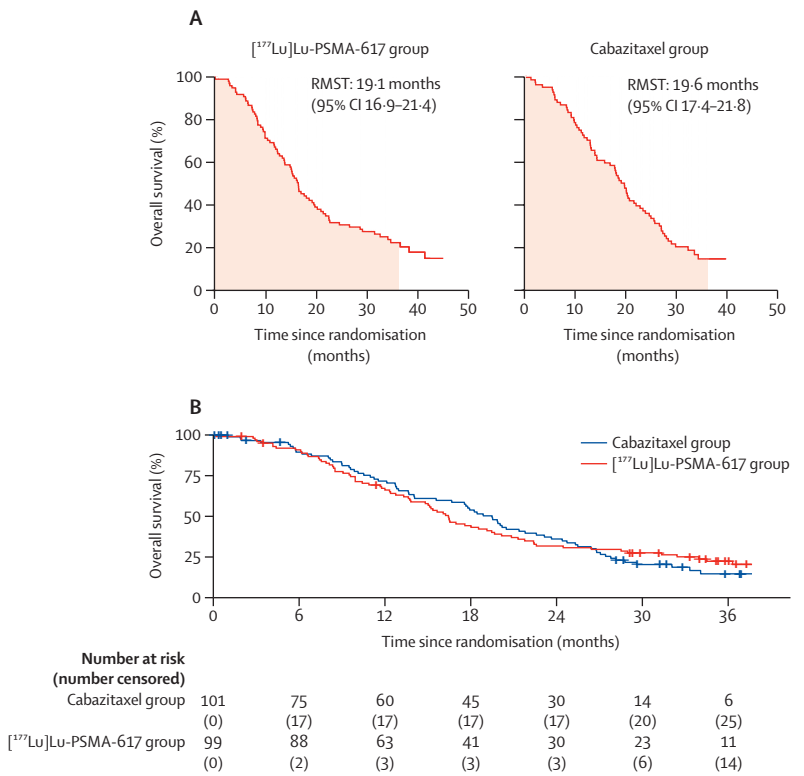

Figure 2: **Overall survival**
(A) Kaplan-Meier curve with shaded area corresponding to the RMST. (B) Kaplan-Meier curve. ^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. RMST=restricted mean survival time.

PSA or radiographic progression events were documented in 177 participants (93 [94%] in the [^{177}Lu]Lu-PSMA-617 group and 84 [83%] in the cabazitaxel group). [^{177}Lu]Lu-PSMA-617 delayed PSA or radiographic progression, compared with cabazitaxel, with an RMST for progression-free survival of 7·1 months (95% CI 5·9–8·4) versus 5·0 months (4·2–5·8; difference 2·1 months [0·7–3·6], p=0·0050; appendix p 6). As previously reported,[2] the effects of treatment on progression-free survival were not constant over time; the benefit of [^{177}Lu]Lu-PSMA-617 on progression-free survival was most apparent after 6 months (appendix p 7). Median progression-free survival was unchanged from our previous report;[2] 5·1 months (95% CI 3·4–5·7) in the [^{177}Lu]Lu-PSMA-617 group and 5·1 months (2·8–6·0) in the cabazitaxel group. Stratification by disease burden did not reveal different effects (data not shown).

Safety, PSA response rate, and RECIST version 1.1 objective response based on CT findings have been previously described[2] and no new findings were observed with longer follow-up (data not shown). No deaths were attributed to study treatment in either randomised group.

80 patients were deemed ineligible by central review of [^{68}Ga]Ga-PSMA-11 or 2-[^{18}F]FDG PET, but met all other eligibility criteria. 61 of these patients consented to follow-up, and their characteristics were similar to those of the randomly assigned participants, except for lower haemoglobin, lower clinician's estimate of expected survival time, and differences in [^{68}Ga]Ga-PSMA-11 and 2-[^{18}F]FDG imaging parameters (table; appendix pp 16–18). Excluded patients had lower SUVmean on [^{68}Ga]Ga-PSMA-11 PET and higher MTV on 2-[^{18}F]FDG PET than randomly assigned participants, in keeping with their reason for exclusion (low [^{68}Ga]Ga-PSMA-11 uptake or discordant 2-[^{18}F]FDG-positive PSMA-negative disease).

The next line of treatment administered for excluded participants was cabazitaxel in 29 (48%) of 61, enzalutamide in four (7%), carboplatin in three (5%), [^{177}Lu]Lu-PSMA in three (5%), mitoxantrone in one (2%), and other in three (5%). Next-line therapy was not recorded in 18 (30%) participants.

