Prognostic and predictive value of baseline PSMA-PET total tumour volume and SUVmean in metastatic castration-resistant prostate cancer in ENZA-p (ANZUP1901): a substudy from a multicentre, open-label, randomised, phase 2 trial

Louise Emmett, Nathan Papa, Shalini Subramaniam, Megan Crumbaker, Andrew Nguyen, Anthony M Joshua, Shahneen Sandhu, Andrew Weickhardt, Sze-Ting Lee, Siobhan Ng, Roslyn J Francis, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Narjess Ayati, Claire Niu, Michael S Hofman, Andrew James Martin, Hayley Thomas, Ian D Davis, Martin R Stockler*, for the ENZA-p Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

Summary

Background Quantitative parameters derived from gallium-68 [^{68}Ga]Ga-prostate-specific membrane antigen (PSMA)-11 PET-CT (PSMA-PET-CT) such as whole-body standardised uptake value (SUV)mean and total tumour volume (PSMA-TTV) have shown prognostic value for response to lutetium-177 [^{177}Lu]Lu-PSMA-617 monotherapy in patients with prostate cancer. Adding [^{177}Lu]Lu-PSMA-617 to enzalutamide improved overall survival compared with enzalutamide in patients with metastatic castration-resistant prostate cancer in the ENZA-p trial. This prespecified substudy of ENZA-p evaluated baseline PSMA-PET quantitative parameters as predictive and prognostic biomarkers for enzalutamide plus [^{177}Lu]Lu-PSMA-617 and enzalutamide monotherapy.

Methods ENZA-p was an open-label, randomised, phase 2 trial done in 15 hospitals in Australia. Participants were aged 18 years or older with progressive metastatic castration-resistant prostate cancer who had not previously been treated with docetaxel or androgen receptor pathway inhibitors (abiraterone permitted) for metastatic castration-resistant prostate cancer, had [^{68}Ga]Ga PSMA-PET-CT-positive disease, an Eastern Cooperative Oncology Group performance status of 0–2, and at least two risk factors for early progression on enzalutamide. Patients were randomly assigned (1:1) by a centralised, web-based system using minimisation with a random component to either enzalutamide 160 mg daily (oral) or enzalutamide 160 mg daily plus adaptive-dosed (two or four doses) intravenous [^{177}Lu]Lu-PSMA-617 7·5 GBq every 6–8 weeks. The primary endpoint was prostate-specific antigen (PSA) progression-free survival, which has been reported previously. All participants underwent baseline [^{68}Ga]Ga-PSMA-11 PET-CT to assess eligibility (SUVmax >15 at a single site and SUVmax >10 at all larger tumour sites). PSMA-PET parameters were quantified with semi-automated software to derive PSMA-TTV and SUVmean and correlated with overall and PSA progression-free survival in a prespecified analysis, with the primary endpoint of this substudy being overall survival. Thresholds were based on SUVmean highest quartile (Q4 *vs* Q1–3) and PSMA-TTV median at baseline. We used the Kaplan–Meier method and Cox regression models and analysed patients on a treatment received basis. The trial is registered with ClinicalTrials.gov, NCT04419402, and follow-up is complete.

Findings Between Aug 17, 2020, and July 26, 2022, 162 participants were randomly assigned to enzalutamide (n=79) or enzalutamide plus [^{177}Lu]Lu-PSMA-617 (n=83). This substudy included the 160 of the 162 randomly assigned patients who received study treatment (79 in the enzalutamide group and 81 in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group). Median follow-up at the final data cutoff (July 31, 2024) was 34 months (IQR 29–39), with 96 overall survival events (53 with enzalutamide and 43 with enzalutamide plus [^{177}Lu]Lu-PSMA-617). Baseline median SUVmean was 7·7 (IQR 6·5–9·8) and median PSMA-TTV was 234 mL (76–687). Median overall survival for PSMA-TTV below or above the median in the enzalutamide group was 39 months (95% CI 31–not estimable) versus 20 months (13–24; HR 0·23 [95% CI 0·13–0·42], log-rank p<0·0001). The corresponding median overall survival for PSMA-TTV below or above the median in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group was 35 months (95% CI 32–37) versus 28 months (26–34; HR 0·66 [0·36–1·21], log-rank p=0·18). The test for interaction between PSMA-TTV and treatment group for overall survival was p=0·0078. Median overall survival for SUVmean Q4 versus Q1–3 in the enzalutamide group was 29 months (95% CI 17–39) versus 25 months (21–31; HR 0·84 [0·44–1·60], log-rank p=0·59). For enzalutamide plus [^{177}Lu]Lu-PSMA-617, median overall survival for SUVmean Q4 versus Q1–3 was 32 months (95% CI 21–not estimable) versus 34 months (27–35; HR 0·80 [0·38–1·68], log-rank p=0·56). The test for interaction between SUVmean (Q4 *vs* Q1–3) and treatment group for overall survival was p=0·88.

Interpretation Baseline PSMA-TTV is prognostic for overall survival and predictive for a beneficial effect on overall survival with the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide as first-line treatment for high-risk metastatic

Lancet Oncol 2025

Published **Online** July 30, 2025 https://doi.org/10.1016/S1470-2045(25)00339-0

*Co-last authors

†All ENZA-p trial collaborators are listed in the appendix (pp 20–21)

Department of Theranostics and Nuclear Medicine (Prof L Emmett MD, A Nguyen MBBS, N Ayati MBBS) **and Department of Medical Oncology, Kinghorn Cancer Centre** (M Crumbaker PhD, Prof A M Joshua PhD), **St Vincent's Hospital, Sydney, NSW, Australia; St Vincent's Clinical School, University of New South Wales, Sydney, NSW, Australia** (Prof L Emmett, M Crumbaker, A Nguyen, Prof A M Joshua, N Ayati); **Garvan Institute of Medical Research, Sydney, NSW, Australia** (Prof L Emmett, N Papa PhD, M Crumbaker, Prof A M Joshua, N Ayati); **NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia** (S Subramaniam MBBS, C Niu MSc, Prof A J Martin PhD, H Thomas MBiostat, Prof M R Stockler MBBS); **Department of Medical Oncology, Bankstown-Lidcombe Hospital, Sydney, NSW, Australia** (S Subramaniam); **Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia** (Prof S Sandhu MBBS, Prof M S Hofman MBBS); **ULTRA The University of Queensland Clinical Trials Capability, Centre for Clinical Research, Brisbane, QLD, Australia** (Prof A J Martin); **Olivia Newton-John Cancer and Wellness Centre**

