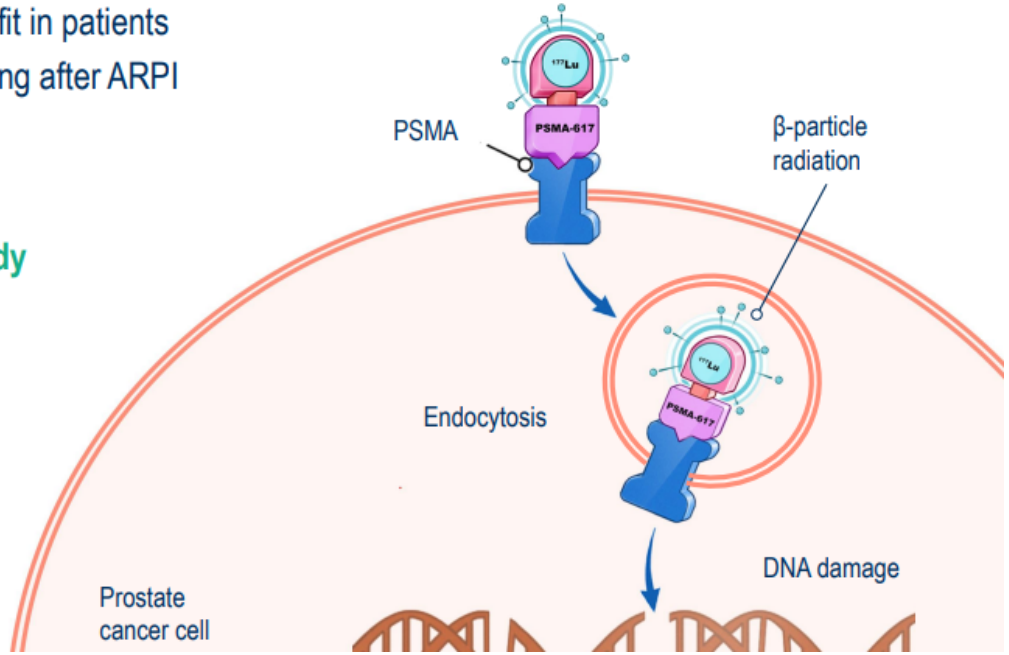
Phase 3 trial of [^{177}Lu]Lu-PSMA-617 combined with ADT + ARPI in patients with PSMA-positive metastatic hormone-sensitive prostate cancer (PSMAddition)

^{177}Lu-PSMA-617

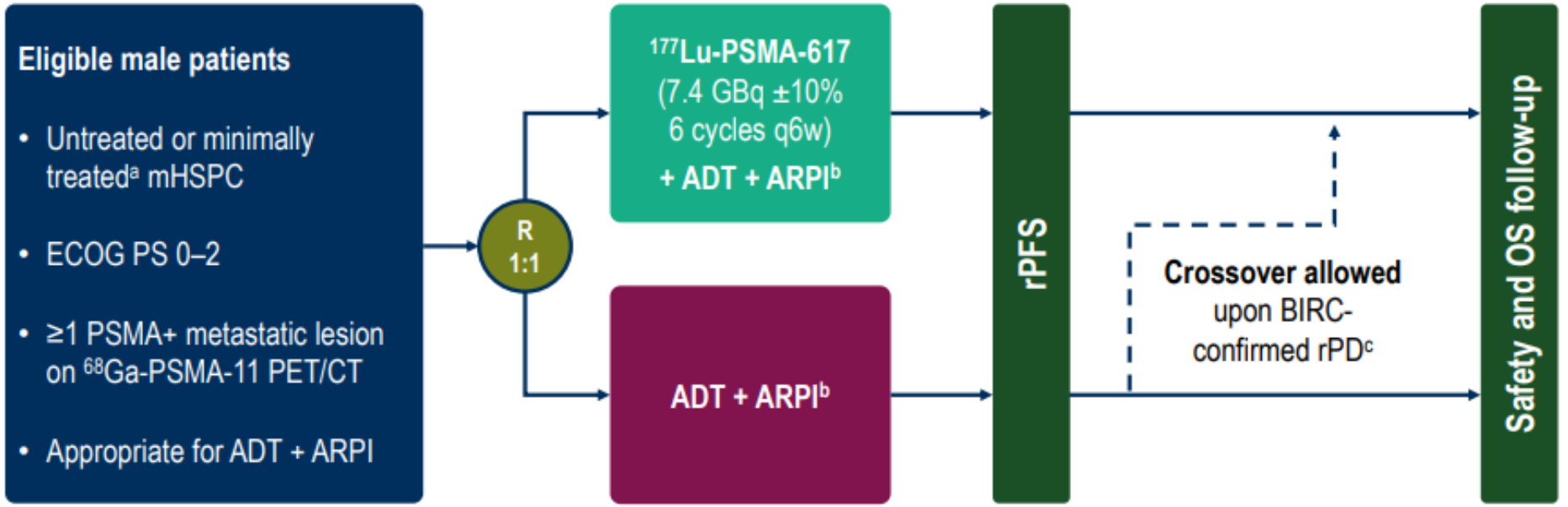
- [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a PSMA-targeted radioligand therapy
- ^{177}Lu-PSMA-617 provides clinical benefit in patients with PSMA-positive mCRPC progressing after ARPI
  - in the taxane-naive setting (PSMAfore)[1,a]
  - in the post-taxane setting (VISION)[2]
- **PSMAddition is the first phase 3 study of targeted radioligand therapy in patients with mHSPC**



