URO TODAY® 21+ years GU ONC TODAY™
PARTNERING WITH THE PROSTATE CANCER FOUNDATION
Powering Education Driven by Evidence

Final OS and Safety Analysis of the Phase 3 PSMAfore Trial of [^{177}Lu]Lu-PSMA -617 vs Change of ARPI in Taxane-Naïve Patients with mCRPC

Rashid Sayyid, MD, MSc
Robotic Urologic Oncology Fellow
Department of Urology
University of Southern California

Zachary Klaassen, MD, MSc
Associate Professor
Department of Urology
Wellstar MCG Health

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Final overall survival and safety analyses of the phase 3 PSMAfore trial of [^{177}Lu]Lu-PSMA-617 versus change of androgen receptor pathway inhibitor in taxane-naive patients with metastatic castration-resistant prostate cancer

K. Fizazi, K.N. Chi, N.D. Shore, K. Herrmann, J.S. de Bono, D. Castellano, J.M. Piulats, A. Fléchon, X.X. Wei, H. Mahammedi, G. Roubaud, M. Fleming, T. Haas, S. Ghebremariam, T.N. Kreisl, S. Rajagopalan, O. Sartor, M.J. Morris, for the PSMAfore Investigators

Treatment Options for mCRPC Patients Post-ARPI: Pre-PSMAfore Era

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Prostate Cancer

Progression on prior novel hormone therapy/no prior docetaxel[qqq]

- **Preferred regimens**
  - **Docetaxel (category 1)[lll]**
  - **Olaparib for *BRCA* mutation[yyy] (category 1)**
  - **Rucaparib for *BRCA* mutation[zzz] (category 1)**
- **Useful in certain circumstances**
  - **Cabazitaxel/carboplatin[lll,mmm]**
  - **Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 2B)**
  - **Olaparib for HRR mutation other than *BRCA1/2*[yyy]**
  - **Pembrolizumab for MSI-H/dMMR[lll] (category 2B)**
  - **Radium-223[u,vvv] for symptomatic bone metastases (category 1)**
  - **Sipuleucel-T[lll,www]**
  - **Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 2B)**
- **Other recommended regimens**
  - **Other secondary hormone therapy[aaaa]**

Limited Options

Treatment Options for mCRPC Patients Post-ARPI: Pre-PSMAfore Era

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Prostate Cancer

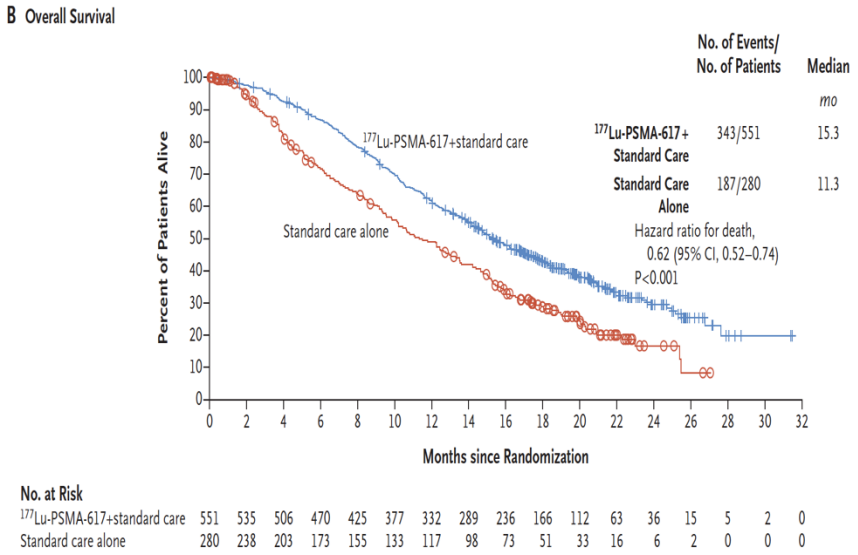
But…what about patients who refuse/unable to tolerate taxanes and do not harbor a *BRCA* mutation?

Limited Options

- **Useful in certain circumstances**
  - **Cabazitaxel/carboplatin[lll,mmm]**
  - **Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 2B)**
  - **Olaparib for HRR mutation other than *BRCA1/2*[yyy]**
  - **Pembrolizumab for MSI-H/dMMR[lll] (category 2B)**
  - **Radium-223[u,vvv] for symptomatic bone metastases (category 1)**
  - **Sipuleucel-T[lll,www]**
  - **Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 2B)**
- **Other recommended regimens**
  - **Other secondary hormone therapy[aaaa]**

Can We Move ^{177}Lu-PSMA 'Up' the Treatment Algorithm?

- Prior to 2025: ^{177}Lu-PSMA approved for mCRPC pts post-ARPI **and** taxanes



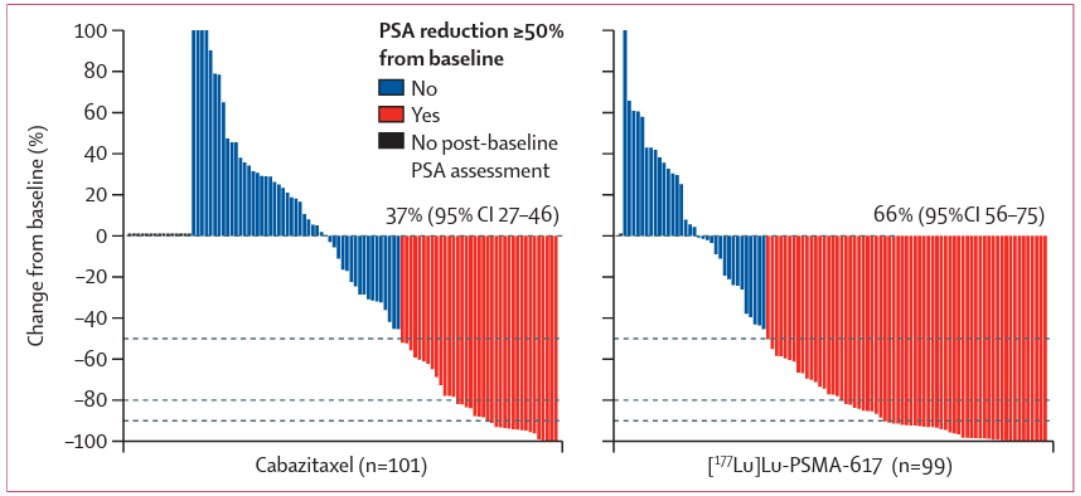


Figure 2: **PSA response**
PSA=prostate-specific antigen. ^{177}Lu=lutetium-177.

