[^{177}Lu]Lu-PSMA-617 in patients with PSMA-positive metastatic androgen pathway modulator-naive/sensitive prostate cancer (PSMAddition): a phase 3 randomised, controlled trial

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Summary

Background A contemporary standard of care for patients with metastatic androgen pathway modulator-naive/sensitive (APMN/S) prostate cancer (also known as metastatic hormone-sensitive prostate cancer) is androgen deprivation therapy (ADT) plus an androgen receptor pathway inhibitor (ARPI) until progression. PSMAddition aimed to evaluate the efficacy and safety of [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) combined with ADT plus ARPI in prostate-specific membrane antigen (PSMA)-positive metastatic APMN/S prostate cancer.

Methods PSMAddition is an ongoing, randomised, controlled, phase 3 superiority trial conducted at 169 sites across 20 countries, including hospitals, medical centres, and specialist cancer centres. Eligible male patients had treatment-naive or minimally treated metastatic APMN/S prostate cancer diagnosed by CT, MRI, or bone scan and one or more PSMA-positive metastatic lesion on centrally read baseline [^{68}Ga]Ga-PSMA-11 PET. Patients were randomly assigned 1:1 to open-label, intravenous ^{177}Lu-PSMA-617 (7·4 GBq [200 mCi] ±10% every 6 weeks for up to six cycles) with ADT plus ARPI (^{177}Lu-PSMA-617 arm) or ADT plus ARPI (control arm). ADT and ARPI were investigator-chosen according to local authorisation and administered per local product labelling. Control arm patients with centrally confirmed radiographic progression could cross over to ^{177}Lu-PSMA-617. The primary endpoint was radiographic progression-free survival (centrally assessed per Prostate Cancer Clinical Trials Working Group 3-modified RECIST 1.1 or death); secondary endpoints included safety and tolerability. We report the second interim analysis of radiographic progression-free survival in the intention-to-treat population (all randomly assigned participants; data cutoff Jan 13, 2025). Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT04720157, and is ongoing.

Findings From June 15, 2021, to July 25, 2023, 1529 patients were screened and 1144 were randomly assigned (n=572 per arm; 1144 [100%] male, 572 [50%] with de novo metastatic APMN/S prostate cancer, 779 [68%] with high-volume disease; median age 68·0 years [IQR 62·0–73·0]). Baseline characteristics were balanced between arms. At second interim analysis for radiographic progression-free survival (median time from randomisation to data cutoff 23·6 months [IQR 20·3–29·2]; median radiographic progression-free survival follow-up time 19·6 months [IQR 14·0–24·1]), 139 (24%) of 572 participants in the ^{177}Lu-PSMA-617 arm and 172 (30%) of 572 participants in the control arm had radiographic disease progression or death. Radiographic progression-free survival was significantly improved in the ^{177}Lu-PSMA-617 arm versus the control arm, with a 28% reduction in the relative risk of radiographic progression or death (HR 0·72 [95% CI 0·58–0·90]; p=0·0021; median radiographic progression-free survival not reached in either arm). The primary endpoint was thus met. Grade 3 or worse adverse events occurred in 286 (51%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 243 (43%) of 565 patients in the control arm. Serious adverse events occurred in 180 (32%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 162 (29%) of 565 in the control arm; of which 17 (3%) in the ^{177}Lu-PSMA-617 arm were ^{177}Lu-PSMA-617-related. The most common adverse event was dry mouth, in 258 (46%) patients in the ^{177}Lu-PSMA-617 arm and 21 (4%) patients in the control arm; all were grade 1 or 2 and none were serious. Other common adverse events with higher incidence in the ^{177}Lu-PSMA-617 arm included cytopenias and gastrointestinal disturbances.

Interpretation Combining ^{177}Lu-PSMA-617 with ADT plus ARPI prolonged radiographic progression-free survival in patients with PSMA-positive metastatic APMN/S prostate cancer. Although adverse events were more frequent, there were no unexpected safety findings associated with the drug combination. Therefore, combining ^{177}Lu-PSMA-617 with ADT plus ARPI might be a new treatment option in metastatic APMN/S prostate cancer.

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Introduction

Prostate cancer is the second-most common cancer in men worldwide.[1] Metastatic androgen pathway modulator-naive/sensitive (APMN/S) prostate cancer (in accordance with the recently updated Prostate Cancer Working Group 4 framework;[2] also referred to as metastatic hormone-sensitive prostate cancer) has spread beyond the pelvis but is naive or initially responsive to hormonal therapy. Despite major advances in treatment, almost all metastatic APMN/S prostate cancer progresses to metastatic androgen pathway modulator-resistant (APMR) prostate cancer (in accordance with the recently updated Prostate Cancer Working Group 4 framework;[2] also referred to as metastatic castration-resistant prostate cancer), which is associated with markedly reduced survival and quality of life.[3–5]

Multiple phase 3 trials over the past decade established doublet therapy with addition of either an androgen receptor pathway inhibitor (ARPI) or docetaxel to androgen deprivation therapy (ADT) as treatments for metastatic APMN/S prostate cancer, with ADT plus ARPI now superseding ADT plus docetaxel as standard of care.[6] Most recently, triplet therapy with ARPI added to ADT plus docetaxel has been shown to provide further benefit, particularly for patients with de novo metastatic APMN/S prostate cancer, in the PEACE-1, ARASENS, and ENZAMET trials.[7–9] Adding radiotherapy to the prostate has been shown to prevent symptomatic local progression in patients with de novo metastatic APMN/S prostate cancer,[10] but not to improve overall survival.[11] Although no phase 3 trial has investigated adding docetaxel to ADT plus ARPI, the most contemporary standard of care for metastatic APMN/S prostate cancer is widely considered to be ADT plus ARPI, with or without docetaxel and with or without local radiotherapy.[12] A triplet therapy combining a novel mechanism of action with ADT plus ARPI to build upon the efficacy of hormonal therapy could provide urgently needed improvement in outcomes for patients with metastatic APMN/S prostate cancer.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is highly expressed on prostate cancer cells in both APMN/S and APMR metastatic prostate cancer, with some variation in

Research in context

Evidence before this study

[^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy for the treatment of prostate cancer. To assess evidence from clinical trials of ^{177}Lu-PSMA-617 in patients with metastatic androgen modulator-naive/sensitive (APMN/S) prostate cancer (also known as metastatic hormone-sensitive prostate cancer), we used the terms "(metastatic hormone-sensitive prostate cancer) AND (lutetium OR radioligand) AND randomised NOT review[pt]" to search PubMed for English-language publications from the past 10 years to Nov 1, 2025. No previous phase 3 trials of radioligand therapy in metastatic APMN/S prostate cancer were identified. We identified two completed and published randomised controlled phase 2 trials of ^{177}Lu-PSMA-617. Both trials had primary endpoints based on PSA changes, and therefore neither was fit for regulatory drug approval. In the CONSOLIDATE study in patients with synchronous high-volume metastatic APMN/S prostate cancer and residual disease after chemohormonal treatment, prostate-specific antigen (PSA) nadir concentrations below 0·2 ng/mL were more frequent with ^{177}Lu-PSMA-617 than placebo (risk ratio 4·5 [95% CI 1·2–17·4]; p=0·008) with no grade 3–4 toxicity. In the UpFrontPSMA study in patients with de novo high-volume metastatic APMN/S prostate cancer receiving androgen deprivation therapy (ADT), undetectable PSA concentrations were more frequent with ^{177}Lu-PSMA-617 followed by docetaxel versus docetaxel alone (odds ratio 3·88, 95% CI 1·61–9·38; p=0·002), without increased toxicity.

Added value of this study

PSMAddition is the first phase 3 trial of any targeted radionuclide therapy in patients with metastatic APMN/S prostate cancer. These findings complement those of two previous phase 3 trials in patients with metastatic androgen pathway modulator-resistant (APMR) prostate cancer (also known as metastatic castration-resistant prostate cancer), which led to regulatory recognition in some countries, where it is now standard of care. PSMAddition extends evidence for the therapeutic benefit of PSMA-targeted radioligand therapy from metastatic APMR to APMN/S prostate cancer. This study addresses whether radioligand therapy can be integrated into the contemporary standard of care of ADT plus an androgen receptor pathway inhibitor (ARPI), informing treatment intensification strategies in earlier disease.