[a] When appropriate to delay taxane

ARPI, androgen receptor pathway inhibitor
mCRPC, metastatic castration-resistant prostate cancer
mHSPC, metastatic hormone-sensitive prostate cancer
PSMA, prostate-specific membrane antigen

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



Stratification factors
- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

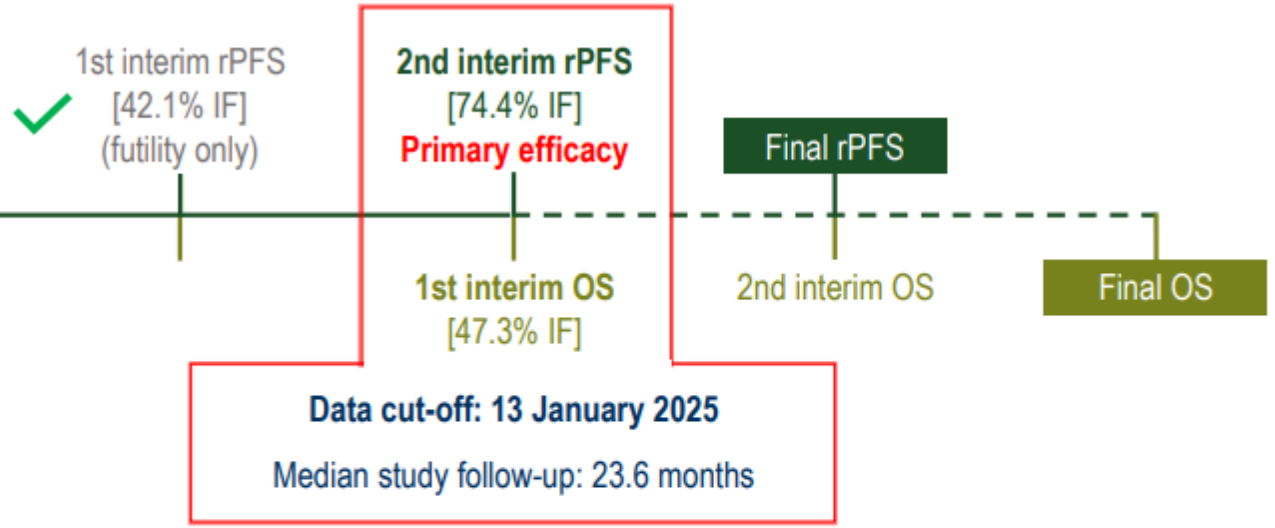
Follow-up periods
- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact

[a] ADT in the neo-/adjuvant setting and/or up to 45 days of ADT/ARPI for metastatic disease was allowed before study entry | [b] Any ARPI with one switch allowed | [c] ADT/ARPI not mandatory after crossover
ADT, androgen deprivation therapy; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival;

Endpoints and analysis plan

PRIMARY ENDPOINT
rPFS
BIRC per PCWG3/RECIST v1.1[a]

