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Participants

Shreeram Aradhye, MD

President, Development &
Chief Medical Officer

Jeff Legos, PhD

EVP, Global Head of Oncology
Development

Agenda

1 ***Pluvicto* potential across prostate cancer stages**

2 *Pluvicto* PSMAfore results

3 Q&A

Prostate cancer is the second most common cancer in men worldwide

1.4 million
Prostate cancer cases worldwide per year

30%
5-year survival prognosis for mCRPC patients

+4 months
median OS benefit from current SoC seen in VISION study

SoC
heavily reliant on hormonal therapies (castration)

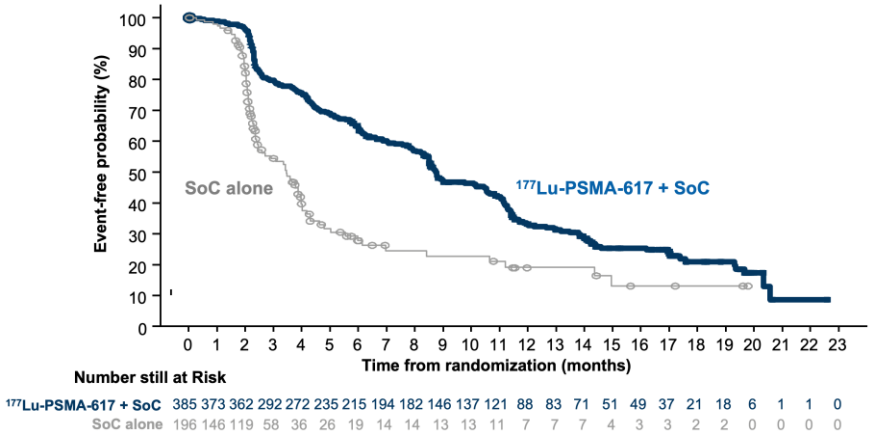
>375k
Prostate cancer deaths per year WW

Source: Wang L. Et all, Front. Public Health, 16 February 2022 (Frontiers | Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019 (frontiersin.org))

Ph3 VISION study: *Pluvicto* met both primary endpoints of rPFS and OS in the mCRPC post-taxane setting, as published in NEJM[1]

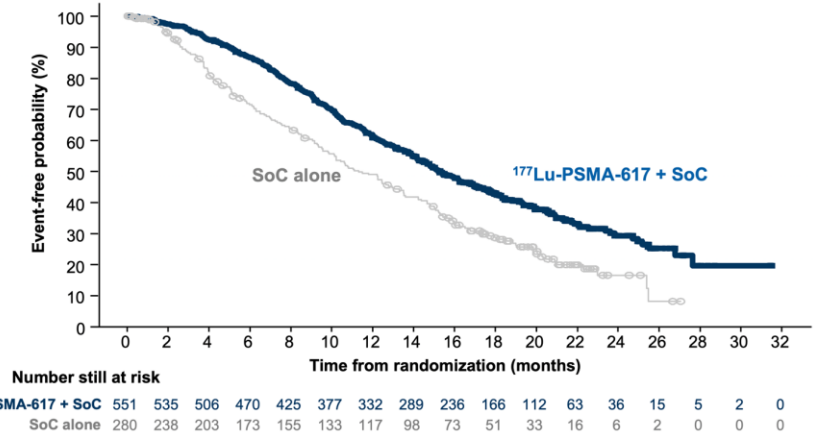
Reduced risk of progression or death by 60%

rPFS HR: **0.40** (99.2% CI: 0.29, 0.57), p<0.001 (one-sided)
Median rPFS, months: **8.7** vs. **3.4**



Reduced risk of death by 38%

OS HR: **0.62** (95% CI: 0.52, 0.74), p<0.001 (one-sided)
Median OS, months: **15.3** vs. **11.3**



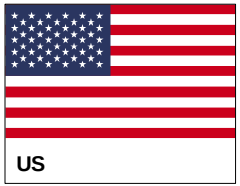
1. Sartor, N Engl J Med 2021;385:1091-103

Pluvicto approved in 37 countries including US and EU; RoW submissions ongoing

FDA indication statement

PLUVICTO is a radioligand therapeutic agent indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

