Overall survival and quality of life with [^{177}Lu]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

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Summary

Background Interim analysis of the ENZA-p trial showed improved prostate-specific antigen (PSA) progression-free survival with the addition of lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 to enzalutamide as first-line treatment of metastatic castration-resistant prostate cancer. Here, we report the secondary endpoints of overall survival and health-related quality of life (HRQOL) with longer follow-up.

Methods ENZA-p was a multicentre, open-label, randomised, phase 2 trial done at 15 hospitals in Australia. Participants were men aged 18 years or older who had not previously been treated with docetaxel or androgen receptor pathway inhibitors for metastatic castration-resistant prostate cancer, gallium-68 [^{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. Participants were randomly assigned (1:1) by a centralised, web-based system using minimisation with a random component to stratify for study site, disease burden, early docetaxel, and previous treatment with abiraterone. Treatment was oral enzalutamide 160 mg daily alone or with adaptive-dosed (two or four doses) intravenous 7·5 GBq [^{177}Lu]Lu-PSMA-617 every 6–8 weeks. The primary endpoint was prostate-specific antigen (PSA) progression-free survival, which has been previously reported. Overall survival, defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive, and HRQOL were key secondary endpoints. HRQOL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the Patient Disease and Treatment Assessment Form. For HRQOL analyses, deterioration-free survival was measured from randomisation until the earliest occurrence of death, clinical progression, discontinuation of study treatment; or a worsening of 10 points or more from baseline in physical function, or in overall health and QOL. Analyses of these secondary endpoints were prespecified and are by intention to treat. The trial is registered with ClinicalTrials.gov, NCT04419402, and follow-up is complete.

Findings Between Aug 17, 2020, and July 26, 2022, 79 patients were randomly assigned to enzalutamide and 83 to enzalutamide plus [^{177}Lu]Lu-PSMA-617. 96 deaths was reported after a median follow-up of 34 months (IQR 29–39): 53 (67%) in the enzalutamide group and 43 (52%) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Overall survival was longer in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group than the enzalutamide group (median 34 months [95% CI 30–37] *vs* 26 months [23–31]; HR 0·55 [95% CI 0·36–0·84], log-rank p=0·0053). HRQOL was rated by 154 (95%) of 162 participants. Deterioration-free survival at 12 months and stratified log-rank p values favoured enzalutamide plus [^{177}Lu]Lu-PSMA-617 for both physical function (median 10·64 months [95% CI 7·66–12·42] *vs* 3·42 months [3·19–7·89]; HR 0·51 [95% CI 0·36–0·72], log-rank p<0·0001) and overall health and QOL (8·71 months [6·41–11·56] *vs* 3·32 months [3·09–5·26]; HR 0·47 [95% CI 0·33–0·67], log-rank p=0·0001). Mean scores for pain until progression favoured enzalutamide plus [^{177}Lu]Lu-PSMA-617 over enzalutamide (difference 7·3 [95% CI 1·6–12·9]; p=0·012). Mean scores for fatigue until progression favoured enzalutamide plus [^{177}Lu]Lu-PSMA-617 over enzalutamide (difference 5·9 [95% CI 1·1–10·7]; p=0·016). The frequency of self-rated xerostomia was lower in the enzalutamide group than in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (43 [57%] of 75 *vs* 58 [74%] of 78; p=0·039), and scores were not significantly different between groups for all other domains. Grade 3–5 adverse events occurred in 35 (44%) of 79 patients in the enzalutamide group and 37 (46%) of 81 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. No deaths were attributed to study treatment in either group.

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Interpretation The addition of [^{177}Lu] Lu-PSMA-617 to enzalutamide was associated with improved survival and some aspects of HRQOL in patients with high-risk metastatic castration-resistant prostate cancer. Our findings warrant phase 3 evaluation of adaptive-dosed [^{177}Lu] Lu-PSMA-617 in combination with androgen receptor pathway inhibitors in people with metastatic prostate cancer.

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Introduction

Both lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 and androgen receptor pathway inhibitors improve overall survival in patients with metastatic castrate-resistant prostate cancer, although early treatment failure can occur with either treatment given as monotherapy.[1–4] PSMA is a transmembrane receptor involved in the PI3K–mTOR growth pathway, with increased expression observed during androgen blockade in clonal subpopulations in metastatic castration-resistant prostate cancer.[5,6] We hypothesised that targeting both androgen signalling and PSMA receptors concurrently would improve anticancer activity in metastatic castration-resistant prostate cancer. The randomised phase 2 ENZA-p trial compared standard-of-care enzalutamide versus enzalutamide plus adaptive-dosed [^{177}Lu]Lu-PSMA-617 in participants with metastatic castration-resistant prostate cancer with prostate-specific antigen (PSA) progression-free survival as the primary endpoint. The trial demonstrated both improved PSA progression-free survival and depth of PSA response in a prespecified interim analysis that occurred after a median follow-up of 20 months (IQR 18–21).[7,8] Here, we report secondary endpoints of overall survival and health-related quality-of-life (HRQOL) outcomes in the ENZA-p trial, with an additional 14 months of follow-up.