KEY SECONDARY ENDPOINT
OS
Intent-to-treat analysis

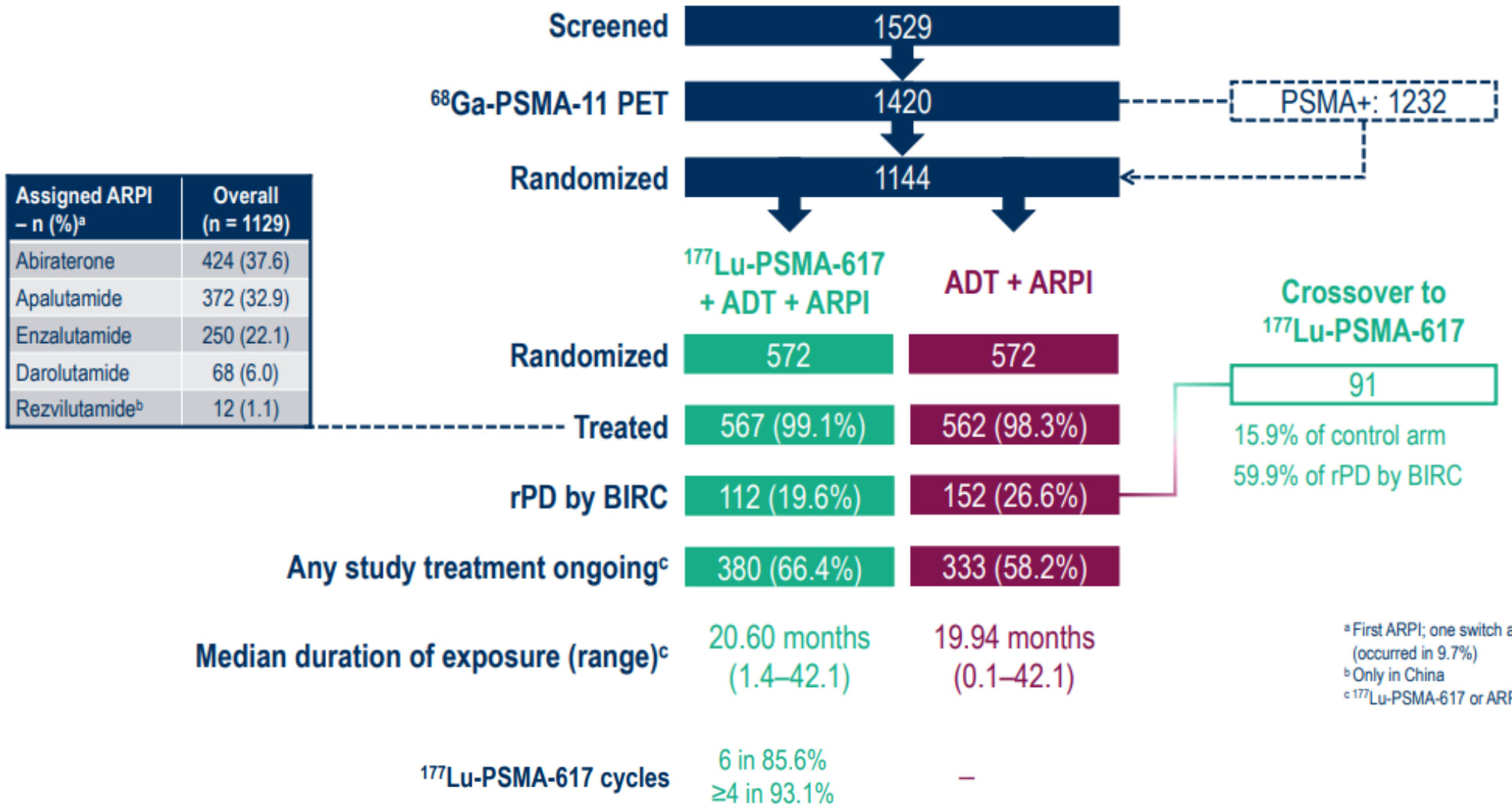


OTHER SECONDARY ENDPOINTS

- PSA90 response rate
- Time to mCRPC
- PFS and PFS2
- PSA <0.2 ng/mL at 12, 24 and 48 weeks
- ORR, DCR, TTR, DOR and TTSTP by BIRC per RECIST v1.1[a]
- Safety and tolerability
- Time to worsening in patient-reported HRQoL and pain
- Time to first SSE

- Overall alpha = 0.025 (one-sided)
- Alpha spending (three-look) and hierarchical testing
- Stratified Cox proportional-hazards model
- Significance threshold for rPFS at 2nd interim analysis: HR ≤ 0.765

Patient disposition (at time of data cut-off)



Assigned ARPI – n (%)[a]	Overall (n = 1129)
Abiraterone	424 (37.6)
Apalutamide	372 (32.9)
Enzalutamide	250 (22.1)
Darolutamide	68 (6.0)
Rezvilutamide[b]	12 (1.1)

