[^{177}Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial

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Summary

Background Enzalutamide and lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 both improve overall survival in patients with metastatic castration-resistant prostate cancer. Androgen and PSMA receptors have a close intracellular relationship, with data suggesting complementary benefit if targeted concurrently. In this study, we assessed the activity and safety of enzalutamide plus adaptive-dosed [^{177}Lu]Lu-PSMA-617 versus enzalutamide alone as first-line treatment for metastatic castration-resistant prostate cancer.

Methods ENZA-p was an open-label, randomised, controlled phase 2 trial done at 15 hospitals in Australia. Participants were men aged 18 years or older with metastatic castration-resistant prostate cancer not previously treated with docetaxel or androgen receptor pathway inhibitors for metastatic castration-resistant prostate cancer, gallium-68 [^{68}Ga]Ga-PSMA-PET-CT (PSMA-PET-CT) positive disease, 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, use of early docetaxel, and previous treatment with abiraterone acetate. Patients were either given 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 dependent on an interim PSMA-PET-CT (week 12). The primary endpoint was prostate-specific antigen (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. The analysis was done in the intention-to-treat population, using stratified Cox proportional hazards regression. This trial is registered with ClinicalTrials.gov, NCT04419402, and participant follow-up is ongoing.

Findings 162 participants were randomly assigned between Aug 17, 2020, and July 26, 2022. 83 men were assigned to the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group, and 79 were assigned to the enzalutamide group. Median follow-up in this interim analysis was 20 months (IQR 18–21), with 32 (39%) of 83 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 16 (20%) of 79 patients in the enzalutamide group remaining on treatment at the data cutoff date. Median age was 71 years (IQR 64–76). Median PSA progression-free survival was 13·0 months (95% CI 11·0–17·0) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 7·8 months (95% CI 4·3–11·0) in the enzalutamide group (hazard ratio 0·43, 95% CI 0·29–0·63, p<0·0001). The most common adverse events (all grades) were fatigue (61 [75%] of 81 patients), nausea (38 [47%]), and dry mouth (32 [40%]) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and fatigue (55 [70%] of 79), nausea (21 [27%]), and constipation (18 [23%]) in the enzalutamide group. Grade 3–5 adverse events occurred in 32 (40%) of 81 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 32 (41%) of 79 patients in the enzalutamide group. Grade 3 events that occurred only in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group included anaemia (three [4%] of 81 participants) and decreased platelet count (one [1%] participant). No grade 4 or 5 events were attributed to treatment on central review in either group.

Interpretation The addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide improved PSA progression-free survival providing evidence of enhanced anticancer activity in patients with metastatic castration-resistant prostate cancer with risk factors for early progression on enzalutamide and warrants further evaluation of the combination more broadly in metastatic prostate cancer.

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Introduction

Androgen receptor pathway inhibitors including enzalutamide have been shown to improve overall survival in men with metastatic prostate cancer.[1,2] However, a subset of patients with poor prognostic features have short duration of disease control with androgen receptor pathway inhibitors.[3] Prostate-specific membrane antigen (PSMA) is a transmembrane protein involved in the PI3K–mTOR signalling pathway, with increased expression on androgen blockade in clonal subpopulations in metastatic castration-resistant prostate cancer.[4–7] The VISION trial established that lutetium-177 [^{177}Lu]Lu-PSMA-617 improved overall survival in conjunction with standard of care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer; however, improvement in survival was modest.[8] Targeting the androgen and PSMA receptors concurrently might improve anticancer activity and disease control in metastatic castration-resistant prostate cancer.[9] We sought to evaluate the safety and efficacy of the combination of enzalutamide and adaptive-dosed [^{177}Lu]Lu-PSMA-617 compared with enzalutamide alone in patients with clinical risk factors for early progression on enzalutamide monotherapy.

Methods

Study design and participants

ENZA-p (Australian and New Zealand Urogenital and Prostate [ANZUP] trial 1901) was a multicentre, open-label, randomised, phase 2 trial done at 15 hospitals in Australia (appendix pp 2–3). The trial protocol has been published[10] and is provided in the appendix. The trial had ethical and regulatory approvals at all participating sites. Participants provided signed, written, informed consent.