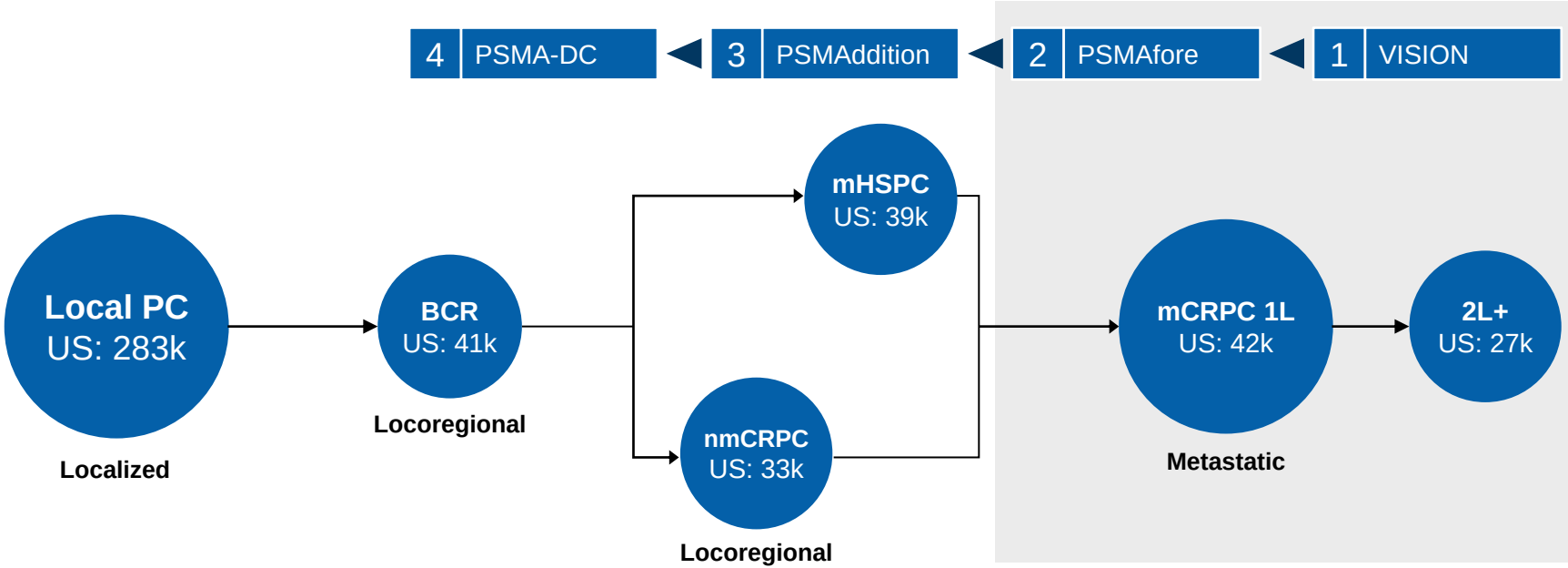
More than 7,400 patients treated across 37 countries[1]



Other selected countries

1. In commercial setting

Ambition to transform advanced prostate cancer across four main segments with *Pluvicto* studies



Source: Cerner Enviza 2023 US Prostate Cancer Incidence PC = prostate cancer BCR = biochemical recurrence nmCRPC = non-metastatic castration-resistant prostate cancer mHSPC = metastatic hormone-sensitive prostate cancer mCRPC = metastatic castration-resistant prostate cancer

PSMAfore met primary endpoint[1] with clinically meaningful and highly statistically significant rPFS benefit in pre-taxane setting

1

***Pluvicto* demonstrated robust efficacy...**

- ☑ More than doubled median rPFS[2]
- ☑ Consistent benefit across subgroups[2]
- ☑ Improved QoL compared to daily oral ARPI[2]
- ☑ Pre-specified crossover-adjusted OS analysis HR 0.80[2]

2

... with a favorable safety profile

- ☑ Lower rate of Grade ≥3 AEs compared to daily oral ARPI
- ☑ Low rate of AE-driven discontinuations
- ☑ Fewer patients required dose adjustment
- ☑ Even better tolerability than in VISION

1. Primary rPFS analysis based on centrally confirmed rPFS events with Oct. 2022 data cutoff. 2. Updated rPFS analysis (at time of 2nd interim OS analysis) based on Jun. 2023 data cutoff.