VISION
^{177}LuPSMA-617 + SOC vs SOC

Sartor et al. *N Engl J Med,* 2021.

TheraP
^{177}LuPSMA-617 vs Cabazitaxel

Hofman et al. *Lancet*, 2021.

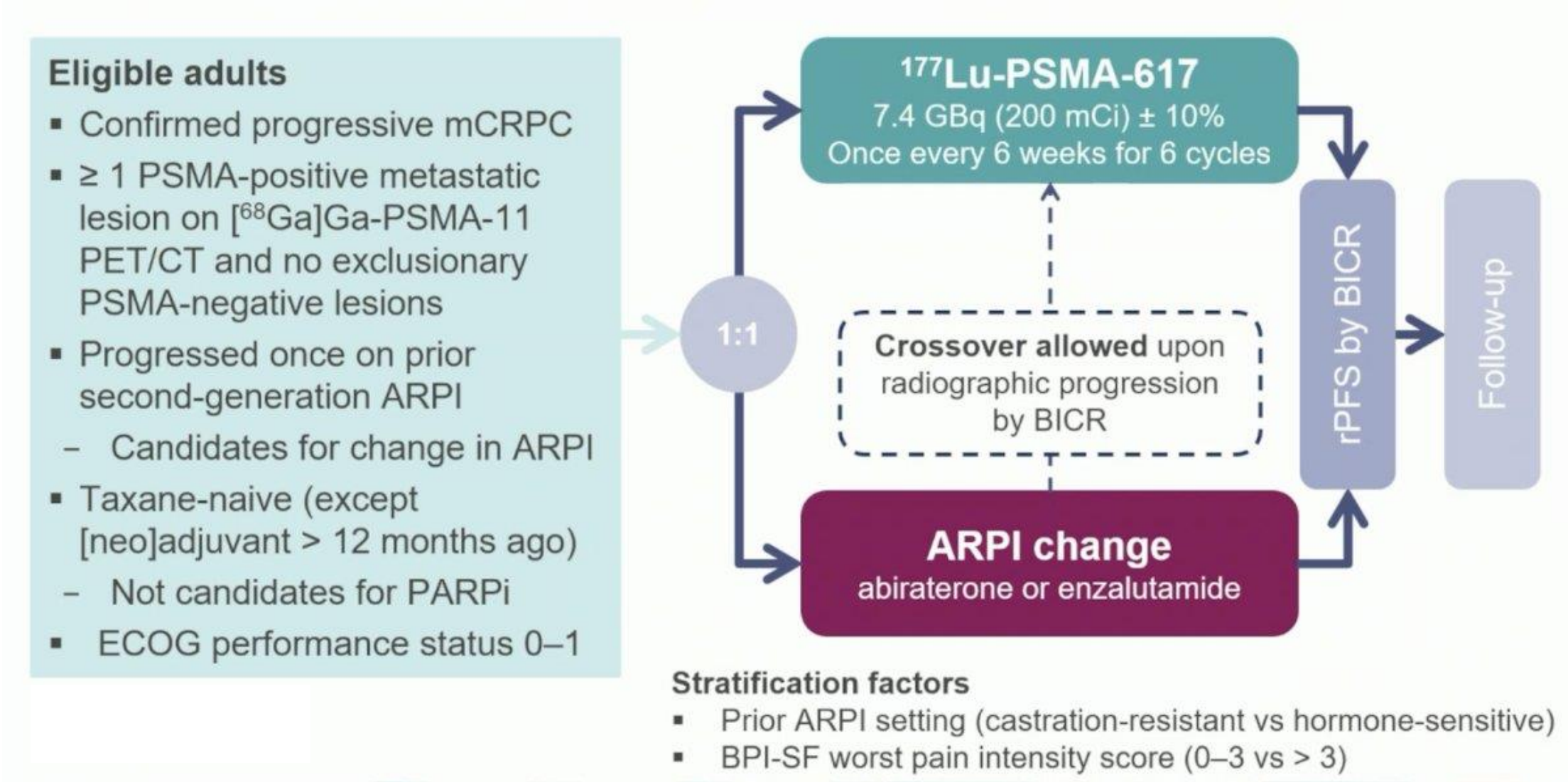
September 2024

THE LANCET

^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

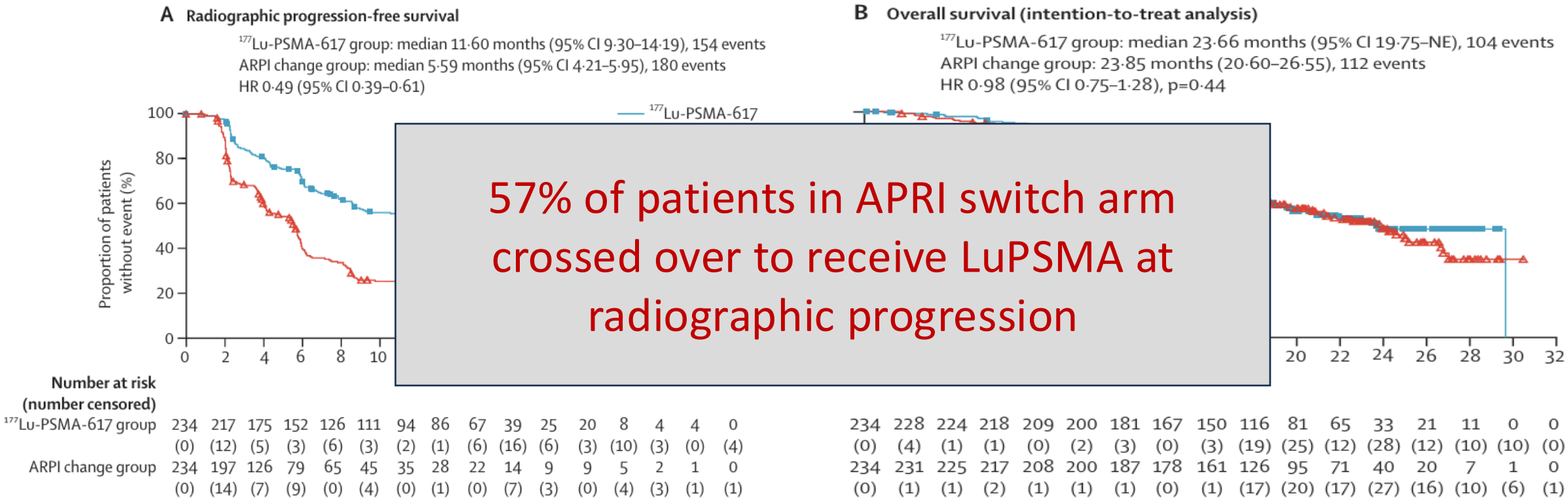
Michael J Morris, Daniel Castellano, Ken Herrmann, Johann S de Bono, Neal D Shore, Kim N Chi, Michael Crosby, Josep M Piulats, Aude Fléchon, Xiao X Wei, Hakim Mahammedi, Guilhem Roubaud, Hana Študentová, James Nagarajah, Begoña Mellado, Álvaro Montesa-Pino, Euloge Kpamegan, Samson Ghebremariam, Teri N Kreisl, Celine Wilke, Katja Lehnhoff, Oliver Sartor*, Karim Fizazi*, for the PSMAfore Investigators†*

PSMAfore Study Design



^{177}Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial

Michael J Morris, Daniel Castellano, Ken Herrmann, Johann S de Bono, Neal D Shore, Kim N Chi, Michael Crosby, Josep M Piulats, Aude Fléchon, Xiao X