Eligible patients were men aged 18 years or older with metastatic castration-resistant prostate cancer, not previously treated with docetaxel or an androgen receptor pathway inhibitor for metastatic castration-resistant prostate cancer, with evidence of progressive disease defined by Prostate Cancer Working Group 3 (PCWG3) criteria and prostate-specific antigen (PSA) more than 5 ng/mL. Previous treatment with abiraterone acetate or docetaxel for metastatic hormone-sensitive prostate cancer was permitted. Participants were required to have metastatic adenocarcinoma of the prostate defined by histopathology or metastatic disease typical of prostate cancer, without significant sarcomatoid, spindle cell, or neuroendocrine small cell components; two or more risk factors for early progression on enzalutamide alone[3,11] (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 or visceral metastases [conventional imaging], PSA doubling time of less than 84 days, pain requiring opiates for more than 14 days, or previous treatment with abiraterone acetate for hormone-sensitive

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 trial 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 of lutetium-177 [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617 in patients with metastatic castration-resistant prostate cancer, showing improved quality of life compared with second-line chemotherapy and improved overall survival compared with best standard of care excluding chemotherapy. We identified no trials assessing [^{177}Lu]Lu-PSMA-617 in combination with enzalutamide or other androgen receptor pathway inhibitors. Therefore, we designed a randomised phase 2 trial to compare activity and safety of enzalutamide plus adaptive-dosed [^{177}Lu]Lu-PSMA-617 versus enzalutamide alone before chemotherapy in patients with metastatic castration-resistant prostate cancer.

Added value of this study

To our knowledge, this is the first randomised study to evaluate the activity and safety of combination enzalutamide and [^{177}Lu]Lu-PSMA-617 versus enzalutamide alone (an active comparator group known to improve overall survival) before chemotherapy for metastatic castration-resistant prostate cancer. The trial addresses the issue of tumour heterogeneity with the use of two targeted therapies with activity on different cancer cell subtypes.

Implications of all the available evidence

This trial provides evidence that the addition of adaptive-dosed [^{177}Lu]Lu-PSMA-617 to enzalutamide improves PSA response rate and PSA progression-free survival compared with enzalutamide alone in patients with metastatic castration-resistant prostate cancer, with a favourable safety profile. Furthermore, the study demonstrates the feasibility of biomarker-guided adaptive dosing of [^{177}Lu]Lu-PSMA-617 using interim molecular imaging, in conjunction with other active treatments, to improve patient outcomes.

prostate cancer); normal renal, haematological, and liver function; and an Eastern Cooperative Oncology Group performance status of 0–2. Patients with other active malignancies within 5 years before consent and seizures or conditions predisposing to seizures were excluded. All potential participants underwent screening with gallium-68 [^{68}Ga]Ga-PSMA-11 PET-CT (PSMA-PET-CT). PET eligibility criteria for the trial were PSMA-positive disease with a maximum standardised uptake value (SUVmax) of at least 15 at a minimum of one site of disease, and SUVmax of at least 10 at all larger sites of disease (not affected by partial volume effect). Conventional imaging with diagnostic CT and [^{18}F]fluorodeoxyglucose-PET-CT was done at screening, but not used to assess screening imaging eligibility. For a full list of inclusion and exclusion criteria, please see the study protocol (appendix).

Randomisation and masking

Participants were randomly assigned (1:1) to enzalutamide plus adaptive-dosed [^{177}Lu]Lu-PSMA-617 or enzalutamide alone by a centralised, web-based system (Medidata RTSM) using minimisation with a random component to stratify for study site, disease burden (more than 20 lesions *vs* 20 lesions or less on PSMA-PET-CT), use of early docetaxel for hormone-sensitive disease, and previous treatment with abiraterone acetate for metastatic hormone-sensitive prostate cancer. 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)-CT 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 (appendix). Blood samples for circulating tumour DNA analysis were obtained at screening, week 12, and at first progression (biochemical or radiographic; appendix p 4).

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 [^{99m}Tc]technetium bone scans were done every 12 weeks until radiographic progression. PSMA-PET-CT scans for biomarker analysis were obtained at baseline, week 2 after commencing enzalutamide, week 12, and at first progression (PSA or radiographic). Patient-reported outcome measures included the McGill–Melzack Present Pain Intensity scale, 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. Patient-reported outcome measures were completed every 4 weeks until the end of study treatment, and then every 6 weeks until radiographic progression. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) 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 deemed most likely to occur with the two investigational treatments and were prespecified by the trial team.

