

Improving Treatment in Advanced Prostate Cancer ECHO



Session 4

Optimal Sequencing of Systemic Therapy
in Androgen Deprivation-Resistant
Prostate Cancer

Thursday, March 6, 2025

11:00 AM - 12:00 PM EST

Improving Treatment in Advanced Prostate Cancer ECHO

Housekeeping & Disclosures



Each ECHO session will be recorded and will be posted to a publicly-facing ACS ECHO website, <https://echo.cancer.org>



Use the buttons in the *black* menu bar to unmute your line and to turn on your video.



Remember: Do **NOT** share any personal health information (PHI) about any patient.



Questions about Zoom? Type in the chat box @Mindi Odom



Have a question? Don't wait to ask! Feel free to enter in the Chat at any time.

Palliative Radiation of Bone Metastases

Agenda Item	Moderator/Presenters	Time
Welcome & Announcements	Mindi Odom	3 minutes
Introductions	Sarah Wienke	2 minutes
Clinical Presentation with Q&A	Vivek Narayan, MD, MS Hospital of the University of Pennsylvania	25 minutes
Case Presentation	L. Crain Garrot, MD Northside Hospital Cancer Institute	5 minutes
Group Discussion	All	20 minutes
Wrap-Up	Mindi Odom	5 minutes

ECHO Hub Team

Subject Matter Experts (SMEs)



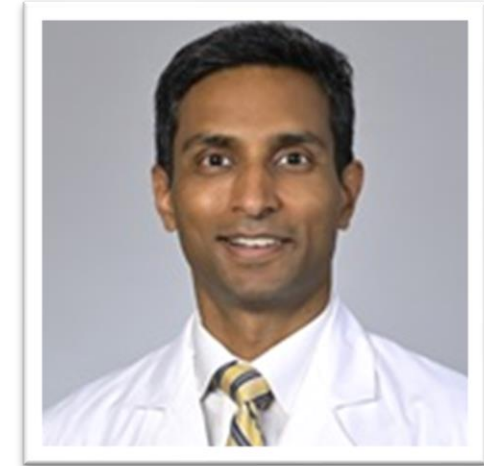
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Vivek Narayan, MD MSCE
Assistant Professor of Medicine
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Optimal Sequencing of Systemic Therapy in Androgen Deprivation– Resistant Prostate Cancer

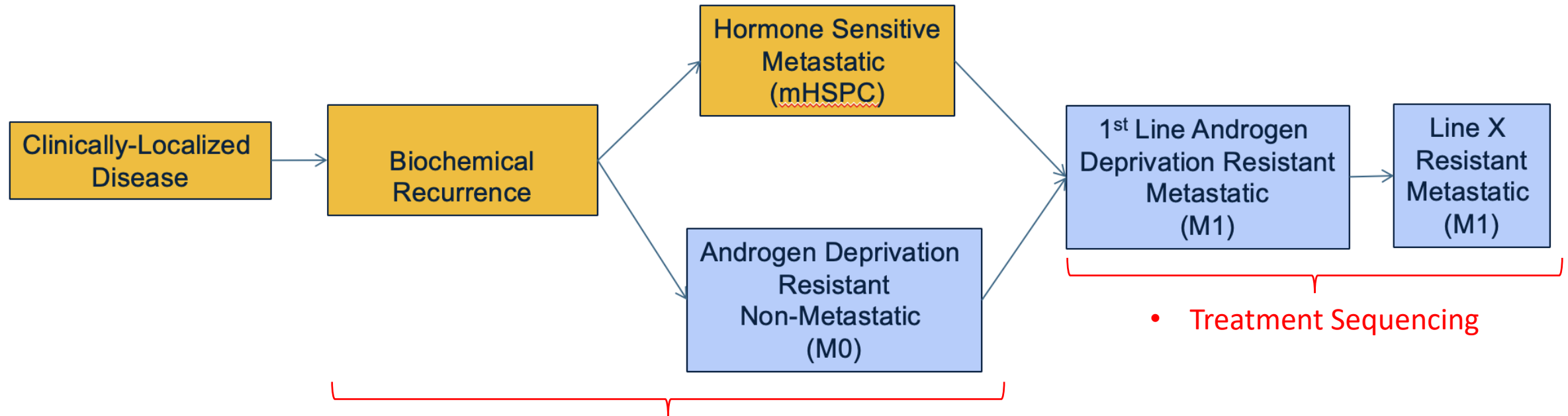
Consulting: Janssen Oncology, Pfizer, Regeneron, Merck, SumitomoPharma, Eisai, Xencor, Exelixis

Research Funding (Institution): Pfizer, Merck, Janssen, Xencor, Bristol-Myers Squibb, Regeneron, BioNTech

Learning Objectives

- 1 Briefly review **real world practice patterns** on treatment sequencing
- 2 Discuss the **challenges** with **choosing “optimal” systemic therapy sequence** in metastatic androgen deprivation resistant prostate cancer
- 3 Review the **prospective clinical trial evidence (and limitations)** informing treatment sequencing

PROSTATE CANCER CLINICAL DISEASE STATES



ADT and ARPI Combination Strategies

[enzalutamide, apalutamide, darolutamide, abiraterone/prednisone]