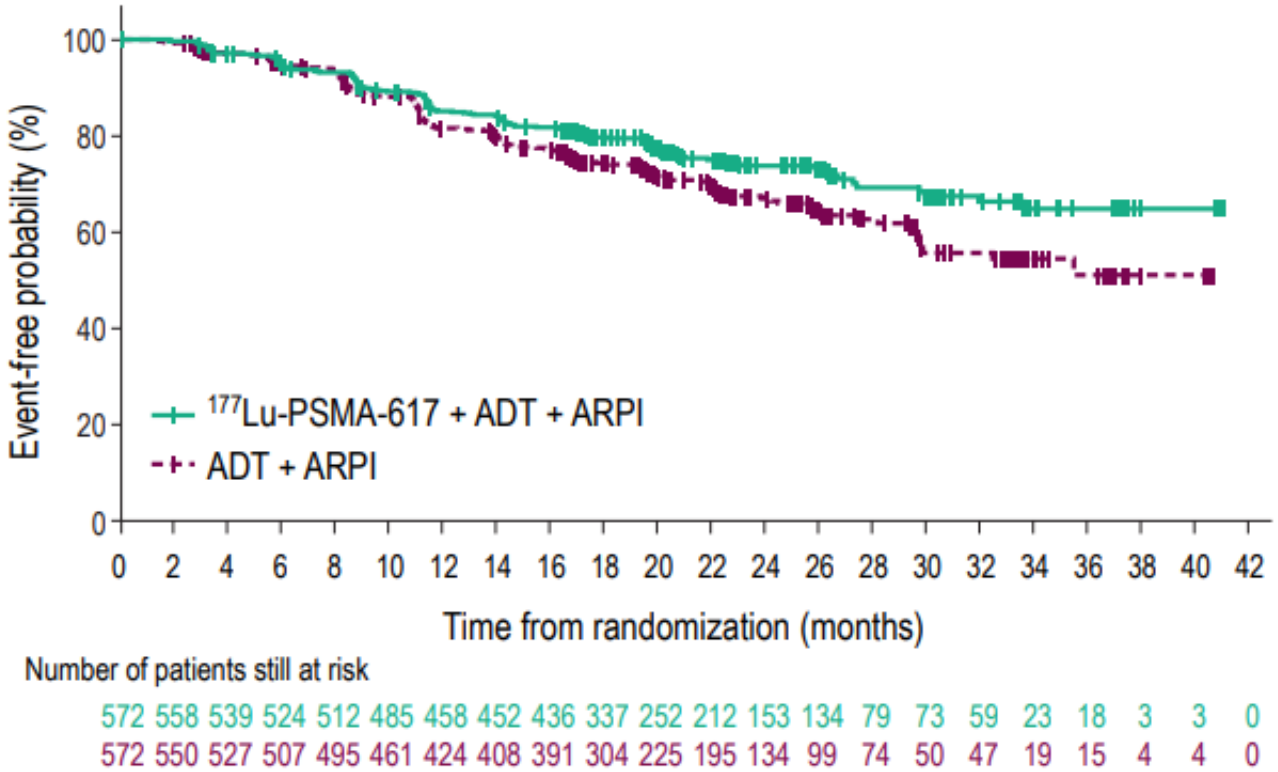
[a] First ARPI; one switch allowed (occurred in 9.7%)
[b] Only in China
[c] 177Lu-PSMA-617 or ARPI

Baseline characteristics were balanced between arms

	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)	Overall (N = 1144)
Age, years – median (range)	68.0 (38–91)	68.0 (36–90)	68.0 (36–91)
≥70 years – n (%)	246 (43.0)	246 (43.0)	492 (43.0)
ECOG performance status – n (%)			
0	397 (69.4)	407 (71.2)	804 (70.3)
1	174 (30.4)	155 (27.1)	329 (28.8)
2	1 (0.2)	7 (1.2)	8 (0.7)
Site of disease – n (%)			
Soft tissue	342 (59.8)	338 (59.1)	680 (59.4)
Bone	522 (91.3)	521 (91.1)	1043 (91.2)
Visceral	225 (39.3)	238 (41.6)	463 (40.5)
PSA level, ng/mL – median (interquartile range)	12.06 (3.16–53.24)	11.64 (2.83–44.15)	11.91 (3.01–50.34)
Gleason score 8–10 (grade group 4–5) – n (%)	389 (68.0)	406 (71.0)	795 (69.5)
High tumour volume[a] – n (%)	389 (68.0)	390 (68.2)	779 (68.1)
De novo mHSPC[b] – n (%)	298 (52.1)	274 (47.9)	572 (50.0)