Wei, Hakim Mahammedi, Guilhem Roubaud, Hana Študentová, James Nagarajah, Begoña Mellado, Álvaro Montesa-Pino, Euloge Kpamegan, Samson Ghebremariam, Teri N Kreisl, Celine Wilke, Katja Lehnhoff, Oliver Sartor*, Karim Fizazi*, for the PSMAfore Investigators†*



57% of patients in APRI switch arm crossed over to receive LuPSMA at radiographic progression

Median rPFS (final analysis)
11.6 vs 5.6 mo (HR 0.49, p<0.0010)

Median OS (interim analysis; f/u: 18 mo)
23.7 vs 23.9 mo (HR 0.98, p=0.44)

March 2025

FDA expands Pluvicto's metastatic castration-resistant prostate cancer indication

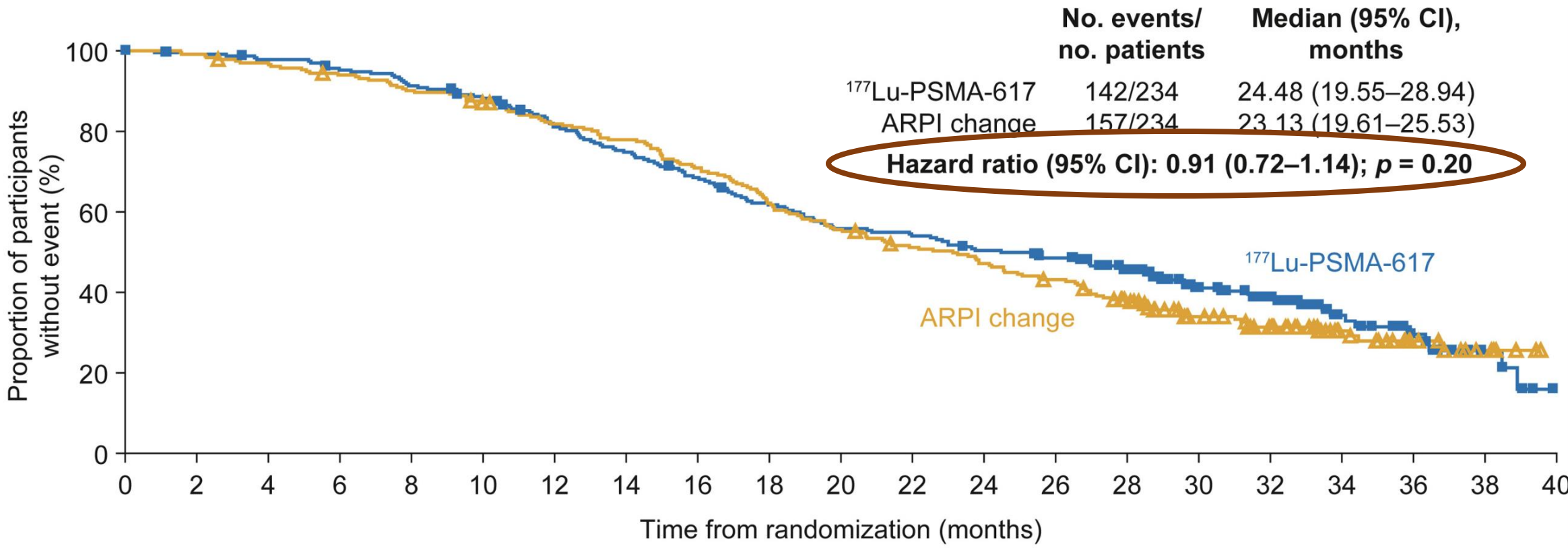
On March 28, 2025, the Food and Drug Administration expanded the indication for lutetium Lu 177 vipivotide tetraxetan (Pluvicto, Novartis Pharmaceuticals Corporation) to include adults with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibitor (ARPI) therapy and are considered appropriate to delay taxane-based chemotherapy.