Implications of all the available evidence

The results of PSMAddition provide evidence for the benefit of combining ^{177}Lu-PSMA-617 with ADT and ARPI in patients with PSMA-positive metastatic APMN/S prostate cancer who are appropriate for treatment with ADT plus ARPI. Together with existing phase 3 evidence from metastatic APMR prostate cancer, these findings support the use of PSMA-targeted radioligand therapy earlier in the disease course and establish ^{177}Lu-PSMA-617 plus ADT and ARPI as a potential new standard-of-care treatment option in this setting.

expression levels among patients, across disease stage, and with treatment exposure.[13–17] [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617; also known as lutetium (^{177}Lu) vipivotide tetraxetan), is a PSMA-targeted radioligand therapy that selectively delivers β-particle radiation to PSMA-positive cells and the surrounding tumour microenvironment. In two pivotal phase 3 trials, VISION and PSMAfore, ^{177}Lu-PSMA-617 significantly improved radiographic progression-free survival and was well tolerated with a favourable benefit–risk profile.[18–20] Both studies used a treatment regimen of ^{177}Lu-PSMA-617 7·4 GBq (200 mCi) every 6 weeks for up to six cycles, depending on tolerability and disease progression.[18–20] ^{177}Lu-PSMA-617 was also associated with delayed time to worsening in patient-reported health-related quality of life (HRQoL) and pain, and time to symptomatic skeletal events.[21,22] On the basis of these findings, the US Food and Drug Administration (FDA) approved ^{177}Lu-PSMA-617 for treatment of PSMA-positive metastatic APMR prostate cancer in patients previously treated with ARPI in both the post-taxane and taxane-naive settings.[23,24]

Combining ^{177}Lu-PSMA-617 with hormonal therapy could enhance efficacy by increasing anti-tumour effects and improving activity against heterogeneous tumours in both APMN/S and APMR metastatic prostate cancer.[25–31] The phase 3 PSMAddition study was designed to compare the efficacy and safety of ^{177}Lu-PSMA-617 combined with ADT plus ARPI versus ADT plus ARPI in patients with treatment-naive or minimally treated PSMA-positive metastatic APMN/S prostate cancer, using a similar six-cycle ^{177}Lu-PSMA-617 regimen as was established in the metastatic APMR prostate cancer setting. Here, we report preplanned interim analyses of the primary endpoint of radiographic progression-free survival, the key secondary endpoint of overall survival, safety and tolerability, and other secondary endpoints in PSMAddition.

Methods

Study design

PSMAddition is an ongoing, international, randomised, open-label, phase 3 superiority trial using a 1:1 allocation ratio to compare ^{177}Lu-PSMA-617 plus standard of care versus standard of care alone in patients with metastatic APMN/S prostate cancer. The trial is conducted at 169 sites across 20 countries (appendix pp 3–10) in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable local regulations. The protocol and amendments (appendix pp 42–272) were ethically approved by institutional review boards or independent ethics committees at all participating sites (appendix pp 11–16).

All patients provided written informed consent before participating and could withdraw consent at any time. There was no patient or public involvement in the study design, conduct, and reporting of the trial.

An independent data monitoring committee regularly and systematically assesses trial progress, safety, and interim efficacy. A steering committee comprising investigators and sponsor representatives provides scientific oversight.

This trial is registered with ClinicalTrials.gov, NCT04720157, and is ongoing.

Participants

Eligible patients were male adults with adenocarcinoma of the prostate and at least one distant soft tissue, visceral, or bone metastatic lesion documented by CT, MRI, or radiotracer technetium-99m (^{99m}Tc) bone scintigraphy. At least one distant metastatic lesion had to be PSMA-positive on centrally read baseline [^{68}Ga]Ga-PSMA-11 (^{68}Ga-PSMA-11) positron emission tomography (PET) scans. Lesion PSMA positivity was defined as uptake greater than that of the liver. In patients with liver metastases, at least one of these had to be PSMA-positive.

Eligible patients were treatment-naive, had received no more than 45 days' previous treatment with ADT or ARPI, or both, for metastatic disease, or had received neoadjuvant or adjuvant ADT for local disease if discontinued for more than 12 months without disease progression. Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function were required. Patients with rapidly progressing tumours that required urgent taxane-based chemotherapy as judged by the investigator were ineligible. A complete list of the selection criteria and further details are given in the appendix (pp 19–20).

Baseline demographics and disease characteristics were collected at screening. Investigators recorded data on race as per the US Office of Management and Budget categories, based on patient self-reports during discussion: one or more of American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Unknown (if collection of this information was permitted in their jurisdiction). Concomitant medications, procedures, and significant non-drug therapies administered from enrolment until 30 days after the last ARPI dose or 42 days after the last ^{177}Lu-PSMA-617 dose (whichever was longer) were recorded.

Randomisation and masking

Enrolled patients were randomly assigned 1:1 to six cycles of ^{177}Lu-PSMA-617 with ADT plus ARPI (^{177}Lu-PSMA-617 arm) or to ADT plus ARPI (control arm) via a validated automated system (appendix p 35). The randomisation list was kept strictly confidential until primary analysis was conducted. Randomisation was stratified by tumour volume (high *vs* low, defined per CHAARTED study[32] criteria on CT, MRI, or bone scan), age (≥70 years *vs* <70 years), and previous or planned prostatectomy or definitive radiotherapy to the prostate (yes *vs* no). Assigned


1529 patients assessed for eligibility
109 excluded
73 did not meet eligibility criteria
33 withdrew
1 adverse event
1 died
1 technical problem*
1420 underwent 68Ga-PSMA-11 PET–CT
1421 with status independent of trial enrolement†
1239 had ≥1 PSMA-positive lesion
1232 met 68Ga-PSMA-11 imaging criteria
159 did not meet 68Ga-PSMA-11 imaging criteria
30 missing data
276 excluded
264 did not meet eligibility criteria
1 withdrawn by investigator
10 withdrew
1 technical problem*
1144 randomly assigned
572 assigned to receive 177Lu-PSMA-617 with ADT plus ARPI
572 assigned to receive ADT plus ARPI
5 did not receive 177Lu-PSMA-617 with ADT plus ARPI
3 withdrew
2 protocol deviation
10 did not receive ADT plus ARPI
5 withdrew
2 protocol deviation
3 withdrawn by investigator
567 received 177Lu-PSMA-617 with ADT plus ARPI
562 received ADT plus ARPI
187 discontinued 177Lu-PSMA-617 with ADT plus ARPI
64 progressive disease
49 withdrawn by investigator
27 adverse event
28 withdrew
16 died
2 protocol deviation
1 lost to follow-up
229 discontinued ADT plus ARPI
118 had progressive disease
42 withdrawn by investigator
20 adverse event
31 withdrew
15 died
3 protocol deviation
380 ongoing treatment with 177Lu-PSMA-617 with ADT plus ARPI
91 crossed over to 177Lu-PSM A-617 with ADT plus ARPI
333 ongoing treatment with ADT plus ARPI
60 discontinued 177Lu-PSMA-617 with ADT plus ARPI
38 progressive disease
14 withdrawn by investigator
5 adverse event
1 withdrew
2 died
20 were still receiving 177Lu-PSMA-617
30 did not enter post-treatment follow-up
33 ongoing in follow-up
12 completed follow-up
112 discontinued the trial during follow-up
48 died
40 withdrew
11 withdrawn by investigator
9 progressive disease
2 adverse event
1 lost to follow-up
1 protocol deviation
7 did not enter post-treatment follow-up
24 ongoing follow-up
5 completed follow-up
35 discontinued the trial during follow-up
23 died
6 withdrew
2 withdrawn by investigator
2 progressive disease
2 adverse event
41 did not enter post-treatment follow-up
22 ongoing follow-up
8 completed follow-up
67 discontinued the trial during follow-up
32 died
22 withdrew
7 withdrawn by investigator
3 progressive disease
2 adverse event
1 lost to follow-up

treatment was concealed only from the blinded, independent review committee (BIRC).

Procedures

^{177}Lu-PSMA-617 was administered as intravenous infusions of 7·4 GBq (200 mCi) ±10% once every 6 weeks for up to six cycles, starting within 14 days of randomisation. The protocol specified criteria for ^{177}Lu-PSMA-617 discontinuation, dose reduction, or dose delay in response to adverse drug reactions.

ADT and ARPI were administered per local product labelling and guidelines. ARPI was chosen by investigators (abiraterone, enzalutamide, apalutamide, darolutamide, or rezvilutamide, depending on local authorisation). One change in ARPI was allowed during study treatment in the absence of disease progression. All patients received ADT plus ARPI, and those in the ^{177}Lu-PSMA-617 arm continued to receive ADT plus ARPI after completing all six cycles of ^{177}Lu-PSMA-617. Protocol deviations were identified through site, monitoring audits, inspections, and sponsor data review activities, assessed in accordance with Good Clinical Practice, sponsor standard operating procedures, and applicable local regulations, and the protocol deviation listing was reviewed and approved by the study medical lead at least monthly.

Patients received full supportive care while on the study but were not to receive any other anti-cancer treatment except planned prostatectomy or definitive radiotherapy to the primary prostate tumour (to be given after completion of ^{177}Lu-PSMA-617 treatment or within 6 months of randomisation in the control arm).

Treatment with ADT plus ARPI, with or without ^{177}Lu-PSMA-617, continued until BIRC-confirmed radiographic progression, investigator or patient decision to discontinue, emergence of a safety concern, or occurrence of an adverse event necessitating treatment cessation. Patients in the control arm could opt to cross over and receive ^{177}Lu-PSMA-617 upon BIRC-confirmed radiographic progression, if eligible. Additional ADT or ARPI, or both treatments, after crossover was at the investigator's discretion.

Patients underwent CT or MRI and ^{99m}Tc bone scans, every 12 weeks for 24 months, then every 16 weeks, from start of treatment (appendix p 35). Patients attended clinic visits for safety evaluations throughout treatment, at end of treatment, then 30 days, 24 weeks, and 48 weeks thereafter. Patients were followed up for survival by telephone every 90 days after last contact. Patients who received ^{177}Lu-PSMA-617 have or will have the option to enrol in a separate long-term safety study (NCT05803941) at participating sites while on survival follow-up in the present study.