Methods

Study design and participants

ENZA-p (Australian and New Zealand Urogenital and Prostate [ANZUP] trial 1901) was an academic-led, multicentre, open-label, randomised, phase 2 trial performed at 15 hospitals in Australia. The trial protocol,[8] primary endpoint (PSA progression-free survival), and

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published in any language up to the finalisation of the protocol on Sept 25, 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. We found two randomised trials with lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 in patients with metastatic castration-resistant prostate cancer suggesting improved quality of life compared with second-line chemotherapy and improved overall survival compared with best standard of care excluding chemotherapy. No trials were identified that evaluated [^{177}Lu] Lu-PSMA-617 in combination with enzalutamide or other androgen receptor pathway inhibitors.

Added value of this study

ENZA-p is the first randomised trial to evaluate enzalutamide and adaptive-dosed [^{177}Lu]Lu-PSMA-617 versus enzalutamide alone before chemotherapy in patients with metastatic castration-resistant prostate cancer at high risk of early progression on enzalutamide. The ENZA-p trial addressed tumour heterogeneity by using two established therapies directed at different therapeutic targets. Our trial findings established that the addition of adaptive-dosed ^{177}[Lu]Lu-PSMA-617 to enzalutamide improved overall survival, pain, fatigue, and deterioration-free survival for both physical function and for overall health and quality of life, in addition to prostate-specific antigen (PSA) progression-free survival and depth of PSA response shown previously. Furthermore, this trial is the first to demonstrate the feasibility and efficacy of using real-time PSMA-PET and PSA biomarkers to guide adaptive dosing of [^{177}Lu]Lu-PSMA-617 used together with enzalutamide in patients with metastatic castration-resistant prostate cancer, an approach that maximises patient benefit and minimises toxicity.

Implications of all the available evidence

Data from this randomised trial and others provide evidence that [^{177}Lu]Lu-PSMA-617 is active in castration-resistant prostate cancer, both before and after chemotherapy with docetaxel, and during or after androgen receptor-directed therapy. Side-effects and patient-reported outcomes favour the use of [^{177}Lu]Lu-PSMA-617 over cabazitaxel after chemotherapy with docetaxel. The findings from this trial favour the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide over enzalutamide alone before docetaxel in metastatic castration-resistant prostate cancer in patients with risk factors for early treatment failure on enzalutamide.

key secondary outcomes up to a median follow-up of 20 months have been previously reported.[7]

We enrolled individuals aged 18 years or older with metastatic castration-resistant prostate cancer not previously treated with an androgen receptor antagonist or docetaxel, with evidence of progressive disease defined by a rising serum PSA as per Prostate Cancer Working Group 3 criteria and serum PSA higher than 5 ng/mL. Previous docetaxel or abiraterone for metastatic hormone-sensitive prostate cancer was permitted. Eligible participants were those for whom enzalutamide alone was considered the appropriate, next standard treatment, and had two or more of the following risk factors for early progression on enzalutamide alone: 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 of less than 84 days, pain requiring opiates longer than 14 days, or previous treatment with abiraterone for hormone-sensitive prostate cancer.[3,9] Eligibility also required adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Screening of potential participants included central review of gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT (PSMA-PET-CT). Imaging criteria for inclusion were PSMA-positive disease with a maximum standardised uptake value (SUVmax) of at least 15 at a single site of disease, and SUVmax more than 10 at all sites of measurable disease not affected by partial volume effect on PSMA-PET-CT. Ethnicity data were not collected.

All participants provided signed, 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. The trial is registered with ClinicalTrials.gov, NCT04419402.

Randomisation and masking

We randomly assigned participants (1:1) to enzalutamide or 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 (ie, yes *vs* no), and previous treatment with abiraterone for hormone-sensitive disease (ie, 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 oral enzalutamide 160 mg daily. Participants in the experimental group received 7·5 GBq [^{177}Lu]Lu-PSMA-617 intravenously given in week 2 and week 8 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. Participants with persistent PSMA-PET-CT-positive disease (defined as evidence of tumour PSMA expression above blood-pool intensity) at week 12 received a further two doses of 7·5 GBq [^{177}Lu]Lu-PSMA-617 at week 16 and week 24. Single-photon-emission CT (SPECT) was done 24 h after each dose of [^{177}Lu]Lu-PSMA-617. Dose modifications and delays for toxicity were specified in the trial protocol.[8] We collected blood samples for translational correlative objectives at screening, week 12, and first progression, matching the translational imaging timepoints (appendix p 16).