Study Objective

To report:

1. Final OS analyses of PSMAfore based on the ITT principle
2. Crossover-adjusted OS analyses
   - Inverse probability of censoring weighting (IPCW)
   - Rank-preserving structure failure time (RPSFT)
3. Updated safety outcomes, including exposure-adjusted outcomes

Overall Survival



Number at risk

177Lu-PSMA-617 arm	234	229	225	218	209	200	181	167	152	136	123	119	110	103	85	57	45	24	15	6	0
ARPI change arm	234	232	226	218	209	200	187	178	162	142	127	115	106	96	79	56	44	25	14	7	0

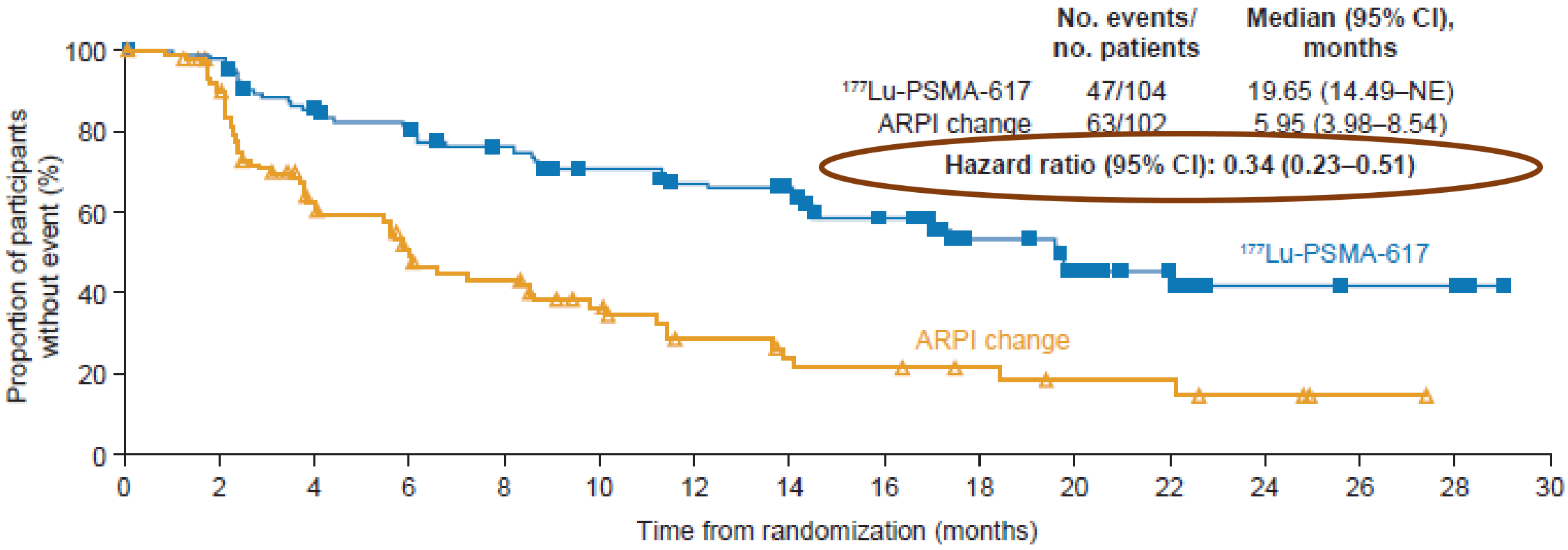
Crossover-Adjusted OS by IPCW and RPSFT

	^{177}Lu-PSMA-617 (*n* = 234)	ARPI change (*n* = 234)
IPCW-adjusted OS hazard ratio (95% CI)[a]		
Model 1	0.56 (0.35, 0.88)	
Model 2	0.54 (0.32, 0.89)	
Model 3 (full model)	0.59 (0.37, 0.94)	
Model 4	0.60 (0.37, 0.96)	
Model 5	0.60 (0.38, 0.96)	
Model 6	0.55 (0.36, 0.86)	
Model 7 (full model)	**0.59 (0.38, 0.91)**	
Model 8	0.62 (0.42, 0.94)	
RPSFT-adjusted OS hazard ratio (95% CI)	**0.84 (0.55, 1.28)**	

