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LBA6

Phase III trial of [177Lu]Lu-PSMA-617 combined with ADT + ARPI in patients with PSMA-positive metastatic hormone-sensitive prostate cancer (PSMAddition)

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Background

ADT + androgen receptor pathway inhibitor (ARPI) is a standard of care for mHSPC but outcomes remain suboptimal. PSMAddition (NCT04720157) evaluates [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) combined with ADT + ARPI in PSMA+ mHSPC.

Methods

Eligible adults had treatment-naïve/minimally treated (≤45 days) mHSPC and ≥1 PSMA+ metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT. Randomization was 1:1 to open-label ^{177}Lu-PSMA-617 (7.4 GBq q6w, 6 cycles) + ADT + ARPI (^{177}Lu-PSMA-617 arm) or ADT + ARPI (control arm), stratified by disease volume (high/low), age (≥/<70 years) and previous/planned primary tumor treatment (yes/no). Control arm patients with centrally confirmed rPD could cross over to ^{177}Lu-PSMA-617 if eligible. The primary endpoint was rPFS (per centrally assessed PCWG3 RECIST v1.1 or death); secondary endpoints included OS (key), ORR, safety/tolerability and QoL. We report rPFS interim analysis (IA) 2, the first efficacy IA.

Results

1144 patients were randomized (de novo mHSPC, 50.0%; high-volume disease, 68.1%). Baseline characteristics were balanced between arms. At rPFS IA2 (median study follow-up, 23.6 months; ^{177}Lu-PSMA-617 cycles, 6 in 85.6% and ≥4 in 93.1%), the primary endpoint was met, with significantly improved rPFS (Table). There was a positive trend in intent-to-treat OS; ORR favored the ^{177}Lu-PSMA-617 arm (Table). Overall incidence of AEs was slightly higher with addition of ^{177}Lu-PSMA-617 (Table). Dry mouth was the most common AE (all grade 1–2; ^{177}Lu-PSMA-617 vs control arm: 41.0% vs 3.4 % grade 1, 4.8% vs 0.4% grade 2). Grade ≥3 cytopenias were more frequent with added ^{177}Lu-PSMA-617 (14.4% vs 5.0%). Time to worsening in QoL (FACT-P, EQ-5D) did not differ meaningfully between arms.Table: LBA6

DCO 13 Jan 2025	^{177}Lu-PSMA-617 + ADT + ARPI	ADT + ARPI
Efficacy	N = 572	N = 572
rPFS[a]		
Events, n (%)	139 (24.3)	172 (30.1)
Median (95% CI), months	NE (NE, NE)	NE (29.73, NE)
HR (95% CI), *p*	0.72 (0.58, 0.90), 0.002	
OS[b]		
Events, n (%)	85 (14.9)	99 (17.3)
Median (95% CI), months	NE (NE, NE)	NE (NE, NE)

DCO 13 Jan 2025	^{177}Lu-PSMA-617 + ADT + ARPI	ADT + ARPI
Efficacy	N = 572	N = 572
HR (95% CI), *p*	0.84 (0.63, 1.13), 0.125	
ORR[c], % (95% CI), n	85.3 (79.9, 89.6), 224	80.8 (74.8, 85.8), 213
Safety	N = 564	N = 565
Any AE, %	98.4	96.6
Grade ≥3, %	50.7	43.0
Serious, %	31.9	28.7

[a]rPD or death; significance threshold at IA2, 0.009; IF, 74.4%. [b]IF, 47.3%. [c]Soft tissue and bone; patients with measurable disease at baseline. CI, confidence interval; DCO, data cut off; IA, interim analysis; IF, information fraction; NE, not estimable.

Conclusions

Combining ^{177}Lu-PSMA-617 with ADT + ARPI significantly improved rPFS in this first phase 3 trial of radioligand therapy in mHSPC. Safety findings were consistent with the known profile and QoL was not adversely affected.

Clinical trial identification

NCT04720157.

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Legal entity responsible for the study

Novartis.

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