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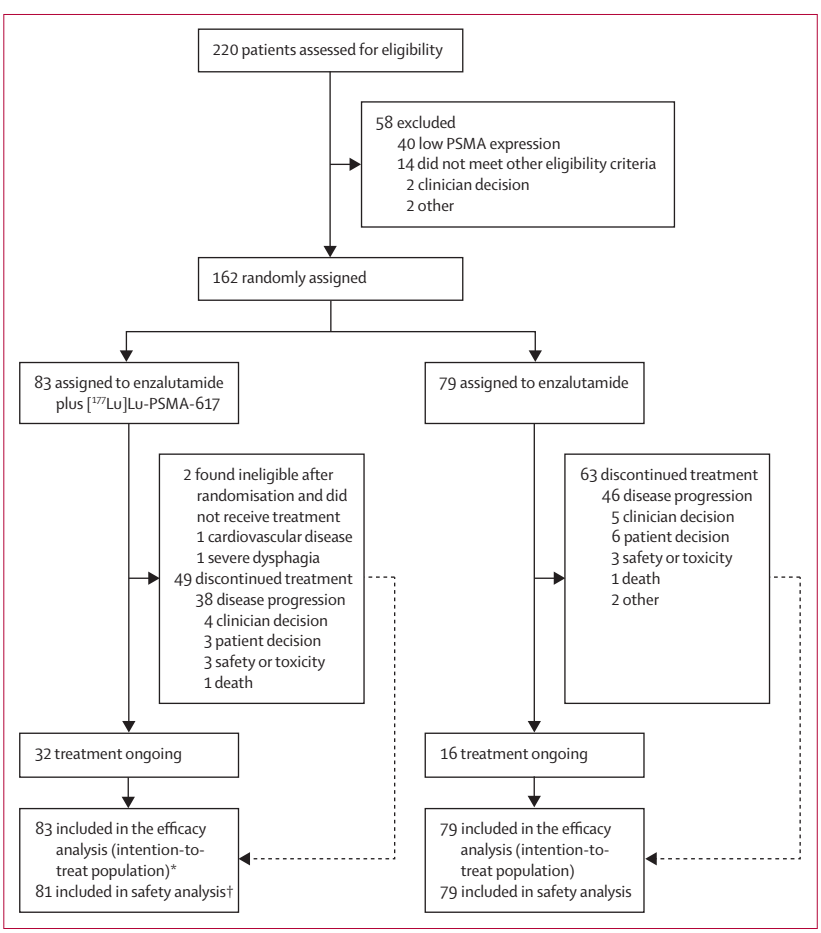

Figure 1: **Trial profile**
^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. *Two additional participants were recruited and randomly assigned to account for the two participants determined to be ineligible after randomisation but before starting study treatment. Both patients were randomly assigned to the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group. †The two patients originally randomly assigned who did not receive any treatment because of ineligibility were not included in the safety population.

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See Online for appendix

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, or the date of last PSA test without PSA progression (at which point the observation was censored). PSA progression was defined as an increase in PSA of at least 25% and at least 2 ng/mL higher than the nadir value, with confirmation at least 3 weeks later. Secondary endpoints included radiographic progression-free survival, defined as the interval from the date of randomisation to the date of first evidence of radiographic progression on imaging (PCWG3 criteria for bone lesions and Response Evaluation Criteria in Solid Tumours [RECIST] 1.1 criteria for soft-tissue lesions) or death from any cause; clinical progression-free survival, defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression, determined by the first occurrence of progression on imaging (PCWG3 criteria for bone lesions and RECIST 1.1 for soft-tissue lesions), development of new symptoms attributable to cancer progression, the need for radiotherapy to new metastases, initiation of other anticancer treatment for prostate cancer, or death from any cause; and pain response, defined as a reduction of 2 or more points for participants with a baseline McGill–Melzack Present Pain Intensity score of at least 2.

Other secondary endpoints included PSA response rate (defined as the proportion of patients with 50% or 90% reduction in PSA from baseline), health-related quality of life, overall survival, and toxicity. Resource use and cost effectiveness were tertiary endpoints. Response endpoints were centrally reviewed.

Translational objectives included the identification of associations between clinical outcomes and candidate biomarkers based on molecular imaging, tissue samples, circulating tumour DNA, and other circulating biomarkers. These translational endpoints, health-related quality of life, and overall survival will be reported separately when data for secondary endpoints are more mature.

	Enzalutamide plus [^{177}Lu]Lu-PSMA-617 (n=83)	Enzalutamide (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 for >14 days	9 (11%)	12 (15%)
Previous early docetaxel for hormone-sensitive disease	44 (53%)	45 (57%)
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 diagnosis	43 (52%)	46 (58%)
<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 for >14 days	9 (11%)	12 (15%)
Previous treatment with abiraterone acetate	12 (14%)	9 (11%)

Data are median (IQR) or n (%). ^{177}Lu=lutetium-177. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. IULN=institutional upper limit of normal.

