PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [^{177}Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial

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Summary

Background Previously, results from the TheraP trial showed that treatment with lutetium-177 [^{177}Lu]Lu-PSMA-617 improved frequency of prostate-specific antigen (PSA) response rate and progression-free survival compared with cabazitaxel in men with metastatic castration-resistant prostate cancer. In this study, we aimed to analyse gallium-68 [^{68}Ga]Ga-PSMA-11 PET (PSMA-PET) and 2-[^{18}F]fluoro-2-deoxy-D-glucose PET (FDG-PET) imaging parameters as predictive and prognostic biomarkers in this patient population.

Methods TheraP was a multicentre, open-label, randomised phase 2 trial that recruited men with metastatic castration-resistant prostate cancer after treatment with docetaxel who were suitable for cabazitaxel from 11 hospitals in Australia. Participants were required to be 18 years old or older; have adequate haematological, renal, and liver function; and an Eastern Cooperative Oncology Group performance status of 0–2. Participants were randomly assigned (1:1) using a centralised system using minimisation with a random component and that stratified patients by disease burden, previous treatment with enzalutamide or abiraterone, and study site. Patients were either given cabazitaxel (20 mg/m² intravenously every 3 weeks for up to ten cycles) or [^{177}Lu]Lu-PSMA-617 (6·0–8·5 GBq intravenously every 6 weeks for up to six cycles). The primary study endpoint, analysed previously, was PSA response rate. The prespecified tertiary study endpoint was association between total tumour quantitative parameters on PSMA-PET, FDG-PET, and baseline characteristics with clinical outcomes. A SUVmean of 10 or higher on PSMA-PET was evaluated as a predictive biomarker for response to [^{177}Lu]Lu-PSMA-617 versus cabazitaxel. A metabolic tumour volume (MTV) of 200 mL or higher on FDG-PET was tested as a prognostic biomarker. Both cutoff points were prespecified. The analysis was intention-to-treat, using logistic regression. This trial is registered with ClinicalTrials.gov, NCT03392428.

Findings 200 patients were randomly assigned between Feb 6, 2018, and Sept 3, 2019. 101 men were assigned to the cabazitaxel group and 99 were assigned to the [^{177}Lu]Lu-PSMA-617 group. The median follow-up at data cutoff of July 20, 2020, was 18·4 months (IQR 12·8–21·8). 35 (35%) of 99 men who were assigned [^{177}Lu]Lu-PSMA-617 and 30 (30%) of 101 men who were assigned cabazitaxel had high PSMA uptake (SUVmean of ≥10). Odds of PSA response to [^{177}Lu]Lu-PSMA-617 versus cabazitaxel were significantly higher for men with SUVmean of 10 or higher compared with those with SUVmean of less than 10 (odds ratio [OR] 12·19 [95% CI 3·42–58·76] *vs* 2·22 [1·11–4·51]; p_{adj}=0·039 for treatment-by-SUVmean interaction). PSA response rate for [^{177}Lu]Lu-PSMA-617 compared with cabazitaxel was 32 (91% [95% CI 76–98]) of 35 men versus 14 (47% [29–65]) of 30 men in patients with SUVmean of 10 or higher, and 33 (52% [39–64]) of 64 men versus 23 (32% [22–45]) of 71 men in those with SUVmean of less than 10. High-volume disease on FDG-PET (MTV ≥200 mL) was seen in 30 (30%) of 99 men who were assigned [^{177}Lu]Lu-PSMA-617 and 30 (30%) of 101 men who were assigned cabazitaxel. PSA response rate for both treatment groups combined for FDG-PET MTV of 200 mL or higher versus FDG-PET MTV of less than 200 mL was 23 (38% [95% CI 26–52]) of 60 men versus 79 (56% [48–65]) of 140 men (OR 0·44, 95% CI 0·23–0·84; p_{adj}=0·035).

Interpretation In men with metastatic castration-resistant prostate cancer, PSMA-PET SUVmean was predictive of higher likelihood of favourable response to [^{177}Lu]Lu-PSMA-617 than cabazitaxel, which provides guidance for optimal [^{177}Lu]Lu-PSMA-617 use. High FDG-PET MTV was associated with lower responses regardless of randomly assigned treatment, warranting further research for treatment intensification. A strength of this analysis is the validation of pre-specified cutpoints within a multicentre, randomised, controlled trial. Quantitative PET parameters used, however, require specialised software and are not yet routinely available in most clinics.

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See Online for appendix

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Introduction

The randomised, open-label, phase 2, TheraP trial showed higher prostate-specific antigen (PSA) response rates and longer progression-free survival in men with metastatic castration-resistant prostate cancer treated with lutetium-177 [^{177}Lu]Lu-PSMA-617 than in those treated with cabazitaxel.[1] On pre-treatment PET imaging, patients were required to have highly prostate-specific membrane antigen(PSMA)-positive disease, as well as no sites of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-positive, and PSMA-negative disease. [^{177}Lu]Lu-PSMA-617 delivers targeted radiation to tumour sites expressing PSMA. Although there is a wide variation in mean radiation absorbed doses, PSA response has been shown to correlate with tumour absorbed radiation.[2]

Metastatic castration-resistant prostate cancer is known to have substantial molecular interpatient and intrapatient heterogeneity.[3,4] PSMA-PET imaging can show that there is heterogeneity in PSMA expression among different metastases, representing a surrogate of [^{177}Lu]Lu-PSMA-617 radiation delivery. This association supports the rationale of using PSMA-PET imaging as a predictive biomarker of response to [^{177}Lu]Lu-PSMA-617. FDG-PET reveals tumour deposits with high glucose metabolism, a surrogate for measuring tumour proliferation, some of which might not be targeted with [^{177}Lu]Lu-PSMA-617 and confer a poor prognosis.[5,6] There is no causal association to support the use of FDG-PET as a predictive biomarker of response to [^{177}Lu]Lu-PSMA-617. Rather, we hypothesise worse outcomes for patients who have higher volumes of disease on FDG-PET, regardless of treatment. On FDG-PET imaging, metabolic tumour volume (MTV) can be measured, representing the amount of these highly proliferative sites (appendix p 5). On PET imaging, maximum standardised uptake value (SUVmax) measures the metastasis with the highest concentration of the radiotracer, while mean SUV (SUVmean) measures the average concentration of the radiotracer within the entire tumour volume (appendix p 5). Accordingly, PSMA-PET SUVmean better takes into account PSMA expression heterogeneity, both at the interlesional and intralesional level, reflecting the variation in radiation delivery to different sites with [^{177}Lu]Lu-PSMA-617.