(A Weickhardt PhD) and Department of Molecular Imaging and Therapy (Prof S-T Lee PhD), Austin Health, Melbourne, VIC, Australia; School of Cancer Medicine, La Trobe University, Melbourne, VIC, Australia (A Weickhardt, Prof S-T Lee); Olivia Newton-John Cancer Research Institute, Melbourne, VIC, Australia (Prof S-T Lee); Department of Oncology (S Ng MBBS) and Department of Nuclear Medicine (R J Francis PhD), Sir Charles Gairdner Hospital and University of Western Australia, Perth, WA, Australia; Medical School, University of Western Australia, Perth, WA, Australia (R J Francis); Department of Oncology (Prof J C Goh MBBS) and Department of Nuclear Medicine and Specialised PET Services (D A Pattison MBBS), Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; Queensland University of Technology, Brisbane, QLD, Australia (Prof J C Goh); School of Medicine (D A Pattison) and Centre for Clinical Research (Prof A J Martin), University of Queensland, Brisbane, QLD, Australia; Department of Medical Oncology (T H Tan MBBS) and Nuclear Medicine, PET and Bone Densitometry (I D Kirkwood MBBS), Royal Adelaide Hospital, Adelaide, SA, Australia; Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, SA, Australia (I D Kirkwood); Prostate Cancer Theranostics and Imaging Centre of Excellence (ProsTIC) and Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (Prof M S Hofman); Australian and New Zealand Urogenital and Prostate Cancer Trials Group, Sydney, NSW, Australia (Prof I D Davis PhD); Monash University Eastern Health Clinical School, Melbourne, Australia (Prof I D Davis); Eastern Health, Melbourne, VIC, Australia (Prof I D Davis); Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, NSW, Australia (Prof M R Stockler)

castration-resistant prostate cancer. By contrast, PSMA SUVmean was not prognostic for PSA progression-free survival or overall survival when [^{177}Lu]Lu-PSMA-617 was administered with enzalutamide.

Funding The Prostate Cancer Research Alliance initiative (Movember and Australian Federal Government), Prostate Cancer Foundation Challenge Award, St Vincent's Clinic Foundation, GenesisCare, RoyMorgan, Endocyte (a Novartis company), and Astellas.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Introduction

Combination enzalutamide plus lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 improves overall survival compared with enzalutamide alone, with an 8-month survival difference in early metastatic castration-resistant prostate cancer.[1] Identifying which patients will most likely benefit from therapy intensification is a key translational goal of the ENZA-p trial. Imaging biomarkers, including standardised uptake value (SUV)mean on PSMA-PET have been evaluated with [^{177}Lu]Lu-PSMA-617 monotherapy, showing that SUVmean is prognostic for depth of response and radiographic progression-free survival.[2,3] PSMA-total tumour volume (TTV) has been shown to be prognostic for overall survival with [^{177}Lu]Lu-PSMA-617, but not other systemic therapies.[4] The aim of this prespecified trial substudy was to determine the prognostic and predictive value of PSMA SUVmean and PSMA-TTV for PSA progression-free survival and overall survival with enzalutamide and combination enzalutamide plus [^{177}Lu]Lu-PSMA-617.

Methods

Study design and participants

ENZA-p (ANZUP 1901) is a multicentre, open-label, randomised, phase 2 trial performed at 15 hospitals in Australia. The trial protocol, primary, and key secondary outcomes up to a median follow-up of 34 months have been previously reported.[1,5,6] ENZA-p enrolled individuals aged 18 years or older with adenocarcinoma of the prostate defined by histopathology or metastatic disease typical of prostate cancer, without substantial

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published between July 13, 2012, and Jan 15, 2019, using the search terms "lutetium-177", "Lu-177", "PSMA" or "prostate specific membrane antigen", and "enzalutamide". We also reviewed key journals and congress abstracts in the fields of urological oncology and nuclear medicine. No publications were found. We designed an imaging-based translational programme as a tertiary endpoint in ENZAp to evaluate the prognostic and predictive benefit of prostate-specific membrane antigen (PSMA)-PET imaging, including at screening, to be done concurrently embedded into the ENZAp therapy trial. Subsequent to commencing the ENZAp trial, two sub-analyses from randomised trials with lutetium-177 [^{177}Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer demonstrated the prognostic value of PSMA quantitative standardised uptake value (SUV)mean for [^{177}Lu]Lu-PSMA-617 monotherapy. A further prospective trial demonstrated the prognostic value of PSMA total tumour volume in patients receiving [^{177}Lu]Lu-PSMA-617.

Added value of this study

To our knowledge, this ENZA-p substudy is the first trial to show that PSMA-PET total tumour volume is a prognostic biomarker for enzalutamide in metastatic castration-resistant prostate cancer, with longer overall survival in patients with low volume compared with those with high volume of prostate cancer treated with enzalutamide monotherapy. PSMA-PET total tumour volume is also predictive of longer overall survival with the addition of ^{177}Lu]Lu-PSMA-617 to enzalutamide in patients with metastatic castration-resistant prostate cancer and risk factors for early treatment failure on enzalutamide alone. In contrast to the studies that have found that PSMA SUVmean to be predictive for a good response to [^{177}Lu]Lu-PSMA-617 monotherapy, this study found no such predictive or prognostic value with SUVmean when [^{177}Lu]Lu-PSMA-617 was added to first-line enzalutamide therapy for metastatic castration-resistant prostate cancer.

Implications of all the available evidence

PSMA-PET quantitative parameters have increasing value in guiding treatment choices in metastatic castration-resistant prostate cancer. Patients with high PSMA-PET total tumour volume commencing enzalutamide should be considered for intensification with the addition of [^{177}Lu]Lu-PSMA-617 to increase overall survival. Furthermore, although PSMA SUVmean has prognostic and predictive value with [^{177}Lu]Lu-PSMA-617 monotherapy in metastatic castration-resistant prostate cancer, it does not when [^{177}Lu]Lu-PSMA-617 is added to enzalutamide. This has implications for decisions around optimal treatments for patients based on PSMA SUVmean and broadens our understanding of how and when these imaging biomarkers should be used. Further research is needed to fully understand the impact of combination therapies on biomarkers with known prognostic and predictive value for monotherapies.

sarcomatoid, spindle cell, or neuroendocrine small-cell components. Participants had metastatic castration-resistant prostate cancer and an Eastern Cooperative Oncology Group performance status of 0–2, with progressive disease defined by a rising serum prostate-specific antigen (PSA) as per Prostate Cancer Working Group 3 criteria and serum PSA higher than 5 ng/mL. Participants had metastatic castration-resistant prostate cancer not previously treated with androgen receptor antagonist (previous abiraterone was permitted) and with no previous docetaxel for metastatic castration-resistant prostate cancer. Docetaxel for metastatic hormone-sensitive prostate cancer was permitted. Eligible participants were those for whom enzalutamide alone was considered the appropriate next standard treatment and who had two or more risk factors for early progression on enzalutamide alone.[7,8] These risk factors included serum lactate dehydrogenase more than or equal to the institutional upper limit of normal (IULN), alkaline phosphatase more than or equal to the IULN, albumin less than 35 g/L, M1 disease at initial diagnosis, less than 3 years from initial diagnosis to randomisation, more than five bone metastases, visceral metastases, PSA doubling time less than 84 days, pain requiring opiates for longer than 14 days, or previous treatment with abiraterone for hormone-sensitive prostate cancer.[7,8] Patients with other active malignancies within 5 years before consent and seizures or conditions predisposing to seizures were excluded. Eligibility also required adequate renal, haematological, and liver function. Screening of potential participants included central review of a gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT (PSMA-PET-CT). Imaging criteria for inclusion were PSMA-positive disease with a maximum SUV (SUVmax) of 15 or more at a single site of disease, and SUVmax of more than 10 at all sites of measurable disease not affected by partial volume effect on PSMA-PET.

