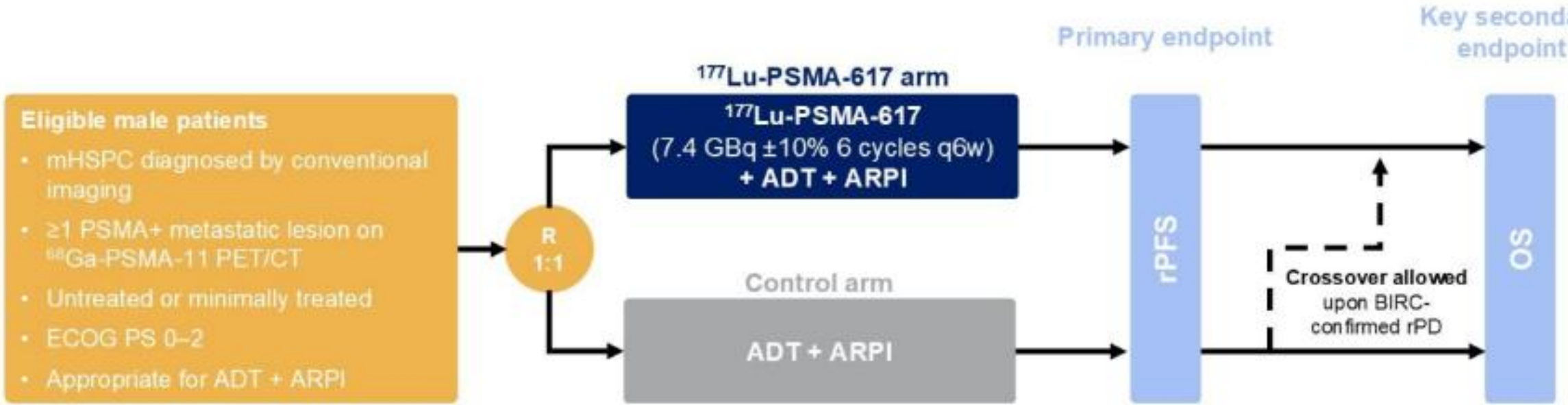
Subgroup analyses by disease volume and *de novo*/recurrent mHSPC in the PSMAddition study of [^{177}Lu]Lu-PSMA-617

PSMAddition: phase 3 trial of ^{177}Lu-PSMA-617 in mHSPC[1]



23.6 months median study follow-up (range 17.7–42.8)

We now report data by subgroups of patients by:

Disease volume per CHAARTED criteria using conventional imaging
- **High:** presence of visceral metastases and/or ≥4 bone lesions with ≥1 lesions beyond the vertebral bodies and pelvis
- **Low:** absence of high disease volume

mHSPC status
- ***De novo*:** stage IVB at initial diagnosis[2]
- **Recurrent:** stage below IVB at initial diagnosis[2]

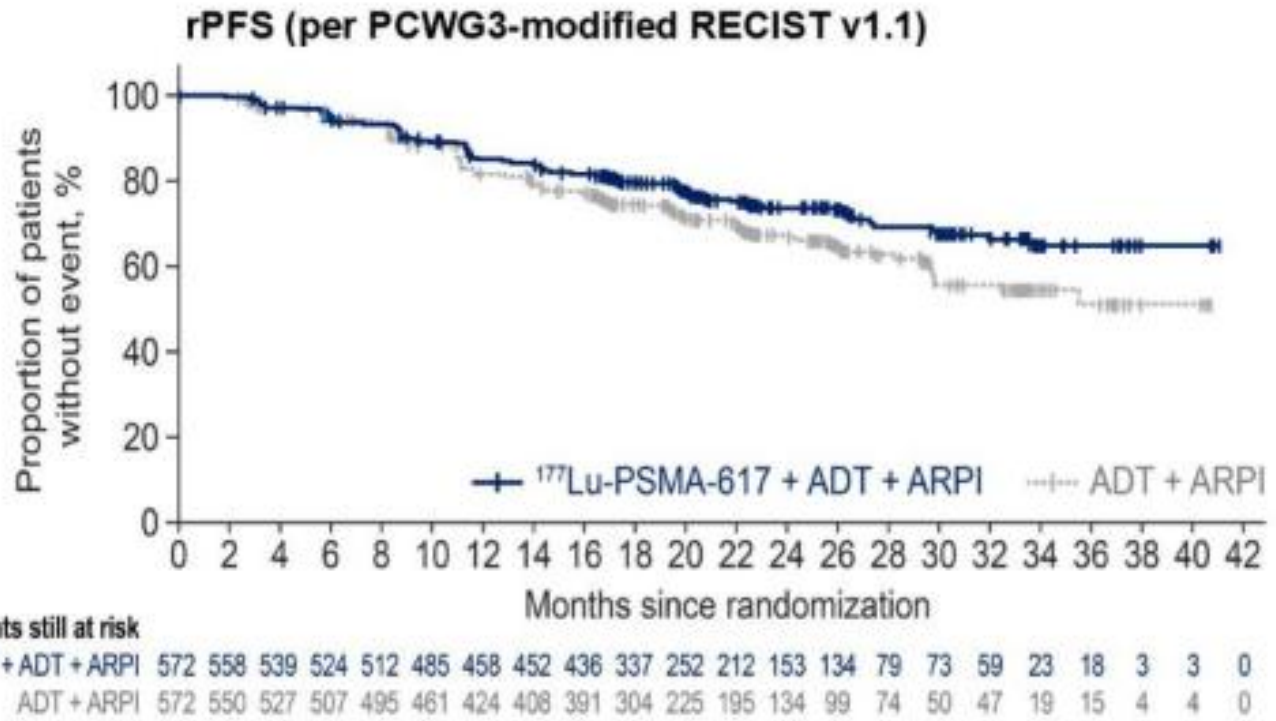
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BIRC, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IA2, second interim analysis; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PET/CT, positron emission therapy/computed tomography; PSMA, prostate-specific membrane antigen; rPD, radiographic progression of disease; rPFS, radiographic progression-free survival.