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

Statistical analysis

The sample size of 160 patients followed up until 150 PSA progression-free survival events were reported was to provide 80% power if the true hazard ratio (HR) was 0·625, using a two-sided, type I error rate of 0·05. An interim analysis at 113 events (75% of total planned) was later added to the design without knowledge of outcomes in each treatment group.[12] The trial executive committee added the interim analysis in response to external evidence of the effectiveness of [^{177}Lu]Lu-PSMA-617 on progression-free survival and overall survival.[8,13] The boundary for rejection of the null hypothesis at the interim analysis was prespecified, set at 2·268, and corresponds to a two-sided p value of 0·023. Details of prespecified endpoint derivations and analysis are available in a statistical analysis plan and addendum (appendix). Control of the study-wide type I error rate was confined to the primary endpoint; therefore, analyses of secondary endpoints are reported with 95% CIs, and without p values. Efficacy analyses were done in the intention-to-treat analysis set, comprising all randomly assigned participants. The safety analyses included all randomly assigned participants who received at least one dose of study treatment. The Kaplan–Meier method was used to summarise time-to-event endpoints, with a stratified log-rank test used for the primary comparison between randomly assigned groups on time-to-event endpoints. We used stratified Cox proportional hazards regression to estimate HRs and their 95% CIs.

Schoenfeld residuals were used to assess whether the proportional hazards assumption was met. Restricted mean survival times were calculated at the median follow-up time and used in the event of evidence of non-proportional hazards. There was evidence of violation of the proportional hazards' assumption. Analyses based on restricted mean survival times gave similar estimates of effect, 95% CIs, and p values. Binary endpoints were compared in the two treatment groups using 95% CIs based on the stratified Cochran–Mantel–Haenszel χ^2 test. Statistical analysis was done with R version 4.3 and SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT04419402.

Role of the funding source

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

Results

From Aug 17, 2020, to July 26, 2022, 220 screened participants were registered (figure 1). Of these, 40 (18%) patients were ineligible because of low PSMA expression and 18 (8%) did not meet other eligibility criteria. 162 participants were randomly assigned, 83 to enzalutamide plus [^{177}Lu]Lu-PSMA-617 and 79 to enzalutamide alone. Two additional participants were recruited and randomly assigned to account for two participants determined to be ineligible after randomisation but before starting study treatment: one had clinically significant cardiovascular disease, the other developed severe dysphagia and was no longer able to swallow capsules.

The trigger for the interim analysis was reached on May 18, 2023, and a sweep for events to that date yielded 117 PSA progression-free survival events. The ANZUP Cancer Trials Group Independent Data Safety Monitoring Committee reviewed the interim analysis of PSA progression-free survival and informed the trial executive committee of convincing evidence of benefit for combination therapy, as the test statistic of 4·372 had crossed the prespecified boundary of 2·268 for rejection of the null hypothesis. The trial executive committee decided to report on outcomes to the May 18, 2023, data cutoff date and to continue follow-up to provide more mature data on overall survival and other secondary endpoints.

Median follow-up for this interim analysis was 20 months (IQR 18–21). At data cutoff, trial treatment was ongoing in 48 (30%) of 162 participants: 32 (39%) of 83 in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 16 (20%) of 79 in the enzalutamide group.

Median age was 71 years (IQR 64–76); table 1. 98 (60%) of 162 participants had more than 20 sites of PSMA-avid metastatic disease; 89 (55%) had M1 disease at diagnosis; 89 (55%) were treated with docetaxel for metastatic hormone-sensitive prostate cancer; and 21 (13%) had received abiraterone acetate for metastatic hormone-sensitive prostate cancer. Ethnicity data were not collected.

In the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group, nine (11%) of 83 participants received up to two doses due to no residual PSMA positive disease on the week 12 PSMA-PET-CT, while five (6%) participants received only