The RMST for overall survival was 18·8 months (95% CI 16·8–20·8) in randomly assigned participants and 11·0 months (9·0–13·1) in ineligible individuals (difference 7·8 months [95% CI 4·1–10·6], p<0·0001; appendix p 8). Compared with ineligible individuals, the HR for overall survival in the cabazitaxel randomised group was 0·42 (95% CI 0·30–0·61) and was 0·41 (0·29–0·59) in the [^{177}Lu]Lu-PSMA-617 randomised group (p<0·0001 for each; appendix p 9).

High uptake on [^{68}Ga]Ga-PSMA-11 PET (SUVmean ≥10) was present in 35 (35%) of 99 participants assigned to treatment with [^{177}Lu]Lu-PSMA-617 and 30 (30%) of 101 participants assigned to treatment with cabazitaxel. For overall survival, the HR for [^{177}Lu]Lu-PSMA-617 versus cabazitaxel was 0·96 (95% CI 0·51–1·79; p=0·89) in participants with high SUVmean (≥10) on [^{68}Ga]Ga-PSMA-11 PET and 1·07 (0·73–1·57; p=0·74) in those with lower SUVmean (<10) on [^{68}Ga]Ga-PSMA-11 PET. The treatment-by-SUVmean interaction test was not significant (p=0·70). Kaplan-Meier curves illustrate these findings (appendix p 10). The quartile splitting analysis showed no clear pattern of association between [^{68}Ga]Ga-PSMA-11 PET SUVmean cutoff values and the magnitude of the effect of [^{177}Lu]Lu-PSMA-617 on overall survival (appendix p 11). However, after adjusting for randomised treatment, SUVmean was a prognostic biomarker with longer overall survival among all participants with an SUVmean of at least 10 versus those with an SUVmean below 10 (HR 0·58 [95% CI 0·40–0·83], p=0·0033), and similar findings among those assigned to [^{177}Lu]Lu-PSMA-617 and those assigned to cabazitaxel (HR 0·56 [0·35–0·92] and 0·62 [0·36–1·07]; difference in HRs, p=0·70; figure 3A). In a post-hoc analysis in which we varied the maximum reduction in PSA from baseline to 12 weeks (<50%, 50% to <90%, and ≥90%), we found associations with overall survival (appendix p 12).

High-volume disease on 2-[^{18}F]FDG PET (MTV ≥200 mL) was present in 30 (30%) of 99 participants assigned to [^{177}Lu]Lu-PSMA-617 and 30 (30%) of 101 participants assigned to cabazitaxel. After adjusting for randomised treatment, participants with 2-[^{18}F]FDG PET MTV of at least 200 mL versus those with MTV