Hormone Sensitive



Androgen Deprivation Resistant

Clinical Considerations for Treatment Sequencing Decisions

- Patient Fitness, Preferences
- Prior Treatment Exposures and Related Toxicities
- Disease burden / Metastatic site
- Pace of cancer growth
- Presence of symptoms
- Molecular Information / PSMA PET imaging
- Clinical Trial data (where available)



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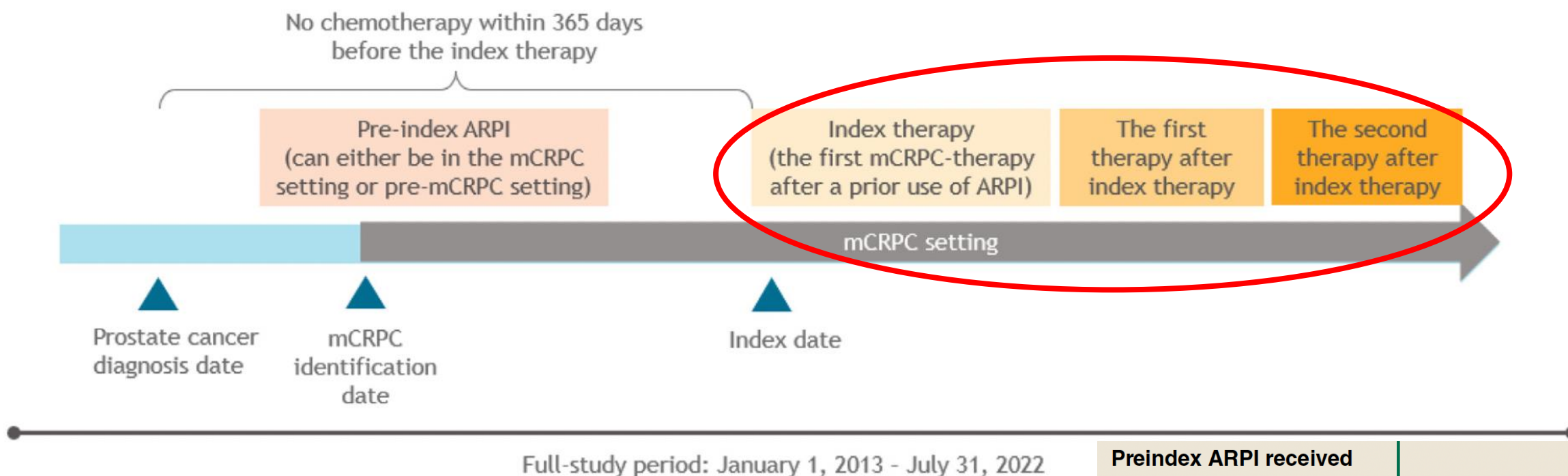
NCCN Guidelines Version 1.2025

Prostate Cancer

[NCCN Guidelines Index](#)
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[Discussion](#)

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA^{f,fff,ggg,hhh,iii}

No prior docetaxel/no prior novel hormone therapy ^{jjj}	Progression on prior novel hormone therapy/no prior docetaxel ^{jjj}
• Preferred regimens ▶ Abiraterone^{z,kkk} (category 1 if no visceral metastases) ▶ Docetaxel^{ddd} (category 1) ▶ Enzalutamide^z (category 1) • Useful in certain circumstances ▶ Niraparib/abiraterone^{z,III,mmm} for <i>BRCA</i> mutation (category 1) ▶ Olaparib/abiraterone^{z,kkk,III} for <i>BRCA</i> mutation (category 1) ▶ Pembrolizumab for MSI-high (MSI-H)/dMMR^{ddd} (category 2B) ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Sipuleucel-T^{ddd,ooo} (category 1) ▶ Talazoparib/enzalutamide for HRR mutation^{z,III} (category 1) • Other recommended regimens ▶ Other secondary hormone therapy^z	• Preferred regimens ▶ Docetaxel (category 1)^{ddd} ▶ Olaparib for <i>BRCA</i> mutation^{III} (category 1) ▶ Rucaparib for <i>BRCA</i> mutation^{III} (category 1) • Useful in certain circumstances ▶ Cabazitaxel/carboplatin^{ddd} ▶ Niraparib/abiraterone^{z,III,mmm} for <i>BRCA</i> mutation (category 2B) ▶ Olaparib for HRR mutation other than <i>BRCA1/2</i>^{III} ▶ Pembrolizumab for MSI-H/dMMR or TMB ≥10 mut/Mb^{ddd} (category 2B) ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Sipuleucel-T^{ddd,ooo} ▶ Talazoparib/enzalutamide for HRR mutation^{z,III} (category 2B) • Other recommended regimens ▶ Other secondary hormone therapy^z
Progression on prior docetaxel/no prior novel hormone therapy ^{jjj}	Progression on prior docetaxel and a novel hormone therapy ^{jjj}
• Preferred regimens ▶ Abiraterone^{z,kkk} (category 1) ▶ Cabazitaxel^{ddd} ▶ Enzalutamide^z (category 1) • Useful in certain circumstances ▶ Cabazitaxel/carboplatin^{ddd} ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{ddd} ▶ Niraparib/abiraterone^{z,III,mmm} for <i>BRCA</i> mutation ▶ Olaparib/abiraterone^{z,kkk,III} for <i>BRCA</i> mutation ▶ Pembrolizumab for MSI-H/dMMR^{ddd} (category 2B) ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Sipuleucel-T^{ddd,ooo} ▶ Talazoparib/enzalutamide for HRR mutation^{z,III} • Other recommended regimens ▶ Other secondary hormone therapy^z	• Preferred regimens ▶ Cabazitaxel^{ddd} (category 1) ▶ Docetaxel rechallenge^{ddd} • Useful in certain circumstances ▶ Cabazitaxel/carboplatin^{ddd} ▶ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) for PSMA-positive metastases^{PPP} (category 1) ▶ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies^{ddd} ▶ Olaparib for HRR mutation^{III} (category 1 for <i>BRCA</i> mutation) ▶ Pembrolizumab for MSI-H/dMMR, or TMB ≥10 mut/Mb^{ddd} ▶ Radium-223^{s,nnn} for symptomatic bone metastases (category 1) ▶ Rucaparib for <i>BRCA</i> mutation^{III} • Other recommended regimens ▶ Other secondary hormone therapy^z