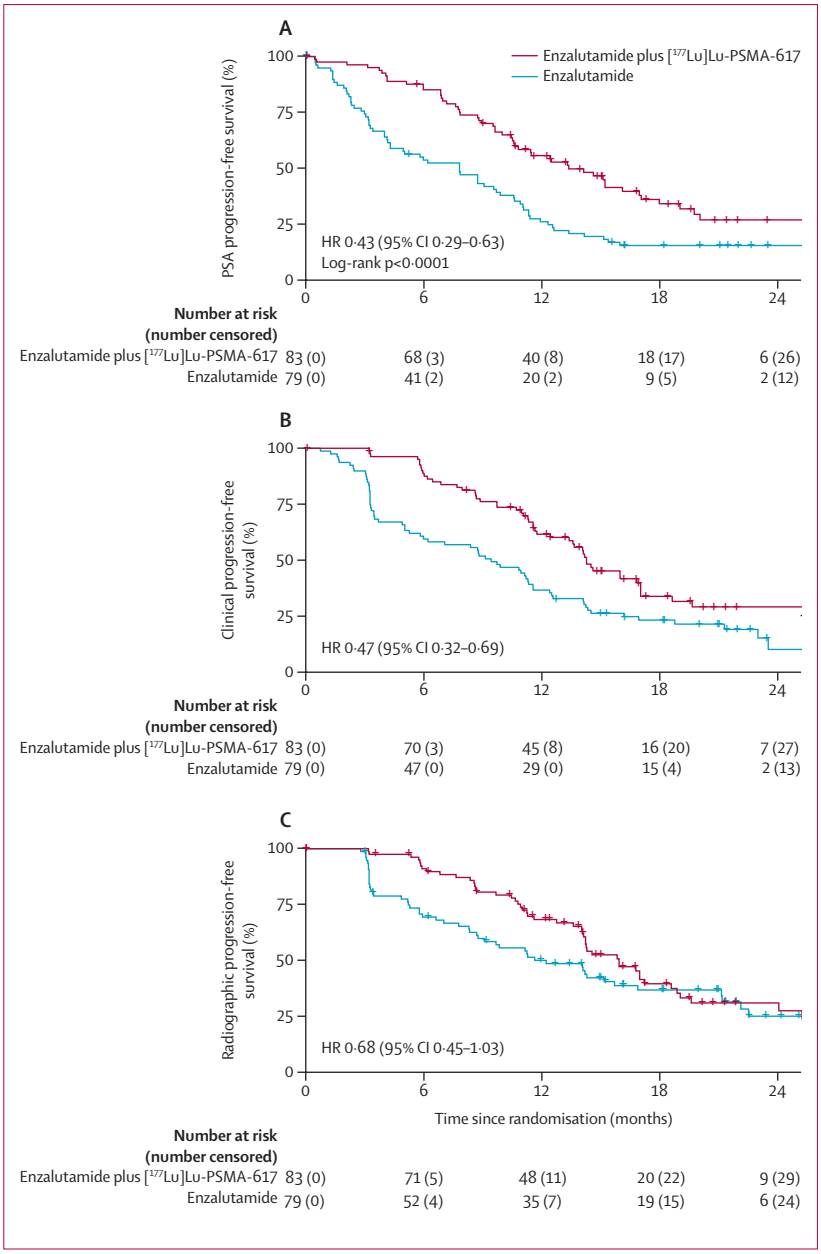

Figure 2: **PSA progression-free survival, clinical progression-free survival, and radiographic progression-free survival**

Kaplan–Meier curves for PSA progression-free survival (A), clinical progression-free survival as determined by results on imaging, symptoms, or changes in therapy (B), and radiographic progression-free survival as determined by results on imaging (C). Control of the study-wide type I error rate was confined to the primary endpoint (PSA progression-free survival); therefore, analyses of secondary endpoints are reported with 95% CIs, and without p values. ^{177}Lu=lutetium-177. HR=hazard ratio. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.