Agenda

1 *Pluvicto* potential across prostate cancer stages

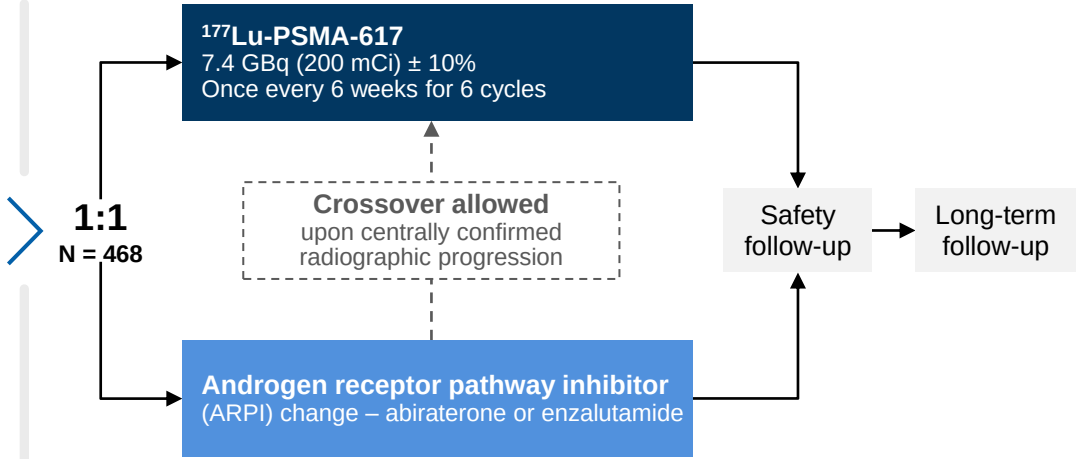
2 ***Pluvicto* PSMAfore results**

3 Q&A

PSMAfore study design

Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on ^{68}Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- **Progressed once on prior second-generation ARPI**
  - Candidates for change in ARPI
- **Taxane-naive (except [neo]adjuvant > 12 months ago)**
  - Not candidates for PARP inhibition
- ECOG performance status 0–1



Randomization stratification factors

Prior ARPI setting (castration-resistant vs. hormone-sensitive prostate cancer)

BPI-SF worst pain intensity score (0–3 vs. >3)

PSMAfore was specifically designed to address key unmet needs in mCRPC

	Insights	PSMAfore trial design
Dosing regimen	Low kidney uptake enables 6 cycles of *Pluvicto* at 7.4 GBq, already proven in the sicker post-taxane setting	Maintain dosing regimen for pre-taxane population to optimize radiation delivery
Choice of comparator	Many patients unwilling or ineligible to take taxane-based chemotherapy, due to debilitating side effects	Compare to change in ARPI, to potentially allow patients to reduce, eliminate or delay chemo
Crossover design	Strong results in VISION increased risk of dropout in PSMAfore control arm	Study allowed patients on control arm to receive *Pluvicto* after centrally confirmed radiographic progression **Pre-specified primary OS analysis adjusted for crossover because of this confounding factor**

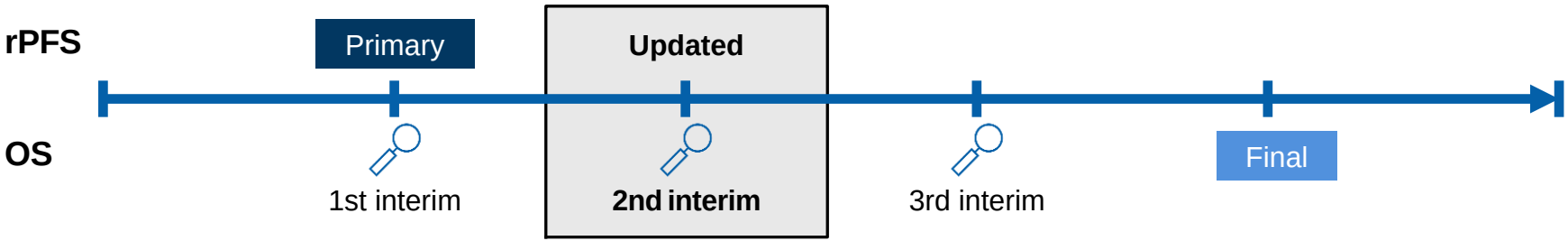
PSMAfore analysis plan

PRIMARY ENDPOINT

rPFS
BICR per PCWG3/
RECIST v1.1

KEY SECONDARY ENDPOINT

OS
prespecified for RPSFT
crossover-adjusted analysis



Other secondary endpoints

- rPFS2
- PFS, PFS2
- PSA50
- Time to SSE
- Time to soft tissue progression
- Time to chemotherapy
- HRQoL
- Safety and tolerability

Exploratory endpoints

- ORR, DCR, DOR
- Time to PSA progression
- Time to pain progression
- Biomarker associations

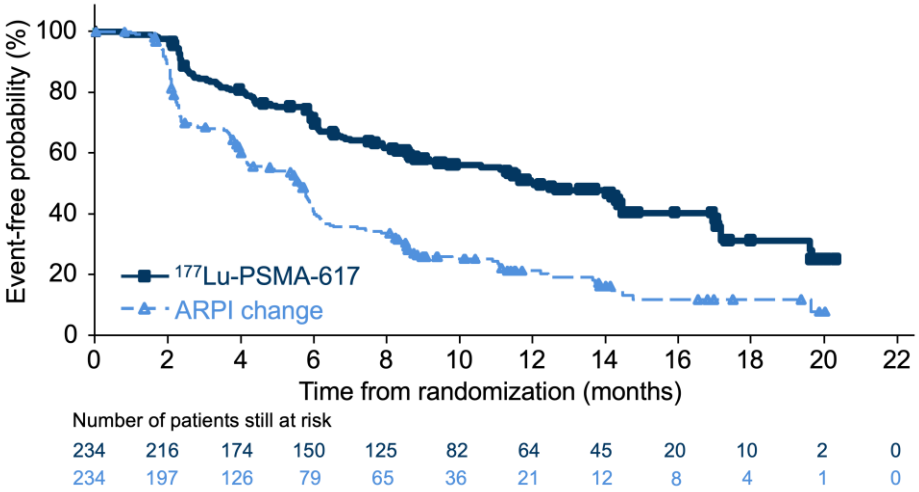
Baseline patient characteristics similar between the two arms and representative of intended population