Assumes there are no unmeasured confounders

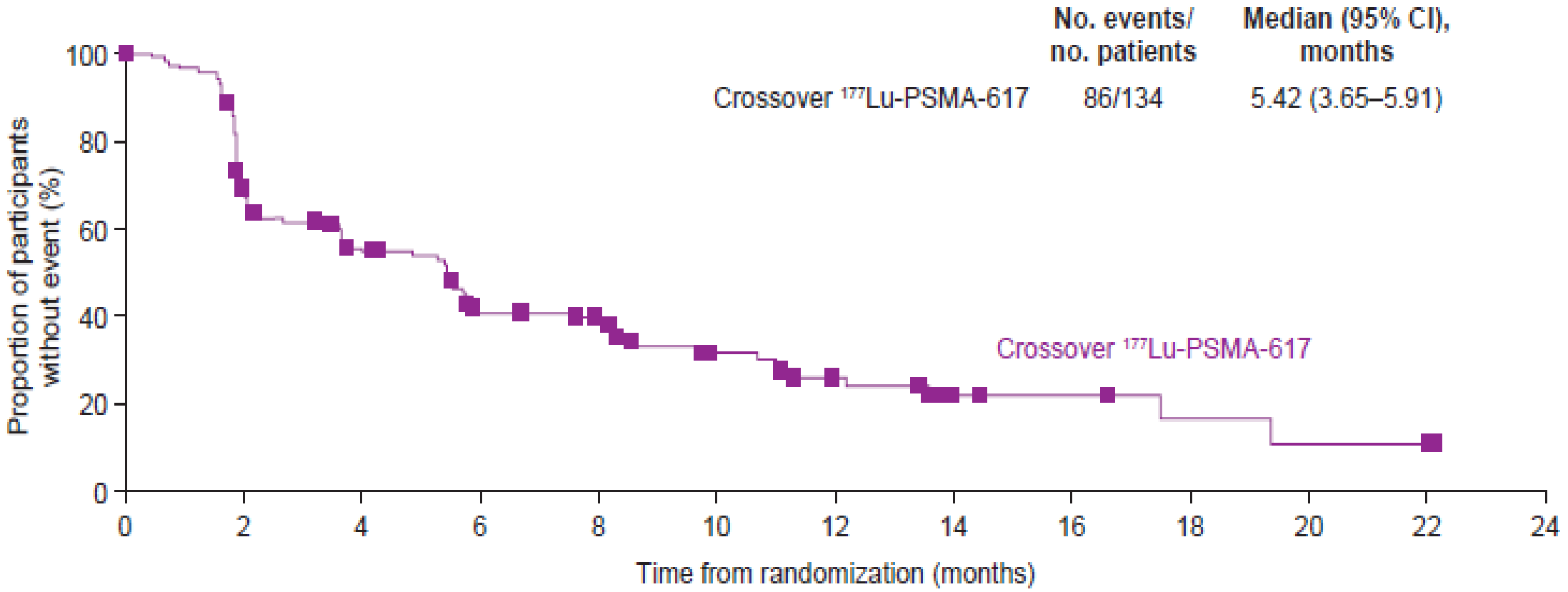
The common treatment assumption was likely not met and the method fails to adjust for confounding in the context of overlapping ITT survival curves

Time to Soft Tissue Progression



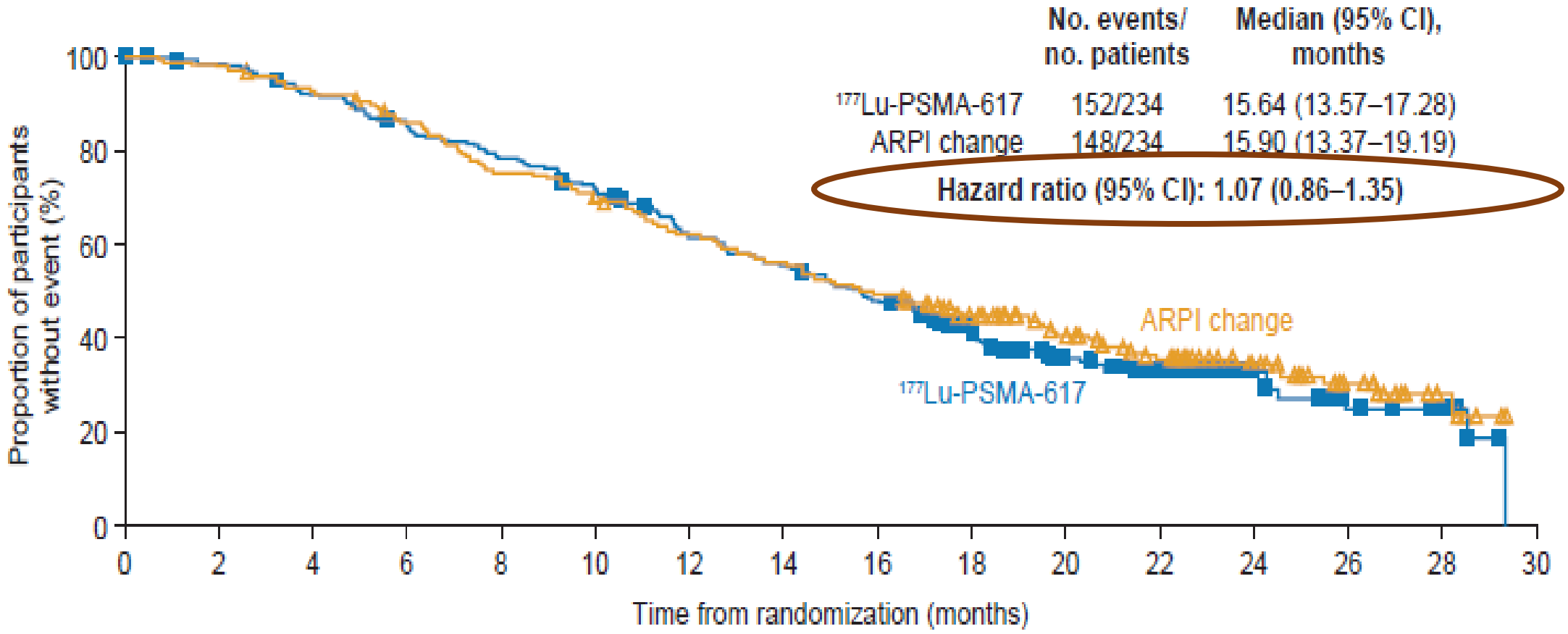
Number at risk																
177Lu-PSMA-617 arm	104	101	85	78	70	62	57	54	44	28	20	13	5	4	4	0
ARPI change arm	102	86	52	35	29	20	13	10	9	7	5	5	3	1	0	0