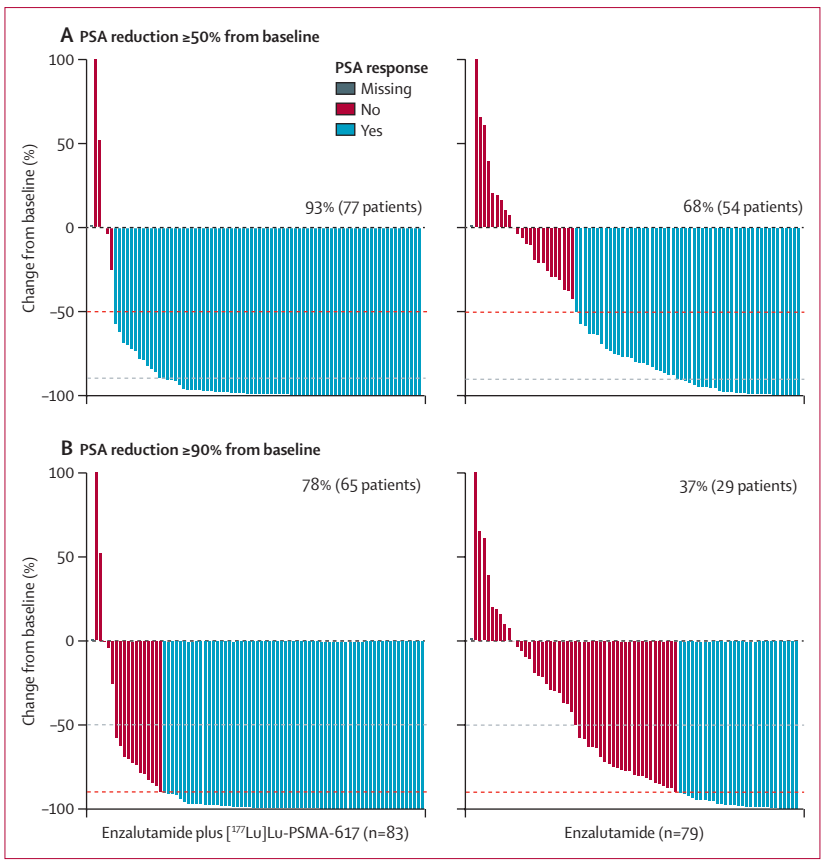

Figure 3: **PSA response**
Waterfall plots depicting the proportion of participants who had reduction in PSA of 50% (A) and 90% (B). ^{177}Lu=lutetium-177. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen.

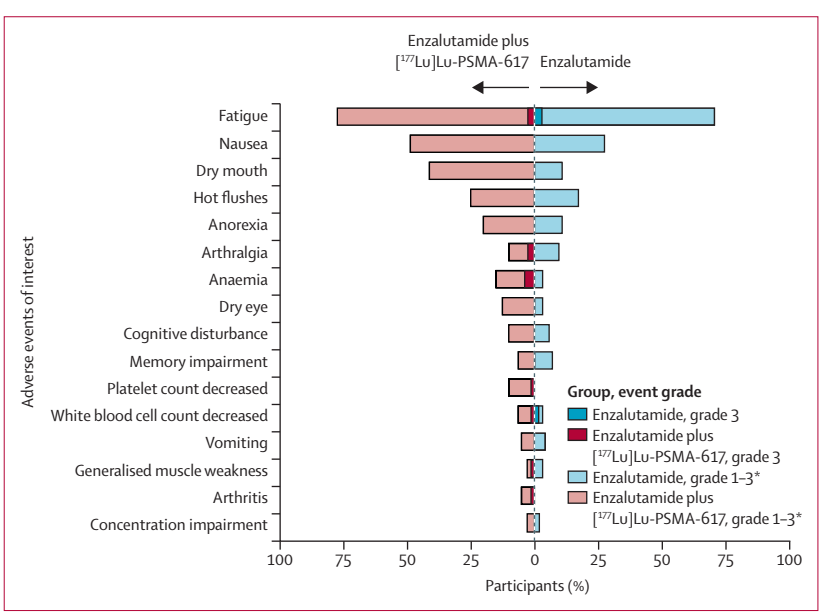

Figure 4: **Adverse events of interest**
Treatment-related adverse events were not separated out in the trial, apart from serious adverse events, which were attributed by local investigators and centrally reviewed. ^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. *No grade 4 or grade 5 adverse events of interest were reported.

three doses due to progression, and 67 (81%) received all four doses (two withdrew before treatment).

The primary endpoint, median PSA progression-free survival, was 13·0 months (95% CI 11·0–17·0) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group compared with 7·8 months (95% CI 4·3–11·0) in the enzalutamide group (HR 0·43, 95% CI 0·29–0·63, p<0·0001; figure 2A). Restricted mean survival time estimates at 20 months were 13·2 months (95% CI 11·9–14·6) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group versus 8·5 months (95% CI 7·1–10·0) in the enzalutamide group.

Median clinical progression-free survival was 14·0 months (95% CI 13·0–17·0) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 9·4 months (95% CI 5·9–12·0) in the enzalutamide group (HR 0·47, 95% CI 0·32–0·69; figure 2B) and median radiographic progression-free survival was 16·0 months (95% CI 14·0–19·0) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group versus 12·0 months (95% CI 8.8–21·0) in the enzalutamide group (HR 0·68, 95% CI 0·45–1·03; figure 2C).

The proportion of patients with a reduction in PSA of 50% of more was 77 (93%) of 83 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group versus 54 (68%) of 79 in the enzalutamide group, and the proportion of patients with a PSA reduction of 90% or more was 65 (78%) of 83 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group versus 29 (37%) of 79 in the enzalutamide group (figure 3).