PSMAddition: key results from second interim analysis[1]

rPFS primary endpoint (met)[1]

- Significantly improved rPFS with ^{177}Lu-PSMA-617 + ADT + ARPI versus ADT + ARPI at IA2

	^{177}Lu-PSMA-617 + ADT + ARPI n = 572	ADT + ARPI n = 572
Median rPFS (95% CI) – months	NR (NE–NE)	NR (29.7–NE)
HR (95% CI)[a]	**0.72 (0.58, 0.90)**	
	***p* = 0.002**	



We now present data by subgroups of patients by disease volume and recurrent/*de novo* mHSPC

[a]Significance threshold at rPFS IA2: 0.009 (one-sided; stratified log-rank test); information fraction, 74.4%

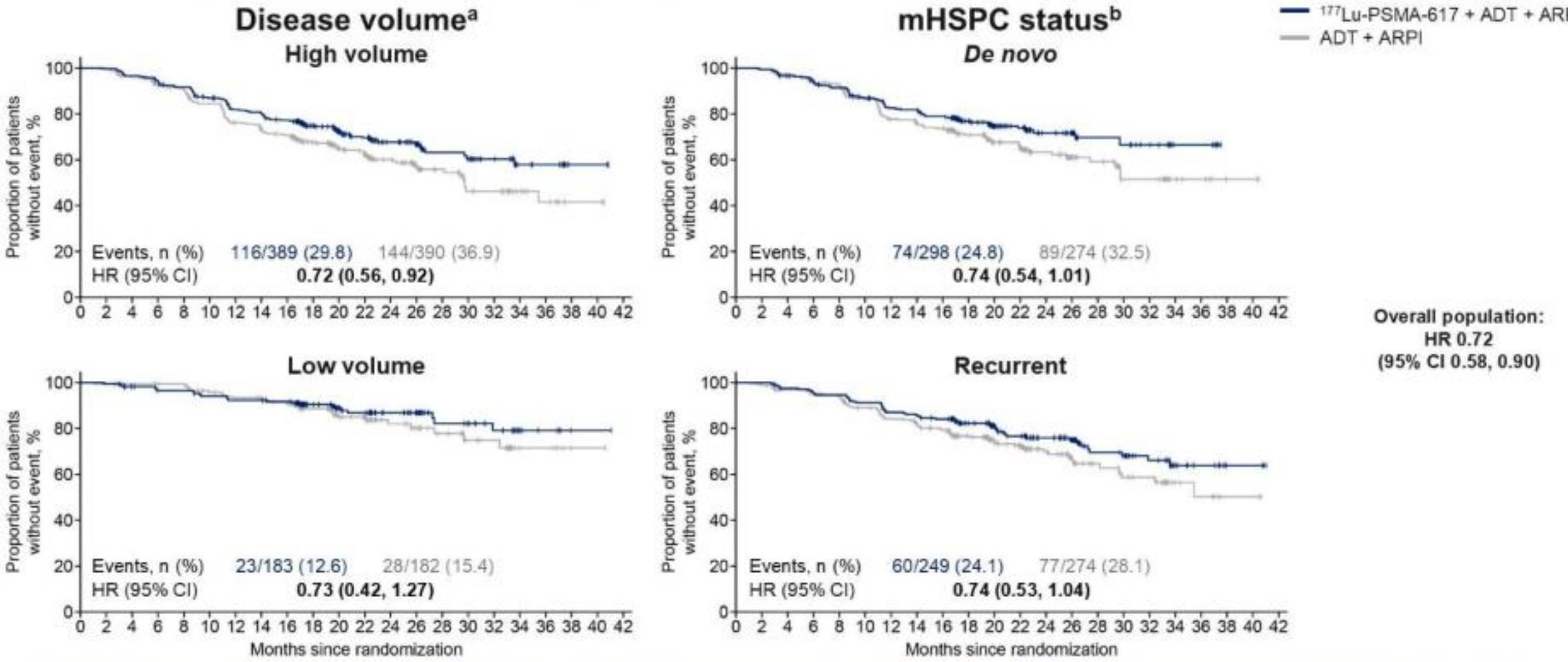
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; IA2, second interim analysis; NE, not evaluable; NR, not reached; rPFS, radiographic progression-free survival.