Data cut-off: 13 January 2025

rPFS by BIRC – the primary endpoint was met

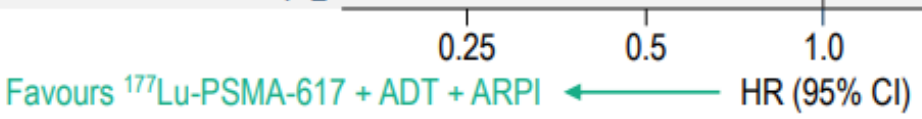


	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

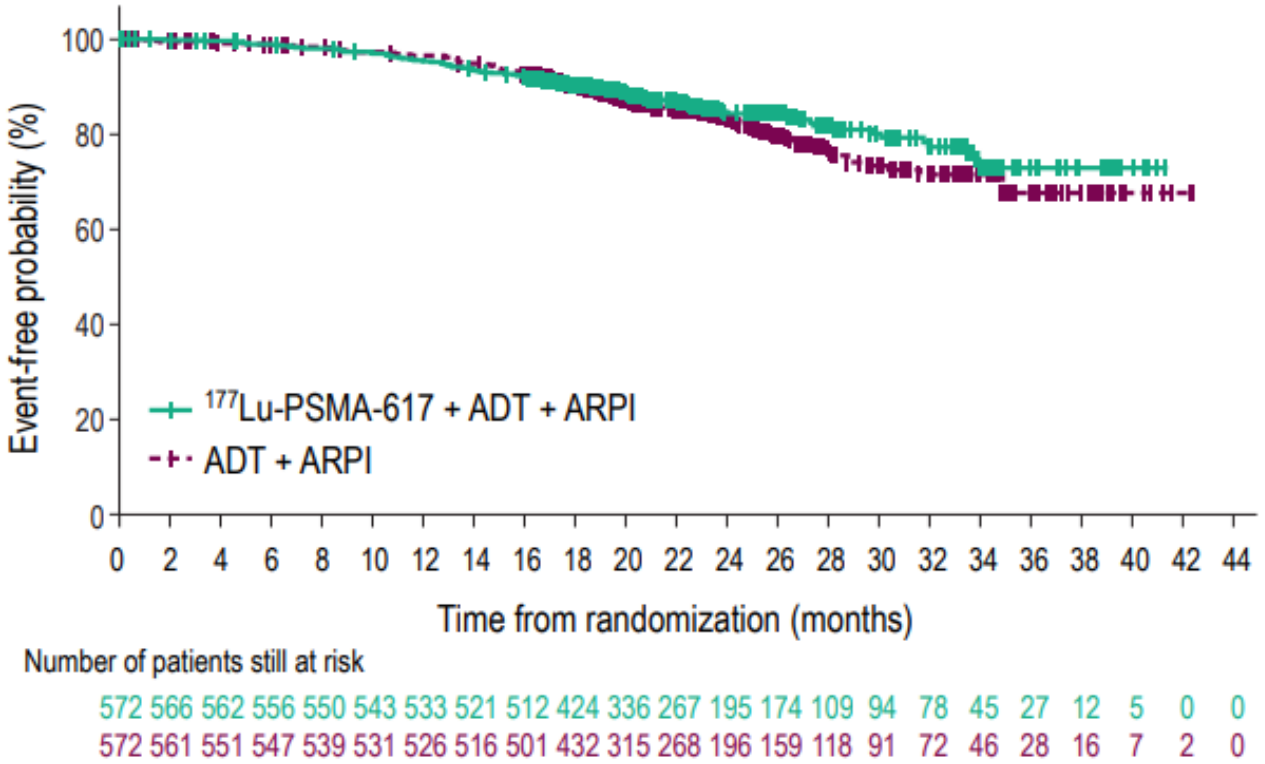
Data cut-off: 13 January 202

rPFS benefit was consistent across subgroups

		HR (95% CI)	Events, n/N (%)	
			^{177}Lu-PSMA-617 + ADT + ARPI	ADT + ARPI
All patients		0.72 (0.58, 0.90)	139/572 (24.3)	172/572 (30.1)
Tumour volume[a]	High	0.72 (0.56, 0.92)	116/389 (29.8)	144/390 (36.9)
	Low	0.73 (0.42, 1.27)	23/183 (12.6)	28/182 (15.4)
Age	< 70 years	0.68 (0.50, 0.92)	75/326 (23.0)	99/326 (30.4)
	≥ 70 years	0.78 (0.56, 1.10)	64/246 (26.0)	73/246 (29.7)
mHSPC[b]	De novo[c]	0.74 (0.54, 1.01)	74/298 (24.8)	89/274 (32.5)
	Recurrent	0.74 (0.53, 1.04)	60/249 (24.1)	77/274 (28.1)
Previous/planned treatment to primary tumour[d]	Yes	0.75 (0.46, 1.22)	31/156 (19.9)	35/155 (22.6)
	No	0.71 (0.55, 0.92)	108/416 (26.0)	137/417 (32.9)
Initial Gleason score	< 8	0.54 (0.33, 0.88)	29/152 (19.1)	39/134 (29.1)
	≥ 8	0.76 (0.58, 0.99)	99/389 (25.4)	122/406 (30.0)
Baseline LDH level	≤ 260 IU/L	0.69 (0.53, 0.89)	104/471 (22.1)	143/489 (29.2)
	> 260 IU/L	0.61 (0.30, 1.26)	20/37 (54.1)	18/33 (54.5)
Baseline PSA level	< Median	0.85 (0.62, 1.16)	73/279 (26.2)	83/287 (28.9)
	≥ Median	0.60 (0.44, 0.83)	63/284 (22.2)	89/283 (31.4)
ECOG performance status	0	0.78 (0.59, 1.03)	92/397 (23.2)	107/407 (26.3)
	1–2	0.63 (0.43, 0.92)	47/175 (26.9)	64/162 (39.5)