All participants provided written informed consent. The study and protocol had ethical and regulatory approval at all participating sites. Consumer research advocates contributed to grant applications, protocol development, and trial conduct. The trial was conducted in accordance with the principles of the Good Clinical Practice guidelines and the Declaration of Helsinki. Data on gender and race were not collected. The trial is registered with ClinicalTrials.gov, NCT04419402.

Randomisation and masking

We randomly assigned participants (1:1) to enzalutamide or adaptive-dosed enzalutamide plus [^{177}Lu]Lu-PSMA-617 with a centralised, web-based system using minimisation with a random component to stratify for study site, disease burden (>20 lesions *vs* ≤20 lesions by PSMA-PET-CT), use of early docetaxel for hormone-sensitive disease (yes *vs* no), and previous treatment with abiraterone for hormone-sensitive disease (yes *vs* no). Treatment allocation was concealed until after registration was completed. Neither participants nor investigators were masked to the group assignment.

Procedures

Participants in both groups received enzalutamide 160 mg orally daily until disease progression or unacceptable toxicity. The experimental group received two doses of [^{177}Lu]Lu-PSMA-617 intravenously 2 weeks and 8 weeks after commencing enzalutamide. All participants had a repeat PSMA-PET-CT at week 12, which was centrally reviewed to guide adaptive dosing of either two or four doses of [^{177}Lu]Lu-PSMA-617 in the experimental group. Patients with persistent PSMA-positive disease (defined as evidence of tumour PSMA expression above blood-pool intensity) on a centrally reviewed PSMA-PET-CT at week 12 were treated with up to a further two doses of [^{177}Lu]Lu-PSMA-617 16 weeks and 24 weeks after commencing enzalutamide. All administered doses of [^{177}Lu]Lu-PSMA-617 were 7·5 GBq. Participants were reviewed every 4 weeks during which they underwent blood tests for haematology, biochemistry, and serum PSA while on study treatment, then every 6 weeks until radiological progression. Participants with dose-limiting toxic effects attributable to [^{177}Lu]Lu-PSMA-617 could receive a 20% dose reduction in [^{177}Lu]Lu-PSMA-617 with no re-escalation allowed. Similarly, participants who had toxic effects attributable to enzalutamide could interrupt study treatment, restarting at the original dose (160 mg per day), or the dose of enzalutamide could be reduced to 120 mg per day for chronic long-term grade 2 adverse events.[5] CT of the chest, abdomen, and pelvis, and technetium-99m bone scans were performed every 12 weeks until radiological progression. Study treatment was discontinued for progressive disease, unacceptable toxicity, substantial treatment delays, or patient choice, or if the participant was no longer clinically benefitting. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). A safety assessment was done at 6 weeks and 12 weeks after the last dose of study treatment, and follow-up continued every 6 weeks thereafter until radiographic progression, after which survival and subsequent treatment follow-up occurred every 12 weeks.

[^{68}Ga]Ga-PSMA-11 was required for PSMA-PET-CT imaging at all timepoints. Both the PSMA PET-CT imaging protocol and acquisition procedures were standardised across sites with phantom certification of PET cameras and [^{68}Ga]Ga-PSMA-11 radiopharmacy production through the Australian Radiopharmaceutical Trials Network.[5] All PSMA-PET-CT timepoints were uploaded to a de-identified cloud-based server specific to the ENZA-p trial (WIDEN) and pushed automatically to a cloud-based image quantification software (MIM encore, MIM Software, a GE HealthCare Company, Beechwood, OH, USA) specifically designed for the trial.

Correspondence to:
Prof Louise Emmett, Department of Theranostics and Nuclear Medicine, St Vincent's Hospital, Sydney, NSW 2010, Australia
louise.emmett@svha.org.au

See Online for appendix

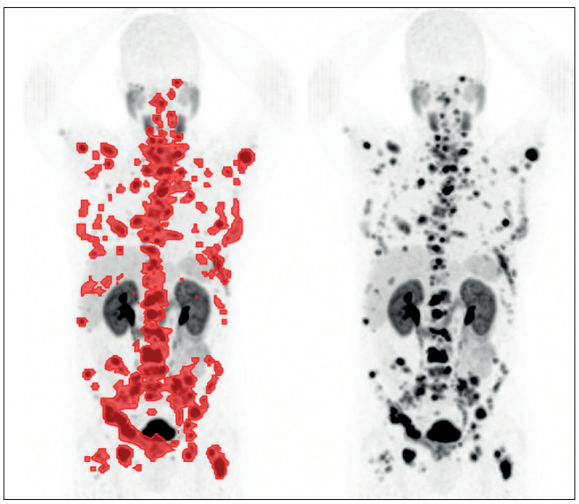

Figure 1: **PSMA-PET total tumour quantitation**
PSMA-TTV is the volume (mL) of all tumour quantified on PSMA-PET using deposits identified as tumour and PSMA positive with an SUVmax >3 and 0·2 mL minimum lesion size. SUVmean is the mean SUVmax of all voxels included in the total tumour volume. In this case, PSMA-TTV is 1431 mL and SUVmax is 8·5. PSMA=prostate-specific membrane antigen. SUV=standardised uptake value. TTV=total tumour volume.