Baseline characteristics were generally similar across treatment arms within subgroups

	Disease volume[a]				mHSPC status[b,c]			
	^{177}Lu-PSMA-617 + ADT + ARPI		ADT + ARPI		^{177}Lu-PSMA-617 + ADT + ARPI		ADT + ARPI	
	High (n = 389)	Low (n = 183)	High (n = 390)	Low (n = 182)	*De novo* (n = 298)	Recurrent (n = 249)	*De novo* (n = 274)	Recurrent (n = 274)
Number of patients – n/N (%)	389/572 (68.0)	183/572 (32.0)	390/572 (68.2)	182/572 (31.8)	298/572 (52.1)	249/572 (43.5)	274/572 (47.9)	274/572 (47.9)
Age, years – median (range)	68.0 (38–90)	68.0 (45–91)	68.0 (36–90)	67.0 (45–89)	68.0 (38–87)	68.0 (43–90)	67.0 (41–89)	69.0 (36–90)
ECOG performance status – n (%)								
0	253 (65.0)	144 (78.7)	256 (65.6)	151 (83.0)	204 (68.5)	179 (71.9)	192 (70.1)	198 (72.3)
1	135 (34.7)	39 (21.3)	126 (32.3)	29 (15.9)	94 (31.5)	69 (27.7)	76 (27.7)	72 (26.3)
2	1 (0.3)	0	5 (1.3)	2 (1.1)	0	1 (0.4)	4 (1.5)	3 (1.1)
Missing	0	0	3 (0.8)	0	0	0	2 (0.7)	1 (0.4)
PSA level, ng/mL – median (Q1–Q3)	17.8 (4.4–85.4), n = 383	8.0 (1.8–24.3), n = 180	17.0 (3.8–77.1), n = 388	5.5 (1.8–20.0), n = 182	14.0 (4.4–85.4), n = 297	9.3 (2.6–40.2), n = 242	16.4 (3.5–71.8), n = 273	8.6 (2.1–34.7), n = 273
Gleason score – n (%)								
8–10 (grade 4–5)	266 (68.4)	123 (67.2)	279 (71.5)	127 (69.8)	225 (75.5)	154 (61.8)	222 (81.0)	169 (61.7)
Missing	27 (6.9)	4 (2.2)	27 (6.9)	5 (2.7)	24 (8.1)	4 (1.6)	22 (8.0)	8 (2.9)

[a]Per CHAARTED criteria using conventional imaging. [b]Subgroup not prespecified; *de novo*: stage IVB at initial diagnosis (*AJCC Cancer Staging Manual* 8th edition). [c]49 patients had missing mHSPC stage at initial diagnosis (25 in the ^{177}Lu-PSMA-617 arm; 24 in the control arm). ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; ECOG, Eastern Cooperative Oncology Group performance status; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen

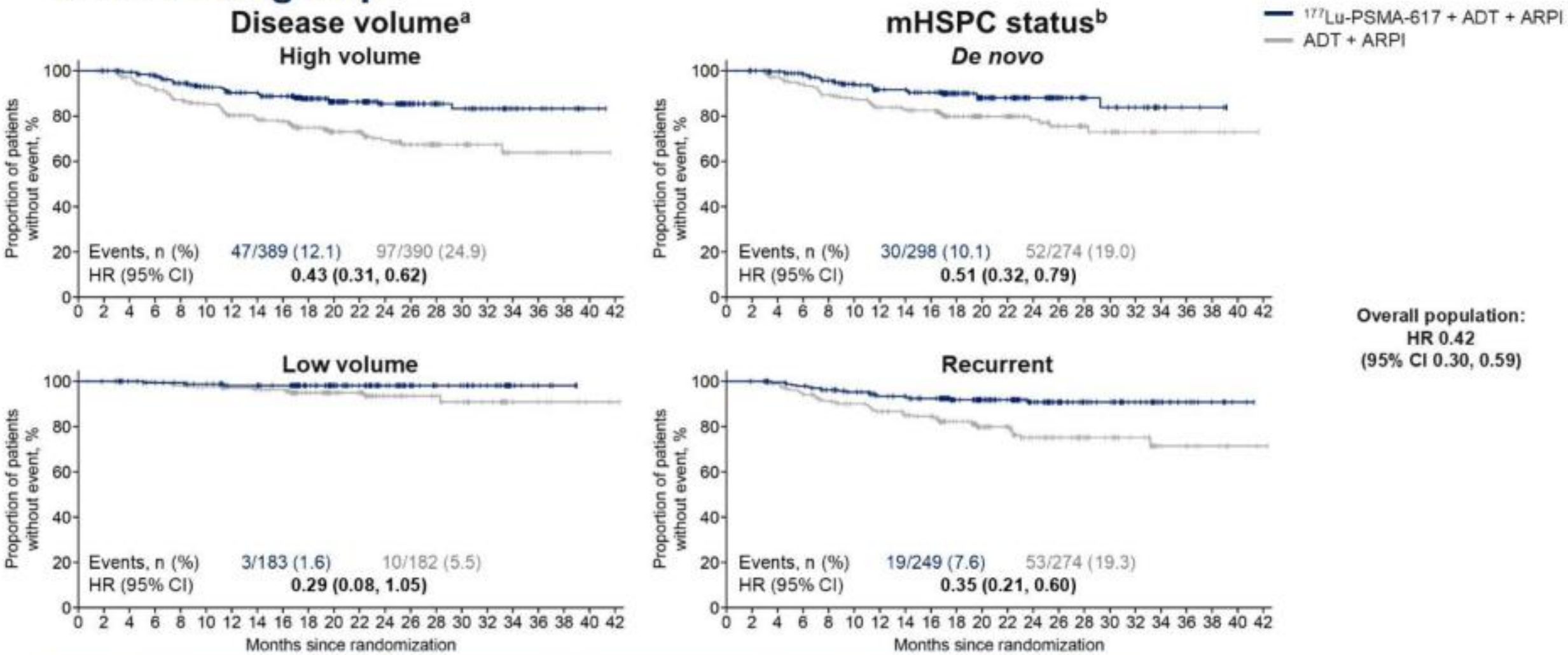
Consistent rPFS benefit with ^{177}Lu-PSMA-617 across subgroups



rPFS per PCWG3-modified RECIST v1.1 (primary endpoint). [a]Per CHAARTED criteria using conventional imaging. [b]Subgroup not prespecified; *de novo*: stage IVB at initial diagnosis (*AJCC Cancer Staging Manual* 8th edition). ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; rPFS, radiographic progression-free survival

Data cut-off: 13 January 2025

Consistent time to PSA progression benefit with ^{177}Lu-PSMA-617 across subgroups