The initial phase 2 single-arm trial[7,8] of [^{177}Lu]Lu-PSMA-617 used a similar patient selection approach and also investigated baseline PSMA and FDG-PET as prognostic biomarkers of overall survival.[9] Quantitative PET parameters were obtained after segmenting tumours on whole body scans. Higher PSMA-PET uptake, defined

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published up to the finalisation of the TheraP protocol on Oct 31, 2017, using the search terms "Lutetium-177", "Lu-177", "PSMA-PET", "FDG-PET", and "biomarkers". We also reviewed PubMed journals and congress abstracts in the fields of urologic oncology and nuclear medicine. There were no studies meeting these criteria. Since commencement of the trial, a prospective single-centre study in 50 men who were treated with lutetium-177 [^{177}Lu]Lu-PSMA-617 identified quantitative prostate specific membrane antigen (PSMA) and 2-[^{18}F]fluoro-2-deoxy-D-glucose PET (FDG-PET) as potential biomarkers. PSMA-PET has been incorporated into externally validated nomograms predictive of outcomes in men treated with [^{177}Lu]Lu-PSMA-617; however, no randomised data were available. Therefore, we analysed the phase 2 TheraP trial to evaluate pre-defined PSMA-PET predictive biomarkers and FDG-PET prognostic biomarkers for men with metastatic castration-resistant prostate cancer given [^{177}Lu]Lu-PSMA-617 versus cabazitaxel.

Added value of this study

In this study, we showed that PSMA-PET SUVmean is a predictive biomarker, indicating that a patient has a much higher likelihood of responding to [^{177}Lu]Lu-PSMA-617 than cabazitaxel when tumour PSMA expression is very high. We further show that FDG-PET metabolic tumour volume (MTV) is a prognostic biomarker, with lower responses in men with high metabolic tumour volumes regardless of treatment received.

Implications of all the available evidence

The TheraP and VISION trials both provide evidence to show the effectiveness of [^{177}Lu]Lu-PSMA-617 with different imaging-based patient selection. Our data provide evidence that PSMA-PET SUVmean is a predictive biomarker for response to [^{177}Lu]Lu-PSMA-617. Patients with very high PSMA expression should have access prioritised for [^{177}Lu]Lu-PSMA-617. With increasing treatment options for men with metastatic castration-resistant prostate cancer, PSMA-PET could enable optimal sequencing. Further research is needed to define whether other treatments (eg, cabazitaxel) should be sequenced first if PSMA-PET SUVmean is in the lower quartile or using combinations (eg, [^{177}Lu]Lu-PSMA-617 with PSMA upregulators). FDG-PET MTV is a prognostic biomarker for worse outcomes, regardless of treatment with [^{177}Lu]Lu-PSMA-617 or cabazitaxel. This group of patients could benefit from treatment intensification, warranting further research.

as SUVmean greater than or equal to 10·55 in whole-body tumour volume, was associated with improved overall survival versus SUVmean less than 10·55 (9·8 *vs* 6·3 months; p=0·002). A higher FDG-PET volume, defined by MTV of 207 mL or higher, was associated with poorer overall survival than MTV less than 207 mL (6·1 *vs* 9·6 months; p<0·001). Other PET parameters were not prognostic in multivariate analyses.

PSMA and FDG-PET image data were centrally collected in the TheraP study with quantitative PET analysis, which represented an ideal opportunity for defining predictive and prognostic imaging biomarkers. As a tertiary objective of the TheraP trial, we sought to validate gallium-68 [^{68}Ga]Ga-PSMA-11 PET SUVmean as a predictive biomarker of response to [^{177}Lu]Lu-PSMA-617 versus cabazitaxel, and FDG-PET MTV as a prognostic biomarker of outcome regardless of treatment group.

Methods

Study design and participants

TheraP (ANZUP 1603)[1] was a randomised, open-label, phase 2 trial conducted in 11 hospitals in Australia (appendix pp 3–4). Men with metastatic castration-resistant prostate cancer who had been previously treated with an androgen receptor pathway inhibitor and docetaxel and who had progressive disease (defined by a rising PSA as per prostate cancer working group 3 [PCWG3] criteria) were eligible.[10] Patients were required to be at least 18 years old; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; as well as adequate haematological, liver, and renal function. All patients underwent PSMA and FDG-PET scans. PET eligibility criteria for the trial were PSMA-positive disease with SUVmax of at least 20 at a site of disease and SUVmax greater than 10 at all other measurable sites of metastatic disease, and no sites of discordant FDG-positive and PSMA-negative disease. PSMA and FDG-PET scans were collected in a central database using the WIDEN system for this analysis. The study received ethics approval at participating sites and all participants provided signed, written, and informed consent. The trial protocol has been previously published,[1] and the research plan for this tertiary analysis is in the appendix.

Randomisation and masking

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

Procedures

Patients who were randomly assigned to cabazitaxel received 20 mg/m² intravenously every 3 weeks, for a maximum of ten cycles. Patients who were randomly assigned to [^{177}Lu]Lu-PSMA-617 received a starting dose of 8·5 GBq intravenously every 6 weeks, for a maximum of six cycles. The dose of [^{177}Lu]Lu-PSMA-617 decreased by 0·5 GBq every cycle, to a minimum dose of 6·0 GBq. [^{177}Lu]Lu-PSMA-617 was suspended if the single-photon emission CT (SPECT-CT) showed little or no PSMA uptake at sites of metastatic disease (uptake less than liver). Treatment could be recommenced for symptomatic progression, PSA progression, or radiological progression if patients had received fewer than six cycles. Dose reductions and delays for toxicity were specified in the trial protocol. During the treatment phase, participants had serum PSA measurements every 3 weeks. They were assessed with CT of the chest, abdomen, and pelvis, as well as whole-body bone scans every 12 weeks, until radiological progression.