Figure 1: **Trial profile**
Dashed boxes represent follow-up after completion or discontinuation of study treatment. ADT=androgen deprivation therapy. ARPI=androgen receptor pathway inhibitor. PSMA=prostate-specific membrane antigen. Per-protocol deviations are detailed in the appendix (p 22). *Technical problem refers to a temporary ^{177}Lu-PSMA-617 production hold in May 2022 that precluded randomisation for non-medical reasons. †If patient was re-screened, results of initial assessment and re-screening have been reported in the output.

Outcomes

The primary endpoint was radiographic progression-free survival, defined as time from randomisation to first documented radiographic disease progression or death, assessed by the BIRC per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3)-modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[33]

The key secondary endpoint was overall survival, defined as the time from the date of randomisation to the date of death due to any cause (appendix p 21). Other secondary endpoints were: PSA90 response rate at 12, 24, and 48 weeks; proportion of patients with PSA nadir of less than 0·2 ng/mL at week 12, 24, and 48; time to PSA progression; time to development of metastatic APMR prostate cancer; progression-free survival by investigator assessment; second progression-free survival (defined as time from date of randomisation to the first documented radiographic, clinical or PSA progression on next-line therapy, or death) by investigator assessment; objective response rate, disease control rate, time to response, duration of response, and time to soft tissue progression assessed by the BIRC per PCWG3-modified RECIST version 1.1; safety and tolerability; and time to first symptomatic skeletal event (appendix p 21).

HRQoL and pain were also secondary endpoints. Patients were to complete Functional Assessment of Cancer Therapy–Prostate (FACT-P), the European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L), and Brief Pain Inventory–Short Form (BPI-SF) questionnaires on day 1 of each cycle, week 6 of cycle 6, then every 12 weeks to end of treatment and 24 weeks and 48 weeks thereafter. These were prespecified for analysis as composite time to worsening in score by prespecified thresholds, clinical disease progression or death (whichever occurred first; appendix p 21). Prespecified longitudinal analyses were performed using repeated measurement analysis models to estimate differences in change from baseline in HRQoL and pain scores between treatment arms (appendix p 17).

Statistical analysis

Data were analysed according to the statistical analysis plan (appendix pp 273–359). Efficacy endpoints were assessed according to the intention-to-treat principle in the full analysis set, comprising all randomly assigned patients. Safety was assessed according to treatment received in the safety analysis set, comprising all patients who received at least one dose of study treatment. RECIST-based endpoints were assessed in patients in the full analysis set with evaluable soft tissue disease at baseline.

The primary efficacy analysis compared radiographic progression-free survival between treatment arms using a log-rank test stratified by the randomisation factors (overall one-sided α=0·025); a stratified Cox proportional hazards model and the Kaplan–Meier estimator was also applied. The planned sample size of 1126 patients provided at least 95% power to detect a radiographic progression-free survival hazard ratio (HR) of 0·70 at final analysis, based on 418 radiographic progression-free survival events and assuming a 15% rate of loss to follow-up.

Two interim analyses and one final analysis of radiographic progression-free survival were planned, using a three-look sequential design with Lan–DeMets (O'Brien–Fleming) α-spending function and β-spending function (ρ=3).[34] The first radiographic progression-free survival interim analysis was to assess only futility at 167 events. Superior efficacy was not to be tested until the second interim and final radiographic progression-free survival analyses at approximately 314 events (HR threshold, 0·768) and 418 events, respectively. Radiographic progression-free survival events occurring after two or more missing or non-adequate tumour assessments (ie, assessments with missing, incomplete, or unevaluable imaging that precluded determination of disease status by BIRC) were censored at the date of the last adequate assessment. No inferential statistical tests were performed for pre-specified subgroup analyses (appendix p 18).

Overall survival was tested hierarchically only if radiographic progression-free survival was met. Two interim analyses and one final analysis of overall survival were planned, at the time of the second interim and final radiographic progression-free survival analyses (approximately 226 and 315 deaths, respectively) and in a final analysis (389 deaths), using a separate α-spending function. Other secondary endpoints were analysed non-inferentially. Safety was assessed in all patients who received at least one dose of study treatment. Adverse events were summarised by preferred terms using Medical Dictionary for Regulatory Activities (MedDRA) coding and safety topics of interest, comprising prespecified groupings of preferred terms. Analyses of resolution and timing of adverse events are planned, and safety will be assessed further at planned future analysis time points.

	^{177}Lu-PSMA-617 with ADT plus ARPI (n=572)	ADT plus ARPI (n=572)	Overall (n=1144)
Age, years	68·0 (62·0–73·0)	68·0 (63·0–73·0)	68·0 (62·0–73·0)
≥70 years	246 (43%)	246 (43%)	492 (43%)
<70 years	326 (57%)	326 (57%)	652 (57%)
Race			
American Indian or Alaska Native	1 (<1%)	2 (<1%)	3 (<1%)
Asian	101 (18%)	118 (21%)	219 (19%)
Black or African American	26 (5%)	29 (5%)	55 (5%)
Native Hawaiian or Other Pacific Islander	0	1 (<1%)	1 (<1%)
White	356 (62%)	345 (60%)	701 (61%)
Unknown	88 (15%)	77 (13%)	165 (14%)
ECOG performance status			
0	397 (69%)	407 (71%)	804 (70%)
1	174 (30%)	155 (27%)	329 (29%)
2	1 (<1%)	7 (1%)	8 (1%)
Metastatic sites			
Soft tissue	342 (60%)	338 (59%)	680 (59%)
Bone	522 (91%)	521 (91%)	1043 (91%)
Non-nodal soft tissue*			
Lung	66 (12%)	83 (15%)	149 (13%)
Liver	11 (2%)	21 (4%)	32 (3%)
Lung or liver	72 (13%)	95 (17%)	167 (15%)
Adrenal	7 (1%)	5 (1%)	12 (1%)
Central nervous system	1 (<1%)	0	1 (<1%)
Lymph nodes†	202 (35%)	192 (34%)	394 (34%)
None	1 (<1%)	2 (<1%)	3 (<1%)
Missing	2 (<1%)	1 (<1%)	3 (<1%)
Metastatic androgen pathway modulator-naive/sensitive prostate cancer			
De novo‡§	298 (52%)	274 (48%)	572 (50%)
Recurrent¶	249 (44%)	274 (48%)	523 (46%)

(Table 1 continues on next page)

Role of the funding source

The funder was involved in study design, data collection, data analysis, data interpretation, and the writing and review of the report.

Results

Patients were enrolled from June 15, 2021, to July 25, 2023. At futility interim analysis on May 6, 2024, the independent data monitoring committee recommended that the trial continue (176 radiographic progression-free survival events; information fraction 42·1%). The present prespecified interim analysis occurred at 311 radiographic progression-free survival events (data cutoff Jan 13, 2025). Median time on study from randomisation to data cutoff was 23·6 months (IQR 20·3–29·2).

Of 1529 patients screened, 1420 underwent ^{68}Ga-PSMA-11 PET–CT imaging and 1232 (87%) met the ^{68}Ga-PSMA-11 PSMA PET positivity criteria (figure 1). The 1144 patients who also met all other inclusion criteria were randomly assigned 1:1 to ^{177}Lu-PSMA-617 with ADT plus ARPI (^{177}Lu-PSMA-617 arm; n=572) or to ADT plus ARPI (control arm; n=572), and were included in the full analysis set.

ADT or ARPI, or both treatments, were started before randomisation in 526 (92%) of 572 patients in the ^{177}Lu-PSMA-617 arm and 513 (90%) of 572 patients in the control arm (appendix p 22). The safety analysis set comprised 564 patients in the ^{177}Lu-PSMA-617 arm and 565 in the control arm. The main reason for not receiving study treatment was withdrawal by the patient or investigator (figure 1). Protocol deviations are detailed in the appendix (p 22).

Baseline characteristics were generally well balanced between the ^{177}Lu-PSMA-617 and control arms (table 1). Patients had a median age of 68·0 years (IQR 62·0–73·0); of 1144 patients, 779 (68%) had high-volume disease and 572 (50%) had de novo disease (table 1).

The median duration of exposure to any component of study treatment was 20·6 months (IQR 15·5–26·3) in the ^{177}Lu-PSMA-617 arm and 19·9 months (13·8–25·1) in the control arm (appendix p 23). In the ^{177}Lu-PSMA-617 arm, the median duration of ^{177}Lu-PSMA-617 exposure was 8·3 months (IQR 8·3–8·7), with 525 (93%) of 564 patients completing at least four cycles and 483 (86%) completing all six cycles (then continuing to receive ADT plus ARPI). The most received ARPIs were abiraterone and apalutamide (appendix p 23) and a single permitted on-study change in ARPI occurred in 52 (9%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 58 (10%) of 565 patients in the control arm (appendix p 23).

During the study, of 1144 patients, 15 (1%) had concomitant antineoplastic surgery (six [1%] of 572 in the ^{177}Lu-PSMA-617 arm and nine [2%] of 572 in the control arm) and 114 (10%) had concomitant antineoplastic radiotherapy (46 [8%] of 572 and 68 [12%] of 572, respectively). Bone modifying agent use included 65 (12%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 89 (16%) of 565 patients in the control arm receiving denosumab and 46 (8%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 50 (9%) of 565 patients in the control arm receiving bisphosphonates.