Interim OS (prespecified intent-to-treat analysis – follow-up continues)



	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)	85 (14.9)	99 (17.3)
Censored – n (%)	487 (85.1)	473 (82.7)
HR (95% CI)	0.84 (0.63, 1.13)	
p value	0.125[a]	
Median OS (95% CI) – months	NR (NE, NE)	NR (NE, NE)

Selected other secondary efficacy endpoints

	^{177}Lu-PSMA-617 + ADT + ARPI (n = 224)	ADT + ARPI (n = 213)
Best response per RECIST v1.1[a]		
ORR – % (95% CI)	85.3 (79.9, 89.6)	80.8 (74.8, 85.8)
Complete response – %	57.1	42.3

	^{177}Lu-PSMA-617 + ADT + ARPI (n = 572)	ADT + ARPI (n = 572)
Time to PSA progression		
Median (95% CI) – months	NR (NE, NE)	NR (NE, NE)
HR (95% CI)	0.42 (0.30, 0.59)	
PSA nadir < 0.2 ng/mL at 48 weeks		
% (95% CI)	87.4 (83.6, 90.6)	74.9 (70.3, 79.1)

	^{177}Lu-PSMA-617 + ADT + ARPI (n = 572)	ADT + ARPI (n = 572)
Time to symptomatic skeletal event		
Median (95% CI) – months	NR (NE, NE)	NR (NE, NE)
HR (95% CI)	0.89 (0.62, 1.26)	
Time to mCRPC		
Median (95% CI) – months	NR (33.58, NE)	29.63 (25.30, NE)
HR (95% CI)	0.70 (0.58, 0.84)	
PFS per investigator assessment		
Median (95% CI) – months	NR (NE, NE)	NR (29.63, NE)
HR (95% CI)	0.64 (0.51, 0.79)	

Overall incidence of adverse events

Patients with on-treatment AE – n (%)[a]	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	555 (98.4)	286 (50.7)	546 (96.6)	243 (43.0)
Related to any study treatment	504 (89.4)	128 (22.7)	394 (69.7)	69 (12.2)
^{177}Lu-PSMA-617-related	441 (78.2)	78 (13.8)	–	–
ADT and/or ARPI-related	418 (74.1)	81 (14.4)	394 (69.7)	69 (12.2)
Serious	180 (31.9)	150 (26.6)	162 (28.7)	129 (22.8)
Related to any study treatment	39 (6.9)	31 (5.5)	14 (2.5)	12 (2.1)
^{177}Lu-PSMA-617-related	17 (3.0)	13 (2.3)	–	–
ADT and/or ARPI-related	27 (4.8)	22 (3.9)	14 (2.5)	12 (2.1)
Leading to death	15 (2.7)	15 (2.7)	14 (2.5)	14 (2.5)
Treatment-related	0	0	0	0
Leading to discontinuation of any study treatment	91 (16.1)	46 (8.2)	51 (9.0)	23 (4.1)
Leading to ^{177}Lu-PSMA -617…				
Discontinuation	45 (8.0)	28 (5.0)	–	–
Dose reduction	22 (3.9)	13 (2.3)	–	–
Dose delay	68 (12.1)	27 (4.8)	–	–

Safety findings were consistent with known profiles

AEs in ≥10% of patients in the ^{177}Lu-PSMA-617 arm – n (%)	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Dry mouth[a]	258 (45.7)	0	21 (3.7)	0
Fatigue	196 (34.8)	6 (1.1)	158 (28.0)	6 (1.1)
Nausea	193 (34.2)	1 (0.2)	53 (9.4)	0
Hot flush	164 (29.1)	0	205 (36.3)	0
Anaemia	153 (27.1)	28 (5.0)	75 (13.3)	15 (2.7)
Arthralgia	111 (19.7)	5 (0.9)	130 (23.0)	9 (1.6)
Back pain	101 (17.9)	8 (1.4)	110 (19.5)	16 (2.8)
Constipation	101 (17.9)	0	91 (16.1)	0
Asthenia	92 (16.3)	2 (0.4)	73 (12.9)	5 (0.9)
Decreased appetite	81 (14.4)	5 (0.9)	37 (6.5)	1 (0.2)
Vomiting	78 (13.8)	4 (0.7)	21 (3.7)	0
COVID-19	76 (13.5)	5 (0.9)	60 (10.6)	2 (0.4)
Hypertension	76 (13.5)	34 (6.0)	95 (16.8)	35 (6.2)
Diarrhoea	69 (12.2)	1 (0.2)	56 (9.9)	0
Headache	69 (12.2)	0	51 (9.0)	2 (0.4)
Alanine aminotransferase increased	68 (12.1)	19 (3.4)	73 (12.9)	14 (2.5)
Dysgeusia	67 (11.9)	0	23 (4.1)	0
White blood cell count decreased	63 (11.2)	12 (2.1)	18 (3.2)	3 (0.5)
Aspartate aminotransferase increased	61 (10.8)	10 (1.8)	65 (11.5)	11 (1.9)
Lymphocyte count decreased	60 (10.6)	28 (5.0)	21 (3.7)	7 (1.2)