We prospectively collected the quantitative parameters on the pre-treatment PSMA and FDG-PET in a central database using the WIDEN system.[11] Three central reviewers (AI, LE, and MSH) used a semi-automated procedure with MIM software (Cleveland, OH, USA) to measure whole-body tumour MTV, SUVmax, and SUVmean. Using a previously defined method,[9] whole-body tumour volume was delineated automatically with a SUV threshold of 3 or higher for PSMA-PET and a SUV threshold greater than or equal to the liver SUVmean plus 2 SDs for FDG-PET. Physiological uptake was thereafter removed. As previously reported, all participating sites were certified for PET scanner validation[12] and radiopharmaceutical production.

Outcomes

The prespecified tertiary study endpoint was association between total tumour quantitative parameters on PSMA-PET, FDG-PET, and baseline characteristics with clinical outcomes. The primary endpoint was PSA response rate, while radiographic progression-free survival and PSA progression-free survival were secondary endpoints, prespecified for PSMA and FDG-PET as predictive and prognostic biomarkers. PSA response rate was defined as the proportion of men with a PSA reduction of at least 50% from baseline. Radiographic progression-free survival was defined as the interval between randomisation and radiographic progression on CT by Response Evaluation Criteria in Solid Tumours 1.1[13] and bone scans by the PCWG3.[10] PSA progression-free survival was the interval between randomisation and PSA progression, as defined by the PCWG3[10] with an increase of at least 25% and at least 2 ng/mL after 12 weeks.

Statistical analysis

The statistical analysis plan was prespecified before the unblinded analysis. The sample size was dictated by the data available from the TheraP trial, which was not specifically powered for this biomarker analysis. The sample size of 200 participants was designed to provide

	Cabazitaxel (n=101)	[^{177}Lu]Lu-PSMA-617 (n=99)
PSMA-PET MTV (mL)		
Mean (SD)	949 (926)	1082 (994)
Median (IQR)	607 (234–1363)	750 (310–1507)
PSMA-PET SUVmax		
Mean (SD)	57 (32)	66 (49)
Median (IQR)	47 (32–73)	54 (36–83)
PSMA-PET SUVmean		
Mean (SD)	9·3 (3·8)	9·7 (4·0)
Median (IQR)	8·5 (6·7–10·5)	8·4 (7·1–11·5)
FDG-PET MTV (mL)		
Mean (SD)	219 (373)	187 (264)
Median (IQR)	80 (22–257)	88 (23–245)
FDG-PET SUVmax		
Mean (SD)	11 (9)	11 (8)
Median (IQR)	9 (6–13)	9 (7–14)
FDG-PET SUVmean		
Mean (SD)	4·36 (1·70)	4·42 (1·60)
Median (IQR)	4·19 (3·70–5·00)	4·48 (3·70–5·02)
PSMA SUVmean ≥10	30/101 (30%)	35/99 (35%)
FDG MTV ≥200 mL	30/101 (30%)	30/99 (30%)

Data are mean (SD), median (IQR), or n/N (%). ^{177}Lu=lutetium-177. FDG=2-[^{18}F] fluoro-2-deoxy-D-glucose. MTV=metabolic tumour volume. PSMA=prostate-specific membrane antigen. PSMA-PET=prostate-specific membrane antigen-PET. SUVmax=maximum standardised uptake value. SUVmean=mean standardised uptake value.

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

at least 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%. The primary analysis was by intention-to-treat and patients who withdrew following random assignment were not replaced.

Analyses were done in accordance with the intention-to-treat principle. The combination of two biomarkers (PSMA-PET SUVmean and FDG-PET MTV) and three endpoints (PSA response rate, radiographic progression-free survival, and PSA progression-free survival) generated six statistical hypotheses. We applied a sequential testing method[14] to these hypotheses and calculated p values adjusted for multiplicity (ie, p_{adj}) with alpha set to 5% (appendix pp 6–7). Unadjusted p values were also calculated.

The first co-primary hypothesis tested whether a pre-treatment PSMA-PET SUVmean greater than or equal to 10 modified the effect of [^{177}Lu]Lu-PSMA-617 on PSA response rate. This hypothesis was addressed by testing for an interaction between treatment and SUVmean in a logistic regression model. We explored in a post-hoc analysis whether conclusions were sensitive to the choice of cutpoint by re-running the analysis using quartile values of PSMA-PET SUVmean to split the cohort into subsets. The same analysis approach was used with the secondary endpoints of radiographic progression-free survival and PSA progression-free survival using a Cox proportional hazards regression model.

The second co-primary hypothesis tested whether a pre-treatment FDG-PET MTV greater than or equal to 200 mL was prognostic for PSA response rate, adjusting for randomised treatment using a logistic regression model. Analyses were re-run using quartile splitting of FDG-PET MTV in a post-hoc sensitivity analysis. Proportional hazards regression was used with the secondary endpoints of radiographic progression-free survival and PSA progression-free survival. The proportional hazards assumption for models was met as determined by evaluating Schoenfeld residuals against time with p values evaluated against an alpha of 0·01 in acknowledgement of multiplicity.