	Enzalutamide group (n=79)	Enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (n=81)
Age, years	71 (62–76)	71 (66–76)
PSA at enrolment, ng/mL	33 (13–87)	39 (16–75)
>20 PSMA-avid metastases	47 (59%)	51 (63%)
Metastatic disease (M1) at initial diagnosis	46 (58%)	43 (53%)
Pain requiring opiates for >14 days	12 (15%)	9 (11%)
Previous early docetaxel for castration-sensitive disease	44 (56%)	43 (53%)
Previous treatment with abiraterone	9 (11%)	12 (15%)
Time since diagnosis, years	2·8 (1·4–6·6)	2·2 (1·2–6·2)
Haemoglobin, g/L	130 (121–137)	132 (121–140)
Lactate dehydrogenase ≥IULN	19 (24%)	15 (19%)
Alkaline phosphatase ≥IULN	37 (47%)	36 (44%)
Albumin <35 g/L	6 (8%)	8 (10%)
De-novo metastatic disease (M1) at initial diagnosis	46 (58%)	43 (53%)
<3 years since initial diagnosis	44 (56%)	49 (60%)
>5 bone metastases	46 (58%)	46 (57%)
Visceral metastases	10 (13%)	7 (9%)
PSA doubling time <84 days	40 (51%)	51 (63%)
Pain requiring opiates >14 days	12 (15%)	9 (11%)
Previous abiraterone	9 (11%)	12 (15%)
PSMA SUVmean		
Q1: ≤6·4	19 (24%)	20 (25%)
Q2: 6·5–7·6	19 (24%)	20 (25%)
Q3: 7·7–9·8	23 (29%)	19 (23%)
Q4: >9·8	18 (23%)	22 (27%)
PSMA-TTV		
Below median: <234 mL	39 (49%)	41 (51%)
Above median: ≥234 mL	40 (51%)	40 (49%)

Data are median (IQR) or n (%). ^{177}Lu=lutetium-177. IULN=institutional upper limit of normal. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. Q=quartile. SUV=standardised uptake volume. TTV=total tumour volume.

Table 1: **Baseline characteristics**

The semi-quantified workflow used previously developed minimum criteria (SUVmax of 3 and volume of 0·2 mL) to identify each tumour deposit based on the rationale of including all active tumour deposits above blood pool.[9] Whole-body SUVmean and PSMA-TTV were calculated from the derived whole-body tumour regions using this method. All workflow-derived tumour regions were assessed for quality by a nuclear medicine investigator. SUVmean and PSMA-TTV were quantitatively derived for each PSMA-PET-CT scan (figure 1). Enrolment of trial participants required a screening PSMA-PET-CT. PSMA-PET-CT was also undertaken at day 15 after commencing enzalutamide (before [^{177}Lu]Lu-PSMA-617), day 92 after commencing enzalutamide, and at first progression (PSA or radiographic; appendix p 2). For this substudy, only the quantitative analysis of the PSMA-PET-CT at screening was evaluated.

Outcomes

The prespecified tertiary substudy endpoint was to determine the association between screening PSMA-PET total tumour quantitative parameters, SUVmean and PSMA-TTV with clinical outcomes, and by treatment received. This substudy primary endpoint was overall survival, the secondary endpoint was PSA progression-free survival, and the exploratory endpoint was PSA response rate, specifically a 90% reduction in PSA from baseline. Overall survival was defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive. PSA progression free survival was defined as the interval from the date of randomisation to the date of first evidence of PSA progression, commencement of non-protocol anticancer therapy, or death from any cause, whichever occurred first.

Statistical analysis

This analysis was prespecified before the unblinded analysis. The sample size was not powered for this biomarker substudy and was dictated by the data available from the ENZA-p trial. The sample size for the ENZA-p primary endpoint of 160 participants followed up until 150 PSA progression-free survival events had occurred, providing 80% power to detect a true hazard ratio (HR) of 0·625, using a two-sided, type I error rate of 0·05. Analyses for this substudy were undertaken in the 160 participants who received treatment (appendix p 3). This substudy hypothesis was that PSMA-TTV and SUVmean will modify the comparative effect of

enzalutamide versus combination treatment on overall and PSA progression-free survival. We examined the association between survival outcomes and treatment group in all randomly assigned patients who received treatment. As all analyses in this paper are unstratified, the results will differ from those presented previously.[1,6] We elected to follow this approach to maintain statistical efficiency, since a primary goal of this paper was to examine associations between imaging parameters within treatment groups in a smaller sample, not in the whole sample. The quantitative imaging parameters analysed in this study included SUVmean greater or less than the upper quartile (Q4) and PSMA-TTV higher or lower than the median. For SUVmean, this clinically relevant definition was chosen to be concordant with previous prospective studies demonstrating the prognostic value of SUVmean upper quartile.[2,3] With a scarcity of similar previous evidence for PSMA-TTV, above or below the median was chosen as the variable for PSMA-TTV to maximise subgroup sample size. Survival outcomes were analysed by unstratified Cox regression, and by treatment received. Participants without the event of interest at the cutoff date of July 31, 2024, were censored. Effect modification between treatment group and imaging parameter was examined by entering both variables into a Cox model with an interaction term, the p value of which is reported. The proportional hazards assumption was tested by inspection of Schoenfeld residuals and in no case for these outcomes was this violated. Survival curves and median survival time were estimated with the Kaplan–Meier method and compared using unstratified log-rank tests. Exploratory analysis included multivariable Cox regression for overall survival, adjusting for the continuous variables of baseline haemoglobin and PSA (per doubling), and the binary variables: lactate dehydrogenase above upper limit of normal and albumin less than 35 g/L. Additionally, univariable Cox regression was undertaken, entering the imaging parameters as quartiles, with Q4 as the reference category for PSMA-TTV and Q1 the reference category for SUVmean, because these are the putative worst quartiles for survival. The relationship between PSA 90% response rate and the quantitative parameters was visually explored by entering these as restricted cubic splines, with internal knots at the tertiles, into a logistic regression model. The proportion of patients with g a PSA 90% response within each treatment group and above or below the median SUVmean was also calculated. For this substudy, reported p values are nominal and inferences should be interpreted in this context. Analysis was performed with Stata (version 17.0MP).

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 Aug 17, 2020, and July 26, 2022, we randomly assigned 162 participants: 79 to the enzalutamide group and 83 to the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Median follow-up at the final data cutoff of July 31, 2024, was 34 months (IQR 29–39): 34 months (IQR 30–38) in those assigned to the enzalutamide group versus 34 months (IQR 29–39) in those assigned to the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. The substudy analyses presented here include the 160 of 162 participants who underwent therapy: 79 in the enzalutamide group and 81 in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Baseline characteristics are summarised in table 1.

96 deaths were reported: 53 (67%) of 79 occurred in the enzalutamide group and 43 (53%) of 81 in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Median overall survival was 26 months (95% CI 21–31) in the enzalutamide group versus 34 months (29–35) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (HR 0·65 [0·43–0·97]). PSA progression was observed in 133 participants (73 [92%] in the enzalutamide group and 60 [74%] in the enzalutamide plus [^{177}Lu]Lu-PSMA-617