Of the 572 patients in the control arm, 152 (27%) had BIRC-confirmed radiographic progression; of these, 91 (60%; 16% of all in the control arm) had crossed over to on-study ^{177}Lu-PSMA-617 treatment at data cutoff. Median time from randomisation to crossover was 15·0 months (IQR 11·8–18·6); median duration of crossover ^{177}Lu-PSMA-617 treatment was 4·2 months (IQR 3·1–6·9), with a median of three cycles (IQR 2·0–4·0) received at data cutoff. Post-protocol taxane chemotherapy was received by 60 (10%) of 572 patients in the ^{177}Lu-PSMA-617 arm and 81 (14%) of 572 patients in the control arm (after crossover if applicable; appendix p 24).

Median radiographic progression-free survival follow-up time was 19·6 months (IQR 14·0–24·1). At the current data cutoff, 139 (24%) of 572 participants in the ^{177}Lu-PSMA-617 arm and 172 (30%) of 572 participants in the control arm had radiographic disease progression or death. Radiographic progression-free survival was significantly improved in the ^{177}Lu-PSMA-617 with ADT plus ARPI arm versus the ADT plus ARPI arm, with a 28% reduction in the relative risk of radiographic progression or death (HR 0·72; 95% CI 0·58–0·90; p=0·0021; figure 2). The primary endpoint was thus met at interim analysis (data cutoff Jan 13, 2025; information fraction 74·4%; significance threshold p=0·0092). BIRC-confirmed radiographic progression occurred in 112 (20%) of 572 patients in the ^{177}Lu-PSMA-617 arm and 152 (27%) of 572 patients in the control arm (appendix p 25). Median radiographic progression-free survival was not reached in either arm. The radiographic progression-free survival benefit was generally consistent across sensitivity and subgroup analyses, including high versus low disease volume and de novo versus recurrent disease, with HRs similar to those in the overall population (appendix p 36).

There was no significant difference in overall survival between the ^{177}Lu-PSMA-617 arm and the control arm in the present prespecified interim intention-to-treat analysis (figure 2), with a HR of 0·84 (95% CI 0·63–1·13; p=0·13; 184 deaths at data cutoff; significance threshold

	^{177}Lu-PSMA-617 with ADT plus ARPI (n=572)	ADT plus ARPI (n=572)	Overall (n=1144)
(Continued from previous page)			
PSA concentration, ng/mL	12·06 (3·16–53·24)	11·64 (2·83–44·15)	11·91 (3·01–50·34)
eGFR category			
Normal	214 (37%)	206 (36%)	420 (37%)
Mild impairment	308 (54%)	303 (53%)	611 (53%)
Moderate impairment	45 (8%)	52 (9%)	97 (8%)
LDH concentration, IU/L	181 (158–207)	178 (159–203)	179 (158–206)
Gleason score			
<8 (grade group 1–3)	152 (27%)	134 (23%)	286 (25%)
≥8 (grade group 4–5)	389 (68%)	406 (71%)	795 (69%)
Tumour volume‖			
High	389 (68%)	390 (68%)	779 (68%)
Low	183 (32%)	182 (32%)	365 (32%)
Planned or previous prostatectomy or definitive radiotherapy to primary prostate tumour**			
Yes	156 (27%)	155 (27%)	311 (27%)
No	416 (73%)	417 (73%)	883 (73%)
FACT-P			
Total score	123·0 (110·0–135·0)	122·0 (109·0–132·0)	123·0 (109·0–134·0)
Questionnaire completed††	511 (89%)	483 (84%)	994 (87%)
EQ-5D-5L			
Utility score	0·8 (0·8–1·0)	0·8 (0·7–1·0)	0·8 (0·8–1·0)
Questionnaire completed††	512 (90%)	487 (85%)	999 (87%)
BPI-SF			
Pain intensity score	1·0 (0·0–2·8)	1·3 (0·0–2·8)	1·0 (0·0–2·8)
Questionnaire completed††	509 (89%)	481 (84%)	990 (87%)

Data are median (IQR) or n (%). All participants were male (sex was defaulted to male in the clinical database). ADT=androgen deprivation therapy. AJCC=American Joint Committee on Cancer. ARPI=androgen receptor pathway inhibitor. BPI-SF=Brief Pain Inventory–Short Form. ECOG=Eastern Cooperative Oncology Group. eGFR=estimated glomerular filtration rate. EQ-5D-5L=the European Quality of Life 5-Dimensions 5-Levels. FACT-P=Functional Assessment of Cancer Therapy–Prostate. LDH=lactate dehydrogenase. PSA=prostate-specific antigen. Race was recorded according to the US Office of Management and Budget categories, if permitted to be collected by local law. *Excludes reported other visceral sites; other is defined as any metastatic site other than soft tissue, bone, lung, liver, skin, adrenal gland, central nervous system, and lymph nodes and is recorded on the case report form as malignant ascites, pancreas, spleen, or as a free-text entry; 351 patients (31%) were recorded as other (^{177}Lu-PSMA-617 arm: 176 [31%]; control arm 175 [31%]). †Pelvic and/or extra-pelvic lymph node metastasis. ‡Stage IVb at initial diagnosis (AJCC Cancer Staging Manual 8th edition).[35] §62 of 572 received previous treatment. ¶225 of 523 received previous treatment. ||Per CHAARTED study[32] criteria using conventional imaging. **Stratification factor as reported by investigator; does not include any other type of local treatment to primary prostate tumour. ††Questionnaire compliance based on first study visit; completion defined as questionnaire completed and score calculable.