The prognostic value of FDG-PET MTV was further explored in a series of logistic regression models after adjustment for established biomarkers, fitted individually (univariable adjustment) and in combination (multivariable adjustment; appendix p 35), including ECOG performance status (≥1), alkaline phosphatase (continuous), haemoglobin (continuous), bone involvement (binary), and liver involvement (binary). The prognostic and predictive value of other PET parameters (PSMA-PET SUVmax, PSMA-PET MTV, FDG-PET SUVmax, and FDG-PET SUVmean) were investigated in prespecified exploratory analyses (appendix p 32) using similar methods to those described above using logistic regression with PSA response and proportional hazards regression with radiographic progression-free survival and PSA progression-free survival. Quartile splitting was used to construct cutoff points for these parameters.

Analyses were done using R 4.1.0. The TheraP trial is 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

Patients were recruited between Feb 6, 2018, and Sept 3, 2019. Of the 200 participants who were randomly assigned in TheraP, 101 (50%) men were assigned to the cabazitaxel group and 99 (50%) were assigned to the [^{177}Lu]Lu-PSMA-617 group. The median follow-up was 18·4 months (IQR 12·8–21·8). The data cutoff was July 20, 2020. 16 (16%) of 101 patients died or withdrew before receiving treatment in the cabazitaxel group. The PET imaging characteristics of the participants at baseline were similar in both groups (table), as well as the baseline conventional biomarkers (appendix p 9). High uptake on PSMA-PET (defined as SUVmean ≥10) was reported in 35 (35%) of 99 men who were assigned to the [^{177}Lu]Lu-PSMA-617 group and 30 (30%) of 101 men

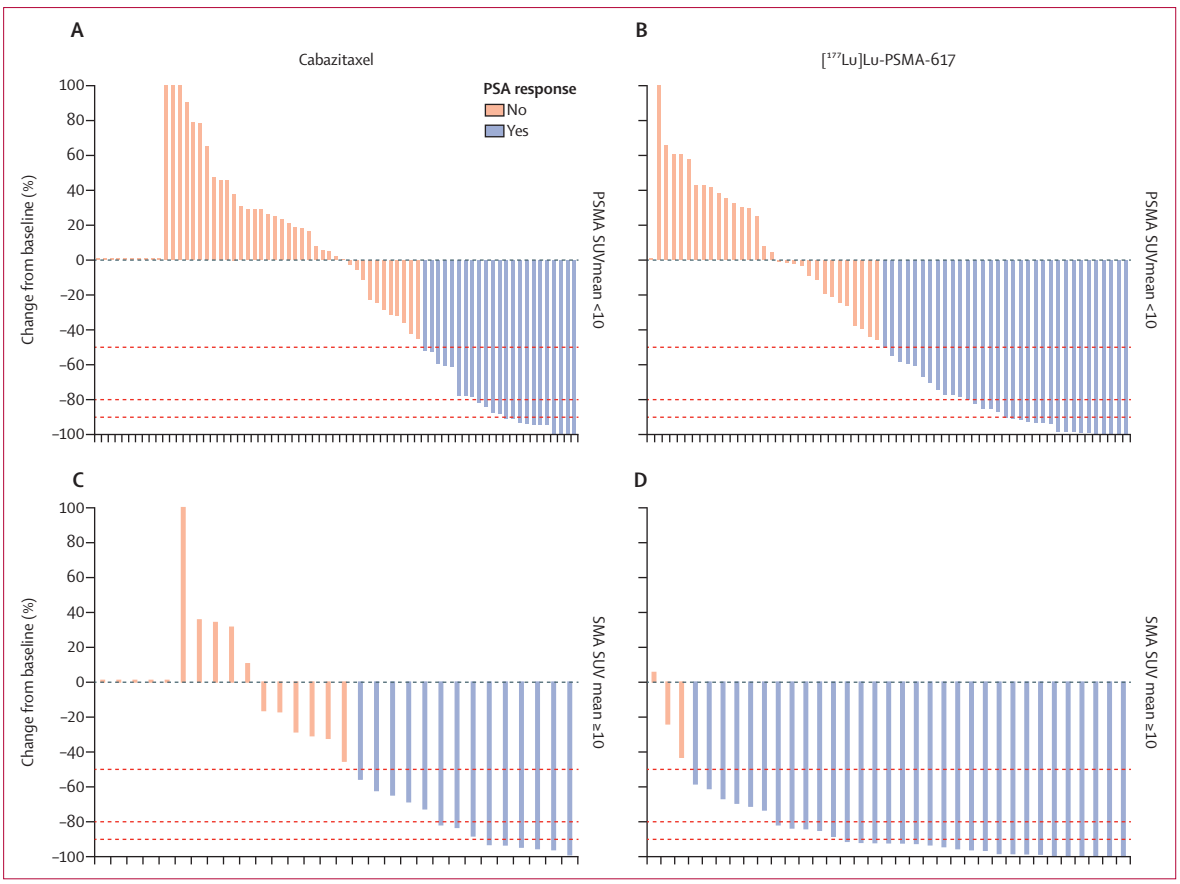

Figure 1: **PSA response according to PSMA-PET SUVmean**

Waterfall plots of the best PSA decline from baseline for patients with PSMA SUVmean <10 (A, B) and PSMA SUV mean ≥10 (C, D) who were allocated cabazitaxel (A, C) *vs* [^{177}Lu]Lu-PSMA-617 (B, D). Participants with missing data were included in the plots as non-responders with a one percentage point increase of PSA. The y-axis is truncated at 100%. The dashed red lines denote 50%, 80%, and 90% PSA response. PSA=prostate-specific antigen. PSMA-PET=prostate-specific membrane antigen-PET. SUVmean=mean standardised uptake value.

who were assigned to the cabazitaxel group. High-volume disease on FDG-PET (MTV ≥200 mL) was reported in 30 (30%) of 99 men who were assigned to [^{177}Lu]Lu-PSMA-617, and 30 (30%) of 101 men who were assigned to cabazitaxel.