Time to Radiographic Disease Progression After Crossover (rPFS2)



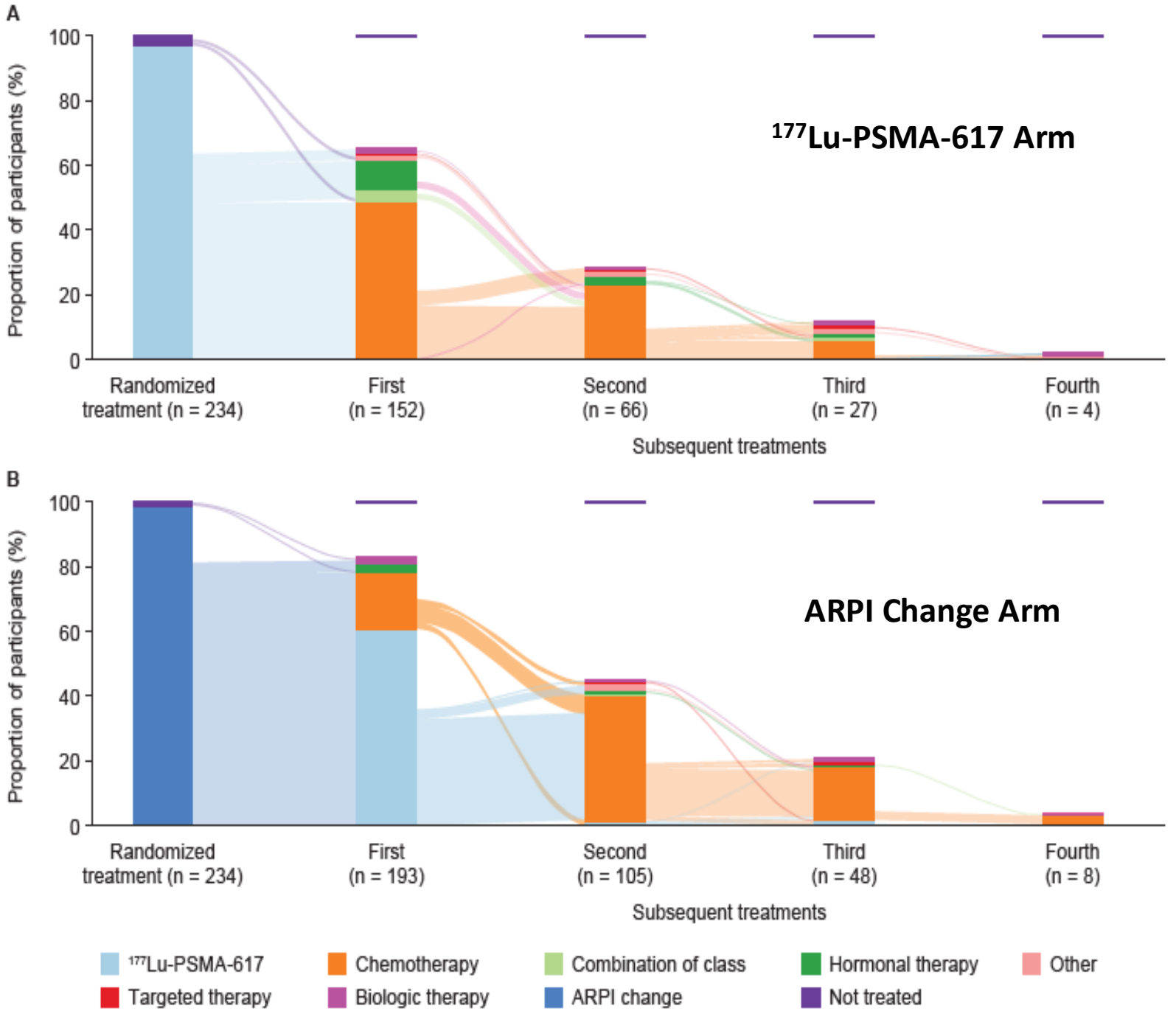
Number at risk												
Crossover 177Lu-PSMA-617 group	134	83	62	42	38	23	14	6	5	3	2	2	0

Time to Chemotherapy



Number at risk																
177Lu-PSMA-617 arm	234	227	211	195	179	164	137	124	106	79	51	39	18	10	7	0
ARPI change arm	234	228	216	199	173	161	141	128	113	92	71	51	30	16	6	0