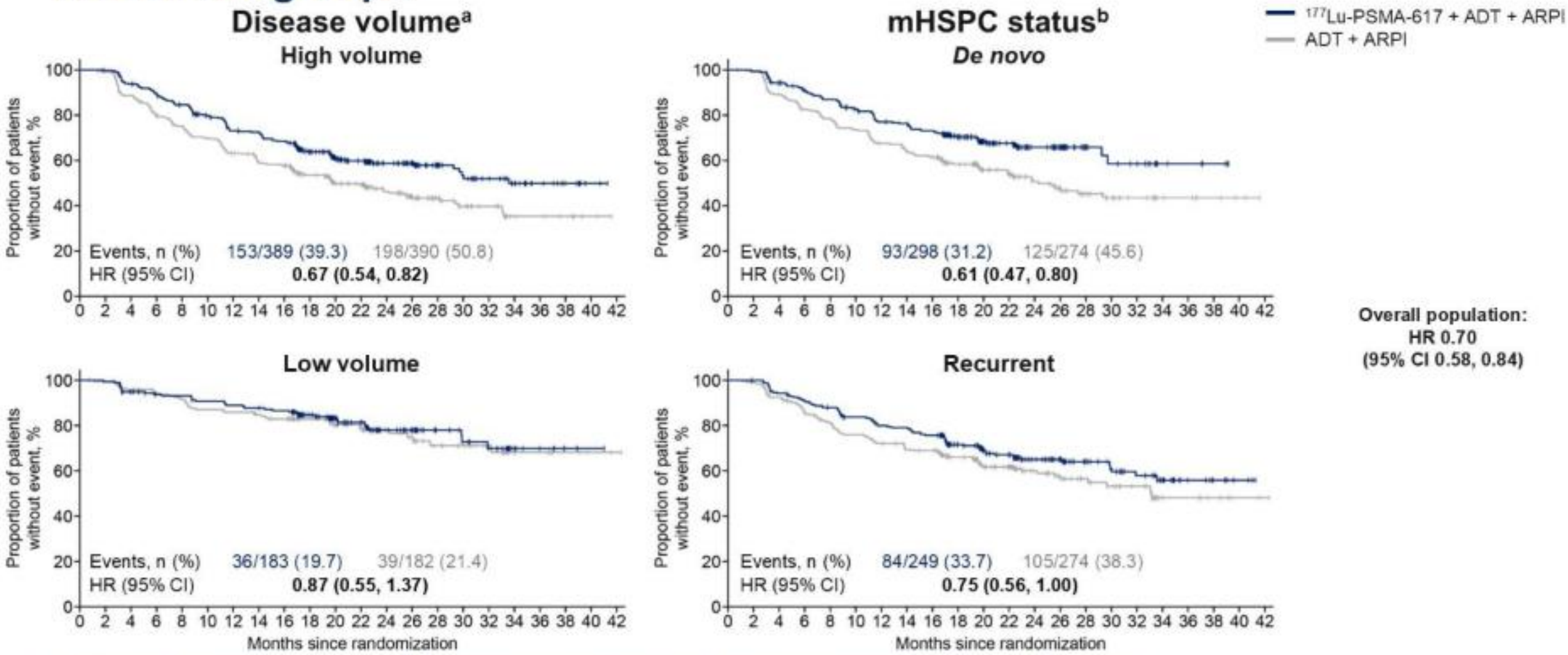


Overall population:
HR 0.42
(95% CI 0.30, 0.59)

[a]Per CHAARTED criteria using conventional imaging. [b]Subgroup not prespecified; *de novo*: stage IVB at initial diagnosis (*AJCC Cancer Staging Manual* 8th edition)
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; PSA, prostate-specific antigen; mHSPC, metastatic hormone-sensitive prostate cancer

Data cut-off: 13 January 2025

Consistent time to mCRPC benefit with ^{177}Lu-PSMA-617 across subgroups

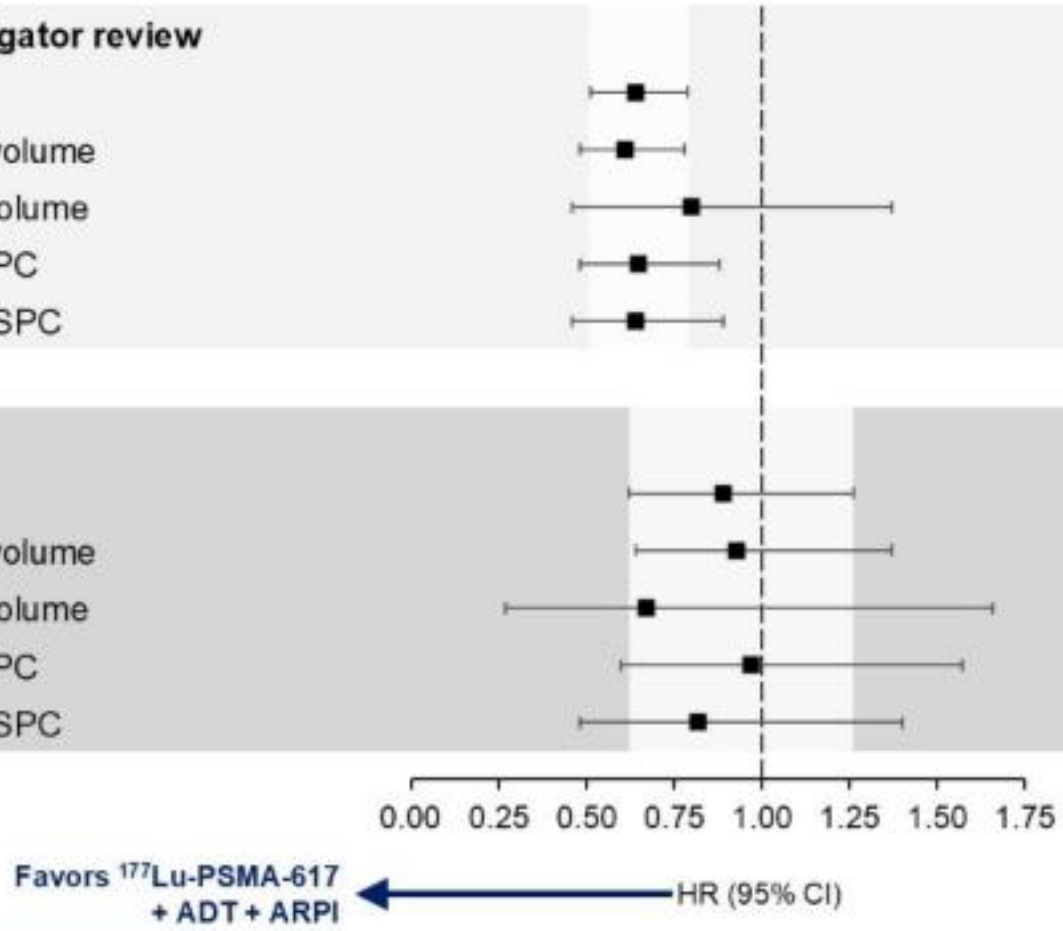


Overall population:
HR 0.70
(95% CI 0.58, 0.84)