Table 1: **Baseline demographics and disease characteristics**

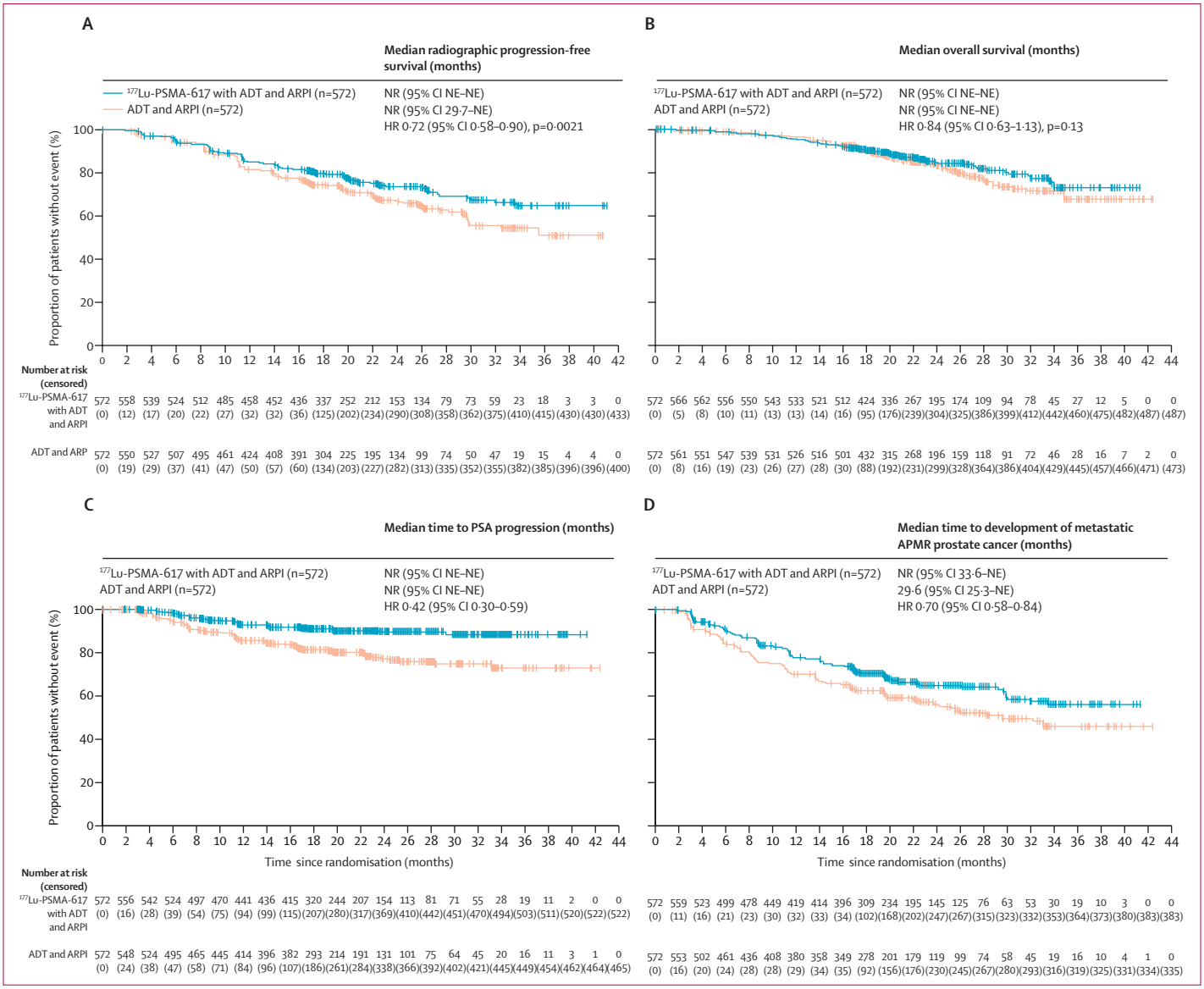


Figure 2: **Radiographic progression-free survival, overall survival, time to PSA progression, and time to metastatic APMR prostate cancer**
(A) Radiographic progression-free survival (primary endpoint). Significance threshold at second interim analysis (Jan 13, 2025) of radiographic progression-free survival p=0·0092 (one-sided; stratified log-rank test); information fraction, 74·4%. (B) Overall survival (key secondary endpoint). Significance threshold at first interim analysis (Jan 13, 2025) of overall survival: 0·0011 (one-sided; stratified log-rank test); information fraction, 47·3%. (C) Time to PSA progression (secondary endpoint); not analysed inferentially. (D) Time to development of metastatic APMR prostate cancer (secondary endpoint); not analysed inferentially. A breakdown of event types in the primary and key secondary endpoints is provided in the appendix (p 25). ADT=androgen deprivation therapy. APMR=androgen pathway modulator-resistant. ARPI=androgen receptor pathway inhibitor. HR=hazard ratio. NE=not estimable. NR=not reached. PSA=prostate-specific antigen.

p=0·0011). Death occurred in 85 (15%) of 572 patients in the ^{177}Lu-PSMA-617 arm and 99 (17%) of 572 patients in the control arm, of which 40 occurred after crossover (appendix p 25). Most deaths were related to prostate cancer progression in both the ^{177}Lu-PSMA-617 arm (54 [9%] of 572 patients) and the control arm (68 [12%] of 572 patients). Median overall survival was not reached in either arm. Overall survival was considered too immature for interpretable subgroup analysis.

PSA90 response rate and the proportion of patients with PSA nadir below 0·2 ng/mL were higher in the ^{177}Lu-PSMA-617 arm than the control arm at weeks 12, 24, and 48 after randomisation (appendix p 25). PSA concentrations decreased from baseline in more than 98% of patients in both arms (appendix p 37). Time to PSA progression was prolonged in the ^{177}Lu-PSMA-617 arm versus the control arm, with a HR of 0·42 (95% CI 0·30–0·59; figure 2).

Time to metastatic APMR prostate cancer was prolonged in the ^{177}Lu-PSMA-617 arm versus the control arm, with a HR of 0·70 (95% CI 0·58–0·84; figure 2). Investigator-determined progression-free survival was

also prolonged, with a HR of 0·64 (95% CI 0·51–0·79; appendix p 38).

Objective response rate by PCWG3-modified RECIST version 1.1 was 85% (95% CI 79·9–89·6; 191 of 224 patients) in the ^{177}Lu-PSMA-617 arm and 81% (95% CI 74·8–85·8; 172 of 213) in the control arm, with complete response rates of 57% (128 of 224) and 42% (90 of 213), respectively, in patients with measurable soft tissue disease at baseline, accounting for bone lesion progression (appendix pp 26, 39). Results were similar in patients with evaluable disease at baseline and when not accounting for bone lesion progression (appendix p 26). Duration of response and second progression-free survival were too immature for interpretation. The HR for time to soft tissue progression was 0·60 (0·41–0·89; appendix p 40), and HR for time to first symptomatic skeletal event or death was 0·89 (95% CI 0·62–1·26); medians were not reached (appendix p 41).

Adverse events occurred in 555 (98%) of 564 patients in the ^{177}Lu-PSMA-617 plus ADT plus ARPI arm and 546 (97%) of 565 in the ADT plus ARPI control arm; these were grade 3 or higher in 286 (51%) and 243 (43%) patients, respectively (table 2).

Among individual adverse event preferred terms, dry mouth was the most common adverse event, occurring in 258 patients (46%) in the ^{177}Lu-PSMA-617 arm and 21 (4%) in the control arm. All were of grade 1 or 2 severity, and none were recorded as serious. In the ^{177}Lu-PSMA-617 arm, grade 1 dry mouth occurred in 231 patients (41%) and grade 2 in 27 patients (5%; table 2). Other common adverse events occurring more frequently in the ^{177}Lu-PSMA-617 versus control arm included nausea, anaemia, decreased appetite, vomiting, dysgeusia, white blood cell count decreased, and lymphocytes decreased (table 2). All adverse events grouped by system organ class categories are reported in the appendix (p 27).

Serious adverse events occurred in 180/564 patients (32%) in the ^{177}Lu-PSMA-617 arm and 162/565 (29%) in the control arm. These were considered related to ^{177}Lu-PSMA-617 by the investigator in 17 patients (3%) in the ^{177}Lu-PSMA-617 arm. Fatal adverse events occurred in 15 patients (3%) in the ^{177}Lu-PSMA-617 arm and 14 (2%) in the control arm; none were considered related to study treatment (table 2; appendix pp 28–29).

Adverse events led to discontinuation of any component of study treatment in 91 (16%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 51 (9%) of 565 patients in the control arm. Adverse events led to ^{177}Lu-PSMA-617 discontinuation, dose reduction, or dose delay in 45 (8%), 22 (4%), and 68 (12%) patients, respectively, in the ^{177}Lu-PSMA-617 arm (table 2; appendix pp 30–32).

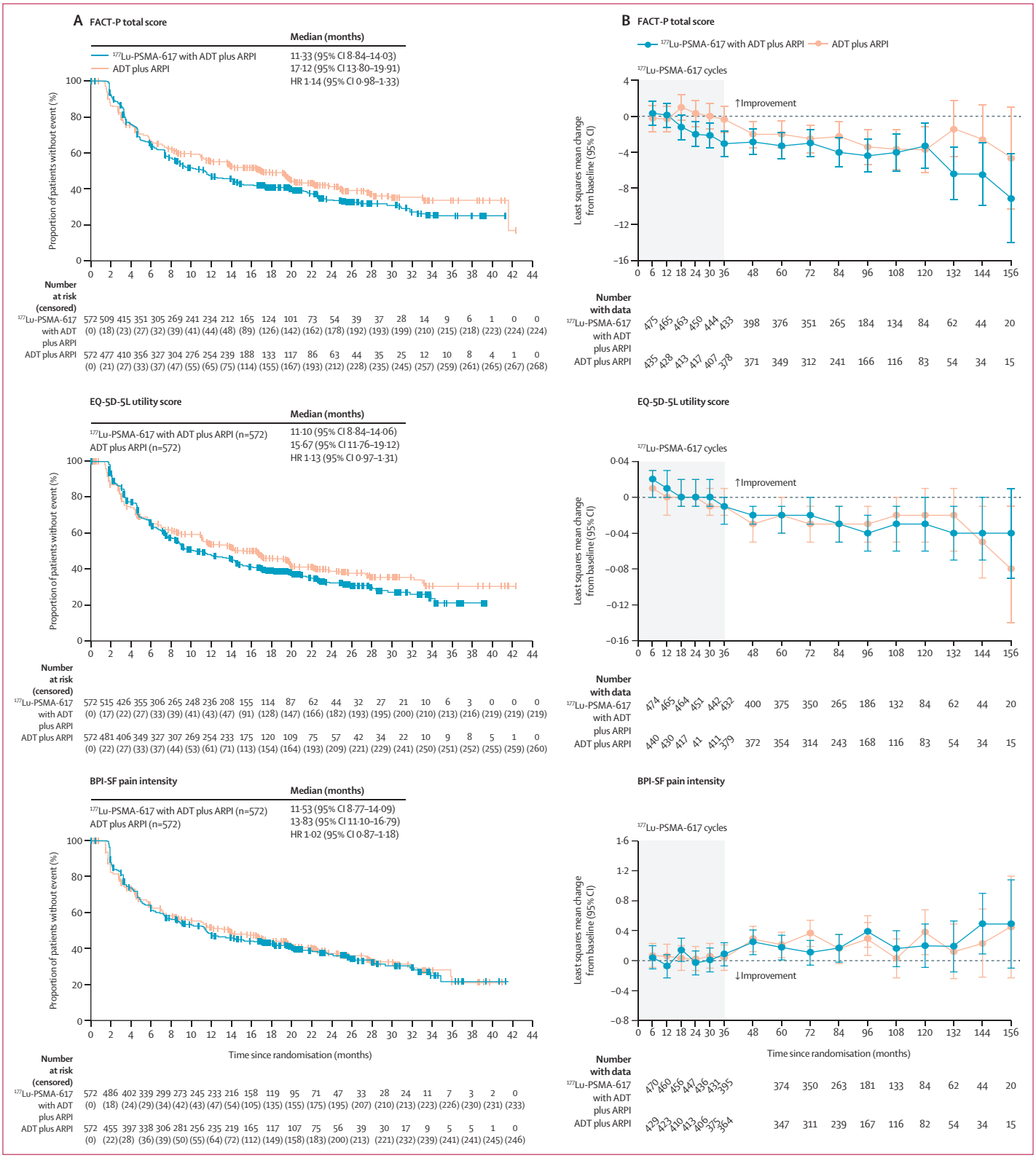
When combining all individual xerostomia-related preferred terms, adverse events in the dry mouth safety topic of interest grouping occurred in 262 patients (46%) in the ^{177}Lu-PSMA-617 arm and 22 (4%) in the control arm (appendix p 33).