Treatments Received After Discontinuation



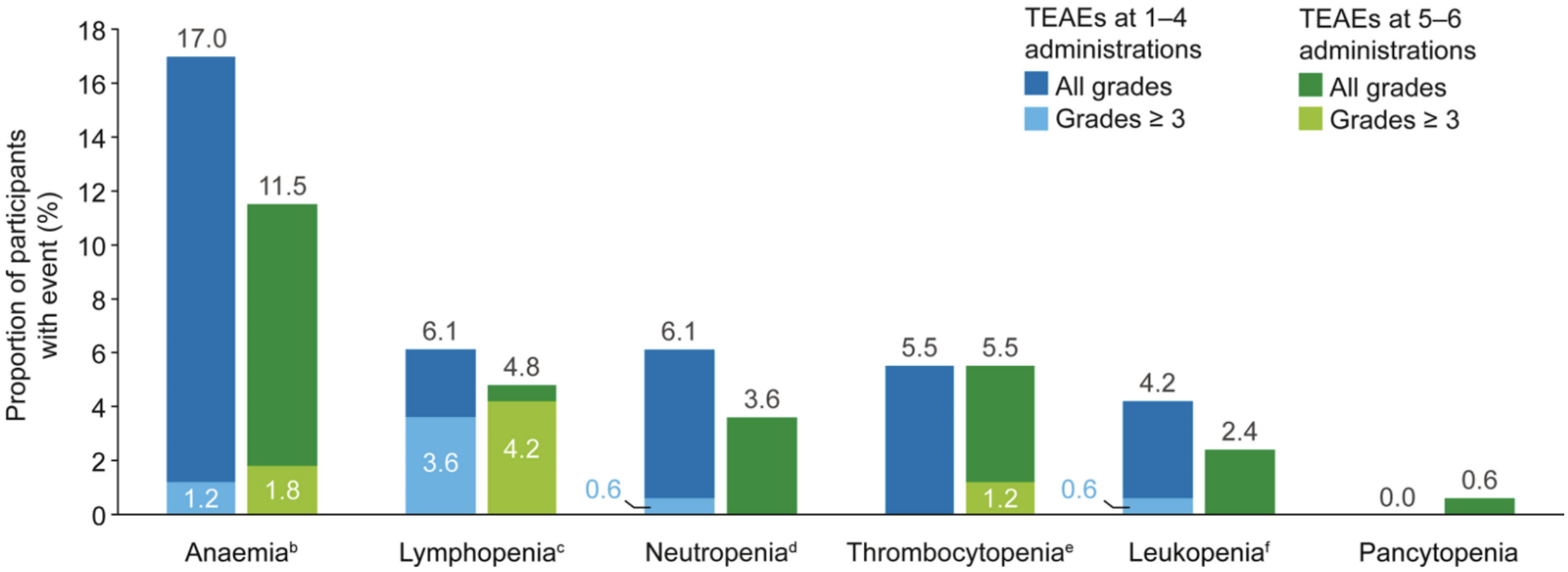
Exposure-Adjusted Safety During Randomized Treatment

Participants with treatment-emergent adverse events – no. (incidence per 100 patient-treatment years)	^{177}Lu-PSMA-617 (*n* = 227)		ARPI change (*n* = 232)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any	224 (1513.1)	80 (60.8)	228 (894.7)	114 (85.1)
Any treatment-related	203 (649.1)	31 (21.2)	148 (190.2)	28 (16.1)
Serious	46 (32.5)	41 (28.4)	76 (49.9)	70 (45.7)
Serious treatment-related	9 (5.9)	8 (5.2)	6 (3.2)	6 (3.2)
Leading to death[a]	4 (2.5)	4 (2.5)	5 (2.7)	5 (2.7)
Leading to death, treatment-related	0	0	1 (0.5)	1 (0.5)
Leading to adjustment of dose[b]	8 (5.2)	3 (1.9)	36 (22.1)	7 (3.8)
Leading to interruption of treatment	29 (19.6)	13 (8.5)	45 (27.8)	20 (11.3)
Leading to discontinuation of treatment	12 (7.7)	7 (4.5)	12 (6.4)	9 (4.8)
Occurring with incidence > 10 per 100 patient-years in ^{177}Lu-PSMA-617 arm				
* Dry mouth **59.5%**	135 (164.1	2 (1.3)	6 (3.2)	0
Nausea	74 (64.6)	0	29 (16.4)	1 (0.5)
Asthenia	73 (59.1)	2 (1.3)	67 (48.4)	8 (4.4)
Anaemia	62 (46.5)	14 (9.1)	45 (27.7)	16 (8.7)
Fatigue	54 (42.2)	1 (0.6)	59 (39.7)	4 (2.1)
Constipation	50 (37.4)	1 (0.6)	33 (19.6)	0
Decreased appetite	49 (35.9)	0	44 (25.3)	2 (1.1)
Arthralgia	46 (33.2)	0	54 (36.8)	1 (0.5)
Diarrhoea	38 (27.6)	0	23 (13.1)	1 (0.5)
COVID-19	37 (25.9)	1 (0.6)	29 (17.4)	1 (0.5)
Back pain	31 (21.2)	3 (1.9)	46 (28.6)	6 (3.2)
Vomiting	26 (17.8)	0	12 (6.5)	0
Bone pain	20 (13.4)	1 (0.6)	18 (9.9)	2 (1.1)
Dysgeusia	19 (12.9)	0	6 (3.2)	0
Headache	19 (12.7)	0	11 (6.1)	0
Oedema peripheral	19 (12.9)	0	29 (17.4)	0
Thrombocytopenia	18 (11.8)	5 (3.2)	7 (3.8)	2 (1.1)
Pain in extremity	17 (11.4)	1 (0.6)	27 (15.6)	1 (0.5)