Improvement in pain occurred in 19 (61%) of 31 patients assigned to enzalutamide plus [^{177}Lu]Lu-PSMA-617 compared with eight (27%) of 30 assigned to enzalutamide alone.

The most common adverse events (all grades) were fatigue (61 [75%] of 81 patients), nausea (38 [47%]), and dry mouth (32 [40%]) in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and fatigue (55 [70%] of 79), nausea (21 [27%]), and constipation (18 [23%]) in the enzalutamide group (appendix pp 5–13). Grade 3–5 adverse events occurred in 32 (40%) of 81 patients in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group and 32 (41%) of 79 patients in the enzalutamide group. Grade 3 events that occurred only in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group included anaemia (three [4%] participants) and decreased platelet count (one [1%] participant; figure 4, table 2). There were five grade 4 adverse events, three in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (hyokalaemia, intracranial haemorrhage, and anxiety) versus two in the enzalutamide group (cardiac disorder [other] and neoplasm), and four grade 5 adverse events, three in the enzalutamide plus [^{177}Lu]Lu-PSMA-617 group (sudden death, sepsis, and intracranial haemorrhage) and one in the enzalutamide group (sudden death; appendix pp 5–13). No deaths were attributed to treatment on central review in either group.

Discussion

Although enzalutamide improves overall survival as first-line treatment for metastatic castration-resistant prostate cancer, many patients have a short duration of response.[1,11] 5-year overall survival rates in patients treated with enzalutamide for metastatic castration-resistant prostate cancer without previous chemotherapy are 26% overall, falling to 5% in those with features indicating increased risk of early progression.[3] This study showed improved progression-free survival with the addition of adaptive-dosed [^{177}Lu]Lu-PSMA-617 to enzalutamide in patients with two or more risk factors for early progression compared with enzalutamide alone. This enhanced anticancer effect of the combination of an androgen receptor pathway inhibitor and [^{177}Lu]Lu-PSMA-617 has implications for how [^{177}Lu]Lu-PSMA-617 could be administered and combined in the treatment of metastatic prostate cancer.

[^{177}Lu]Lu-PSMA-617 is a targeted radionuclide therapy that prolonged overall survival in patients with metastatic castration-resistant prostate cancer after progression on chemotherapy.[8,13] Toxicity was lower, and health-related quality of life was better, with [^{177}Lu]Lu-PSMA-617 than with cabazitaxel chemotherapy.[13,14] However, the improvement in overall survival with [^{177}Lu]Lu-PSMA-617 was modest at 15 months versus 11 months with a standard of care comparator that excluded chemotherapy.[8] Treatment resistance to [^{177}Lu]Lu-PSMA-617 is likely to be multifactorial, including heterogeneous expression of the PSMA receptor in metastatic castration-resistant prostate cancer as well as radiation resistance.[15,16] In the current trial, the addition of [^{177}Lu]Lu-PSMA-617 to enzalutamide directly addressed the issue of tumour heterogeneity by combining two targeted therapies with complementary activity.[4]

PSMA and androgen receptors are both cell proliferation receptors that have a strong intracellular relationship in metastatic prostate cancer.[6,15,17–19] Androgen receptor blockade increases PSMA expression in clonal subpopulations.[7,20–22] Patients with increasing PSMA expression when treated with an androgen receptor pathway inhibitor have shorter overall survival, particularly in metastatic castration-resistant prostate cancer.[18,19] High PSMA expression is required to deliver sufficient radiation with [^{177}Lu]Lu-PSMA-617 therapy, and correlates to improved treatment responses.[16,17,23] The rationale of the ENZA-p trial is that the two therapies will have anticancer activity on different cancer cell subtypes, with additive effect. Furthermore, PSMA upregulation with enzalutamide before [^{177}Lu]Lu-PSMA-617 therapy might drive deeper responses in the androgen-resistant clones, leaving a cell population more responsive to androgen receptor pathway inhibitors, resulting in longer treatment responses through treatment synergy. This trial has confirmed enhanced anticancer effect, improvement in pain, and longer progression-free survival with the combination.