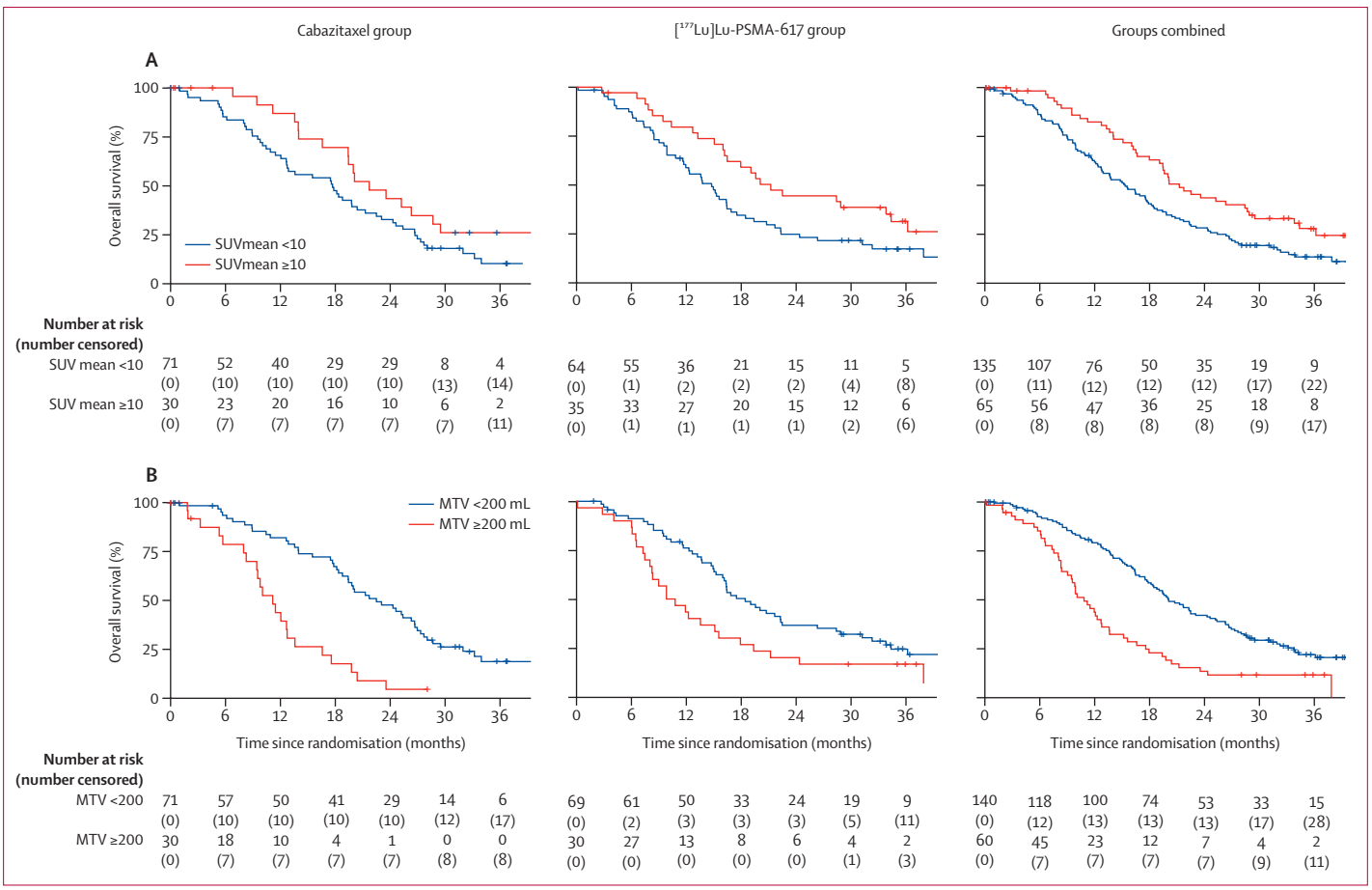

Figure 3: **Subgroup analysis for overall survival**
(A) SUVmean measured on [^{68}Ga]Ga-PSMA-11 PET-CT. (B) MTV measured on 2-[^{18}F]FDG PET-CT. 2-[^{18}F]FDG=2-[^{18}F]fluoro-2-deoxy-D-glucose. ^{18}F=fluorine-18. ^{68}Ga=gallium-68. MTV=metabolic tumour volume. PSMA=prostate-specific membrane antigen. SUVmean=mean standardised uptake value.

lower than 200 mL at baseline had worse overall survival, with a HR of 2·28 (95% CI 1·60–3·25; p<0·0001; figure 3B). The quartile-splitting analysis also showed this trend (appendix p 13). 2-[^{18}F]FDG PET MTV remained a prognostic marker after adjusting for conventional prognostic biomarkers (ECOG performance status, alkaline phosphatase, haemoglobin, and presence of bone or liver metastases; appendix p 19).

Discussion

Therapy for men with metastatic castration-resistant prostate cancer continues to evolve.[14,15] To our knowledge, TheraP is the first reported randomised trial comparing [^{177}Lu]Lu-PSMA-617 with an active comparator, cabazitaxel. The VISION and CARD trials have separately shown that [^{177}Lu]Lu-PSMA-617 and cabazitaxel are both superior to use of a second-line androgen-receptor pathway inhibitor or best supportive care.[4,8]

In TheraP, we previously observed improvements in radiographic progression-free survival, PSA-progression-free survival, PSA response rate, and objective tumour response rate after treatment with [^{177}Lu]Lu-PSMA-617.[2] In this updated analysis, we show that improvements in these surrogate outcomes did not translate into improved overall survival, although the study was not powered for this outcome. Nevertheless, given fewer grade 3–4 adverse events and improved patient-reported outcomes with [^{177}Lu]Lu-PSMA-617, it is reasonable to conclude that quality of life during treatment was better with [^{177}Lu]Lu-PSMA-617 than cabazitaxel. Treatment with [^{177}Lu]Lu-PSMA-617 also requires fewer visits and injections than cabazitaxel.