[a] Grade 1 in 231 (41.0%) and grade 2 in 27 (4.8%) in the ^{177}Lu-PSMA-617 + ADT + ARPI arm; grade 1 in 19 (3.4) and grade 2 in 2 (0.4%) in the ADT + ARPI arm

Data cut-off: 13 Janua

AEs grouped by safety topics of interest

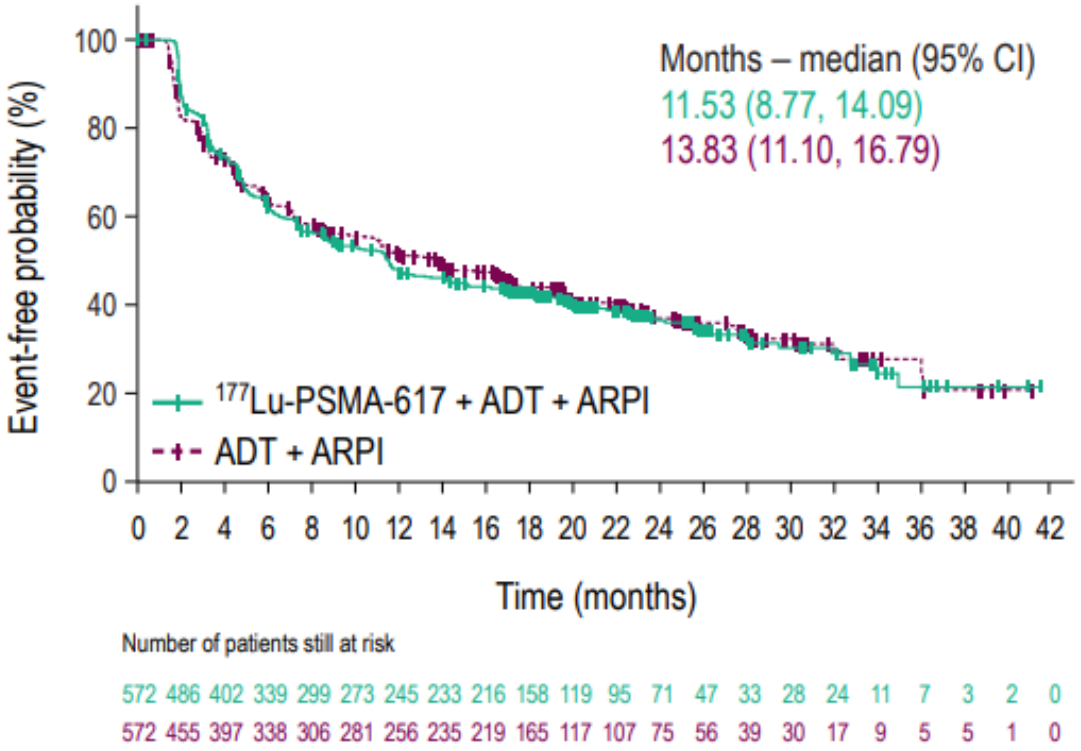
Patients with AE in grouping – n (%)	^{177}Lu-PSMA-617 + ADT + ARPI (N = 564)		ADT + ARPI (N = 565)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Dry mouth[a]	262 (46.5)	0	22 (3.9)	0
Cytopenias	248 (44.0)	81 (14.4)	115 (20.4)	28 (5.0)
Anaemia[b]	158 (28.0)	28 (5.0)	79 (14.0)	16 (2.8)
Neutropenia[c]	83 (14.7)	21 (3.7)	24 (4.2)	5 (0.9)
Thrombocytopenia[d]	63 (11.2)	10 (1.8)	19 (3.4)	3 (0.5)
Fractures	52 (9.2)	16 (2.8)	43 (7.6)	15 (2.7)
Renal events[e]	40 (7.1)	9 (1.6)	26 (4.6)	5 (0.9)
Second primary malignancies	37 (6.6)	24 (4.3)	31 (5.5)	14 (2.5)
Dry eye	33 (5.9)	0	3 (0.5)	0
Intracranial haemorrhage	6 (1.1)	4 (0.7)	4 (0.7)	2 (0.4)

