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Symptomatic skeletal events, health-related quality of life and pain in a phase 3 study of [^{177}Lu]Lu-PSMA-617 in taxane-naive patients with PSMA-positive metastatic castration-resistant prostate cancer: third interim analysis of PSMAfore

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KEY FINDINGS & CONCLUSIONS

- ^{177}Lu-PSMA-617 significantly prolonged time to SSE and time to worsening in self-reported HRQoL and pain versus ARPI change in patients with PSMA-positive mCRPC whose disease had progressed once on previous ARPI, as assessed using validated instruments and questionnaires.
- These results support the use of ^{177}Lu-PSMA-617 as a new standard of care for patients with mCRPC who are being considered for an ARPI change after one progression on previous ARPI.

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INTRODUCTION

- [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy that delivers β-particle radiation to PSMA-expressing cancer cells and the surrounding microenvironment.[1,2]
- The VISION study demonstrated the efficacy of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC) who had previously been treated with at least one androgen receptor pathway inhibitor (ARPI) and one or two taxanes.[3,4]
- In PSMAfore, ^{177}Lu-PSMA-617 prolonged radiographic progression-free survival compared with change of ARPI in patients with PSMA-positive mCRPC.
- We now present the time to first symptomatic skeletal event (SSE) and time to worsening in health-related quality of life (HRQoL) and pain at the third interim overall survival analysis of PSMAfore (data cutoff: 27 Feb 2024).

METHODS

- PSMAfore (NCT04689828) was an international, open-label study of ^{177}Lu-PSMA-617 in patients with PSMA-positive mCRPC who had not received taxane-based chemotherapy (except ≤ 6 cycles [neo] adjuvant ≥ 12 months ago) and were candidates for ARPI change after one progression on previous second-generation ARPI.
- Participants were randomized 1:1 to receive ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks, ≤ 6 cycles) or ARPI change.
  - Those in the ARPI change group could cross over to ^{177}Lu-PSMA-617 upon blinded independent central review (BICR)-confirmed radiographic disease progression.
- The primary endpoint was BICR-confirmed radiographic progression-free survival and the key secondary endpoint was overall survival.
- Secondary endpoints included time to SSE and time to worsening in self-reported HRQoL (Functional Assessment of Cancer Therapy-Prostate [FACT-P], EQ-5D-5L) and pain (Brief Pain Inventory-Short Form [BPI-SF]) (**Table 1**).
- Patient-reported outcome (PRO) questionnaires were completed and SSEs were monitored throughout treatment and at end of treatment.

Table 1. Time-to-event endpoint definitions for patient-reported outcomes and SSEs

Worsening in …	Time from randomization to …	Or …
FACT-P		clinical disease progression[a] (excluding radiographic and PSA progression) or death
Total score	a ≥ 10-point decrease from baseline	
Subscales	a ≥ 3-point decrease from baseline	
EQ-5D-5L utility score	a 0.08-point decrease from baseline	
BPI-SF pain intensity/ pain interference	a ≥ 30% or a ≥ 2-point increase from baseline	
Time to …	**Time from randomization to …**	**Or …**
SSE	the first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention or requirement for radiation therapy to relieve bone pain	death from any cause[b]

[a]Clinical progression was investigator-assessed as cancer-related pain escalation, immediate need for new treatment, ECOG status deterioration or progression requiring treatment discontinuation. [b]*Post hoc* analyses excluded death.
BPI-SF, Brief Pain Inventory-Short Form; ECOG, Eastern Cooperative Oncology Group; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PSA, prostate-specific antigen; SSE, symptomatic skeletal event.

RESULTS

- Overall, 468 patients were randomized (^{177}Lu-PSMA-617, n = 234; ARPI change, n = 234) and all were included in the analysis.

Time to first symptomatic skeletal event

- ^{177}Lu-PSMA-617 prolonged time to first SSE and fewer bone fractures were reported versus ARPI change (**Table 2**; **Figure 1**).

Patient-reported outcomes

- ^{177}Lu-PSMA-617 prolonged time to worsening in all scales and subscales of the FACT-P, EQ-5D-5L and BPI-SF versus ARPI change (**Figures 2** and **3**).

Safety

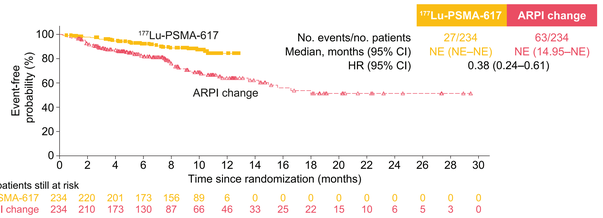
- Incidences of grade ≥ 3 adverse events (AEs), serious AEs and AEs leading to discontinuation for ^{177}Lu-PSMA-617 and ARPI change were 36% and 48%, 20% and 32%, and 6% and 5%, respectively.