Preindex ARPI received

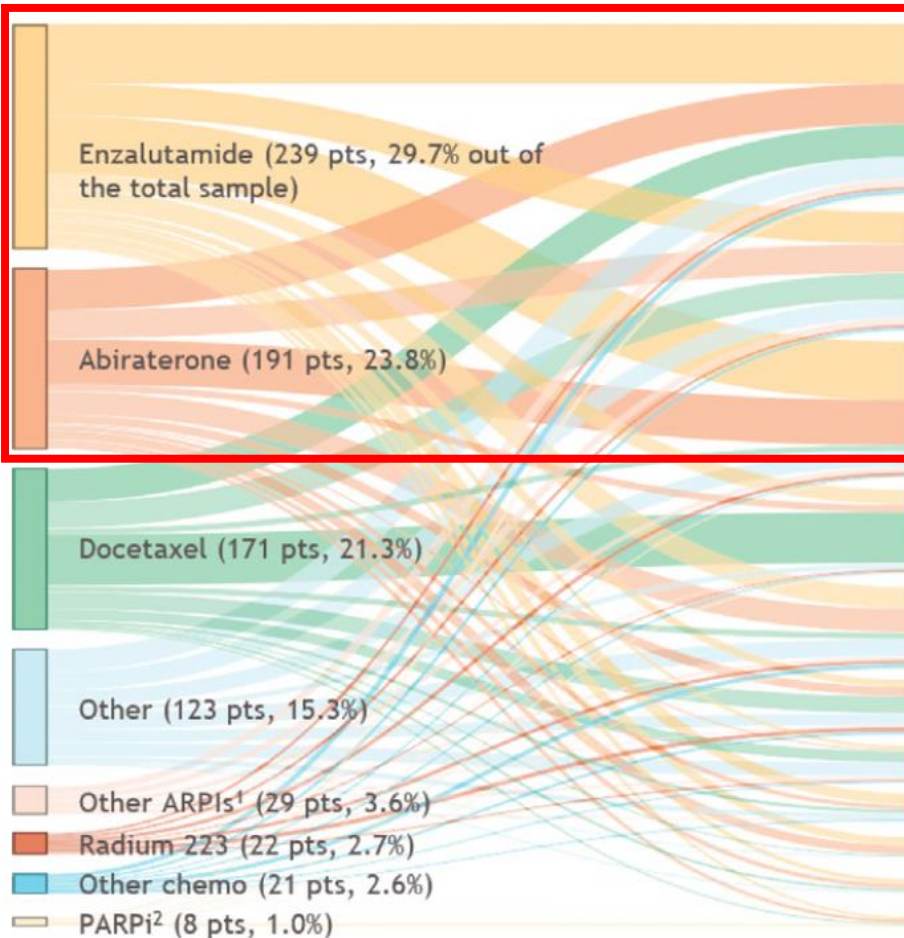
Number of ARPI-containing LOTs received, *n* (%)

1	791 (98.4)
2	10 (1.2)
3	2 (0.2)
4	1 (0.1)