PSA responses were more frequent in men with a PSMA-PET SUVmean of at least 10 who were assigned to [^{177}Lu]Lu-PSMA-617 than in those assigned to cabazitaxel (32 [91%; 95% CI 76–98] of 35 men *vs* 14 [47%; 29–65] of 30 men). With a PSMA-PET SUVmean of less than 10, PSA responses were also more frequent in men who were assigned to [^{177}Lu]Lu-PSMA-617 (33 [52%; 39–64] of 64 men) versus cabazitaxel (23 [32%; 22–45] of 71 men). The odds of a PSA response was significantly greater in men who received [^{177}Lu]Lu-PSMA-617 than men receiving cabazitaxel for PSMA-PET SUVmean of 10 or higher versus SUVmean of less than 10 (odds ratio [OR] 12·19; 95% CI 3·42–58·76 vs 2·22; 1·11–4·51; p=0·031, padj=0·039 for treatment-by-SUVmean interaction test). Waterfall plots of PSA response for each treatment group and PSMA-PET SUVmean status are in figure 1. Post-hoc sensitivity analysis using quartile splitting supported these findings (figure 2).

Lower PSA response rates were seen in men with FDG-PET MTV of 200 mL or higher than in men with FDG-PET MTV less than 200 mL (23 [38%; 95% CI 26–52] of 60 men *vs* 79 [56%; 48–65] of 140 men). Adjusting for randomised treatment, the odds of PSA responses were significantly lower in patients who had FDG-PET MTV of 200 mL or higher versus patients who had FDG-PET MTV of less than 200 mL (OR 0·44, 95% CI 0·23–0·84; p=0·014, p_{adj}=0·035). Waterfall plots of PSA response for treatment groups combined and FDG-PET MTV status are in figure 3. The odds of response for FDG-PET MTV of 200 mL or higher versus MTV less than 200 mL in the [^{177}Lu]Lu-PSMA-617 group was 0·57 (95% CI 0·24–1·40) and, for the cabazitaxel group, was 0·32 (0·11–0·84). Although FDG-PET MTV was prognostic, there was no evidence that it was a predictive biomarker for effectiveness of [^{177}Lu]Lu-PSMA-617 (p=0·40). A pre-planned step in evaluating the prognostic value of FDG-PET MTV involved confirming that there was no evidence of effect

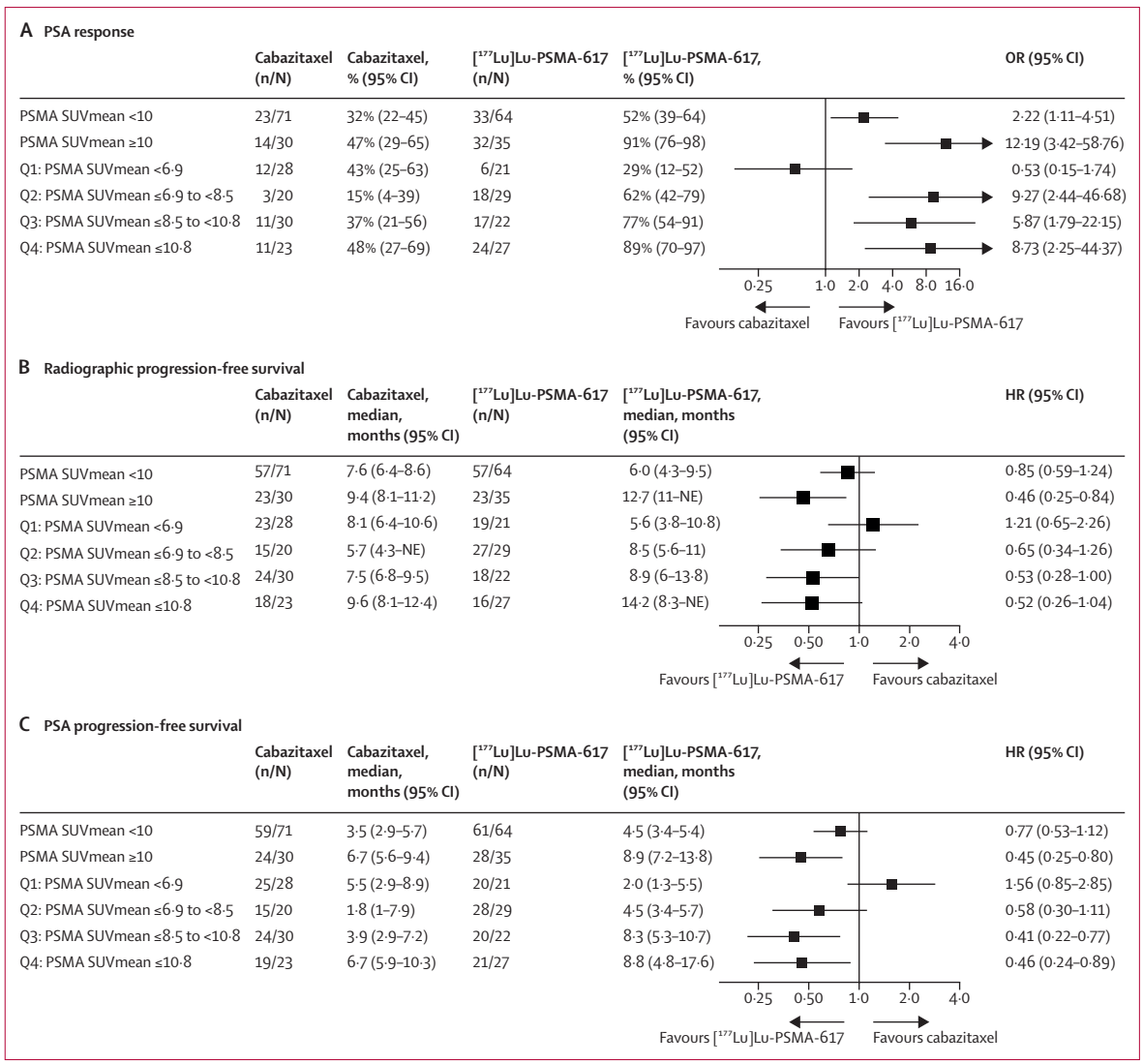

Figure 2: **Post-hoc sensitivity analyses of clinical outcomes according to PSMA-PET SUVmean**
Forest plots by PSMA-PET SUVmean status (≥10 *vs* <10) and quartile subsets for PSA response (A), radiographic progression-free survival (B), and PSA progression-free survival (C). HR=hazard ratio. NE=not estimable. OR=odds ratio. PSA=prostate-specific antigen. PSMA=prostate specific membrane antigen. SUVmean=mean standardised uptake value.

modification by testing for a treatment-by-MTV interaction. The post-hoc sensitivity analysis using quartile splitting showed that the odds of a PSA response decreased with higher FDG-PET MTV (figure 4).