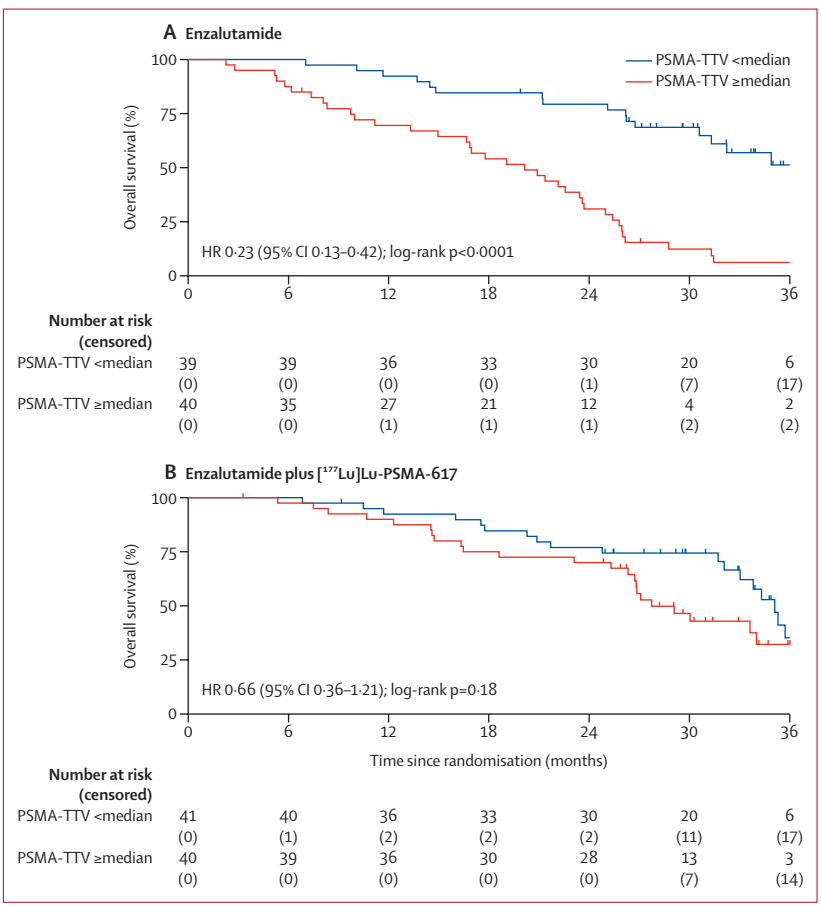

Figure 2: **Kaplan–Meier plots for overall survival with enzalutamide plus [^{177}Lu]Lu-PSMA-617 and enzalutamide alone based on PSMA-TTV above the median and below the median**
^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. TTV=total tumour volume.

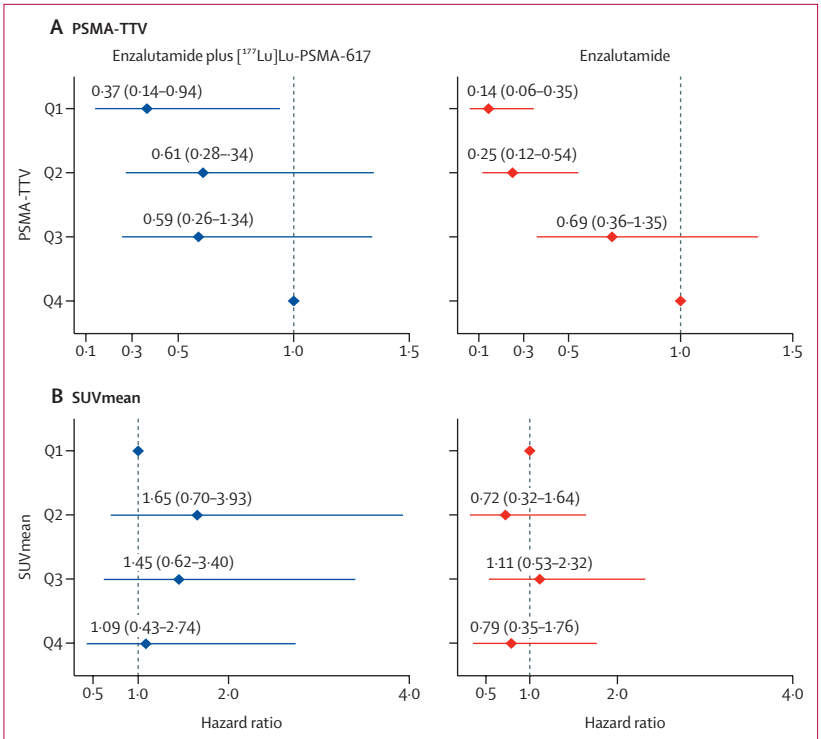

Figure 3: **Hazard ratios for overall survival with enzalutamide and enzalutamide plus [^{177}Lu]Lu-PSMA-617 based on PSMA-TTV and SUVmean**

^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. SUV=standardised uptake value. TTV=total tumour volume.

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
PSMA-TTV ≥median (ref) *vs* <median		
Enzalutamide	0·23 (0·13–0·42)	0·33 (0·15–0·72)
Enzalutamide plus [^{177}Lu]Lu-PSMA-617	0·66 (0·36–1·21)	0·66 (0·31–1·40)
SUVmean Q1–3 (ref) *vs* Q4		
Enzalutamide	0·84 (0·44–1·60)	0·87 (0·44–1·72)
Enzalutamide plus [^{177}Lu]Lu-PSMA-617	0·80 (0·38–1·68)	0·86 (0·41–1·84)

^{177}Lu=lutetium-177. HR=hazard ratio. IULN=institutional upper limit of normal. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. SUV=standardised uptake value. TTV=total tumour volume. PSA range was 1·7–1737 ng/mL. Haemoglobin range was 92–177 g/dL. *Adjusted for baseline haemoglobin (continuous), PSA (per doubling), lactate dehydrogenase at or above in the IULN, and albumin less than 35 g/L.

Table 2: **Unadjusted and adjusted overall survival HRs (95% CIs) by imaging parameter and treatment group**

group), with a median PSA progression-free survival of 8 months (95% CI 4–10) in the enzalutamide group versus 13 months (11–17) with enzalutamide plus [^{177}Lu]Lu-PSMA-617 (HR 0·49 [0·34–0·69]). PSA 90% response was observed in 29 (37%) of 79 patients in the enzalutamide group versus 65 (80%) of 81 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group.

The median PSMA-TTV at baseline was 234 mL (IQR 76–687) in all patients, with PSMA-TTV above the median reported in 40 (49%) of 81 patients in the enzalutamide group and 40 (51%) of 79 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Median overall survival for PSMA-TTV below versus above the median in the enzalutamide group was 39 months (95% CI 31–not estimable) versus 20 months (13–24; HR 0·23 [0·13–0·42], log-rank p<0·0001). The corresponding median overall survival in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group was 35 months (95% CI 32–37) versus 28 months (26–34; HR 0·66 [0·36–1·21], log-rank p=0·18; figure 2). The p value for an interaction term between PSMA-TTV and treatment group was p=0·0078.

Predominately increasing hazard ratios were observed as quartiles of PSMA-TTV increased for both treatments (figure 3). In the multivariable analysis including clinical prognostic factors (haemoglobin, lactate dehydrogenase, albumin, and PSA levels), PSMA-TTV remained independently prognostic for overall survival in the enzalutamide group (HR 0·33 [95% CI 0·15–0·72]) but not in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (0·66 [0·31–1·40]; table 2; appendix p 6).