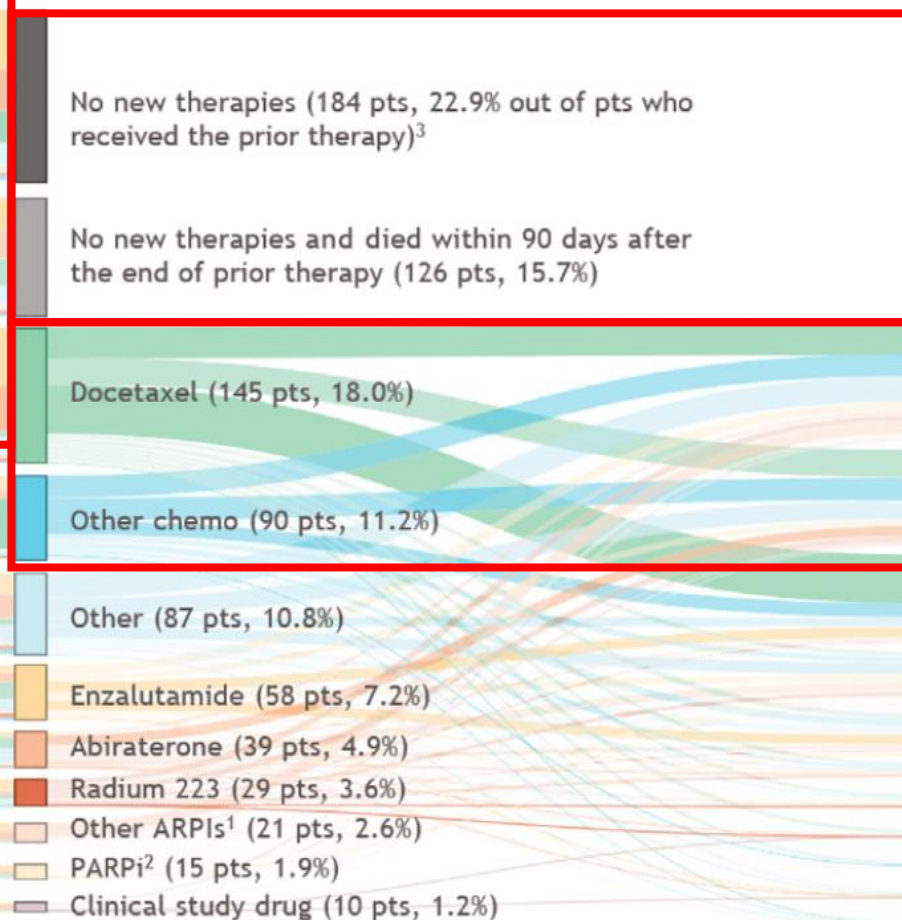
Types of ARPI received, *n* (%)

Abiraterone	435 (54.1%)
Enzalutamide	352 (43.8%)
Apalutamide	26 (3.2%)
Darolutamide	2 (0.2%)

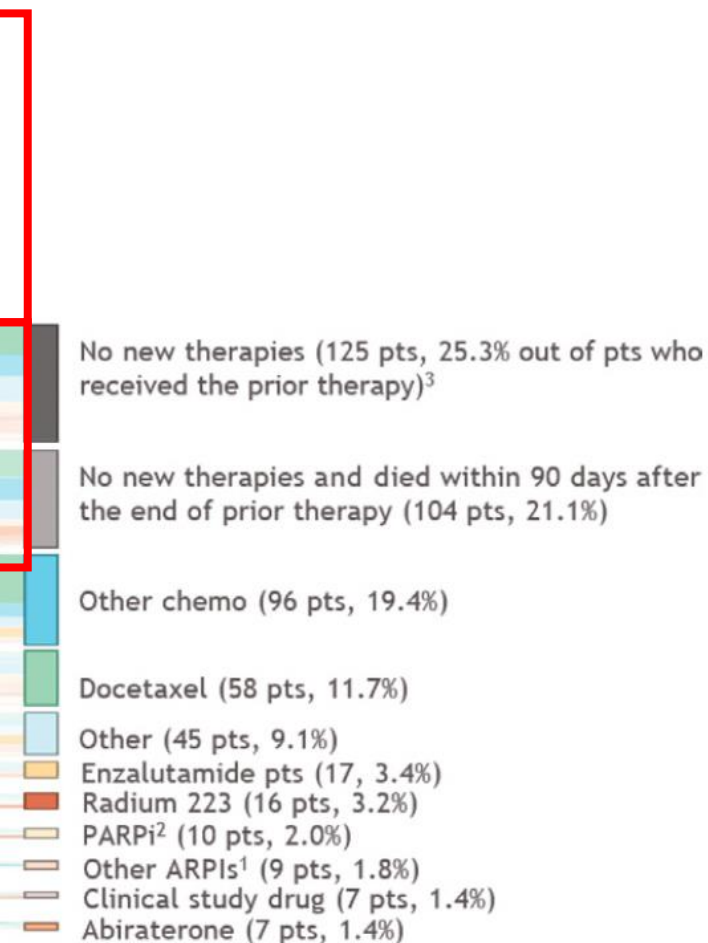
Index therapy (804 pts received)



The first therapy after index therapy (494 pts received)