	^{177}Lu-PSMA-617 with ADT plus ARPI (n=564)		ADT plus ARPI (n=565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with adverse event				
Any	555 (98%)	286 (51%)	546 (97%)	243 (43%)
Related to any study treatment	504 (89%)	128 (23%)	394 (70%)	69 (12%)
^{177}Lu-PSMA-617-related	441 (78%)	78 (14%)	..	..
ADT-related or ARPI-related	418 (74%)	81 (14%)	394 (70%)	69 (12%)
Serious	180 (32%)	150 (27%)	162 (29%)	129 (23%)
Related to any study treatment	39 (7%)	31 (5%)	14 (2%)	12 (2%)
^{177}Lu-PSMA-617-related	17 (3%)	13 (2%)	..	..
ADT-related or ARPI-related	27 (5%)	22 (4%)	14 (2%)	12 (2%)
Leading to death	15 (3%)	15 (3%)	14 (2%)	14 (2%)
Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16%)	46 (8%)	51 (9%)	23 (4%)
Leading to ^{177}Lu-PSMA-617				
Discontinuation*	45 (8%)	28 (5%)	..	..
Dose reduction†	22 (4%)	13 (2%)	..	..
Dose delay‡	68 (12%)	27 (5%)	..	..
Occurring in ≥10% of patients in the ^{177}Lu-PSMA-617 with ADT plus ARPI arm				
Dry mouth§	258 (46%)	0	21 (4%)	0
Fatigue	196 (35%)	6 (1%)	158 (28%)	6 (1%)
Nausea¶	193 (34%)	1 (<1%)	53 (9%)	0
Hot flush	164 (29%)	0	205 (36%)	0
Anaemia	153 (27%)	28 (5%)	75 (13%)	15 (3%)
Arthralgia	111 (20%)	5 (1%)	130 (23%)	9 (2%)
Back pain	101 (18%)	8 (1%)	110 (19%)	16 (3%)
Constipation	101 (18%)	0	91 (16%)	0
Asthenia	92 (16%)	2 (<1%)	73 (13%)	5 (1%)
Decreased appetite	81 (14%)	5 (1%)	37 (7%)	1 (<1%)
Vomiting‖	78 (14%)	4 (1%)	21 (4%)	0
COVID-19	76 (13%)	5 (1%)	60 (11%)	2 (<1%)
Hypertension	76 (13%)	34 (6%)	95 (17%)	35 (6%)
Diarrhoea**	69 (12%)	1 (<1%)	56 (10%)	0
Headache	69 (12%)	0	51 (9%)	2 (<1%)
ALT increased	68 (12%)	19 (3%)	73 (13%)	14 (2%)
Dysgeusia	67 (12%)	0	23 (4%)	0
White blood cell count decreased	63 (11%)	12 (2%)	18 (3%)	3 (1%)
AST increased	61 (11%)	10 (2%)	65 (12%)	11 (2%)
Lymphocyte count decreased	60 (11%)	28 (5%)	21 (4%)	7 (1%)

Data are n (%). ADT=androgen deprivation therapy. ALT=alanine aminotransferase. ARPI=androgen receptor pathway inhibitor. AST=aspartate aminotransferase. *Listed in the appendix (p 30). †Listed in the appendix (p 31). ‡Listed in the appendix (p 32). §Dry mouth: grade 1 in 231 patients (41%) and grade 2 in 27 patients (5%) in the ^{177}Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 19 patients (3%) and grade 2 in two patients (<1%) in the ADT plus ARPI arm. ¶Nausea: grade 1 in 156 patients (28%) and grade 2 in 36 patients (6%) in the ^{177}Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 39 patients (7%) and grade 2 in 14 patients (2%) in the ADT plus ARPI arm. ‖Vomiting: grade 1 in 47 patients (8%) and grade 2 in 27 patients (5%) in the ^{177}Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 13 patients (2%) and grade 2 in eight patients (1%) in the ADT plus ARPI arm. **Diarrhoea: grade 1 in 52 patients (9%) and grade 2 in 16 patients (3%) in the ^{177}Lu-PSMA-617 with ADT plus ARPI arm; grade 1 in 43 patients (8%) and grade 2 in 13 patients (2%) in the ADT plus ARPI arm.

Table 2: **Adverse events**

Adverse events in the cytopenias grouping occurred in 248 (44%) of 564 patients in the ^{177}Lu-PSMA-617 arm and 115 (20%) of 565 patients in the control arm; these were grade 3 or worse in 81 (14%) and 28 (5%) patients,


A FACT-P total score
Median (months)
177Lu-PSMA-617 with ADT plus ARPI
ADT plus ARPI
11·33 (95% CI 8·84–14·03)
17·12 (95% CI 13·80–19·91)
HR 1·14 (95% CI 0·98–1·33)
Proportion of patients without event (%)
Number at risk (censored)
177Lu-PSMA-617 with ADT plus ARPI 572 509 415 351 305 269 241 234 212 165 124 101 73 54 39 37 28 14 9 6 1 0 0
(0) (18) (23) (27) (32) (39) (41) (44) (48) (89) (126) (142) (162) (178) (192) (193) (199) (210) (215) (218) (223) (224) (224)
ADT plus ARPI 572 477 410 356 327 304 276 254 239 188 133 117 86 63 44 35 25 12 10 8 4 1 0
(0) (21) (27) (33) (37) (47) (55) (65) (75) (114) (155) (167) (193) (212) (228) (235) (245) (257) (259) (261) (265) (267) (268)
B FACT-P total score
177Lu-PSMA-617 with ADT plus ARPI
ADT plus ARPI
177Lu-PSMA-617 cycles
↑Improvement
Least squares mean change from baseline (95% CI)
Number with data
177Lu-PSMA-617 with ADT plus ARPI 475 465 463 450 444 433 398 376 351 265 184 134 84 62 44 20
ADT plus ARPI 435 428 423 417 407 378 371 349 312 241 166 116 83 54 34 15
EQ-5D-5L utility score
Median (months)
177Lu-PSMA-617 with ADT plus ARPI (n=572)
ADT plus ARPI (n=572)
11·10 (95% CI 8·84–14·06)
15·67 (95% CI 11·76–19·12)
HR 1·13 (95% CI 0·97–1·31)
Proportion of patients without event (%)
Number at risk (censored)
177Lu-PSMA-617 with ADT plus ARPI 572 515 426 355 306 265 248 236 208 155 114 87 62 44 32 27 21 10 6 3 0 0 0
(0) (17) (22) (27) (33) (39) (41) (43) (47) (91) (128) (147) (166) (182) (193) (195) (200) (210) (213) (216) (219) (219) (219)
ADT plus ARPI 572 481 406 349 327 307 269 254 233 175 120 109 75 57 42 34 22 10 9 8 5 1 0
(0) (22) (27) (33) (37) (44) (53) (61) (71) (113) (154) (164) (193) (209) (221) (229) (241) (250) (251) (252) (255) (259) (260)
EQ-5D-5L utility score
177Lu-PSMA-617 cycles
↑Improvement
Least squares mean change from baseline (95% CI)
Number with data
177Lu-PSMA-617 with ADT plus ARPI 474 465 464 451 442 432 400 375 350 265 186 132 84 62 44 20
ADT plus ARPI 440 430 417 41 411 379 372 354 314 243 168 116 83 54 34 15
BPI-SF pain intensity
Median (months)
177Lu-PSMA-617 with ADT plus ARPI (n=572)
ADT plus ARPI (n=572)
11·53 (95% CI 8·77–14·09)
13·83 (95% CI 11·10–16·79)
HR 1·02 (95% CI 0·87–1·18)
Proportion of patients without event (%)
Time since randomisation (months)
Number at risk (censored)
177Lu-PSMA-617 with ADT plus ARPI 572 486 402 339 299 273 245 233 216 158 119 95 71 47 33 28 24 11 7 3 2 0
(0) (18) (24) (29) (34) (42) (43) (47) (54) (105) (135) (155) (175) (195) (207) (210) (213) (223) (226) (230) (231) (233)
ADT plus ARPI 572 455 397 338 306 281 256 235 219 165 117 107 75 56 39 30 17 9 5 5 1 0
(0) (22) (28) (36) (39) (50) (55) (64) (72) (112) (149) (158) (183) (200) (213) (221) (232) (239) (241) (241) (245) (246)
BPI-SF pain intensity
177Lu-PSMA-617 cycles
↓Improvement
Least squares mean change from baseline (95% CI)
Time since randomisation (months)
Number with data
177Lu-PSMA-617 with ADT plus ARPI 470 460 456 447 436 431 395 374 350 263 181 133 84 62 44 20
ADT plus ARPI 429 423 410 413 406 375 364 347 311 239 167 116 82 54 34 15

respectively (appendix p 33). Within this grouping, grade 3 or worse adverse events of anaemia, neutropenia, and thrombocytopenia occurred in 28 (5%), 21 (4%), and ten (2%) patients, respectively, in the ^{177}Lu-PSMA-617 arm and 16 (3%), five (1%), and three (1%) patients, respectively, in the control arm.