A strength of TheraP is that it used cabazitaxel, an active treatment that prolongs survival in patients with metastatic castration-resistant prostate cancer,[7] and was deemed the next appropriate standard treatment option for patients recruited to TheraP. TheraP provides data that supports the notion that [^{177}Lu]Lu-PSMA-617 and cabazitaxel are viable options for the treatment of metastatic castration-resistant prostate cancer.

The results of TheraP should be interpreted in the knowledge that 15 participants assigned to cabazitaxel withdrew from the trial after randomisation, and that 20 participants assigned to cabazitaxel in the study were

subsequently treated with [177Lu]Lu-PSMA-617 as a post-protocol regimen. [177Lu]Lu-PSMA became available in Australia in other clinicals trials and outside of trials (via the Therapeutic Goods Administration Special Access Scheme) while TheraP was ongoing. Analyses accounting for crossover have not been used in this report, but are planned to be reported separately. TheraP was an open-label trial, and participants with high PSMA-expression assigned to cabazitaxel might have sought [177Lu]Lu-PSMA following study treatment.

We previously reported that PSMA expression defined by SUVmean on [68Ga]Ga-PSMA-11 PET-CT was a predictive biomarker for PSA response.[3] In this updated analysis of associations with overall survival, [68Ga]Ga-PSMA-11 SUVmean was also prognostic, but not predictive. Findings from VISION also support a SUVmean threshold of 10 as prognostic for overall survival.[16] MTV on 2-[18F]FDG PET-CT was also a robust prognostic biomarker for overall survival, with substantially better stratification than previously reported surrogate endpoints.[3] 2-[18F]FDG PET showing high MTV might be useful for selecting patients with short overall survival who might be suitable for trials of novel combinations or alternatives.

Our results are complementary to those from VISION, which showed a median survival benefit of approximately 4 months with [177Lu]Lu-PSMA-617 versus protocol-defined therapy (15·3 months *vs* 11·3 months; HR 0·62 [95% CI 0·52–0·74], p<0·001).[4] Notably, 38% of all participants in VISION had been treated previously with cabazitaxel. Both TheraP and VISION reported better quality of life in patients assigned to [177Lu]Lu-PSMA-617 versus control.[2,5] In TheraP, we recorded significantly less fatigue, diarrhoea, neuropathy (sore hands and feet), hair loss, and change in taste in men who received [177Lu]Lu-PSMA-617 versus those who received cabazitaxel.[2] In the VISION trial, the time to a symptomatic skeletal event or death was delayed with [177Lu]Lu-PSMA-617 versus protocol-defined therapy (11·5 months *vs* 6·8 months) and time to worsening pain measured by pain intensity score was also delayed (HR 0·52 [95% CI 0·42–0·63]).[5]

In conclusion, the results of TheraP support the use of [177Lu]Lu-PSMA-617 as an alternative to cabazitaxel in PSMA-positive, metastatic castration-resistant prostate cancer progressing after docetaxel and an androgen receptor pathway inhibitor. Compared with cabazitaxel, [177Lu]Lu-PSMA-617 provided a higher PSA-response rate, longer progression-free survival, better patient-reported outcomes, a favourable safety profile and schedule of administration, and similar duration of overall survival. Survival time was shorter for patients excluded on the basis of [68Ga]Ga-PSMA-11 and 2-[18F]FDG PET imaging showing either low PSMA expression, or discordant 2-[18F]FDG-positive disease.

Contributors

MSH, LE, AJM, MRS, and IDD were members of the protocol development working party contributing to study conceptualisation and writing of the first version of the protocol. This group in addition to JPB contributed to the imaging biomarkers analysis. 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 and SGW recruited patients and collected data. MSH, LE, and AI performed the imaging central review. MSH, MRS, AJM, JPB, LE, IDD, and AYZ contributed to the statistical analysis plan. AJM led the statistical analysis. AJM and MSH accessed and verified the underlying data. AYZ reviewed data on adverse events, response, and progression-free survival. MSH was the coordinating principal investigator and wrote the first draft of the manuscript. All authors had full access to all the data in the study. All authors contributed to the writing and approval of this manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Requests for specific analyses or data will be considered by the TheraP trial executive committee from 3 months after publication of the manuscript for researchers who provide a methodologically sound proposal. This includes access to de-identified individual participant data collected during the trial. Proposals should be directed to the corresponding author (michael.hofman@petermac.org); to gain access, data requestors will sign a data access agreement. Data will be made available via email.

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