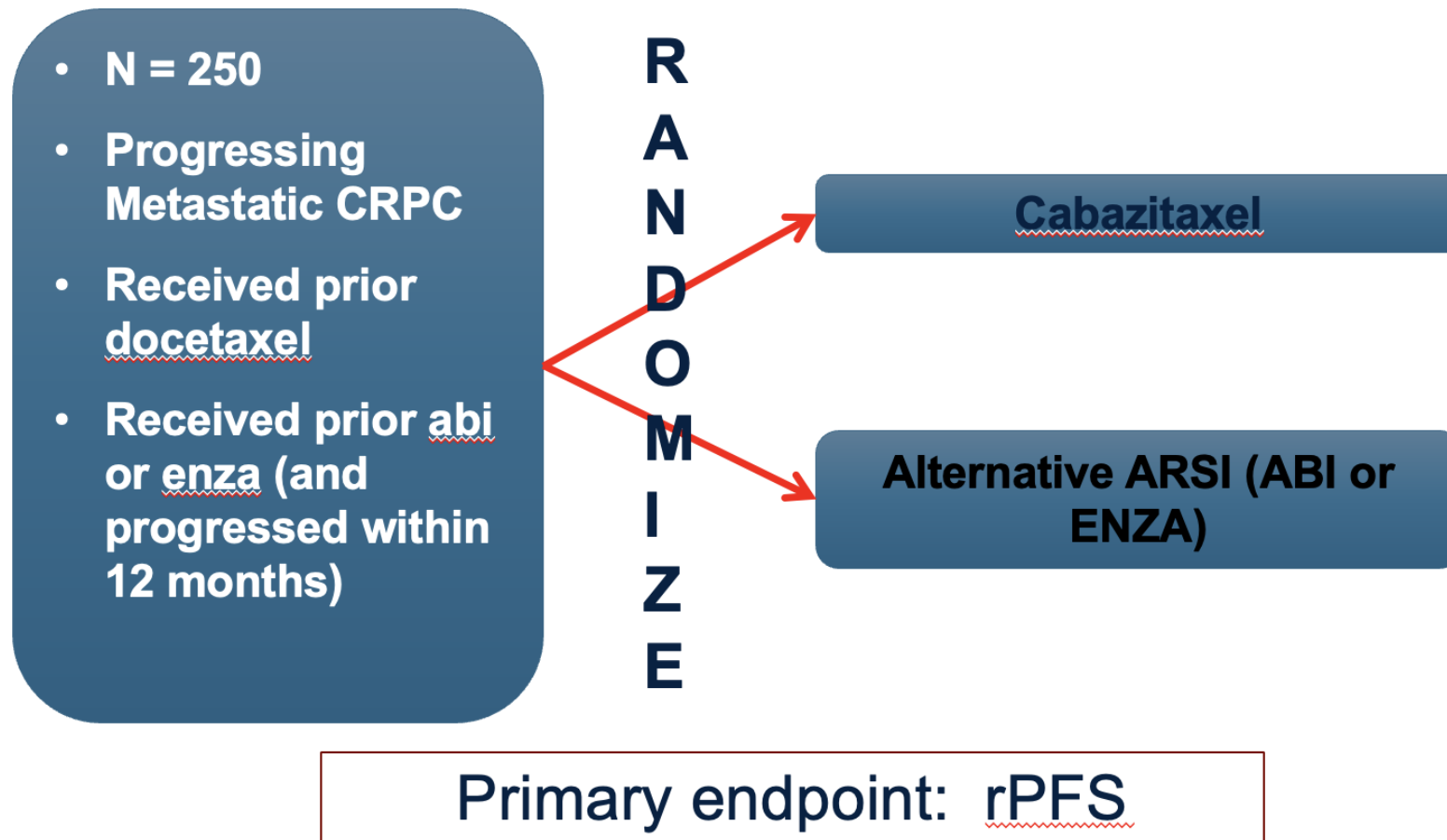


The second therapy after index therapy (265 pts received)