In the univariate analysis for prognostic factors of PSA response, a FDG-PET MTV of 200 mL or higher was a significant biomarker (OR 0·48, 95% CI 0·26–0·89; p=0·020) as well as the allocation of the treatment group (appendix p 9). The OR remained similar after adjustment in the multivariate analysis; however, this was no longer significant (0·50, 0·24–1·00; p=0·053). Conventional biomarkers (ECOG performance status, alkaline phosphatase, haemoglobin, bone metastases, and liver metastases) were not found to be significant for PSA response (appendix p 9).

The hazard ratio (HR) for radiographic progression-free survival for [177Lu]Lu-PSMA-617 versus cabazitaxel in men who had PSMA-PET SUVmean of at least 10 was 0·46 (95% CI 0·25–0·84), and was 0·85 (0·59–1·24) in men who had a PSMA-PET SUVmean of less than 10 (figure 2). The treatment-by-SUVmean interaction test was not significant (p=0·098, p_{adj}=0·37). Results were similar for PSA progression-free survival (appendix p 8). HRs for PSA progression-free survival, were 0·45 (95% CI 0·25–0·80) for PSMA-PET SUVmean of at least 10 and 0·77 (0·53–1·12) for PSMA-PET SUVmean of less than 10 (figure 2). Kaplan Meier curves of radiographic progression-free survival and PSA progression-free survival are shown in the appendix (p 10). Post-hoc sensitivity quartile splitting analyses

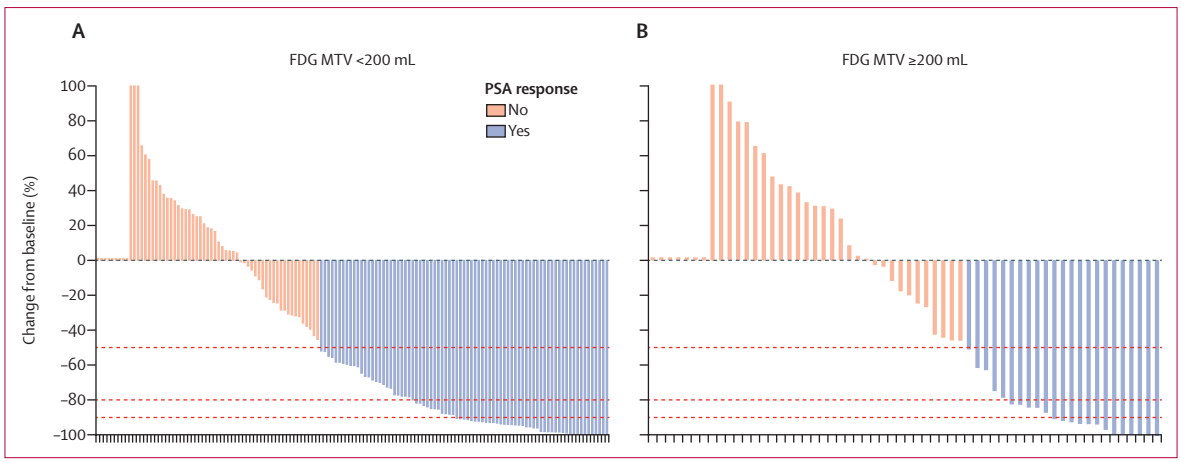

Figure 3: **PSA response according to FDG-PET MTV**
Waterfall plots of the best PSA decline from baseline for patients, treatment groups combined, with FDG-PET MTV less than 200 mL (A) *vs* greater than or equal to 200 mL (B). Participants with missing data were included in the plot as non-responders with a one percentage point increase of PSA. The y-axis is truncated at 100%. The dashed red lines denote 50%, 80%, and 90% PSA response. FDG=2-[18F]fluoro-2-deoxy-D-glucose. MTV=metabolic tumour volume. PSA=prostate-specific antigen.

for radiographic progression-free survival and PSA progression-free survival are shown in figure 2 and the appendix (pp 11–12).

After adjusting for randomised treatment, men who had a FDG-PET MTV greater than or equal to 200 mL status had a worse radiographic progression-free survival outcome with a HR of 1·79 (95% CI 1·28–2·52; p=0·0008, p_{adj}=0·035). Figure 5 shows radiographic progression-free survival for both groups pooled, while radiographic progression-free survival for both groups separately is shown in the appendix (p 13). There was no evidence that FDG-PET MTV modified the effectiveness of [177Lu]Lu-PSMA-617 (p=0·93). A pre-planned step in evaluating the prognostic value of FDG-PET MTV involved confirming there was no evidence of effect modification by testing for a treatment-by-MTV interaction. Results were similar for PSA progression-free survival with a HR of 1·44 (1·03–2·02; p=0·031, p_{adj}=0·067; appendix p 14). Post-hoc sensitivity quartile splitting analyses are shown in figure 4 and the appendix (p 15).

There was no evidence that other PET parameters (PSMA-PET SUVmax, PSMA-PET MTV, FDG-PET SUVmax, and FDG-PET SUVmean) were more valuable markers of response or prognosis than PSMA-PET SUVmean or FDG-PET MTV (appendix p 16–29).