		^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Age, years, median (range)		71 (43–94)	72 (53–91)
White, n (%)		211 (90.2)	214 (91.5)
ECOG performance status n (%)	0	146 (62.4)	115 (49.1)
	1	86 (36.8)	114 (48.7)
Gleason score 8–10, n (%)		136 (58.1)	107 (45.7)
PSA, median (range), µg/L		18.4 (0–1197)	14.9 (0–4224)
Haemoglobin, median (range), g/L		128.0 (88–155)	129.0 (88–156)
Alkaline phosphatase, median (range), U/L		100.0 (36–1727)	103.5 (28–1319)
Lactate dehydrogenase, median (range), U/L		197.0 (66–1314)	196.5 (124–999)
Site of disease n (%)	Liver	13 (5.6)	7 (3.0)
	Lymph node	76 (32.5)	74 (31.6)
	Bone	205 (87.6)	203 (86.8)
Prior ARPI n (%)	Abiraterone	119 (50.9)	130 (55.6)
	Enzalutamide	94 (40.2)	84 (35.9)
	Other	21 (9.0)	20 (8.5)

Pluvicto showed a clinically meaningful and highly statistically significant rPFS benefit in taxane-naive patients with PSMA+ mCRPC

Primary[1] HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Updated[2] HR: 0.43 (95% CI: 0.33, 0.54); p < 0.0001 (nominal)



	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.0 months (9.3, 14.4)	5.6 months (4.2, 6.0)

1. Primary rPFS analysis based on centrally confirmed rPFS events with Oct. 2022 data cutoff. 2. Updated rPFS analysis (at time of 2nd interim OS analysis) based on Jun. 2023 data cutoff.

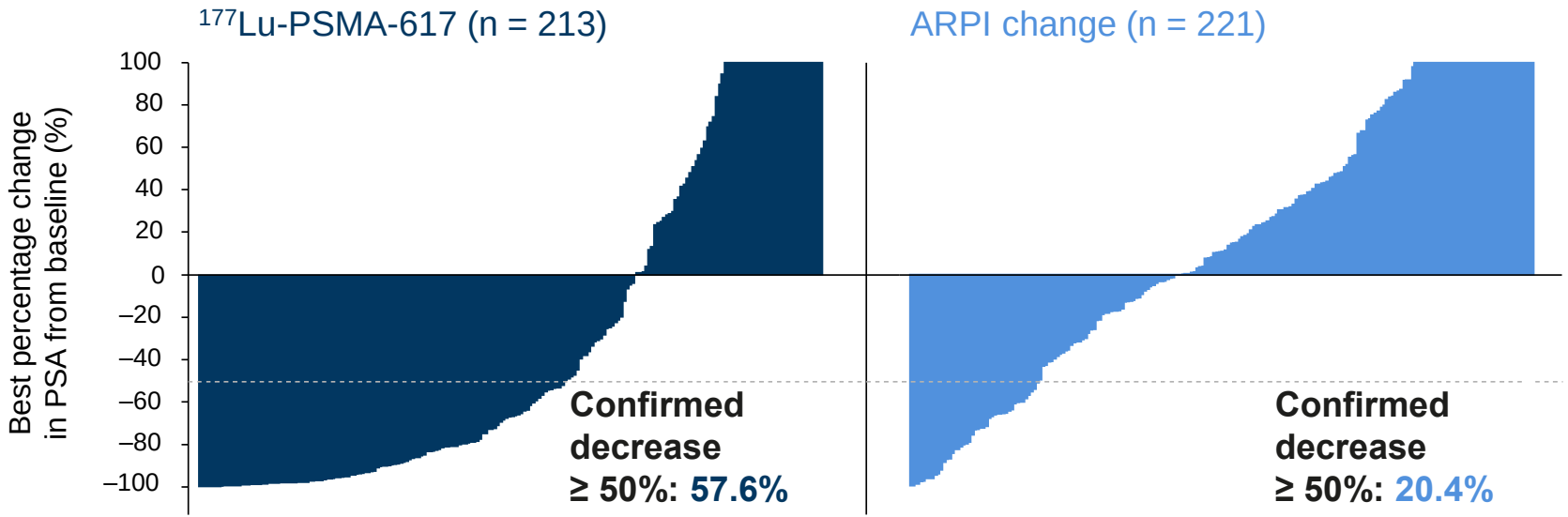
Benefit[1] was consistent across pre-specified subgroups[2]