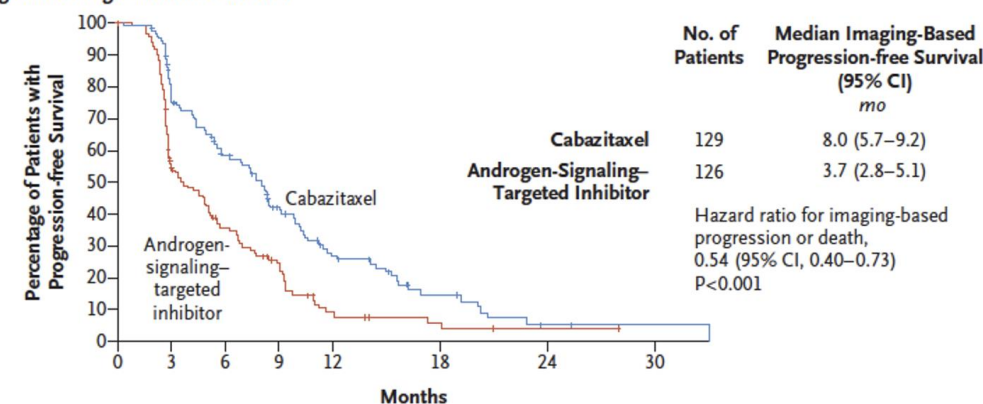
Post-ARPI and Post-Docetaxel Setting

CARD TRIAL



Liver or lung metastases — no. (%)	21 (16.3)	25 (19.8)
PSA — ng/ml		
Mean	264.4±1352.5	232.9±453.8
Median (range)	62.0 (1.1–15,000.0)	60.5 (1.5–2868.0)
Neutrophil count per mm ³		
Mean	5000±2000	4700±1700
Median (range)	4500 (2000–11,000)	4500 (2000–9000)
Hemoglobin — g/liter		
Mean	122.0±14.1	121.2±14.1
Median (range)	121.0 (91–170)	122.0 (82–162)
Alkaline phosphatase — IU/liter		
Mean	226.6±322.2	235.3±306.8
Median (range)	132.5 (41–2275)	122.0 (35–1980)
Lactate dehydrogenase — IU/liter		
Mean	331.0±276.3	348.5±348.3
Median (range)	248.0 (135–2753)	251.0 (50–3374)
Type of progression at trial entry — no. (%)		
PSA only	11 (8.5)	10 (7.9)
Imaging-based, with or without PSA progression	23 (17.8)	16 (12.7)
Pain, with or without PSA or imaging-based progression	86 (66.7)	90 (71.4)
Missing data	9 (7.0)	10 (7.9)
Disease history		
M1 disease at diagnosis — no. (%)‡	49 (38.0)	60 (47.6)
Gleason score 8–10 at diagnosis — no. (%)§	73 (56.6)	81 (64.3)
First androgen-deprivation therapy		
Median duration (range) — mo	13.7 (2–114)	12.6 (3–179)
Duration <12 mo — no. (%)	56 (43.4)	57 (45.2)
Previous androgen-signaling-targeted inhibitor — no. (%)		
Abiraterone	56 (43.4)	67 (53.2)
Enzalutamide	72 (55.8)	59 (46.8)
Missing data	1 (0.8)	0
Timing of previous androgen-signaling-targeted inhibitor — no. (%)		
Before docetaxel	50 (38.8)	49 (38.9)
After docetaxel	79 (61.2)	77 (61.1)
Time from initiation of previous androgen-signaling-targeted inhibitor to progression ≤6 mo — no. (%)	65 (50.4)	62 (49.2)

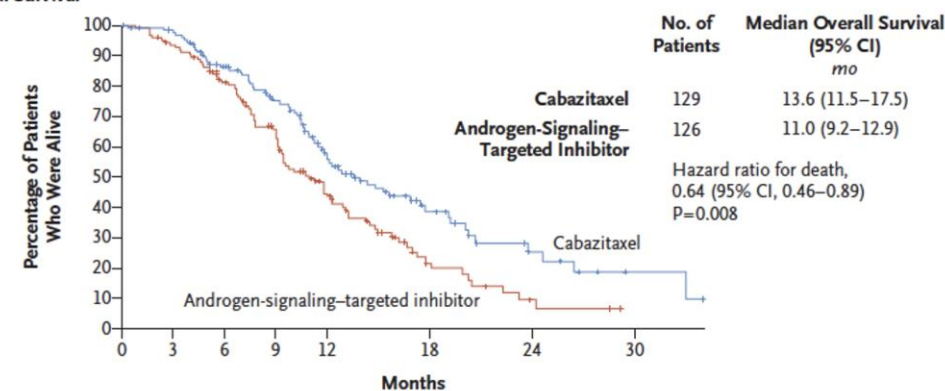
A Imaging-Based Progression-free Survival



No. at Risk

Cabazitaxel	129	91	64	41	23	9	2	1
Androgen-signaling-targeted inhibitor	126	61	36	22	7	3	1	0

A Overall Survival



No. at Risk

Cabazitaxel	129	122	96	77	51	21	8	2
Androgen-signaling-targeted inhibitor	126	116	88	64	39	11	3	0

Post-ARPI and Post-Docetaxel Setting

[¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedy, Natalie K Rutherford, Andrew Weickhardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakhher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet*, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†

KEY ELIGIBILITY

- mCRPC post docetaxel suitable for cabazitaxel
- Progressive disease with rising PSA and PSA ≥ 20 ng/mL
- Adequate renal, haematologic and liver function
- ECOG performance status 0-2



⁶⁸Ga-PSMA + ¹⁸F-FDG PET/CT

- PSMA SUV_{max} > 20 at any site
- Measurable sites SUV_{max} > 10
- No FDG positive/PSMA negative sites of disease
- Centrally reviewed

ELIGIBILITY

Metastatic castration-resistant prostate cancer post docetaxel suitable for cabazitaxel



PSMA + FDG PET/CT
SUV_{max} ≥ 20 at a site of disease
Measurable sites SUV_{max} > 10
No discordant FDG+ PSMA-disease
Centrally reviewed