Data cut-off: 13 January 2025

Time to worsening in patient-reported HRQoL and pain

BPI-SF pain intensity[a]

HR: 1.02 (95% CI: 0.87, 1.18)

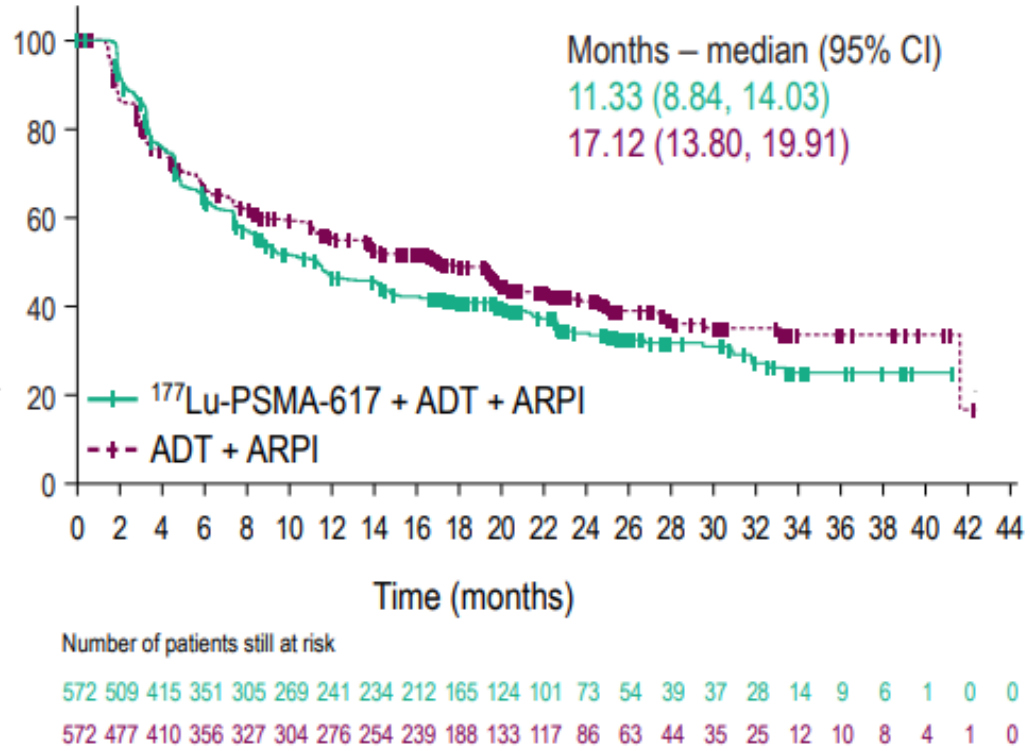


Number of patients still at risk

572	486	402	339	299	273	245	233	216	158	119	95	71	47	33	28	24	11	7	3	2	0
572	455	397	338	306	281	256	235	219	165	117	107	75	56	39	30	17	9	5	5	1	0

FACT-P total score[a]

HR: 1.14 (95% CI: 0.98, 1.33)



Number of patients still at risk

572	509	415	351	305	269	241	234	212	165	124	101	73	54	39	37	28	14	9	6	1	0	0
572	477	410	356	327	304	276	254	239	188	133	117	86	63	44	35	25	12	10	8	4	1	0

Data cut-off: 13 January 2025

PSMAddition conclusions at rPFS IA2 / OS IA1

- **Combining ^{177}Lu-PSMA-617 with ADT + ARPI led to statistically significant improvement in rPFS in patients with PSMA-positive mHSPC, versus ADT + ARPI**
  - rPFS benefit was consistent across subgroups
  - There was a positive trend in OS; follow-up for mature data is ongoing
  - PSA, PFS, mCRPC and SSE results favoured the ^{177}Lu-PSMA-617 combination arm
- **Safety findings were consistent with the known profile of ^{177}Lu-PSMA-617, with no unexpected concerns about combination with ADT+ARPI**
  - AEs were more frequent in the ^{177}Lu-PSMA-617 combination arm, most commonly dry mouth, fatigue and nausea
- **There were no clinically significant differences in time to worsening in HRQoL and pain**

These findings indicate that combining ^{177}Lu-PSMA-617 with ADT + ARPI provides clinically meaningful benefit in patients with PSMA-positive mHSPC

Thank you!