[a]Per CHAARTED criteria using conventional imaging. [b]Subgroup not prespecified; *de novo*: stage IVB at initial diagnosis (*AJCC Cancer Staging Manual* 8th edition)
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer

Efficacy was generally consistent in all patients and subgroups

	HR (95% CI)[a]	Events, n/N (%)	
		^{177}Lu-PSMA-617 + ADT + ARPI	ADT + ARPI
PFS by investigator review			
All patients	0.64 (0.51, 0.79)	139/572 (24.3)	192/572 (33.6)
High disease volume	0.61 (0.48, 0.78)	115/389 (29.6)	163/390 (41.8)
Low disease volume	0.80 (0.46, 1.37)	24/183 (13.1)	29/182 (15.9)
De novo mHSPC	0.65 (0.48, 0.88)	74/298 (24.8)	98/274 (35.8)
Recurrent mHSPC	0.64 (0.46, 0.89)	61/249 (24.5)	89/274 (32.5)
Time to SSE			
All patients	0.89 (0.62, 1.26)	61/572 (10.7)	64/572 (11.2)
High disease volume	0.93 (0.64, 1.37)	53/389 (13.6)	53/390 (13.6)
Low disease volume	0.67 (0.27, 1.66)	8/183 (4.4)	11/182 (6.0)
De novo mHSPC	0.97 (0.60, 1.57)	34/298 (11.4)	32/274 (11.7)
Recurrent mHSPC	0.82 (0.48, 1.40)	25/249 (10.0)	31/274 (11.3)