Adverse events in the second primary malignancies grouping occurred in 37 patients (7%) in the ^{177}Lu-PSMA-617 arm and 31 (5%) in the control arm (appendix p 33). No cases of acute myeloid leukaemia or myelodysplastic syndrome had been reported at data cutoff. The second primary malignancies grouping included change in prostate cancer pathology; neuroendocrine differentiation of prostate cancer was reported in three patients (1%) in the ^{177}Lu-PSMA-617 arm and none in the control arm (appendix p 34). Adverse events in the renal grouping occurred in 40 patients (7%) in the ^{177}Lu-PSMA-617 arm and 26 (5%) in the control arm. Other safety topics of interest are shown in the appendix (p 33).

Median time to worsening in FACT-P total score, clinical disease progression, or death (whichever was first) was 11·33 months (95% CI 8·84–14·03) in the ^{177}Lu-PSMA-617 arm and 17·12 months (13·80–19·91) in the control arm, with a HR of 1·14 (0·98–1·33; figure 3A). Median time to worsening in EQ-5D-5L utility score, clinical disease progression, or death was 11·10 months (95% CI 8·84–14·06) in the ^{177}Lu-PSMA-617 arm and 15·67 months (11·76–19·12) in the control arm, with a HR of 1·13 (0·97–1·31; figure 3A). Median time to worsening in BPI-SF pain intensity, clinical disease progression, or death was 11·53 months (95% CI 8·77–14·09) in the ^{177}Lu-PSMA-617 arm and 13·83 (11·10–16·79) in the control arm, with a HR of 1·02 (0·87–1·18; figure 3A).

In the prespecified longitudinal analyses of HRQoL and pain scores in patients with available data at interim analysis (figure 3B), least-squares mean changes in FACT-P total score from baseline in the ^{177}Lu-PSMA-617 arm and control arm, respectively, were: –3·06 (95% CI –4·45 to –1·67) and –0·34 (–1·81 to 1·12) at week 36 (cycle 6); –2·98 (–4·46 to –1·50) and –2·51 (–4·07 to –0·96) at week 72; and –4·02 (–6·09 to –1·94) and –3·67 (–5·88 to –1·46) at week 108. Least-squares mean changes in EQ-5D-5L utility score from baseline to week 36 were –0·01 (95% CI –0·03 to 0·00) in the ^{177}Lu-PSMA-617 arm and –0·01 (–0·02 to 0·01) in the control arm. Least-squares mean changes in BPI-SF pain intensity from baseline to week 36 were 0·09 (95% CI –0·07 to 0·24) in the ^{177}Lu-PSMA-617 arm and 0·04 (–0·13 to 0·21) in the control arm (figure 3B).

Figure 3: **Time to worsening and longitudinal assessment of health-related quality of life and pain**

(A) Time to worsening in FACT-P total score (composite time to worsening, defined as time from randomisation to the first occurrence of >10 point decrease from baseline, or clinical disease progression, or death). EQ-5D-5L utility score (composite time to worsening, defined as time from randomisation to the first occurrence of 0·08 point decrease from baseline, or clinical disease progression, or death) and BPI-SF pain intensity (composite time to worsening, defined as time from randomisation to the first occurrence of ≥30% or ≥2 point increase from baseline, or clinical disease progression, or death). (B) Longitudinal mixed model repeated measures analysis of change from baseline in FACT-P total score, EQ-5D-5L utility score, and BPI-SF pain intensity. Shaded region represents time on ^{177}Lu-PSMA-617 treatment. ADT=androgen deprivation therapy. BPI-SF=Brief Pain Inventory–Short Form. EQ-5D-5L=the European Quality of Life 5-Dimensions 5-Levels. FACT-P=Functional Assessment of Cancer Therapy–Prostate. HR=hazard ratio.

Discussion

Adding ^{177}Lu-PSMA-617 to ADT plus ARPI significantly improved radiographic progression-free survival versus ADT plus ARPI alone in patients with PSMA-positive metastatic APMN/S prostate cancer suitable for treatment with ADT plus ARPI without chemotherapy in this phase 3 study. The primary endpoint was thus met at the first interim analysis of efficacy. Complete radiographic responses were more frequent when ^{177}Lu-PSMA-617 was combined with ADT plus ARPI, and PSA responses were more frequent and longer-lasting. There was no significant difference in overall survival between arms at the time of the present interim analysis, but data were immature: crossover and follow-up continue.

The most common adverse event was grade 1 dry mouth, which occurred in 41% of patients in the ^{177}Lu-PSMA-617 arm, and is probably associated with normal extra-prostatic PSMA expression. Other undesirable effects of combining ^{177}Lu-PSMA-617 with ADT plus ARPI included cytopenias and gastrointestinal adverse events. Overall, the adverse event findings in the current study are consistent with the safety profile of ^{177}Lu-PSMA-617 established in the VISION and PSMAfore trials.[18,19] No unexpected safety findings associated with combining ^{177}Lu-PSMA-617 with ADT plus ARPI were observed at the present data cutoff (Jan 13, 2025), and discontinuation rates for ADT and ARPI were similar across arms. Analyses of resolution and timing of adverse events are planned, and safety will be assessed further at planned future analysis time points.

In patient-reported outcomes, HRs for composite time to worsening in FACT-P total score, EQ-5D-5L utility score, and BPI-SF pain intensity were above 1·0 but below 1·2, with all 95% CIs including 1·0, for the ^{177}Lu-PSMA-617 arm versus the control arm. These findings might indicate an incremental risk of shortening the time to worsening HRQoL and pain during treatment when combining ^{177}Lu-PSMA-617 with ADT plus ARPI. The thresholds for worsening HRQoL scores were prespecified based on established minimum clinically important differences for these instruments. Time-to-worsening analyses treat the first decline as irreversible and do not capture longitudinal changes such as subsequent recovery or stabilisation. Furthermore, the endpoints were composites that treated disease progression and death as worsening if they occurred first, which can lead to bias.

Longitudinal analyses of changes from baseline in patient-reported outcome measure scores showed continual modest worsening throughout the study in both arms, with high baseline questionnaire completion rates (>80%). Worsening in FACT-P total score was greater in the ^{177}Lu-PSMA-617 arm during ^{177}Lu-PSMA-617 treatment cycles (to week 36), but changes from baseline were nominally different from the control arm thereafter to week 108. Beyond 108 weeks, interpretation was limited because fewer than 100 patients per group had reached later time points and completed questionnaires at the present interim data cutoff. Longitudinal profiles of worsening in EQ-5D-5L utility score and BPI-SF pain intensity were comparable across arms throughout the study. Detailed results on patient-reported outcomes in PSMAddition will be published separately, including post-hoc non-composite time-to-worsening analyses, instrument subscales, and longitudinal analyses of change from baseline in all HRQoL subscales.

The proportion of patients with PSA nadir below 0·2 ng/mL was higher in the ^{177}Lu-PSMA-617 combination arm than the control arm. In PSMAddition, approximately three-quarters of patients started ADT or ARPI, or both treatments, before randomisation, and the 24-week post-randomisation time point (approximately 5·5 months) is closest to the established time point of 6–8 months after start of treatment for prognostication based on PSA nadir.[36] The findings support a deeper and longer PSA response associated with improved radiographic progression-free survival when combining ^{177}Lu-PSMA-617 with ADT plus ARPI.

The definition of PSMA positivity for metastatic APMN/S prostate cancer in PSMAddition differed from that used for metastatic APMR prostate cancer in the VISION and PSMAfore studies. Although all studies required at least one metastatic lesion to be PSMA-positive, VISION and PSMAfore also excluded patients with PSMA-negative lesions with sizes exceeding specified thresholds.[18,19] This difference is because all patients in PSMAddition received ADT plus ARPI for treatment-naive or minimally treated metastatic APMN/S prostate cancer (with or without ^{177}Lu-PSMA-617). Visual assessment of ^{68}Ga-PSMA-11 uptake as greater than liver parenchyma remains a straightforward method for defining lesion PSMA positivity. In the present study, approximately 87% of patients who underwent ^{68}Ga-PSMA-11 PET–CT had PSMA-positive, metastatic APMN/S prostate cancer. The PSMAddition population of patients with metastatic APMN/S prostate cancer eligible for ^{177}Lu-PSMA-617 is broader than the populations eligible for targeted therapy with tyrosine kinase inhibitors and poly(ADP-ribose) polymerase inhibitors.[37–40]