	Enzalutamide plus [^{177}Lu]Lu-PSMA-617 (n=81)		Enzalutamide (n=79)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Any adverse event	68 (84%)	9 (11%)	64 (81%)	3 (4%)
Anaemia	8 (10%)	3 (4%)	2 (3%)	0
Anorexia	16 (20%)	0	8 (10%)	0
Arthralgia	2 (2%)	2 (2%)	7 (9%)	0
Arthritis	3 (4%)	1 (1%)	0	0
Cognitive disturbance	8 (10%)	0	4 (5%)	0
Concentration impairment	2 (2%)	0	1 (1%)	0
Dry eye	10 (12%)	0	2 (3%)	0
Dry mouth	32 (40%)	0	8 (10%)	0
Fatigue	59 (73%)	2 (2%)	53 (67%)	2 (3%)
Generalised muscle weakness	1 (1%)	1 (1%)	2 (3%)	0
Hot flushes	20 (25%)	0	13 (16%)	0
Memory impairment	5 (6%)	0	5 (6%)	0
Nausea	38 (47%)	0	21 (27%)	0
Platelet count decreased	8 (10%)	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 (%). ^{177}Lu=lutetium-177. PSMA=prostate-specific membrane antigen. *No grade 4 or grade 5 adverse events of interest were reported.

Table 2: **Adverse events of interest***

A novel aspect of this trial was adaptive dosing of [^{177}Lu]Lu-PSMA-617. [^{177}Lu]Lu-PSMA-617 dosing was personalised with participants eligible for two or four doses dependent on persistent PSMA-avid disease on an interim PSMA-PET-CT. Few participants (11%) received one or two doses, possibly because of our selection of participants with two or more risk factors for early progression on enzalutamide. However, an adaptive-dosing strategy has the potential to minimise both cost and toxicity by only administering treatment when the PSMA receptor target is present and might be effective in managing potential toxicity as [^{177}Lu]Lu-PSMA-617 is administered earlier in prostate cancer. More flexible adaptive dosing, including recommencement of treatment at the time of PSA progression, might further improve progression-free survival.[24] Translational work within ENZA-p will evaluate whether whole-body SPECT acquired from [^{177}Lu]Lu-PSMA-617 gamma emission is equivalent to PSMA-PET-CT as an interim response biomarker.[25]

PSA progression-free survival was chosen as the primary endpoint for this study because it was considered a sensitive and reliable measure of anticancer activity. It was not intended to be a surrogate measure of overall survival. Although the longer PSA progression-free survival, clinical progression-free survival, and deeper PSA responses support the hypothesis of enhanced anticancer activity with the combination, longer follow-up is needed to assess the effects of enzalutamide plus [^{177}Lu]Lu-PSMA-617 on overall survival, and the durability

of responses in patients treated with fewer doses of [177Lu]Lu-PSMA-617. To our knowledge, ENZA-p is the first randomised trial to embed serial PSMA-PET-CT for translational purposes, including at the time of first progression (PSA or radiographic). In some participants, study treatment was stopped following progression on PSMA-PET-CT, without the subsequent conventional imaging required to determine radiographic progression-free survival. This is a study limitation that might have obscured real effects on radiographic progression-free survival, which is based solely on conventional imaging with CT and technetium bone scans. Longer follow-up will also allow comprehensive evaluation of the predictive and prognostic power of molecular imaging and of liquid biomarkers embedded in the trial.

In this trial, enzalutamide was administered as first-line treatment of metastatic castration-resistant prostate cancer and it is unclear how our findings apply in the treatment of hormone-sensitive prostate cancer. However, the complementary therapeutic effect of an androgen receptor pathway inhibitor and [177Lu]Lu-PSMA-617 shown in this study has implications for the future use of theranostics in prostate cancer. Responses to treatment with [177Lu]Lu-PSMA-617 alone can be short-lived.[13] This trial raises the question of whether PSMA targeted therapy should be used with an androgen receptor pathway inhibitor to prolong treatment responses. The combination of an androgen receptor pathway inhibitor and [177Lu]Lu-PSMA-617 is being evaluated in patients with metastatic hormone-sensitive prostate cancer in the PSMAddition trial (NCT04720157). Further work is required to determine if use of a second-line androgen receptor pathway inhibitor also improves treatment responses to [177Lu]Lu-PSMA-617 in metastatic castration-resistant prostate cancer, and if the improved treatment responses identified in the current trial are additive or synergistic.

Contributors

LE, SSu, MC, AYZ, AJM, SSa, MRS, IDD, and SY were members of the protocol development working party contributing 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 have 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, 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. 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. CG declares consulting fees (unrelated to this work) from Novotech, Cadex Geonomics, and BCAL Diagnostics; and participation on an advisory board for Alloplex. 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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 louise.emmett@svha.org.au; to gain access, data requestors will be asked to sign a data access agreement.

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