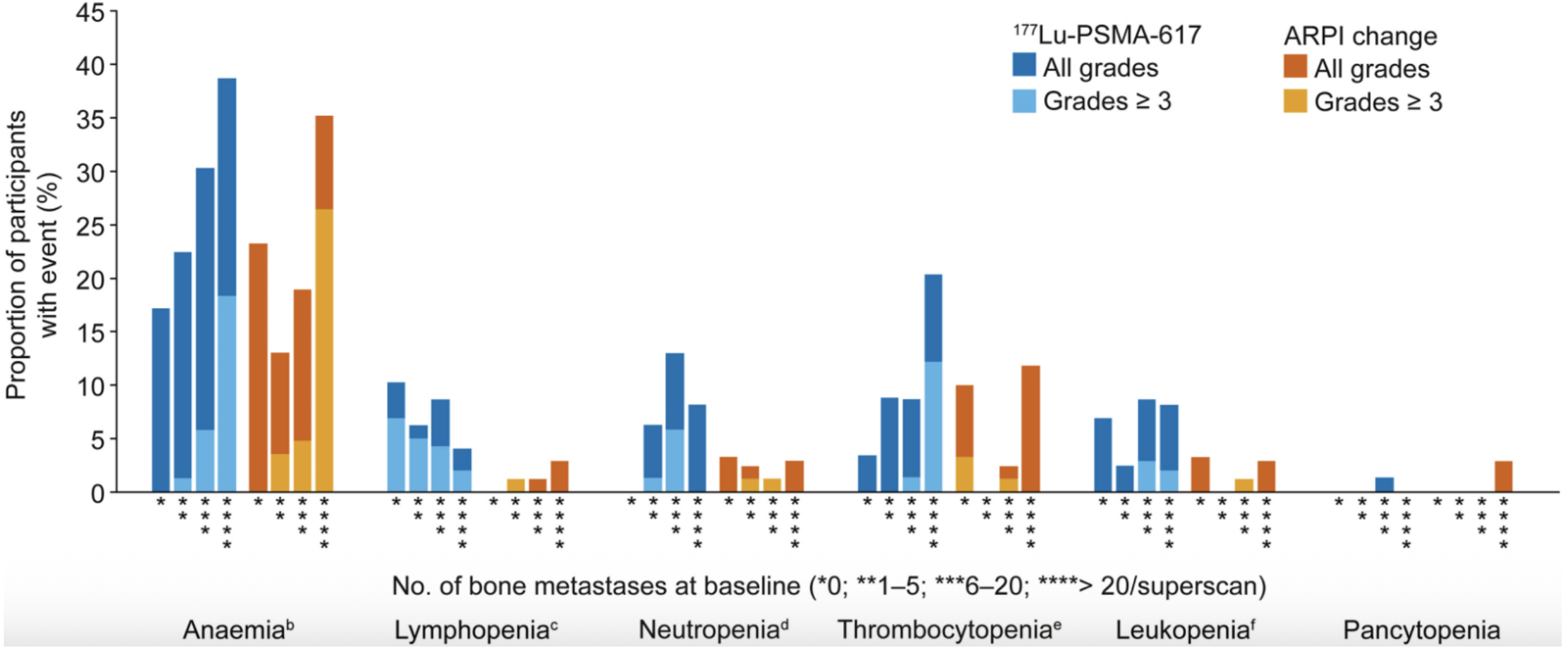
Time to Onset and Resolution of Dry Mouth, Hematologic AEs, and Renal Toxicity

Safety topic of interest	^{177}Lu-PSMA-617 (*n* = 227)	ARPI change (*n* = 232)
Dry mouth[a] – no. (%)	138 (60.8)	6 (2.6)
Time to first occurrence – months, median (95% CI)[b]	4.17 (2.83–5.49)	NE (NE–NE)
Hazard ratio (95% CI)[b]	33.55 (14.80, 76.04)	
Time to resolution – months, median (min–max)[c,d]	1.12 (0.0–27.2)	2.89 (2.9–2.9)
Haematologic adverse events[e] – no. (%)	89 (39.2)	55 (23.7)
Time to first occurrence – months, median (95% CI)[b]	11.40 (11.40–NE)	NE (25.10–NE)
Hazard ratio (95% CI)[b]	1.86 (1.31, 2.63)	
Time to resolution – months, median (min–max)[c,d]	1.77 (0.2–18.0)	0.92 (0.1–9.2)
Renal toxicity[f] – no. (%)	14 (6.2)	19 (8.2)
Time to first occurrence – months, median (95% CI)[b]	NE (NE–NE)	NE (NE–NE)
Hazard ratio (95% CI)[b]	0.70 (0.35, 1.40)	
Time to resolution – months, median (min–max)[c,d]	0.71 (0.0–16.2)	0.20 (0.1–20.7)

Proportion of Pts with Hematologic TEAEs at 1-4 vs 1-6 Doses of ^{177}Lu-PSMA-617



Proportion of Pts with Hematologic TEAEs According to # of Bone Metastases at Baseline



Discussion (1)

- **In the final OS analysis, there was no statistically significant difference in OS between treatment arms based on the ITT principle**
  - IPCW crossover-adjusted OS analyses (HR 0.59, 95% CI 0.38-0.91) suggested crossover confounded the OS analysis
  - Rate of crossover was high: 60.3% of pts in ARPI arm (75.4% with confirmed radiographic progression) crossed over
    - Majority of pts in the ARPI arm received investigational drug, and received it early in the study (median 7.66 mos)
- **Overall safety profile of ^{177}Lu-PSMA-617 at the final OS was favorable and similar to previous analyses → no new safety signals**
  - Overall exposure-adjusted incidence of dry mouth in the ^{177}Lu-PSMA-617 arm (59.5%) was higher than previously observed in VISION (38.8%)
    - Most events were grade 1-2, did not lead to dosage modifications, and had resolved by the time of final OS analysis
  - Rates of renal toxicity were low and comparable between treatment arms

Discussion (2)

- **Important limitations/considerations**:
  1. Selection bias and unmeasured variables may have further affected outcomes in the crossover group because this was a post-randomization event → likely confounded ITT analysis of OS
  2. Other variables, such as PSMA expression, may have influenced outcomes and were not accounted for in the correction models
  3. Pts with known genomic alterations conferring eligibility for other Rx (ie. PARPi) were excluded
  4. The trial may have been underpowered to detect an OS difference (power for OS: 80%), which may have been further reduced by crossover

- *All pts in active therapy or follow-up upon closure of the trial will be eligible for a further long-term follow-up study (NCT05803941), which will provide insights into the long-term safety outcomes of patients receiving ^{177}Lu-PSMA-617*

Take Home Messages

- In the final OS analysis of PSMAfore, OS was not statistically significantly different between ^{177}Lu-PSMA-617 and ARPI change

- Safety profile: acceptable and consistent with previous reports

- ***Given that ^{177}Lu-PSMA-617 prolonged rPFS, time to PSA progression, and time to worsening HRQoL and pain, these results support the use of ^{177}Lu-PSMA-617 for PSMA-positive mCRPC pre-chemotherapy***