Participants were reviewed every 4 weeks during treatment, with blood tests for haematology, biochemistry, and serum PSA. CT scans of the chest, abdomen, and pelvis, and [^{99}mTc]technetium bone scans were done every 12 weeks until radiographic progression. Patient-reported outcome measures were the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the Patient Disease and Treatment Assessment (DATA) Form. Patient-reported outcome measures were completed every 4 weeks until the end of study treatment, and then every 6 weeks until radiographic progression. The QLQ-C30 comprises items scored to produce five functional scales (ie, physical, role, cognitive, emotional, and social), three symptom scales (ie, fatigue, pain, and nausea and vomiting), and global health and quality-of-life scales. The remaining single items assess common cancer-related symptoms (ie, dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea) and perceived financial effects of the disease and treatment.[10] Scores range from from 0 (worst possible) to 100 (best possible) for functional and overall health scales, and from 0 (none) to 100 (worst possible) for symptoms. The Patient DATA Form is a simple, multi-item quality-of-life instrument based on 11-point numeric rating scales for a range of relevant symptoms and functions. Higher scores indicate worse symptoms, whereas, for functional measures, higher scores indicate better functioning and overall wellbeing.

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. Adverse events of interest were events that were deemed most likely to occur with the

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See **Online** for appendix

two investigational treatments and were prespecified by the trial team. 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. Study treatment was discontinued for progressive disease, unacceptable toxicity, substantial treatment delays, or if the participant was no longer clinically benefiting.

Outcomes

The primary endpoint was PSA progression-free survival, 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. Secondary endpoints were overall survival, radiographic and clinical progression-free survival, PSA response rate, pain response and progression-free survival, adverse events, health economics, and translational work. In this Article, we focus on the key secondary outcomes of overall survival, defined as the interval from the date of randomisation to date of death from any cause, or the date last known alive, and HRQOL (ie, EORTC QLQ-C30 and the Patient DATA Form). Other secondary endpoints have been previously reported[7] or have analysis ongoing.

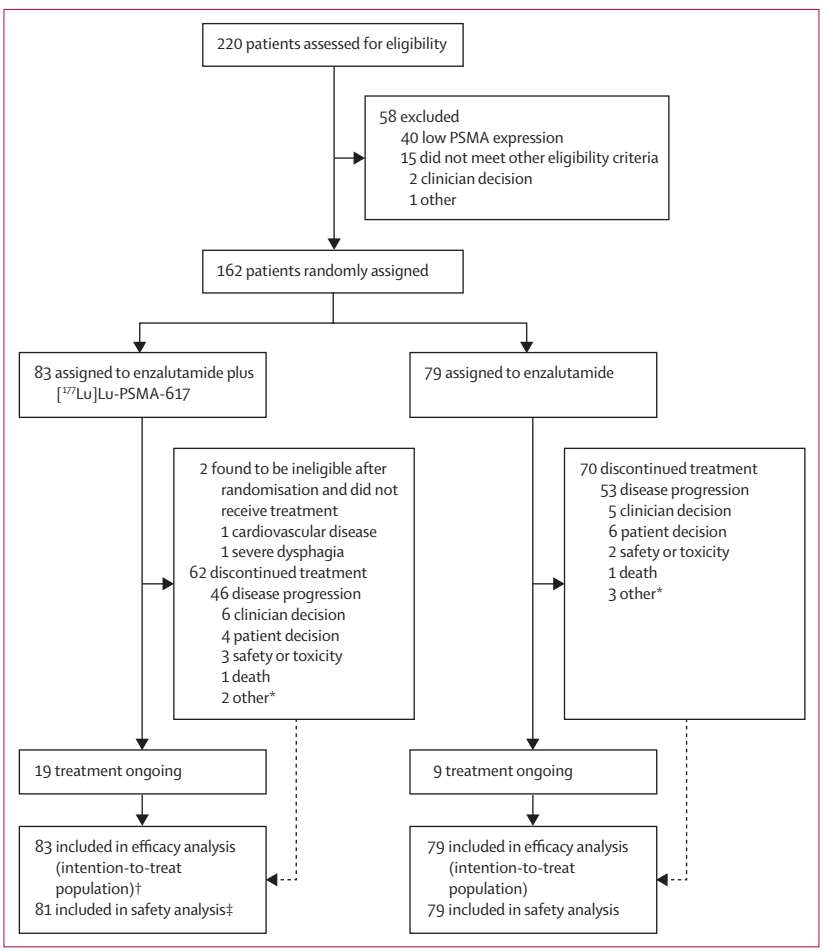

Figure 1: **Trial profile**

^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. *In the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group, other reasons for discontinuation were development of other substantial medical condition (n=1) and end of study (n=1). In the enzalutamide group, other reasons were required use of prohibited concomittant treatment (n=1), patient not complying with study protocol (n=1), and occurence of exclusion criterion affecting patient safety (n=1). †Two additional participants were recruited and randomly assigned to account for the two participants determined to be ineligible after randomisation, but before starting study treatment; both patients were randomly assigned. ‡The two patients originally randomly assigned and who did not receive any treatment because of ineligibility were not included in the safety population.