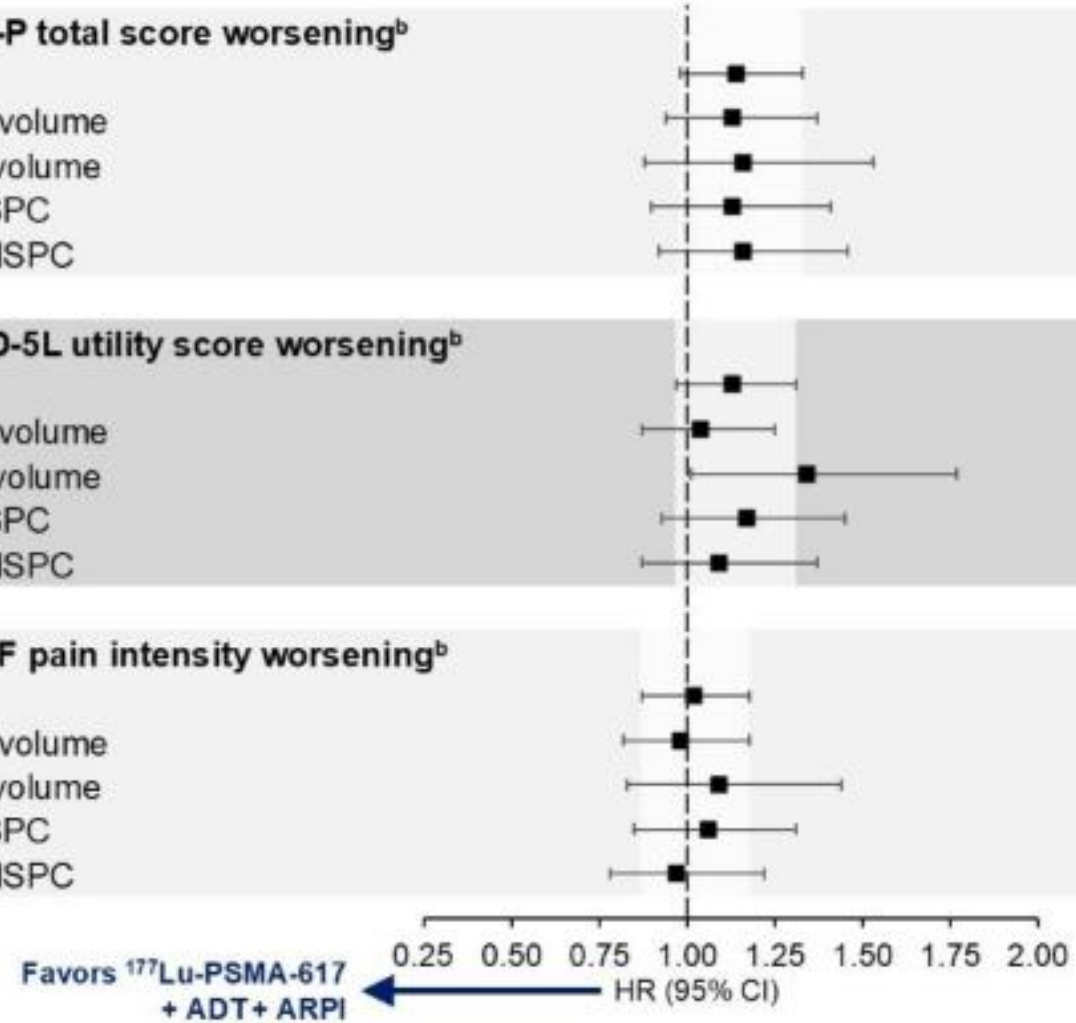


[a]Stratified Cox proportional hazards model

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer; PFS, progression-free survival; SSE, symptomatic skeletal event

Data cut-off: 13 January 2025

HRs for patient-reported outcomes were generally similar in all patients and subgroups