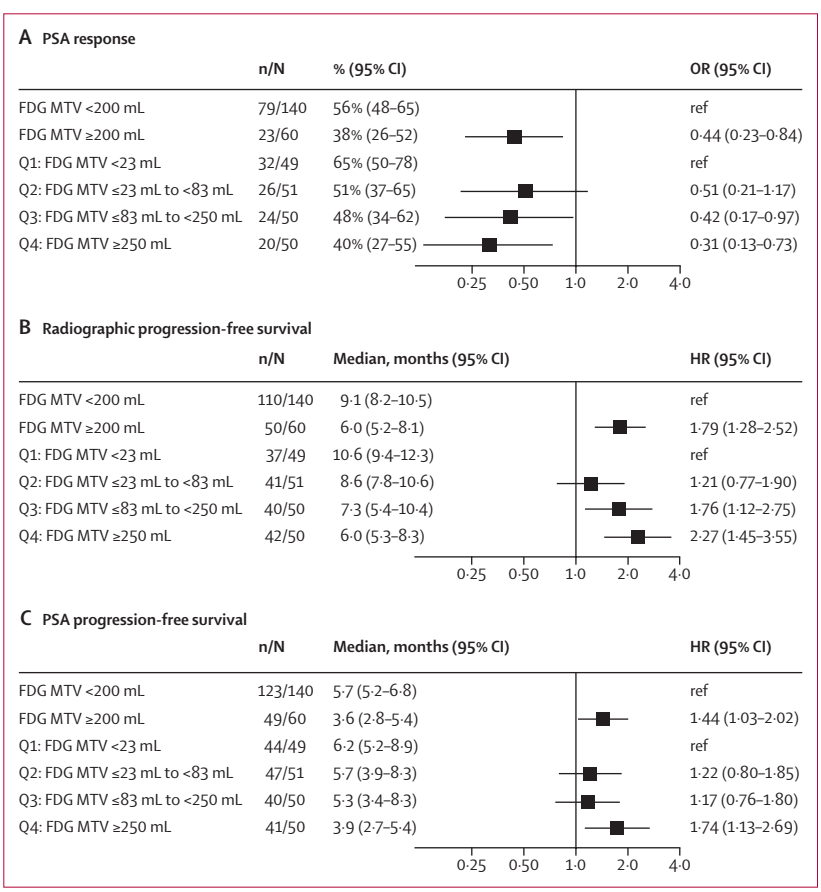

Figure 4: **Post-hoc sensitivity analyses of clinical outcomes according to FDG-PET MTV**
Forest plots by FDG-PET MTV quartile subsets for PSA response (A), radiographic progression-free survival (B), and PSA progression-free survival (C). The treatment groups are combined. FDG-PET MTV less than 200 mL is the reference for FDG-PET MTV greater than or equal to 200 mL. Q1 is the reference for the quartile subsets. FDG=2-[18F]fluoro-2-deoxy-D-glucose. HR=hazard ratio. MTV=metabolic tumour volume. OR=odds ratio. PSA=prostate-specific antigen. ref=reference.

Discussion

The TheraP and VISION[15] studies have both established PSMA-PET imaging to select patients for radionuclide therapy. In this theranostic paradigm, patients with higher PSMA uptake receive higher delivery of beta radiation to sites of metastases.[2] In this study, we showed that pre-treatment PSMA-PET is a predictive biomarker of PSA response for [177Lu]Lu-PSMA-617 treatment compared with cabazitaxel within a randomised controlled setting. We also validated pre-treatment FDG-PET MTV as a

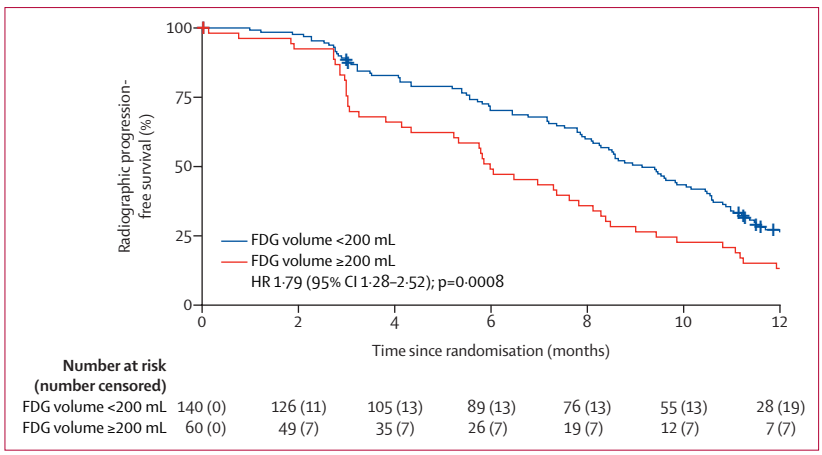

Figure 5: **Radiographic progression-free survival according to FDG-PET MTV**
FDG=2-[18F]fluoro-2-deoxy-D-glucose. MTV=metabolic tumour volume.

prognostic biomarker, with higher metabolic volume of disease conferring a worse prognosis.

Our findings provide guidance for improving optimal use of [177Lu]Lu-PSMA-617 for men with metastatic castration-resistant prostate cancer. In March, 2022, [177Lu]Lu-PSMA-617 was approved by the US Food and Drug Administration (FDA) for clinical use, although resources and capacity will be limited in many centres, both in the USA and worldwide. Although [177Lu]Lu-PSMA-617 resulted in a higher PSA response rate compared with cabazitaxel in the TheraP trial, the use of an additional predictive biomarker could identify the subgroup of men who might benefit most of all in terms of response rate. For these men, providing [177Lu]Lu-PSMA-617 could be prioritised. PSMA-PET has also been integrated in externally validated nomograms[16] that are predictive for outcome in men treated with [177Lu]Lu-PSMA-617, providing further evidence to support the use of PSMA-PET SUVmean as a biomarker. Furthermore, FDG-PET could identify men with metastatic castration-resistant prostate cancer who might have a worse prognosis, regardless of treatment. Trials exploring treatment intensification in men with high FDG-PET MTV, such as higher doses of [177Lu]Lu-PSMA-617, shorter intervals of [177Lu]Lu-PSMA-617 administration, or combination therapies, are warranted.