Table 2. Time to first SSE

	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n (%)	27 (11.5)	63 (26.9)
Symptomatic pathological bone fracture	4 (1.7)	13 (5.6)
Spinal cord compression	6 (2.6)	4 (1.7)
Tumour-related orthopaedic surgery intervention	1 (0.4)	3 (1.3)
Requirement for radiation therapy to relieve bone pain	16 (6.8)	43 (18.4)
Censored,[a] n (%)	207 (88.5)	171 (73.1)
Median, months (95% CI)	NE (NE–NE)	NE (14.95–NE)
HR (95% CI)[b]	0.38 (0.24–0.61)	

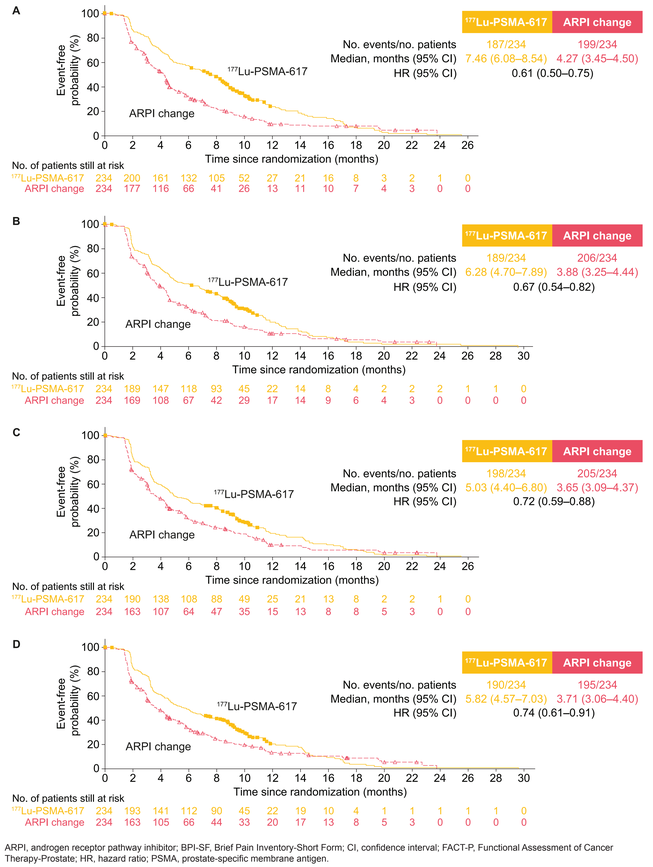
[a]Patients who did not experience an event. [b]Stratified Cox proportional-hazards model.
Post hoc analysis excluding death.
ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PSMA, prostate-specific membrane antigen; SSE, symptomatic skeletal event.

Figure 1. Time to first SSE



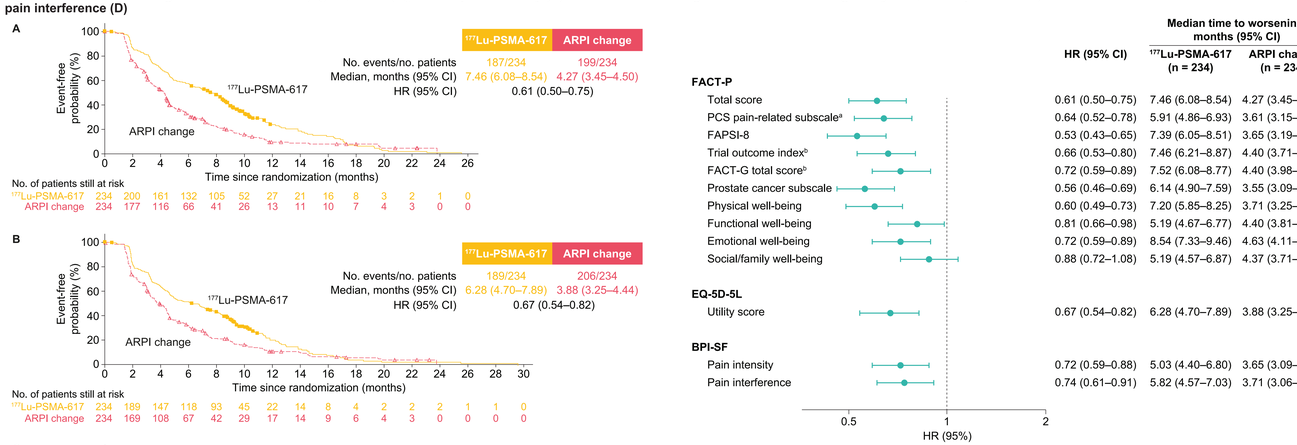
Post hoc analysis excluding death.
ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PSMA, prostate-specific membrane antigen; SSE, symptomatic skeletal event.

Figure 2. Time to worsening in FACT-P total score (A), EQ-5D-5L (B), BPI-SF pain intensity (C) and BPI-SF pain interference (D)



ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; PSMA, prostate-specific membrane antigen.

Figure 3. Time to worsening in key HRQoL and pain indices, domains and sub-domains



Definitions of worsening are shown in **Table 1**. [a]Time from randomization to the first occurrence of a decrease of at least 2 points, clinical disease progression or death. [b]Time from randomization to the first occurrence of a decrease of at least 9 points, clinical disease progression or death.
ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; HR, hazard ratio; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FAPSI-8, Functional Assessment of Cancer Therapy Advanced Prostate Symptom Index-8; HRQoL, health-related quality of life; PCS, prostate cancer subscale; PSMA, prostate-specific membrane antigen.

LIMITATIONS

- The open-label nature of the study may have affected patients' perception of their HRQoL.
- PRO questionnaires were not completed after disease progression or discontinuation of study treatment.
- PRO completion rates and non-completion reasons were not analysed and patients who experienced declining HRQoL may have been unable to complete the questionnaires.

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