Statistical analysis

We used a sample size of 160 patients followed up until 150 PSA progression-free survival events occurred to provide 80% power if the true hazard ratio (HR) was 0·625, using a two-sided, type I error rate of 0·05. Overall survival time was summarised using the Kaplan–Meier method and compared between groups with a stratified log-rank test. HRs with 95% CIs were estimated using Cox proportional hazards regression, accounting for stratification factors, and included all randomly assigned participants. Schoenfeld residuals analysis was used to confirm the proportional hazards assumption for PSA progression-free survival, clinical progression-free survival, radiological progression-free survival, and overall survival. The proportional-hazards assumption was met for overall survival, PSA progression-free survival, and radiological progression-free survival but not for clinical progression-free survival. We calculated restricted mean survival time in the event of evidence of non-proportional hazards and, in this case, gave similar results for all these endpoints, including clinical progression-free survival (appendix p 4). This is the final planned analysis of PSA progression-free survival and overall survival. All reported p values are nominal, without correction for multiple comparisons, and should be interpreted conservatively.

HRQOL analyses followed previously established methods[11] and included the estimation of deterioration-free survival, defined as the time from randomisation to the first occurrence of a decline of at least 10 points in baseline health status (without subsequent ≥10-point improvement), progression, death, or treatment discontinuation, with censoring at the last known QOL assessment. Two deterioration-free survival endpoints were derived from the QLQ-C30: one using the Physical Function Scale (deterioration-free survival for physical function) and the other using the scale for overall health and QOL (deterioration-free survival for overall health and QOL). Deterioration-free survival and the mixed model for repeated measures were applied to QLQ-C30 data. Data from the Patient DATA Form were analysed

using the frequency of troublesome symptoms approach. The McGill-Melzack Present Pain Intensity scale was used in analysis of the pain response and progression-free survival endpoints, which have been previously reported.[7]

Treatment groups were compared using stratified log-rank tests with Kaplan–Meier curves estimating median deterioration-free survival with 95% CI and including all randomly assigned participants. The subset of participants who received study treatment, agreed to participant in HRQOL assessment, and provided a baseline assessment were included in the additional HRQOL analyses. Scale scores from the QLQ-C30 were summarised by treatment group over time and analysed using a mixed model for repeated measures, with a random intercept for participant and fixed effects for baseline score, treatment group, timepoint, and treatment-by-time interaction. Aspects of HRQOL measured by the Patient DATA form were evaluated across the post-baseline period, with symptoms rated as "troublesome" if they reached an intensity of 3 or higher on 11-point scales from 0 to 10, or if the wellbeing scores decreased by 3 or more points from an optimal score of 10. HRQOL analyses did not use imputation methods and assumed missingness was at random. Comparisons between treatment groups were performed using logistic regression, adjusting for baseline values. Statistical analysis was done with R version 4.3 and SAS version 9.4.

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, 79 patients were randomly assigned to enzalutamide and 83 to enzalutamide plus [^{177}Lu]Lu-PSMA-617 (figure 1). Two patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group were found to be ineligible after randomisation and were withdrawn before starting treatment and were not included in the safety analysis. Two additional participants were recruited and randomly assigned to the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and were included in the intention-to-treat population. Baseline characteristics are summarised in table 1. Ethnicity data were not collected. 89 (55%) patients had M1 disease at initial diagnosis (43 [52%] in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 46 [58%] in the enzalutamide group), 89 (55%) had previous treatment with docetaxel (44 [53%] *vs* 45 [57%]), and 21 (13%) had previous treatment with abiraterone for metastatic hormone-sensitive prostate cancer (12 [14%] *vs* nine [11%]).

96 deaths were reported after a median follow-up of 34 months (IQR 29–39): 53 (67%) of 79 patients in the enzalutamide group and 43 (52%) of 83 in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. Overall survival was longer in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group than the enzalutamide group (median 34 months [95% CI 30–37] *vs* 26 months [23–31]; HR 0·55 [95% CI 0·36–0·84], p=0·0053; figure 2).

	Enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (n=83)	Enzalutamide group (n= 79)
Age, years	71 (66–76)	71 (63–76)
PSA at enrolment, ng/mL	39 (13–75)	33 (14–85)
>20 PSMA-avid metastases	51 (61%)	47 (59%)
Metastatic disease (M1) at initial diagnosis	43 (52%)	46 (58%)
Pain requiring opiates >14 days	9 (11%)	12 (15%)
Previous early docetaxel for castration-sensitive disease	44 (53%)	45 (57%)
Previous treatment with abiraterone	12 (14%)	9 (11%)
Time since diagnosis, years	2·2 (1·2–6·0)	2·8 (1·5–6·4)
Features associated with early progression on enzalutamide		
Lactate dehydrogenase ≥IULN	15 (18%)	19 (24%)
Alkaline phosphatase ≥IULN	36 (43%)	37 (47%)
Albumin <35 g/L	8 (10%)	6 (8%)
De novo metastatic disease (M1) at initial diagnosis	43 (52%)	46 (58%)
Less than 3 years since initial diagnosis	49 (59%)	44 (56%)
>5 bone metastases	46 (55%)	46 (58%)
Visceral metastases	7 (8%)	10 (13%)
PSA doubling time <84 days	51 (61%)	40 (51%)
Pain requiring opiates >14 days	9 (11%)	12 (15%)
Previous abiraterone	12 (14%)	9 (11%)
EORTC QLQ-C30 scale scores at baseline		
Physical functioning	81·4 (19·1; n=74)	78·6 (21·0; n=74)
Overall health and QOL	64·8 (19·5; n=72)	65·2 (22·6; n=72)

Data are median (IQR), n (%), or mean (SD; n). ^{177}Lu=lutetium-177. EORTC=European Organisation for Research and Treatment of Cancer. IULN=institutional upper limit of normal. QLQ-C30=Quality of Life Questionnaire Core 30. QOL=quality of life. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.

Table 1: **Baseline characteristics**

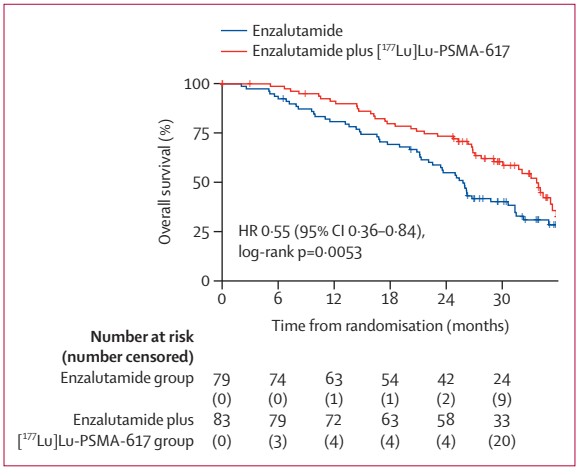

Figure 2: **Overall survival**
^{177}Lu=lutetium-177. HR=hazard ratio.

Longer follow-up confirmed the results reported in the interim analysis.[7] With additional follow-up, the previously reported improved progression-free survival outcomes and depth of PSA response were maintained (appendix pp 2–4).

In the enzalutamide group, the post-protocol treatment was [177Lu]Lu-PSMA-617 in 30 (38%) of 79 patients (19 [24%] received [177Lu]Lu-PSMA-617 as their next line of therapy), cabazitaxel in 23 (29%) of 79 patients, and docetaxel in 18 (23%) of 79 patients. In the enzalutamide plus [177Lu]Lu-PSMA-617 group, post-protocol treatment was cabazitaxel in 27 (33%) of 83 patients, docetaxel in 21 (25%) patients, and [177Lu]Lu-PSMA-617 in nine (11%) patients. Overall, 58 (73%) patients in the enzalutamide group and 48 (58%) patients in the enzalutamide plus [177Lu]Lu-PSMA-617 group received a subsequent non-protocol cancer treatment (appendix p 10).

HRQOL was reported by 148 (91%) of 162 patients, 74 in each group. Median deterioration-free survival for physical function was longer in the enzalutamide plus [177Lu]Lu-PSMA-617 group than in the enzalutamide group (median 10·64 months [95% CI 7·66–12·42] *vs* 3·42 months [3·19–7·89]; HR 0·51 [95% CI 0·36–0·72], log-rank p=0·0001). Median deterioration-free survival for overall health and QOL was also longer in the enzalutamide plus [177Lu]Lu-PSMA-617 group than in the enzalutamide group (8·71 months [6·41–11·56] *vs* 3·32 months [3·09–5·26]; 0·47 [0·33–0·67]; log-rank p<0·0001; figure 3).

Analyses of scores for patient-reported outcomes over time using a mixed model of repeated measures included 154 (95%) of 162 participants. These analyses showed better scores in the enzalutamide plus [177Lu]Lu-PSMA-617 group than in the enzalutamide group for overall health and QOL (difference 5·1 [95% CI 0·5–9·6], p=0·029), fatigue (5·9 [1·1–10·7], p=0·016), and pain (7·3 [1·6–12·9], p=0·012) and scores were not significantly different between groups for all other domains (figure 4; appendix p 6). The frequency of self-rated xerostomia was lower in the enzalutamide group