		HR	95% CI
All patients		0.43	0.33, 0.54
Previous ARPI setting	☑ CRPC	0.40	0.30, 0.52
	☑ HSPC	0.57	0.33, 0.98
Symptomatology	☑ Asymptomatic or mildly symptomatic	0.40	0.30, 0.53
	☑ Symptomatic	0.51	0.32, 0.79
Liver metastases at baseline	☑ Yes	0.42	0.11, 1.61
	☑ No	0.43	0.33, 0.55
Baseline PSA level	☑ < median	0.42	0.29, 0.60
	☑ ≥ median	0.40	0.29, 0.56
Initial Gleason score	☑ < 6	0.55	0.10, 3.09
	☑ ≥ 6	0.42	0.32, 0.54
Baseline LDH level	☑ ≤ 260 IU/L	0.41	0.31, 0.54
	☑ > 260 IU/L	0.53	0.27, 1.07
Previous ARPI	☑ Abiraterone	0.47	0.33, 0.66
	☑ Enzalutamide	0.35	0.24, 0.52

1. rPFS per BIRC HR for *Pluvicto* vs. ARPI change 2. Subgroups with <10 patients in both arms include liver mets at baseline (yes) and initial Gleason score < 6

PSA50 response was >2.5X more frequent with *Pluvicto* than with ARPI change among evaluable patients

Waterfall plots of best percentage change from baseline in PSA

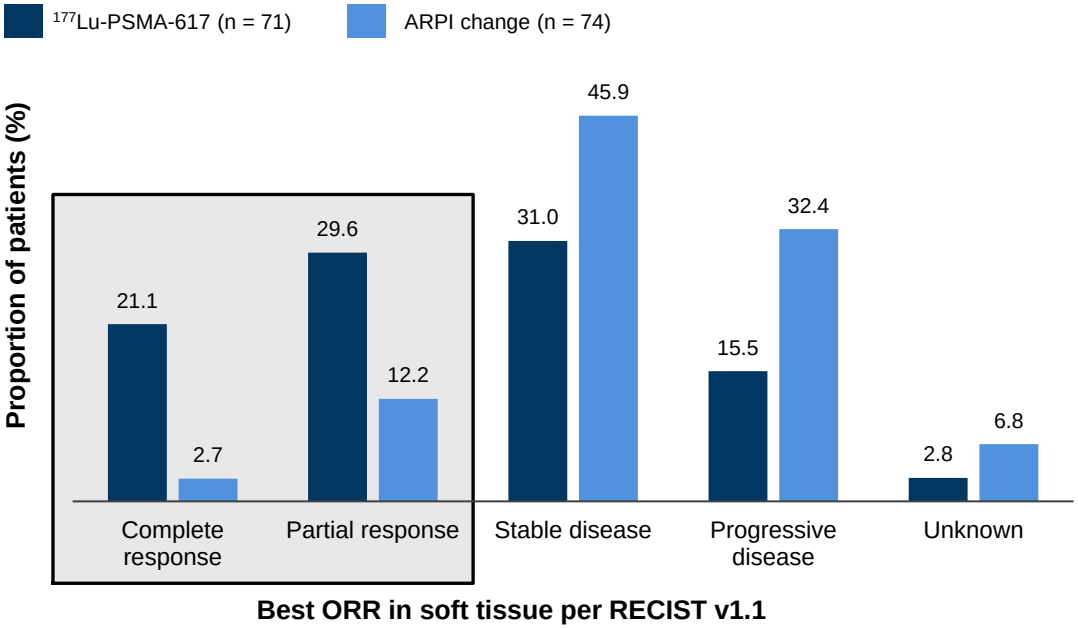


Pluvicto halved the number of symptomatic skeletal events (SSE)[1] and prolonged time without SSE vs. ARPI change

	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Number of events, n (%)	25 (10.7)	59 (25.2)
SSE	21 (9.0)	54 (23.1)
Death	4 (1.7)	5 (2.1)
Median time to SSE, months (95% CI)	NE (NE, NE)	NE (15.6, NE)
HR (95% CI)	**0.35 (0.22, 0.57)**	

1. SSE defined as the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause

Objective response rate (ORR) was higher and duration of response (DOR) was longer with *Pluvicto* versus ARPI change[1]



ORR in soft tissue:

50.7% vs. **14.9%**[2]

Median DOR in soft tissue[3], months:

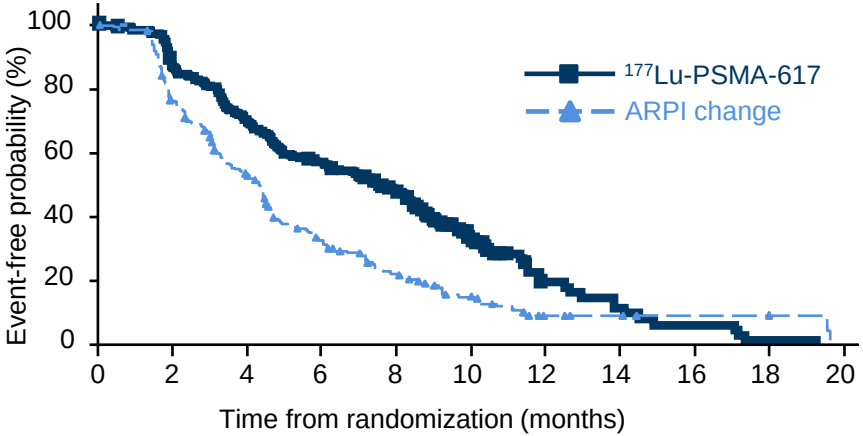
13.6 vs. **10.1**[4]

1. Among patients with measurable disease at baseline. 2. 95% CI: 50.7% (38.6, 62.8) vs. 14.9% (7.7, 25.0) 3. In patients with complete response or partial response 4. 95% CI: 13.6 (11.6, NE), n = 36 vs. 10.0 (4.6, NE), n = 11

Patients on *Pluvicto* demonstrated improved quality of life compared to daily oral ARPI

FACT-P total score[1]

HR: **0.59** (95% CI: 0.47, 0.72)

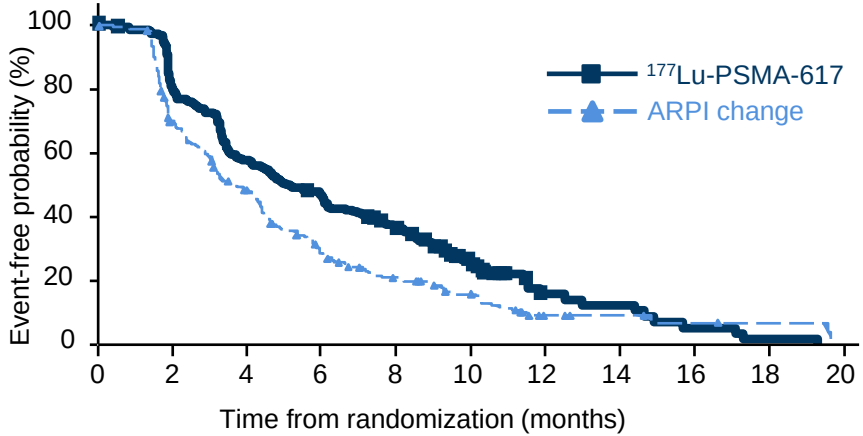


Number of patients still at risk

234	199	160	130	101	38	12	7	4	1	0
234	174	115	64	39	20	8	6	3	2	0

BPI-SF pain intensity scale[2]

HR: **0.69** (95% CI: 0.56, 0.85)

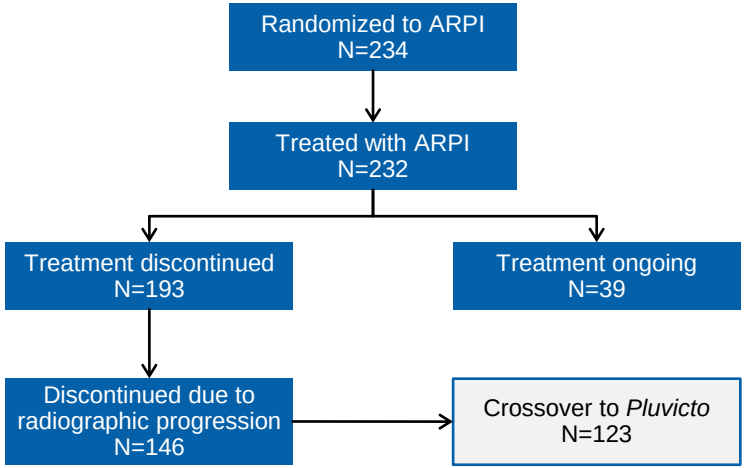


234	190	138	108	88	39	12	9	3	1	0
234	159	105	61	42	24	7	5	2	2	0

1. FACT-P: Median time to worsening, months (95% CI): 7.5 (6.1, 8.5) vs. 4.3 (3.5, 4.5) 2. BPI: Median time to worsening, months (95% CI): 5.0 (4.4, 6.9) vs. 3.7 (3.1, 4.4)