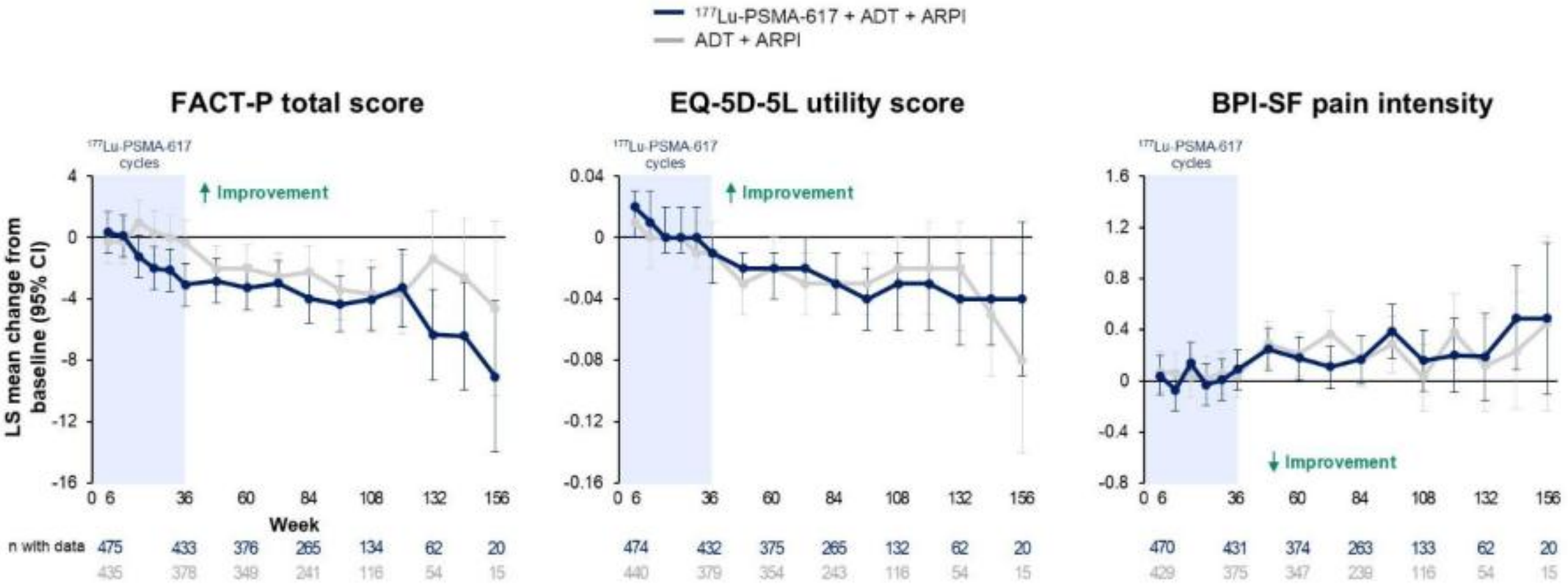


	HR (95% CI)[a]	Events, n/N (%)	
		^{177}Lu-PSMA-617 + ADT + ARPI	ADT + ARPI
Time to FACT-P total score worsening[b]			
All patients	1.14 (0.98, 1.33)	348/572 (60.8)	304/572 (53.1)
High disease volume	1.13 (0.94, 1.37)	237/389 (60.9)	209/390 (53.6)
Low disease volume	1.16 (0.88, 1.53)	111/183 (60.7)	95/182 (52.2)
De novo mHSPC	1.13 (0.90, 1.41)	180/298 (60.4)	144/274 (52.6)
Recurrent mHSPC	1.16 (0.92, 1.46)	155/249 (62.2)	149/274 (54.4)
Time to EQ-5D-5L utility score worsening[b]			
All patients	1.13 (0.97, 1.31)	353/572 (61.7)	312/572 (54.5)
High disease volume	1.04 (0.87, 1.25)	239/389 (61.4)	222/390 (56.9)
Low disease volume	1.34 (1.01, 1.77)	114/183 (62.3)	90/182 (49.5)
De novo mHSPC	1.17 (0.93, 1.45)	182/298 (61.1)	143/274 (52.2)
Recurrent mHSPC	1.09 (0.87, 1.37)	155/249 (62.2)	156/274 (56.9)
Time to BPI-SF pain intensity worsening[b]			
All patients	1.02 (0.87, 1.18)	339/572 (59.3)	326/572 (57.0)
High disease volume	0.98 (0.82, 1.18)	232/389 (59.6)	229/390 (58.7)
Low disease volume	1.09 (0.83, 1.44)	107/183 (58.5)	97/182 (53.3)
De novo mHSPC	1.06 (0.85, 1.31)	174/298 (58.4)	154/274 (56.2)
Recurrent mHSPC	0.97 (0.78, 1.22)	153/249 (61.4)	159/274 (58.0)

[a]Stratified Cox proportional hazards model. [b]Composite of time to worsening, clinical progression, or death. BPI-SF, Brief Pain Inventory-Short Form; FACT-P, Functional Assessment of Cancer Therapy – Prostate; mHSPC, metastatic hormone-sensitive prostate cancer

Data cut-off: 13 January 2025

Longitudinal assessment of change from baseline for patient-reported outcomes in the overall population[1]



LS means from linear mixed-effect model for change from baseline in score
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory-Short Form; FACT-P, Functional Assessment of Cancer Therapy – Prostate; mHSPC, metastatic hormone-sensitive prostate cancer

On-treatment AEs were similar across subgroups within each arm

	Disease volume[a]				mHSPC status[b,c]			
	^{177}Lu-PSMA-617 + ADT + ARPI		ADT + ARPI		^{177}Lu-PSMA-617 + ADT + ARPI		ADT + ARPI	
	High (n = 387)	Low (n = 177)	High (n = 385)	Low (n = 180)	*De novo* (n = 296)	Recurrent (n = 244)	*De novo* (n = 271)	Recurrent (n = 270)
Patients with AE – n (%)								
Any	381 (98.4)	174 (98.3)	373 (96.9)	173 (96.1)	291 (98.3)	240 (98.4)	263 (97.0)	259 (95.9)
Grade ≥3	202 (52.2)	84 (47.5)	173 (44.9)	70 (38.9)	145 (49.0)	129 (52.9)	125 (46.1)	108 (40.0)
Serious	129 (33.3)	51 (28.8)	117 (30.4)	45 (25.0)	94 (31.8)	80 (32.8)	80 (29.5)	72 (26.7)
Leading to ^{177}Lu-PSMA-617 discontinuation	34 (8.8)	11 (6.2)	NA	NA	20 (6.8)	23 (9.4)	NA	NA
Safety topics of interest (patients with AE in grouping)[d]								
Cytopenias	170 (43.9)	78 (44.1)	82 (21.3)	33 (18.3)	121 (40.9)	114 (46.7)	59 (21.8)	52 (19.3)
Dry mouth	170 (43.9)	92 (52.0)	16 (4.2)	6 (3.3)	127 (42.9)	124 (50.8)	9 (3.3)	13 (4.8)
Renal events	27 (7.0)	13 (7.3)	20 (5.2)	6 (3.3)	19 (6.4)	19 (7.8)	10 (3.7)	15 (5.6)
Second primary malignancies	25 (6.5)	12 (6.8)	20 (5.2)	11 (6.1)	16 (5.4)	20 (8.2)	13 (4.8)	15 (5.6)

Conclusions – PSMAddition (at interim analysis)

- Combining ^{177}Lu-PSMA-617 with ADT + ARPI provided a similar magnitude of rPFS benefit versus ADT + ARPI across high and low disease volume and *de novo* and recurrent mHSPC subgroups
- Other efficacy and patient-reported outcome HRs for the ^{177}Lu-PSMA-617 vs control arm for each disease volume and mHSPC status subgroup were generally similar across subgroups and to the overall population
- The safety profile was generally consistent across subgroups within each treatment arm, with similar incidences of AEs, grade ≥3 AEs, and selected safety topics of interest (cytopenias, dry mouth)

In patients with PSMA+ mHSPC, the efficacy, patient-reported outcomes, and safety profile of ^{177}Lu-PSMA-617 combined with ADT + ARPI were consistent across clinically relevant disease volume and mHSPC status subgroups

ADT, androgen deprivation therapy; AE, adverse event; ARPI, androgen receptor pathway inhibitor; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; rPFS, radiographic progression-free survival