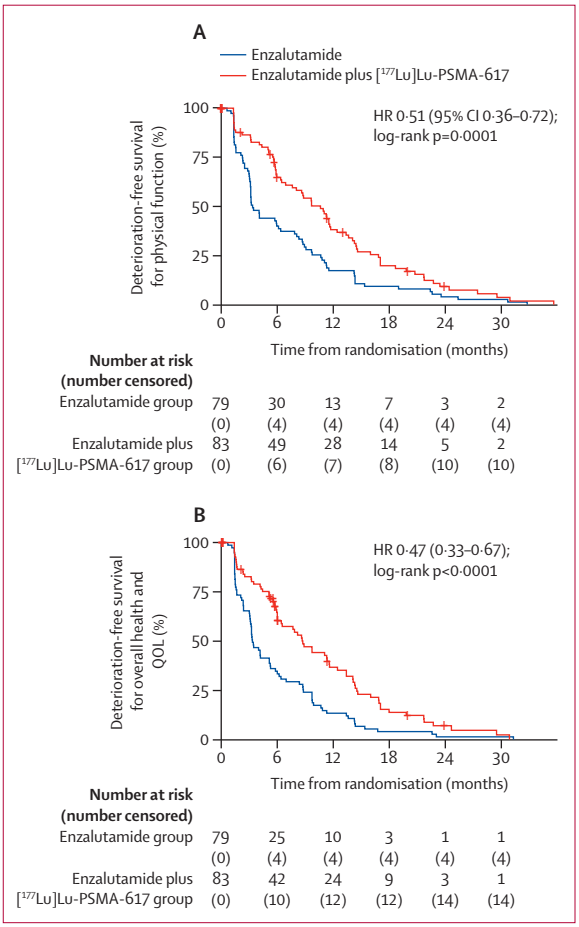

Figure 3: **Deterioration-free survival for physical function (A) and overall health and QOL (B)**
177Lu=lutetium-177. HR=hazard ratio. QOL=quality of life.

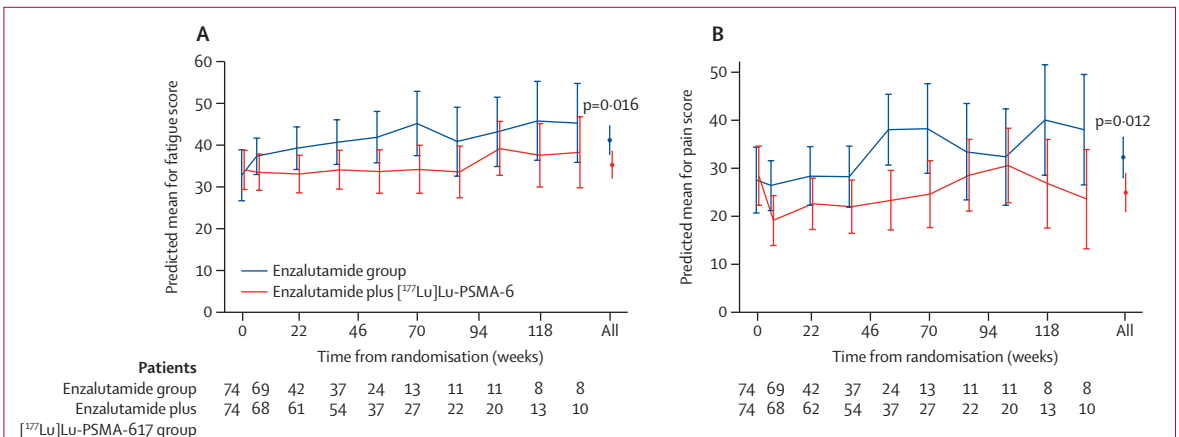

Figure 4: **HRQOL scores over time by randomly assigned treatment for fatigue (A) and pain (B) EORTC QLQ-C30 scales**
Error bars indicate 95% CIs. 177Lu=lutetium-177. EORTC=European Organisation for Research and Treatment of Cancer. HRQOL=health-related quality of life. QLQ-C30=Quality of Life Questionnaire Core 30.

than in the enzalutamide plus [177Lu]Lu-PSMA-617 group (43 [57%] of 75 *vs* 58 [74%] of 78; p=0·039; appendix p 13). The frequency of symptoms rated as troublesome from the Patient Disease and Treatment Assessment Form are summarised in the appendix (p 11–15).

Median time on study treatment was 7·9 months (95% CI 5·3–11·0) for the enzalutamide group and 13·4 months (11·5–15·2) for the enzalutamide plus [177Lu]Lu-PSMA-617 group. The most common all-grade adverse events were fatigue (55 [70%] of 79), nausea (24 [30%]), and constipation (18 [23%]) in the enzalutamide group, and fatigue (62 [77%] of 81), nausea (39 [48%]), and dry mouth (33 [41%]) in the enzalutamide plus [177Lu]Lu-PSMA-617 group (appendix pp 7–9). Grade 3–5 adverse events occurred in 35 (44%) of 79 patients in the enzalutamide group and 37 (46%) of 81 patients in the enzalutamide plus [177Lu]Lu-PSMA-617 group. Five grade 5 adverse events were reported: four in the enzalutamide plus [177Lu]Lu-PSMA-617 group (sudden death, sepsis, colonic obstruction, and intracranial haemorrhage) and one in the enzalutamide group (sudden death). No deaths were attributed to study treatment in either group. Adverse events of interest are detailed in table 2; the most common grade 3 or worse adverse events of interest were anaemia (none in the enzalutamide group *vs* three [4%] in the enzalutamide plus [177Lu]Lu-PSMA-617 group), arthralgia (none *vs* two [2%]), and fatigue (two [3%] *vs* two [2%]).