Median PSA progression-free survival for PSMA-TTV below versus above the median for enzalutamide monotherapy was 11 months (95% CI 9–13) versus 3 months (2–4; HR 0·31 [0·19–0·50]). The corresponding median PSA progression-free survival for enzalutamide plus [^{177}Lu]Lu-PSMA-617 was 15 months (95% CI 11–29) versus 11 months (9–16; HR 0·67 [0·40–1·11]; appendix p 4). The p value for a test of interaction between PSMA-TTV and treatment group was p=0·017.

Overall survival and progression-free survival curves for PSMA-TTV presented as Q1–4 are in the appendix (pp 10–13).

The median SUVmean was 7·7 (IQR 6·5–9·8) in all patients overall. SUVmean in Q4 (SUVmean ≥9·8) was reported in 18 (23%) of 79 patients in the enzalutamide group and in 22 (27%) of 81 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Median overall survival for SUVmean in Q4 versus Q1–3 for the enzalutamide group was 29 months (95% CI 17–39) versus 25 months (21–31; HR 0·84 [0·44–1·60], log-rank p=0·59). The respective median overall survival for the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group was 32 months (95% CI 21–not estimable) versus 34 months (27–35; HR 0·80 [0·38–1·68], log-rank p=0·56; figure 4). The p value for an interaction term between SUVmean and treatment group was p=0·88. No clear relation was seen between hazard of overall survival and increasing quartile of SUVmean in either treatment group (figure 3).

Median PSA progression-free survival for SUVmean in Q4 versus Q1–3 in the enzalutamide group was 5·0 months (95% CI 3·0–9·9) versus 7·8 months (4·0–11; HR 1·17 [0·69–2·01]). The respective median PSA progression-free survival in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group was 15 months (95% CI 7–not estimable) versus 13 months (10–17; HR 0·69 [0·38–1·25]; appendix p 5). The p value for a test of interaction between SUVmean and treatment group was p=0·17.

Survival curves for SUVmean as Q1–4 are presented for both overall survival and progression-free survival (appendix pp 14–17).

For SUVmean split at the median, in the enzalutamide group the PSA 90% response rate with an SUVmean above the median was 11 (27%) of 41 versus 18 (47%) of 38 for an SUVmean below the median. With enzalutamide plus [^{177}Lu]Lu-PSMA-617, the PSA 90% response rate with an SUVmean above the median was 32 (78%) of 41 versus 33 (83%) of 40 for an SUVmean below the median (appendix pp 8–9).

Discussion

Predictive and prognostic biomarkers are crucial for the personalisation of treatments to improve patient outcomes and optimise treatment choices. ENZA-p is a randomised trial that demonstrated improved overall survival with treatment intensification through the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide in men with metastatic castration-resistant prostate cancer with risk factors for early treatment failure on enzalutamide alone.[1,6] This ENZA-p subanalysis has found that screening PSMA-TTV is prognostic for overall survival with enzalutamide monotherapy in metastatic castration-resistant prostate cancer, finding a difference in overall survival of 20 months versus 39 months based on PSMA-TTV above or below the median value. Furthermore, PSMA-TTV remained prognostic of overall survival independent of other prognostic clinical parameters. The prognostic value of PSMA-TTV for enzalutamide identified in this study suggests an additional potential role of PSMA-PET in metastatic prostate cancer above and beyond its current use in defining suitability for [^{177}Lu]Lu-PSMA-617 therapy.

PSMA-TTV has been previously found to be prognostic for progression-free survival and overall survival with [^{177}Lu]Lu-PSMA-617 therapy.[4,10] A prospective trial of [^{177}Lu]Lu-PSMA-617 plus idronoxil showed that baseline PSMA-TTV was independently prognostic for overall survival even when other clinical prognostic predictors were included.[4] However, to our knowledge, this is the first time that the prognostic value of PSMA-TTV for overall survival has been demonstrated for a systemic therapy other than [^{177}Lu]Lu-PSMA-617. Androgen receptor pathway inhibitors such as enzalutamide are used widely in metastatic prostate cancer, and biomarkers that effectively identify patients with poor overall survival without intensification are scarce. Future evaluation of PSMA-TTV should focus on its potential benefit in comparison to other prognostic parameters, including CHAARTED high and low volume criteria on diagnostic CT and bone scan in hormone-sensitive prostate cancer.[11]

This study has also demonstrated that PSMA-TTV is predictive for improvement in overall survival with the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide in metastatic castration-resistant prostate cancer in patients with prognostic risk factors for early treatment failure on enzalutamide alone. In patients with a PSMA-TTV above the median, median overall survival rose from 20 months to 28 months with the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide. However, in patients with a PSMA-TTV below the median, the median overall survival did not improve (39 months *vs* 35 months) with the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide. This predictive value of PSMA-TTV was supported by the p value for an interaction between the effects of treatment group and PSMA-TTV on survival. That PSMA-TTV is less prognostic for enzalutamide plus [^{177}Lu]Lu-PSMA-617 than for enzalutamide alone is likely to be due to the effectiveness of the combined agents even in participants with high-volume disease, through the concurrent targeting of disparate clonal populations. The TheraP trial showed that ctDNA at baseline predicted improved progression free and overall survival with [^{177}Lu]Lu-PSMA-617 monotherapy compared with cabazitaxel chemotherapy.[9,12,13] The interaction between screening circulating tumour DNA and PSMA-PET is being examined within the ENZA-p cohort as part of the trial's translational programme.[5]