Our study has some limitations. First, we did not evaluate these biomarkers with overall survival as a primary endpoint. Our analysis used PSA response rate as a primary endpoint, aligning with the TheraP trial, which was powered for this outcome. We intend to update this analysis with data for overall survival, although radiographic progression-free survival is likely to be more representative because it is not affected by crossover to other treatments following progression. Second, in this study, there was also an insufficient sample size to definitively evaluate all endpoints, considering the number of patients who died or withdrew before treatment in the cabazitaxel group. In our analysis, these patients were counted as PSA non-responders, which might have overestimated the biomarker's value. Lastly, the method for contouring whole-body tumour volume was time consuming and other contouring methods exist that could produce different results in SUVmean.[16] Clinical implementation in the future could be facilitated with validated deep-learning methods and reproducible software tools, reducing time and interobserver variability.

A key strength of our analysis is the multicentre dataset, collected across 11 sites in Australia using a variety of PET–CT systems. All sites had validation of PET scanners and radiopharmaceutical production before site activation. Tumour segmentation was done prospectively, and quantitative parameters (PSMA-PET SUVmean and FDG-PET MTV) were prespecified, including cutoff points. This approach contrasts with other imaging research, in which optimal cutoff points were defined post-hoc. Furthermore, our study conformed to the reporting recommendations for tumour marker prognostic studies.[17]

Our analysis does not inform if patients excluded from the TheraP study because of lower PSMA uptake would benefit from [177Lu]Lu-PSMA-617. In our post-hoc sensitivity analysis by PSMA-PET SUVmean quartile subsets, treatment outcomes remained in favour of [177Lu]Lu-PSMA-617 for most patients, whereby increasing SUVmean was associated with increased odds of a PSA response to [177Lu]Lu-PSMA-617. However, men in the lower quartile with PSMA-PET SUVmean less than 6·9 did not show a superior response to [177Lu]Lu-PSMA-617 versus cabazitaxel. Below a threshold, these patients might not even benefit from [177Lu]Lu-PSMA-617, although our data do not confirm this hypothesis nor provide a definitive threshold. In a post-hoc analysis of the VISION data for quantitative parameters on PSMA-PET, higher SUVmean was associated with improved outcomes,[18] although the findings could not inform of the predictive value because of study design and have yet to be compared with the control group. Further analysis would provide crucial insights for the threshold below which treatment with [177Lu]Lu-PSMA-617 would be futile. This evidence would improve appropriate therapy administration and would also avoid treating a subgroup of patients with low PSMA uptake who would possibly derive no benefit from [177Lu]Lu-PSMA-617.

To conclude, the randomised, controlled trial data with calibrated PET imaging from multiple sites presented here provide evidence that support findings from smaller or retrospective studies of PSMA-PET SUVmean[16,19] and FDG-PET MTV as biomarkers.[5] [177Lu]Lu-PSMA-617 should be prioritised in men with metastatic castration-resistant prostate cancer with high PSMA-PET SUVmean, while FDG-PET MTV can identify men with worse prognosis, warranting further research for treatment intensification.

Contributors
MSH, JPB, LE, AI, AJM, MRS, and IDD were members of the protocol development working party contributing to conceptualisation and writing the first version of the protocol. MSH, JPB, LE, AI, AMJ, SS, RJF, AMS, S-TL, and AAA accrued patients and collected data. MSH, LE, and AI conducted the imaging central review. MSH, JPB, MRS, AJM, LE, 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 for TheraP. JPB and MSH wrote the first draft of the manuscript and visualisation with major input from LE, AJM, MRS, and IDD. MSH, JPB, AJM, and IDD had access to the verified data. All authors contributed to the writing and approval of this manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declarations of interests
MSH reports grants from Novartis, ANSTO, Bayer, Isotopia; and consulting fees for lectures or advisory boards from Astellas, AstraZeneca, Janssen, Merck Sharp and Dohme (MSD), Mundipharma, and Point Biopharma. LE reports personal fees from AstraZeneca, Janssen, Astellas, outside the submitted work. SS reports grants from Novartis, AstraZeneca, MSD, Genentech, Pfizer; and personal fees from AstraZeneca, MSD, Bristol Myer Squibb, and Novartis, outside the submitted work. AYZ reports personal fees from AstraZeneca, Bayer, Astellas, MSD, Novartis, Pfizer, Merck, and Bristol-Myers Squibb, outside the submitted work. AMS reports trial and research funding from AbbVie, EMD Serono, ITM, AVID, Medimmune, Telix, Adalta, Cyclotek, Theramyc; and personal fees from Life Science Pharmaceuticals, and Imagion, all outside the submitted work. AAA reports grants or personal fees from Janssen, Astellas, Novartis, Merck Serono, Tolmar, Amgen, Pfizer, Bayer, Telix Pharmaceuticals, Bristol-Myers Squibb, Sanofi, Noxopharm, AstraZeneca, Ipsen, MSD; and grants from GlaxoSmithKline, Aptevo Therapeutics, MedImmune, Bionomics, SYNthorx, Aculeus Therapeutics, Gilead, Eli Lilly, and Exelixis, all outside the submitted work. MRS reports grants from Astellas, Amgen, AstraZeneca, Bayer, Bionomics, Bristol-Myers Squibb, Celgene, Medivation, MSD, Pfizer, Roche, Sanofi, and Tilray; all outside the submitted work. IDD reports grants from National Health and Medical Research Council, during the conduct of the study; and institutional payments to support prostate cancer trials from Pfizer, ANZUP Cancer Trials Group, Bayer, Astellas, Janssen, Movember Foundation, and MSD, outside the submitted work. IDD also reports being an unremunerated chair of ANZUP Cancer Trials Group. All other authors declare no competing interests.

Data sharing
De-identified participant data will be made available to researchers who are 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 be required to sign a data access agreement. No additional, related documents will be available.

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