The ^{177}Lu-PSMA-617 dose and regimen in PSMAddition (7·4 GBq every 6 weeks for six cycles) was identical to that used in PSMAfore and similar to that used in VISION (four to six cycles) in patients with metastatic APMR prostate cancer.[18,19] All three studies evaluated a predetermined ^{177}Lu-PSMA-617 dose and regimen that could be adjusted for adverse drug reactions or progression but not for response or residual PSMA-positive disease. Although preclinical data indicate that ADT and ARPI might up-regulate PSMA expression within metastatic APMN/S prostate cancer tumour cells, the anti-tumour activity of the treatment in patients with metastatic APMN/S prostate cancer starting on ADT and ARPI reduces radiotracer uptake on PSMA PET scans and this could mask cellular upregulation of PSMA expression in residual viable tumour cells.[41–45] In the present study, baseline ^{68}Ga-PSMA-11 PET imaging was used only to determine PSMA positivity for study eligibility; CT or MRI and bone scans were used for metastatic APMN/S prostate cancer staging, disease volume, and the primary endpoint of radiographic progression-free survival. After a protocol amendment, some patients in both treatment arms underwent a second exploratory ^{68}Ga-PSMA-11 PET scan after BIRC-confirmed radiographic progression (results pending). The present study was not designed to investigate adaptive ^{177}Lu-PSMA-617 dosing based on PSMA PET imaging, but only to assess the efficacy in metastatic APMN/S prostate cancer of the six-cycle regimen already established in metastatic APMR prostate cancer, which is the only regimen with proven efficacy and clinical benefit in a phase 3 trial.[18–20]

The clinical question in PSMAddition was whether combining ^{177}Lu-PSMA-617 with ADT plus ARPI improves outcomes in patients with metastatic APMN/S prostate cancer for whom treatment with ADT plus ARPI without chemotherapy is appropriate. ADT plus ARPI is a contemporary standard of care for patients with metastatic APMN/S prostate cancer, and this was also the case when the study was designed. Chemotherapy (eg, docetaxel) was not considered a relevant comparator in PSMAddition, and evidence of improved overall survival with triplet therapy that includes docetaxel was not available when the present study was designed. Furthermore, at the time of writing it is unknown whether docetaxel improves outcomes when added to the contemporary standard of care of ADT plus ARPI, given that the trials supporting triplet therapy tested addition of ARPI to ADT plus docetaxel.[7–9] The question of whether adding docetaxel to ADT plus ARPI provides clinical benefit is being investigated in the recently initiated ASpiRE (NCT06931340) and TRIPLE-SWITCH (NCT06592924) studies. In the phase 2 UpFrontPSMA study, sequential ^{177}Lu-PSMA-617 followed by docetaxel enhanced anti-tumour activity compared with docetaxel in patients with high-volume de novo metastatic APMN/S prostate cancer receiving ADT but not ARPI.[44] PSMAddition provides the first evidence for the efficacy of ^{177}Lu-PSMA-617 in patients for whom the contemporary standard of ADT plus ARPI doublet treatment without docetaxel is appropriate. This is a necessary foundation for future

studies of optimal treatment intensification strategies in metastatic APMN/S prostate cancer.

The strengths of this study include the relevant and contemporary control arm comprising appropriate doublet therapy with ARPI plus ADT in all patients. The use of the BIRC for PSMA positivity and the primary endpoint is a strength and mitigates the inherent limitations of the open-label design common to radiopharmaceuticals. The crossover design is a strength, because it ensured that patients with BIRC-confirmed radiographic progression and resulting metastatic APMR prostate cancer were able to receive ^{177}Lu-PSMA-617. Other strengths include: the flexibility of investigator's choice of any ARPI and ADT with one allowed change of ARPI before progression; accurate powering; multiplicity-controlled radiographic progression-free survival analyses; overall survival as the key secondary endpoint with multiplicity control (follow-up continues); the applicability to a broad population of patients with PSMA-positive, metastatic APMN/S prostate cancer who are appropriate for ADT plus ARPI; the extended safety monitoring period; the high completion rate of patient-reported outcome questionnaires at baseline; and the inclusion of all patients in the radiographic progression-free survival endpoint regardless of study treatment discontinuation. As discussed here, the study was designed to use visual assessment of PSMA positivity on baseline PET scans (not quantitative parameters) and to evaluate an established predetermined ^{177}Lu-PSMA-617 dose and regimen (with no post-baseline PSMA PET scans and no regimen modification based upon such scans).

The limitations of the study include the short follow-up time for radiographic progression-free survival at the present interim analysis, with the primary endpoint met but medians not reached. Although allowing crossover to ^{177}Lu-PSMA-617 in the control arm after a radiographic progression-free survival event and associated progression to metastatic APMR prostate cancer was desirable and consistent with patient benefit, it might confound interpretation of overall survival (although the influence of crossover on overall survival was not explored at the present interim analysis owing to data immaturity). The composite HRQoL and pain endpoints included disease progression and death, which could bias interpretation, while longitudinal analyses patient-reported outcomes could only include patients with available data. Data on PSMA-negative metastatic lesions at baseline were not collected during screening because the only PSMA-PET eligibility criterion was the presence of at least one metastatic lesion (except in patients with liver metastases where at least one also had to be PSMA-positive). Planned exploratory analyses will investigate associations of quantitative PSMA PET parameters with treatment outcomes. The collection method for baseline visceral metastatic sites appeared to result in classification of a substantial number of patients in the other category, potentially limiting scope for comparison with other studies. Additionally, renal and bone marrow events often occur late in targeted radionuclide therapy and might not have been captured within the present follow-up time. Final radiographic progression-free survival and overall survival analyses and updated safety analyses are planned and will be reported in the future.

In conclusion, the findings of PSMAddition at interim analysis indicate that combining ^{177}Lu-PSMA-617 with ADT plus ARPI prolongs radiographic progression-free survival in patients with PSMA-positive metastatic APMN/S prostate cancer. Although adverse events were more frequent when combining ^{177}Lu-PSMA-617 with ADT plus ARPI, the safety findings were consistent with the known profile.

Contributors

STT, OSar, FS, KF, and MJM contributed to conceptualisation. STT, OSar, FS, KF, LS, EB, AY, OSak, and MJM contributed to methodology. EB and OSak contributed to data curation and analysis. EB and MJM accessed and verified the underlying data in the study. All authors contributed to data investigation, interpretation, and writing and reviewing the manuscript and accept responsibility for the decision to submit for publication. All authors had full access to the data and attest that the data are complete and accurate and that the trial adhered to the protocol.

Declaration of interests

STT declares consulting or advisory fees from AbbVie, Abdera, AIkido Pharma, Ambrx, Astellas, Bayer, Biohaven, Blue Earth Diagnostics, Clarity Pharmaceuticals, Convergent Therapeutics, Daiichi Sankyo, Eisai, EMD Serono, General Electric, Gilead, Janssen, Lilly, Merck, Myovant, Novartis, Pfizer, POINT Biopharma, Regeneron, Seagen, Telix Pharmaceuticals, and 4D Pharma; Data and Safety Monitoring Board membership for Boston Scientific; stock and other ownership in AIkido Pharma and Convergent Therapeutics; patents with Convergent Therapeutics and Gilead; a local principal investigator role for AIQ, Ambrx, Astellas, AstraZeneca, Bayer, BMS, Clovis, Janssen, Janux, Medivation, Merck, and Seagen, and steering committee roles for Ambrx, Clarity, Gilead, Novartis, POINT Biopharma, Promontory, and Telix Pharmaceuticals. OSar declares consulting, advisory, or speaker fees from AbbVie, Advanced Accelerator Applications, ARTBIO, Astellas Pharma, AstraZeneca, Bayer, Blue Earth Diagnostics, Cardinal Health, Clarity Pharmaceuticals, Dendreon, EMD Serono, Endocyte, Fusion, Invitae, Isotopen Technologies, Janssen, Lantheus, Lilly, MacroGenics, Merck, ModeX Therapeutics, Myovant, Myriad, Noria Therapeutics, Norroy Biotech, North Star, Novartis, Pfizer, POINT Biopharma, Precede Biosciences, Progenics, Sanofi, Swiss Roche, Telix Pharmaceuticals, and Tenebio; research grants from Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Endocyte, Invitae, Janssen, Lantheus, Merck, Norroy Biotech, Novartis, Progenics, and Tenebio; stock and other options in AbbVie, ARTBIO, Cardinal Health, Clarity Pharmaceuticals, Convergent, Fusion, Lilly, Pfizer, Ratio, Telix Pharmaceuticals, and United Healthcare; travel or other support from Lantheus, North Star, and Novartis; and payment for expert testimony for Sanofi. JMP declares grants or contracts from BeiGene, Bristol Myers Squibb, Immunocore, Mirati, MSD, and Pfizer; consulting fees from Astellas, AstraZeneca, BeiGene, Bristol Myers Squibb, Clovis, Ideaya, Immunocore, Janssen, MSD, Novartis, and Pfizer; and travel expenses from AstraZeneca, Janssen, and Pfizer. FS declares consulting and advisory fees from AbbVie, Advanced Accelerator Applications, Astellas Pharma, AstraZeneca/MedImmune, Bayer, GSK, Janssen Oncology, Knight Therapeutics, Myovant Sciences, Novartis, Pfizer, Sumitomo Dainippon Pharma Oncology, and Tolmar; honoraria from AbbVie, Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer, BMS, GSK, Janssen Oncology, Knight Therapeutics, Myovant Sciences, Novartis, Pfizer, Sanofi, Sumitomo Dainippon Pharma Oncology, and Tolmar; and research funding from AbbVie, Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen Oncology, Merck,

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Data sharing

Novartis is committed to sharing patient-level data and supporting clinical documents from eligible studies with qualified external researchers. Requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymised to respect the privacy of patients who participated in the trial, in line with applicable laws and regulations. Data availability for this trial is according to the criteria and process described at https://www.clinicalstudydatarequest.com/.

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