	Enzalutamide plus [177Lu]Lu-PSMA-617 group (n=81)		Enzalutamide group (n=79)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Any adverse event	67 (83%)	10 (12%)	64 (81%)	3 (4%)
Anaemia	9 (11%)	3 (4%)	4 (5%)	0
Anorexia	16 (20%)	0	8 (10%)	0
Arthralgia	7 (9%)	2 (2%)	7 (9%)	0
Arthritis	3 (4%)	1 (1%)	0	0
Cognitive disturbance	8 (10%)	1 (1%)	4 (5%)	0
Concentration impairment	2 (2%)	0	1 (1%)	0
Dry eye	10 (12%)	0	2 (3%)	0
Dry mouth	33 (41%)	0	8 (10%)	0
Fatigue	60 (74%)	2 (2%)	53 (67%)	2 (3%)
Generalised muscle weakness	1 (1%)	1 (1%)	2 (3%)	0
Hot flashes	20 (25%)	0	13 (16%)	0
Memory impairment	5 (6%)	0	5 (6%)	0
Nausea	39 (48%)	0	24 (30%)	0
Platelet count decreased	7 (9%)	1 (1%)	0	0
Vomiting	4 (5%)	0	3 (4%)	0
White blood cell count decreased	4 (5%)	1 (1%)	1 (1%)	1 (1%)

Data are n (%). There were no grade 4 or 5 adverse events of interest.

Table 2: **Adverse events of interest**

Discussion

PSMA-targeted radionuclide therapy, in particular [177Lu]Lu-PSMA-617, has changed the treatment landscape for prostate cancer following its approval for use in metastatic castration-resistant prostate cancer. However, although QOL benefits have been clearly demonstrated, improvements in overall survival have been modest, with a 4-month median overall survival benefit demonstrated in the VISION trial, and no survival benefit in other randomised trials of [177Lu]Lu-PSMA-617 monotherapy.[2,12–14] To our knowledge, the ENZA-p trial, which evaluated the addition of [177Lu]Lu-PSMA-617 to enzalutamide in metastatic castration-resistant prostate cancer at high risk of early treatment failure on enzalutamide alone, is the first PSMA-targeted radionuclide trial to show a significant benefit in overall survival versus an active, life-prolonging therapy.[4] This overall survival benefit for the combination, despite the subsequent use of [177Lu]Lu-PSMA in more than a third of participants in the control group, raises important questions about how PSMA-targeted radionuclide therapy should optimally be sequenced and combined for maximal benefit.

Cellular heterogeneity and crosstalk between signalling pathways are inherent characteristics of metastatic castration-resistant prostate cancer that contribute to early treatment failure with both androgen receptor pathway inhibitors and PSMA-targeted therapies.[15] There is a strong relationship between the androgen and PSMA receptors, with the gene that encodes the PSMA receptor, *FOLH1*, indirectly regulated by the androgen receptor.[16,17] Preclinical and clinical data show that blockade of the androgen receptor with androgen receptor pathway inhibitors in metastatic castration-resistant prostate cancer leads to increased PSMA expression.[6,17,18] In concurrent translational work within ENZA-p, an increase in PSMA expression on PSMA-PET-CT 15 days after commencing enzalutamide occurred in 70% of participants. Participants showing this early increase in PSMA expression with enzalutamide had the largest improvement in both depth of PSA response and PSA progression-free survival with the addition of [177Lu]Lu-PSMA-617.[19] The ENZA-p trial addresses cellular heterogeneity by combining two complementary therapies that leverage the relationship between PSMA expression and androgen signalling to limit activation of resistant signalling pathways, while targeting distinct clonal populations. Determination of whether the survival benefits of adding [177Lu]Lu-PSMA-617 to enzalutamide are synergistic or complementary requires further research. The PEACE-3 trial, which evaluated the addition of radium-223 dichloride to enzalutamide versus enzalutamide alone in early metastatic castration-resistant prostate cancer, also

demonstrated improved overall survival, underpinning the potential value of concurrent radionuclide therapy and an androgen receptor pathway inhibitor in metastatic castration-resistant prostate cancer.[20]

38% of participants in the enzalutamide group of ENZA-p received [177Lu]Lu-PSMA as a subsequent therapy off-trial. The PSMAfore trial, a randomised trial of [177Lu]Lu-PSMA-617 versus second-line androgen receptor pathway inhibitors in patients with metastatic castration-resistant prostate cancer before chemotherapy, allowed crossover to [177Lu]Lu-PSMA-617 in the control group, with 57% of patients receiving subsequent [177Lu]Lu-PSMA-617. PSMAfore demonstrated improved radiographic progression-free survival, but not overall survival.[12] The difference in overall survival between these two trials might be in part due to the high-risk features for the lack of a response with enzalutamide used to select participants in ENZA-p, but points to the strength of combining the two therapies.