Overall survival data interpretation confounded by crossover

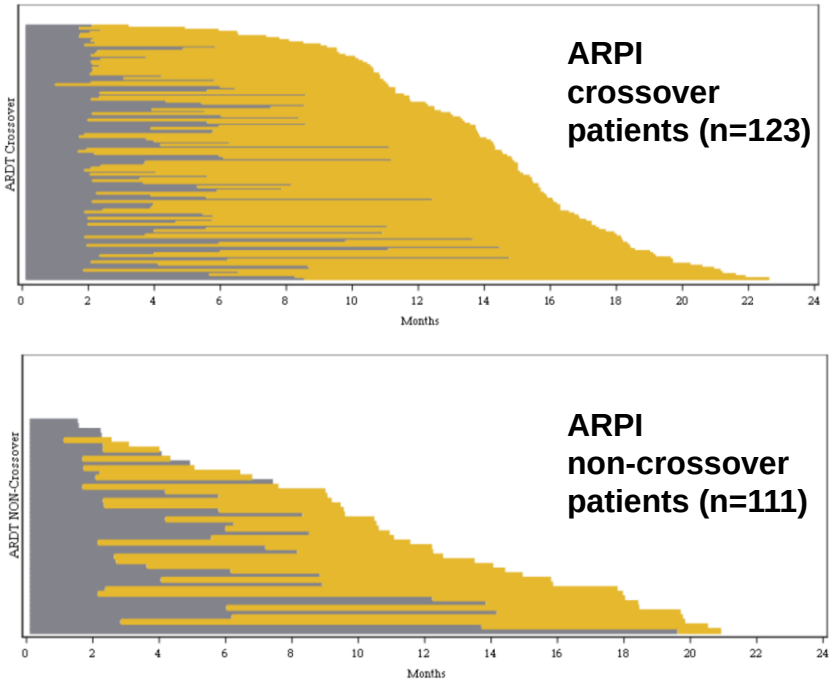
Crossover: 123/146 (84%) patients who discontinued with radiographic progression



45% information fraction at time of 2nd interim OS analysis

OS	HR	95% CI
Pre-specified primary crossover-adjusted analysis	**0.80**	(0.48, 1.33)
Unadjusted ITT analysis	**1.16**	(0.83, 1.64)

ARPI patients who crossed over to *Pluvicto* had a survival benefit over ARPI patients who did not cross over



rPFS time

OS time from rPD

Estimated OS probability at 12 months:

92.1% for pts randomized to ARPI arm who crossed over

68.6% for pts randomized to ARPI arm who did not cross over

Other than *Pluvicto* crossover and concurrent radiation, no major difference in post-progression therapies between treatments arms

Antineoplastic therapy since discontinuation of study drug by medication type[1]

Medication Type	^{177}Lu-PSMA-617 N=234 | n (%)	ARPI N=234 | n (%)
***Pluvicto* as crossover treatment**	**0**	**123 (84.2)**
Radiation therapy	36 (15.4)	66 (28.2)
Concurrent (includes crossover treatment)	7 (3.0)	39 (16.7)
Post-study treatment	29 (12.4)	27 (11.5)
≥ 1 subsequent ANP medication (excluding crossover)	81 (34.6)	68 (29.1)
Chemotherapy	70 (29.9)	61 (26.1)
Hormonal therapy	13 (5.6)	4 (1.7)
Biologic therapy	5 (2.1)	2 (0.9)
Targeted therapy (excluding radioligand therapy)	2 (0.9)	3 (1.3)
PSMA-directed radioligand therapy	1 (0.4)	5 (2.1)
Other	1 (0.4)	0

1. Full analysis set. A medication / therapy can appear with more than one medication type. Only ANP medications that started after the end of randomized treatment date are summarized. For crossover subjects all antineoplastic medications after crossover are included in the ARPI column. Targeted therapies reported: capivasertib, olaparib, and NUV-868 (BETi). PSMA-directed radioligand therapies reported: Pluvicto, 67CuBIPSMA.