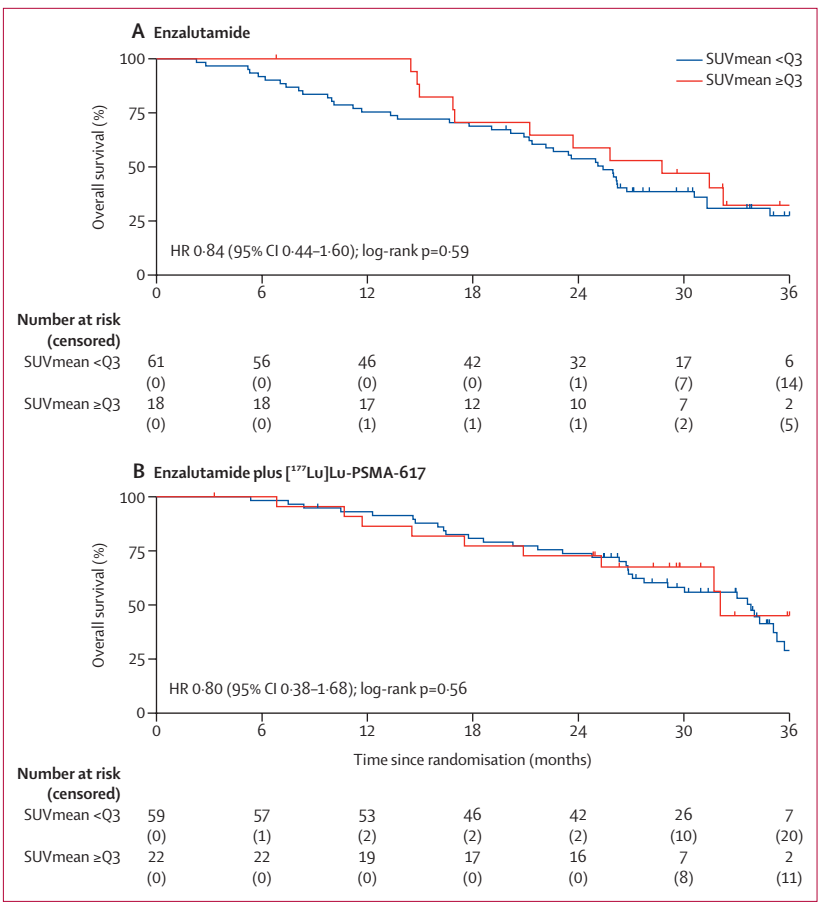

Figure 4: **Kaplan–Meier plots for overall survival with enzalutamide plus [^{177}Lu]Lu-PSMA-617 and enzalutamide alone based on PSMA SUVmean ≥Q3 versus <Q3**
^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. SUV=standardised uptake value.

PSMA-PET whole-body SUVmean is a quantitative PET parameter that measures the mean voxel intensity across all tumour deposits included in the total body tumour volume, capturing both PSMA intensity and heterogeneity of PSMA expression. SUVmean has previously been found to be prognostic for depth of response, progression-free survival, and overall survival with [^{177}Lu]Lu-PSMA-617 monotherapy.[2–4] However, in this study, SUVmean was neither predictive nor prognostic for progression-free survival or overall survival. This lack of association between baseline PSMA SUVmean and treatment response was predicted for this prespecified tertiary endpoint. The rationale for ENZA-p was that complementary therapies targeting clonal populations with disparate PSMA expression would result in deeper and longer responses than monotherapy.[14,15] A recent study found that androgen receptor pathway inhibitors in metastatic castration-resistant prostate cancer have higher response rates in those with lower PSMA intensity.[16] Consistent with this, the current study also found higher PSA 90% response rates with SUVmean below the median with enzalutamide than with SUVmean above the median. This absence of association between high SUVmean and either PSA progression-free survival or overall survival when [^{177}Lu]Lu-PSMA-617 is administered with enzalutamide represents a novel and important finding. Although SUVmean remains an important imaging prognostic biomarker when [^{177}Lu]Lu-PSMA-617 is used as monotherapy, it requires re-evaluation when used in combination with other active therapies such as androgen receptor pathway inhibitors, or if a radionuclide therapy has different PSMA receptor expression requirements (such as targeted alpha therapy).[17]

There are several limitations to this study. Quantitative assessment of PSMA-PET parameters requires semi-automated software that are labour intensive and are not yet in routine clinical use. Although this study demonstrates potential clinical utility of PSMA-TTV for guiding patient treatments, it is not available to imaging specialists without substantial additional input. This situation is changing with recent work demonstrating an automated PSMA-PET quantitative programme to be predictive for treatment response and overall survival with [^{177}Lu]Lu-PSMA therapy without requiring human correction.[18] Until validated and harmonised fully automated PET quantitation programmes become available, the full value of PSMA-PET quantitation will not be realised in routine clinical practice.

Participants in ENZA-p had metastatic castration-resistant prostate cancer with risk factors for early treatment failure on enzalutamide monotherapy. As such ENZA-p represents a higher risk group than the broader metastatic castration-resistant prostate cancer population treated with enzalutamide, and the impact of PSMA-TTV on overall survival might therefore be different in this wider patient population. Furthermore, the ENZA-p trial used first-line enzalutamide in early metastatic castration-resistant prostate cancer, whereas most patients are now receiving androgen receptor pathway inhibitors in the metastatic hormone-sensitive prostate setting. ENZA-p is a randomised, phase 2 trial with a small number of participants in each treatment group, limiting full evaluation of imaging biomarkers. Additionally, due to the sample size, the number of clinical prognostic risk factors evaluated was limited to four, with the stratification risk factor of more than 20 sites of disease not chosen due to its inherent association with PSMA-TTV. Further evaluation of PSMA-TTV in larger prospective trials in a broader-risk group and in earlier settings is warranted given the strength of the findings in this study. Finally, the screening PSMA PET was used to exclude patients with low PSMA expression disease, defined as an SUVmax of more than 15 at a single site and SUVmax of more than 10 at all larger sites of disease. This might have affected the number of patients with low PSMA expression included in the trial, although the median SUVmean in this trial is similar to that in the randomised phase 3 trials using [^{177}Lu]Lu-PSMA-617.[2]

In conclusion, baseline PSMA-TTV is prognostic for overall survival and predictive of a beneficial effect on overall survival with the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide in metastatic castration-resistant prostate cancer. In contrast to previous studies with [^{177}Lu]Lu-PSMA-617 monotherapy, PSMA SUVmean was not prognostic for PSA progression-free survival or overall survival when [^{177}Lu]Lu-PSMA-617 was administered with enzalutamide as a first-line treatment for metastatic castration-resistant prostate cancer.

Contributors

LE, NP, MC, AJM, MRS, SSa, MSH, and IDD were members of the research group that developed the prespecified ENZA-p translational analysis plan and contributed to conceptualisation and writing the first version of the protocol. LE, SSu, MC, AMJ, AN, AW, S-TL, IDK, SN, RJF, JCG, HT, SSa, MSH, THT, DAP, MRS, and IDD accrued patients and collected data. LE, AN, S-TL, and NA performed imaging quantitative analysis. LE, NP, MRS, AJM, and HT contributed to the statistical analysis plan. NP, AJM, and HT led the statistical analysis and verified underlying data. SSu and CN reviewed data on adverse events, response, and progression-free survival. LE, IDD, MRS, AJM, HT, and SSu accessed and verified the data. LE was the coordinating principal investigator and wrote the first draft of the manuscript. 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

LE reports research grant support (to their institution) from Novartis and Clarity Pharma; consulting fees for lectures or advisory boards from Astellas, Janssen, AstraZeneca, Clarity, Novartis, Advancell, and Telix in the past 5 years; and philanthropic grant support from the Prostate Cancer Foundation, St Vincent's Clinic Research Foundation, and Curran Foundation. SSa reports grants from Novartis/AAA, AstraZeneca, Merck Sharp & Dohme, Genentech, Pfizer, Amgen, and Senhwa to their institution; and personal fees from AstraZeneca, Merck Sharp & Dohme, Bristol Myers Squibb, and AstraZeneca to their institution, outside the submitted work. MSH reports grants and receipt of equipment, materials, drugs, medical writing, gifts, or other services from the Prostate Cancer Foundation, the NHRMC, Movember,