Additive toxicities often arise when escalating treatment by using combinations of active drugs, particularly cytotoxic drugs. Good HRQOL is a significant benefit of both androgen receptor pathway inhibitors and [177Lu]Lu-PSMA-617 monotherapy when compared with chemotherapy in patients with prostate cancer. The ENZA-p trial confirmed that the addition of [177Lu]Lu-PSMA-617 to enzalutamide improved pain, fatigue, physical activity, and overall health and QOL, compared with single-agent enzalutamide. The frequency and severity of adverse events were similar for the combination versus monotherapy despite longer treatment time on the combination, with the exception of low-grade xerostomia being more frequent with the addition of [177Lu]Lu-PSMA-617.

There are several limitations to this study. First, it uses enzalutamide as first-line treatment for metastatic castration-resistant prostate cancer restricting broad applicability of the findings, as first-line androgen receptor pathway inhibitors are increasingly used in metastatic hormone-sensitive prostate cancer. Second, ENZA-p is a randomised phase 2 trial of 162 participants with overall survival as a secondary endpoint. Evaluation of combination androgen receptor pathway inhibitors and [177Lu]Lu-PSMA-617 is currently underway in metastatic hormone-sensitive prostate cancer with the randomised phase 3 PSMAddition trial (NCT04720157). In ENZA-p, the [177Lu]Lu-PSMA-617 dosing was personalised with a limited number of doses (two or four) administered based on interim biomarker (PSMA-PET-CT and PSA) responses, in contrast to the six doses administered continuously in other randomised trials evaluating [177Lu]Lu-PSMA-617. This innovation might be even more relevant in the hormone-sensitive setting, in which PSMA expression might decrease rapidly after starting androgen deprivation therapy and non-target organ toxicity might cause long-term harm.[6,21,22] Further evaluation of PSMA-targeted radionuclide therapy in combination with second-line androgen receptor pathway inhibitors or androgen receptor degraders might also be warranted given the overall survival benefit with first-line enzalutamide plus [177Lu]Lu-PSMA-617 observed in this trial. Finally, the ENZA-p trial included participants with risk factors for early lack of response to treatment on enzalutamide, which also limits the general applicability of the findings. However, the trial has confirmed that patients with risk factors associated with limited 5-year survival on enzalutamide can experience survival outcomes equivalent to those for unselected participants on enzalutamide in metastatic castration-resistant prostate cancer, without significant additional toxicity.[3]

In conclusion, the addition of [177Lu] Lu-PSMA-617 to enzalutamide was associated with improved survival, as well as some aspects of HRQOL, in patients with high-risk metastatic castration-resistant prostate cancer.

Contributors

LE, SSu, MC, AYZ, AJM, SSa, MRS, and IDD were members of the protocol development working party that contributed to conceptualisation and writing the first version of the protocol. LE, SSu, MC, AMJ, AN, AW, S-TL, IDK, SN, RJF, CG, NKR, JCG, DP, HT, AL, SSa, MSH, SR, THT, ARK, ADR, WM, MV, DPN, AYZ, LK, GS, PBa, PBu, DAP, PL, LH, WC, MRS, and IDD accrued patients and collected data. LE, AN, and S-TL performed imaging central review. LE, MRS, SSu, IDD, AMJ, AJM, and HT contributed to the statistical analysis plan. AJM and HT led the statistical analysis and verified underlying data. SSu and AYZ reviewed data on adverse events, response, and progression-free survival. MM contributed to writing and approval of the manuscript. 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 the 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. CG donated personal fees from Astellas, Janssen, AstraZeneca, Bristol Myers Squibb, Pfizer/EMD Serono, Ipsen, Astellas, and MSD, direct and complete, to a third party not-for-profit; declares consulting fees (unrelated to this work) from Novotech, Cadex Geonomics, and BCAL Diagnostics; and participation on an advisory board for Alloplex. MSH reports grants and receipt of equipment, materials, drugs, medical writing, gifts, or other services from the Prostate Cancer Foundation, Australian National Health and Medical Research Council (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 the Peter MacCallum Cancer Centre and the University of Melbourne (Melbourne, VIC, Australia). 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

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Data sharing

Requests for specific analyses or data will be considered by the ENZA-p trial executive committee after 3 months following 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 need to sign a data access agreement.

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