Treatment with *Pluvicto* had a favorable safety profile and was well tolerated

63% of patients received 6 cycles of *Pluvicto*

Lower rate of Grade ≥3 AEs compared to daily oral ARPI

Fewer patients on *Pluvicto* required a dose adjustment compared to ARPI

AE-driven discontinuations were low and balanced between the arms

AEs, n (%)	^{177}Lu-PSMA-617 (n = 227)	ARPI change (n = 232)
Any	223 (98.2)	223 (96.1)
Grade 3-4	77 (33.9)	100 (43.1)
Serious	46 (20.3)	65 (28.0)
Treatment-related	7 (3.1)	5 (2.2)
Fatal (Grade 5)	4 (1.8)	5 (2.2)
Treatment-related	0	1 (0.4)
Leading to dose adjustment	8 (3.5)	35 (15.1)
Leading to discontinuation	13 (5.7)	12 (5.2)

Vast majority of AEs were low-grade

Treatment-emergent adverse events in ≥ 10% patients in either arm

	All grades		Grades 3–5	
AEs, n (%)	^{177}Lu-PSMA-617 (n = 227)	ARPI change (n = 232)	^{177}Lu-PSMA-617 (n = 227)	ARPI change (n = 232)
Dry mouth	130 (57.3)	5 (2.2)	3 (1.3)	0
Asthenia	72 (31.7)	67 (28.9)	1 (0.4)	8 (3.4)
Nausea	71 (31.3)	28 (12.1)	0	1 (0.4)
Anaemia	55 (24.2)	39 (16.8)	14 (6.2)	14 (6.0)
Fatigue	52 (22.9)	59 (25.4)	0	4 (1.7)
Constipation	50 (22.0)	31 (13.4)	1 (0.4)	0
Decreased appetite	48 (21.1)	42 (18.1)	0	1 (0.4)
Arthralgia	43 (18.9)	48 (20.7)	0	1 (0.4)
COVID-19	37 (16.3)	26 (11.2)	1 (0.4)	1 (0.4)
Diarrhoea	37 (16.3)	20 (8.6)	0	1 (0.4)
Back pain	28 (12.3)	38 (16.4)	2 (0.9)	5 (2.2)
Vomiting	26 (11.5)	11 (4.7)	0	0
Oedema peripheral	19 (8.4)	26 (11.2)	0	0
Weight loss	15 (6.6)	28 (12.1)	2 (0.9)	5 (2.2)

Exposure-adjusted safety data show even better tolerability in this earlier line of treatment than was seen in the VISION study

	Incidence rate per 100 subject-time years PSMAfore	Incidence rate per 100 subject-time years VISION
AEs (Grade ≥3)	60	88
Treatment related AEs (Grade ≥3)	17	39
SAEs	33	53

~2,000 patient-years of exposure in VISION, PSMAfore and post-marketing experience support favorable safety and tolerability profile of *Pluvicto*

PSMAfore study showed robust efficacy with favorable safety of *Pluvicto* in PSMA+ mCRPC patients in the pre-taxane setting

Robust efficacy	*Pluvicto* vs. ARPI arm
☑ rPFS[1]	HR **0.41** (0.29, 0.56)
☑ Median rPFS[2]	**12.0** vs. 5.6 months
☑ PSA50 response	**57.6%** vs. 20.4%
☑ Time to SSE	HR **0.35** (0.22, 0.57)
☑ ORR[3]	**50.7%** vs. 14.9%
☑ Time to worsening (FACT-P[4])	HR **0.59** (0.47, 0.72)
☑ Time to worsening (BPI-SF[5])	HR **0.69** (0.56, 0.85)
Crossover-adjusted OS	HR **0.80** (0.48, 1.33)
Unadjusted OS **(84% crossover)**	HR 1.16 (0.83, 1.64)

Favorable safety profile

- ☑ Vast majority of AEs low-grade
- ☑ Grade 3-4 AEs: 33.9% *Pluvicto* vs. 43.1% ARPI
- ☑ SAEs: 20.3% *Pluvicto* vs. 28.0% ARPI
- ☑ AEs leading to discontinuation[6]: 5.7% vs. 5.2%
- ☑ AEs leading to dose adjustment[6]: 3.5% vs. 15.1%

Overall exposure to *Pluvicto* ~2,000 patient-years
(incl. VISION, PSMAfore and post-marketing experience)

1. Primary rPFS analysis based on 166 rPFS events per BICR assessment (or centrally confirmed rPFS events); 1-sided p-value: <0.0001. Updated analysis of rPFS (at time of 2nd interim OS analysis) was consistent, with HR 0.43 (0.33, 0.54). All other data points from updated analysis with more mature data. 2. (95% CI): 12.0 (9.3, 14.4) vs. 5.6 (4.2, 5.95) 3. ORR in soft tissue per RECIST 1.1 for pts with measurable disease at baseline; (95% CI): 50.7% (38.6, 62.8) vs. 14.9% (7.7, 25.0) 4. FACT-P: prostate cancer-specific quality of life 5. BPI-SF: severity of pain and impact of pain on daily functions 6. Comparisons for *Pluvicto* vs. ARPI arm

Next steps for *Pluvicto* in the pre-taxane setting

High crossover confounded OS analysis interpretation with 45% information fraction

PSMAfore continues to next interim analysis for OS after ~75% of target events

Submission to health authorities to follow in 2024

Agenda

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3 **Q&A**