US Department of Defense, Medical Research Future Fund, Bayer, Peter MacCallum Foundation, Isotopia, and the Australian Nuclear Science and Technology Organisation; consulting fees from Merck Sharp & Dohme and Novartis; honoraria from Janssen, Novartis, AstraZeneca, and Astellas; support for meetings from Merck Sharp & Dohme, Novartis, Janssen, AstraZeneca, and Astellas; leadership or fiduciary role in other board from Australian Friends of Sheba; and other financial or non-financial interests from Peter MacCallum Cancer Centre and the University of Melbourne. DAP reports personal fees from Ipsen and Eisai, all outside the submitted work. RJF reports institution funding and consulting fees from AIQ Solutions (outside the submitted work), and committee involvement in the Australasian Radiopharmaceutical Trials Network (unpaid). MRS reports grants to his institution from the NHMRC, Cancer Australia, Astellas, Amgen, AstraZeneca, Bayer, Bionomics, Bristol Myers Squibb, Celgene, Medivation, Merck Sharp & Dohme, Pfizer, Roche, Sanofi, and Tilray, all outside the submitted work. IDD reports grants from the NHMRC, during the conduct of the study; reports institutional payments to support prostate cancer trials from Pfizer, ANZUP Cancer Trials Group, Bayer, Astellas, Janssen, Movember Foundation, and Merck Sharp & Dohme, outside the submitted work; and is unremunerated Chair of the ANZUP Cancer Trials Group and is supported in part by an Australian NHMRC Investigator Grant (grant number 2016274). AMJ reports consulting or advisory roles (to their institution) from Janssen Oncology, Pfizer, and Astellas Pharma, and research funding (to their institution) from Bristol Myers Squibb, Janssen Oncology, Merck Sharp & Dohme, Mayne Pharma, Roche/Genentech, Bayer, Lilly, Pfizer, and AstraZeneca. AW declares consulting fees from MSD, Eisai, Bristol Myers Squibb, and Astellas; honoraria from Eisai and MSD; and participation on an advisory board from Loxo-Lilly, MSD, and Astellas. All other authors declare no competing interests.

Data sharing

Requests for specific analyses or data will be considered by the ENZA-p trial executive committee 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; to gain access, data requestors will sign a data access agreement.

Acknowledgments

ENZA-p is an investigator-initiated trial led by the ANZUP Cancer Trials Group in partnership with the Prostate Cancer Research Alliance, a joint initiative between the Australian Federal Government and the Movember Foundation. The ENZA-p translational research programme is funded through a Prostate Cancer Foundation Challenge Award. ENZA-p is a collaboration between ANZUP, the NHMRC Clinical Trials Centre at the University of Sydney and the Australasian Radiopharmaceutical Trials Network with support from AdAcAp (a Novartis company), St Vincent's Clinic Foundation, GenesisCare, and Roy Morgan Research. Astellas provided drug support for the trial. ANZUP receives infrastructure funding from Cancer Australia. We acknowledge and thank the 162 participants for their participation in the ENZA-p study; and the principal investigators, co-investigators, and study coordinators at the 15 centres across Australia for their dedication and enthusiasm.

References

1 Emmett L, Subramaniam S, Crumbaker M, et al. Overall survival and quality of life with [177Lu]Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2025; **26:** 291–99.

2 Kuo PH, Morris MJ, Hesterman J, et al. Quantitative 68Ga-PSMA-11 PET and clinical outcomes in metastatic castration-resistant prostate cancer following 177Lu-PSMA-617 (VISION Trial). *Radiology* 2024; **312:** e233460.

3 Buteau JP, Martin AJ, Emmett L, et al. PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial. *Lancet Oncol* 2022; **23:** 1389–97.

4 Pathmanandavel S, Crumbaker M, Yam AO, et al. 177Lutetium PSMA-617 and idronoxil (NOX66) in men with end-stage metastatic castrate-resistant prostate cancer (LuPIN): patient outcomes and predictors of treatment response of a phase I/II trial. *J Nucl Med* 2022; **63:** 560–66.

5 Emmett L, Subramaniam S, Joshua AM, et al. ENZA-p trial protocol: a randomized phase II trial using prostate-specific membrane antigen as a therapeutic target and prognostic indicator in men with metastatic castration-resistant prostate cancer treated with enzalutamide (ANZUP 1901). *BJU Int* 2021; **128:** 642–51.

6 Emmett L, Subramaniam S, Crumbaker M, et al. [177Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 2024; **25:** 563–71.

7 Armstrong AJ, Lin P, Tombal B, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer from the PREVAIL Trial. *Eur Urol* 2020; **78:** 347–57.

8 Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: the PROPHECY study. *J Clin Oncol* 2019; **37:** 1120–29.

9 Hofman MS, Emmett L, Sandhu S, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet* 2021; **397:** 797–804.

10 Seifert R, Kessel K, Schlack K, et al. PSMA PET total tumor volume predicts outcome of patients with advanced prostate cancer receiving [177Lu]Lu-PSMA-617 radioligand therapy in a bicentric analysis. *Eur J Nucl Med Mol Imaging* 2021; **48:** 1200–10.

11 Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; **373:** 737–46.

12 Kwan EM, Ng SWS, Tolmeijer SH, et al. Lutetium-177-PSMA-617 or cabazitaxel in metastatic prostate cancer: circulating tumor DNA analysis of the randomized phase 2 TheraP trial. *Nat Med* 2025; published online May 27. https://doi.org/10.1038/s41591-025-03704-9.

13 Hofman MS, Emmett L, Sandhu S, et al. Overall survival with [177Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. *Lancet Oncol* 2024; **25:** 99–107.

14 Kaittanis C, Andreou C, Hieronymus H, et al. Prostate-specific membrane antigen cleavage of vitamin B9 stimulates oncogenic signaling through metabotropic glutamate receptors. *J Exp Med* 2018; **215:** 159–75.

15 Bakht MK, Beltran H. Biological determinants of PSMA expression, regulation and heterogeneity in prostate cancer. *Nat Rev Urol* 2025; **22:** 26–45.

16 de Kouchkovsky I, Moradpour M, Zhang L, et al. Impact of baseline PSMA PET in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) starting first-line (1L) androgen receptor signaling inhibitor (ARSI) therapy. *J Clin Oncol* 2025; **43** (suppl): 46 (abstr).

17 Pouget JP, Constanzo J. Revisiting the radiobiology of targeted alpha therapy. *Front Med* 2021; **8:** 692436.

18 Emmett L, Zheng A, Jin C, et al. 'One button push' fully automated PSMA PET quantification: Correlation with progression free and overall survival in patients undergoing [177Lu] Lu PSMA therapy for metastatic castrate resistant prostate cancer. *Proc Am Soc Clin Oncol* 2025; **43** (suppl 16): 5054 (abstr).