Efficacy of [^{177}Lu]Lu-PSMA-617 versus ARPI change in taxane-naive patients with metastatic castration-resistant prostate cancer by pre-randomization ARPI (PSMAfore)

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Background

In the phase 3 PSMAfore study (NCT04689828), [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolonged radiographic progression-free survival (rPFS) versus androgen receptor pathway inhibitor (ARPI) change in patients naive to taxane chemotherapy with prostate-specific membrane antigen (PSMA) positive metastatic castration-resistant prostate cancer (mCRPC; HR 0.41; 95% CI 0.29–0.56; $p < 0.0001$). We now present an exploratory *post hoc* analysis of efficacy outcomes by pre-randomization ARPI treatment at the second interim overall survival (OS) analysis.

Methods

Eligible adults had mCRPC, were suitable for ARPI change after one progression on prior ARPI and had ≥ 1 PSMA-positive lesion and no exclusionary PSMA-negative lesions by [^{68}Ga]Ga-PSMA-11 PET/CT. Ineligible patients were candidates for PARP inhibition or had received prior systemic/hemibody radiotherapy, immunotherapy or chemotherapy. Randomization was 1:1 to open-label ^{177}Lu-PSMA-617 (7.4 GBq Q6W; 6 cycles) or ARPI change (abiraterone/enzalutamide). Endpoints included rPFS (BICR per PCWG3/RECIST v1.1; primary), OS (key secondary), PSA50 response (prostate-specific antigen [PSA] decline ≥ 50% from baseline; secondary) and objective response rate (ORR; exploratory). Median rPFS was estimated using the Kaplan–Meier method and HRs were obtained using the Cox proportional hazards model. Descriptive statistics were used for PSA50 response and ORR.

Results

Of the 234 patients randomized per arm, 50.9% and 40.2% randomized to ^{177}Lu-PSMA-617, and 55.6% and 35.9% randomized to ARPI change received pre-randomization abiraterone and enzalutamide, respectively. ^{177}Lu-PSMA-617 prolonged rPFS versus ARPI change regardless of pre-randomization ARPI; PSA50 responses and ORR also favored the ^{177}Lu-PSMA-617 arm. In both arms, more favorable results were observed in patients receiving pre-randomization abiraterone than enzalutamide (**Table**).

Conclusion

^{177}Lu-PSMA-617 prolonged rPFS and increased PSA50 responses and ORR versus ARPI change in taxane-naive patients with PSMA-positive mCRPC, regardless of pre-randomization ARPI. Results favored patients receiving pre-randomization abiraterone versus enzalutamide.

Table. *Post hoc* analysis of the efficacy of ^{177}Lu-PSMA-617 versus ARPI change by pre-randomization ARPI at second overall survival interim analysis (data cut-off, June 21, 2023; median follow-up, 15.9 months).

	rPFS[a]		**Confirmed PSA50**	**ORR**
	Median time, months (95% CI)	**HR (95% CI)**	**m/M[b] (%) [95% CI]**	**m/M[c]< (%) [95% CI]**
Pre-randomization ARPI: abiraterone				
177Lu-PSMA-617 arm (n = 119)	12.62 (9.56–17.15)	0.47 (0.33–0.66)	70/109 (64.2) [54.5–73.2]	22/36 (61.1) [43.5–76.9]
ARPI change arm (n = 130)	5.78 (4.93–6.44)		32/125 (25.6) [18.2–34.2]	6/37 (16.2) [6.2–32.0]
Pre-randomization ARPI: enzalutamide				
177Lu-PSMA-617 arm (n = 94)	12 02 (7.00–17.05)	0.35 (0.24–0.52)	45/87 (51.7) [40.8–62.6]	12/30 (40.0) [22.7–59.4]
ARPI change arm (n = 84)	4.34 (3.88–5.78)		10/80 (12.5) [6.2–21.8]	4/30 (13.3) [3.8–30.7]

An additional 41 patients received either darolutamide or apalutamide pre-randomization (data not shown; ARPI change arm (n = 20]; ^{177}Lu-PSMA-617 arm [n = 21]).

[a]At primary analysis, the primary endpoint of rPFS was met (HR 0.41; 95% CI 0.29-0.56; $p < 0.0001$; data cut-off, October 2, 2022); the data presented here are of an exploratory analysis conducted at the time of the second overall survival interim analysis (data cut-off, June 21, 2023).

[b]m: patients with a PSA50 and confirmed ≥ 4 weeks later; M: patients with a PSA measurement.

[c]m: patients with ORR (patients with complete or partial response); M: patients with measurable disease at baseline (soft tissue only).

^{177}Lu-PSMA-617, [^{177}Lu]Lu-PSMA-617; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PSA, prostate-specific antigen; PSA50, prostate-specific antigen decline ≥ 50% from baseline; rPFS, radiographic progression-free survival.

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