¹⁷⁷Lu-PSMA-617

8.5 GBq i.v. q6 weekly
↓ 0.5GBq/cycle
Up to 6 cycles

SPECT/CT @ 24 h

suspend Rx if exceptional response; recommence upon progression

1:1 randomization

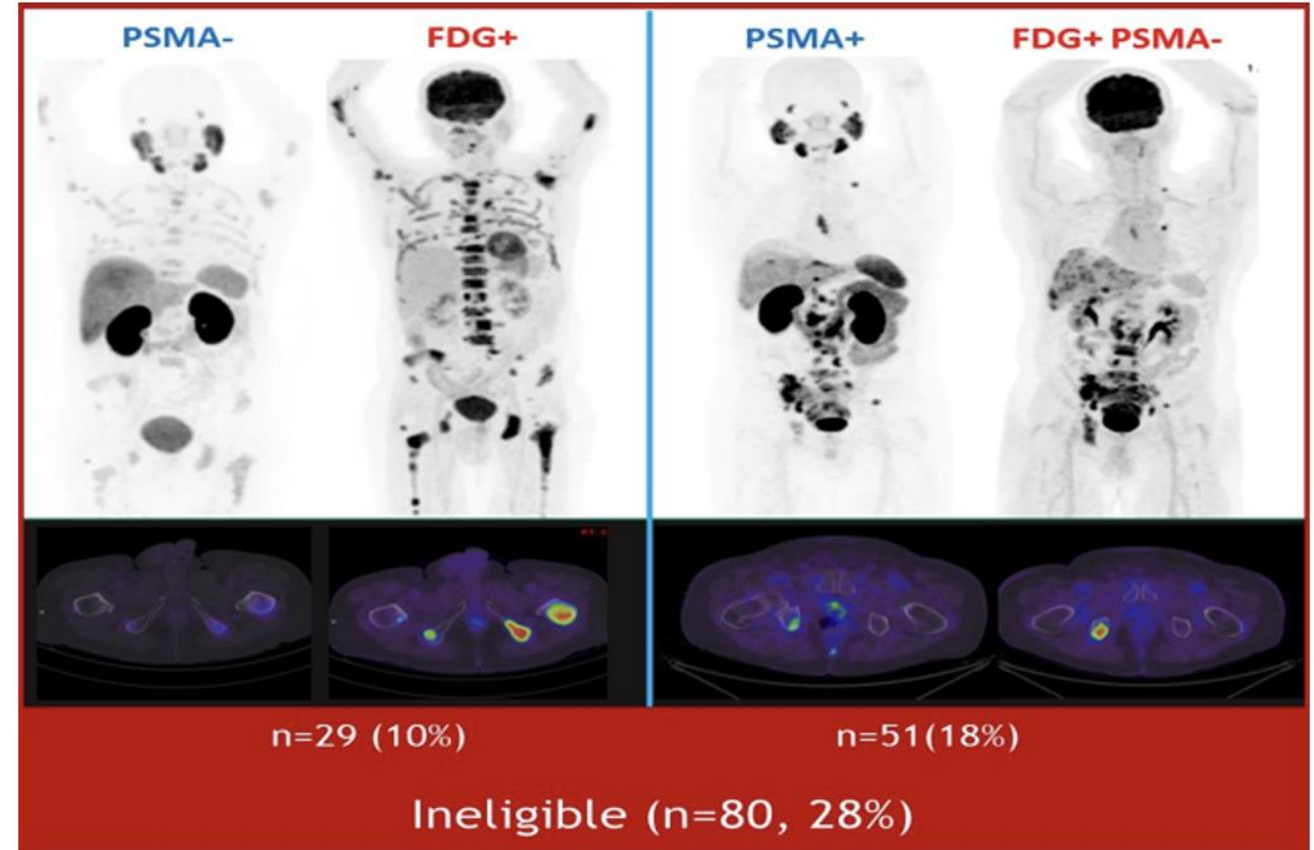
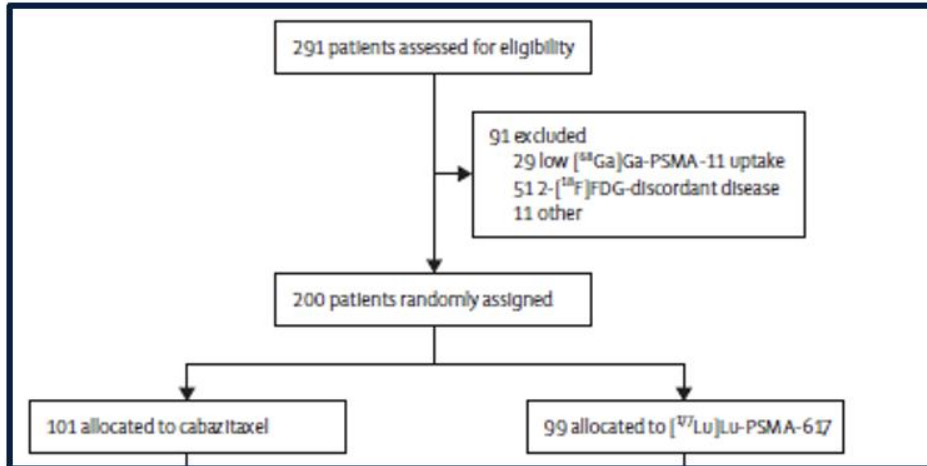
Stratified by:

- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

CABAZITAXEL

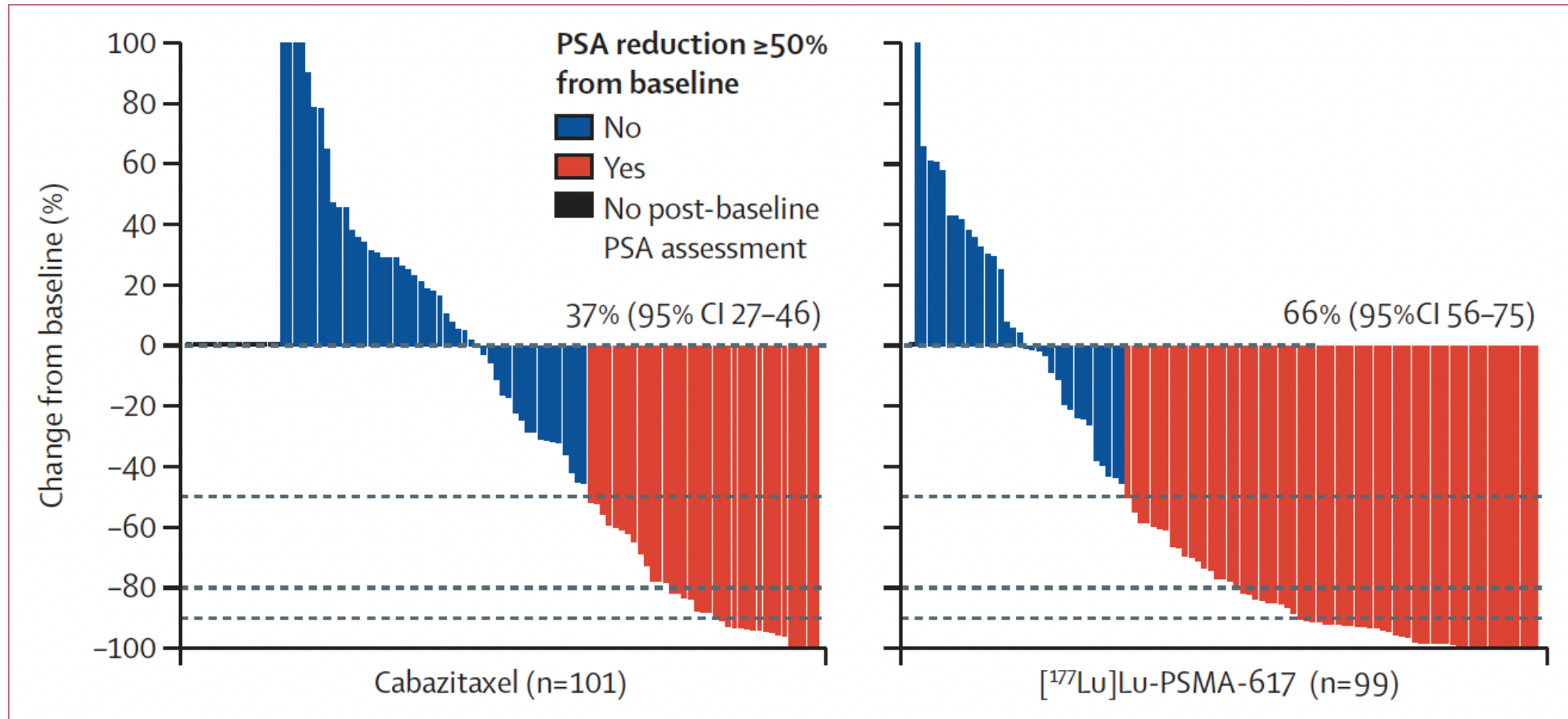
20mg/m² i.v. q3 weekly,
Up to 10 cycles

PSMA PET / FDG PET PATIENT SELECTION

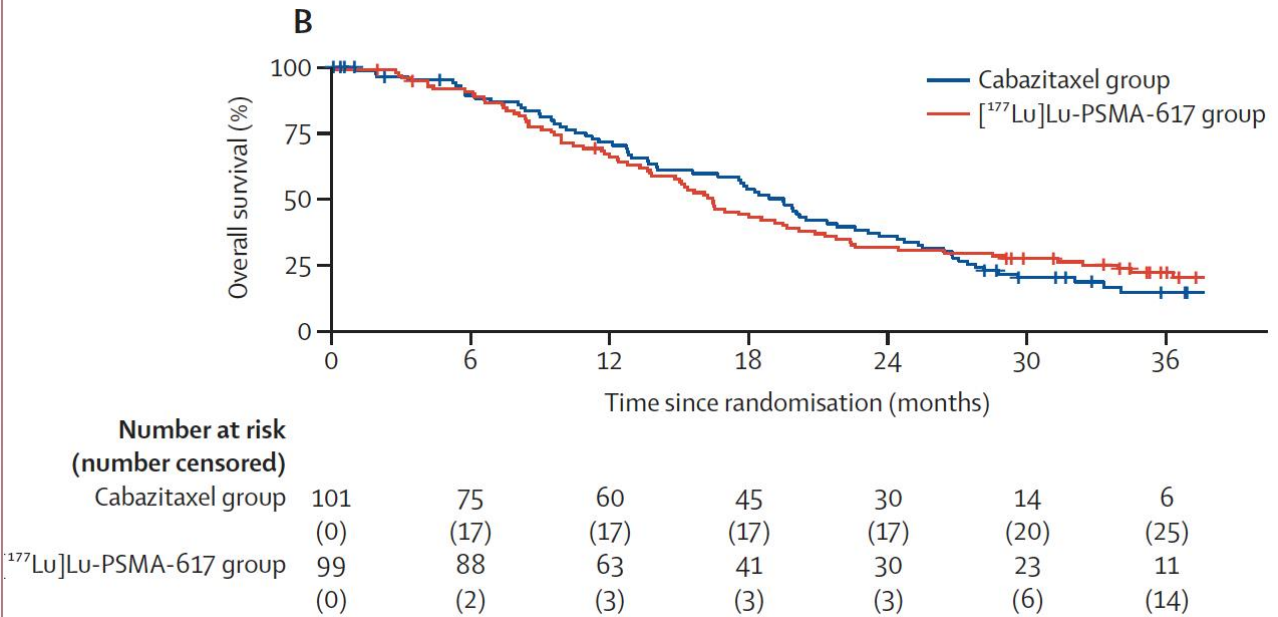
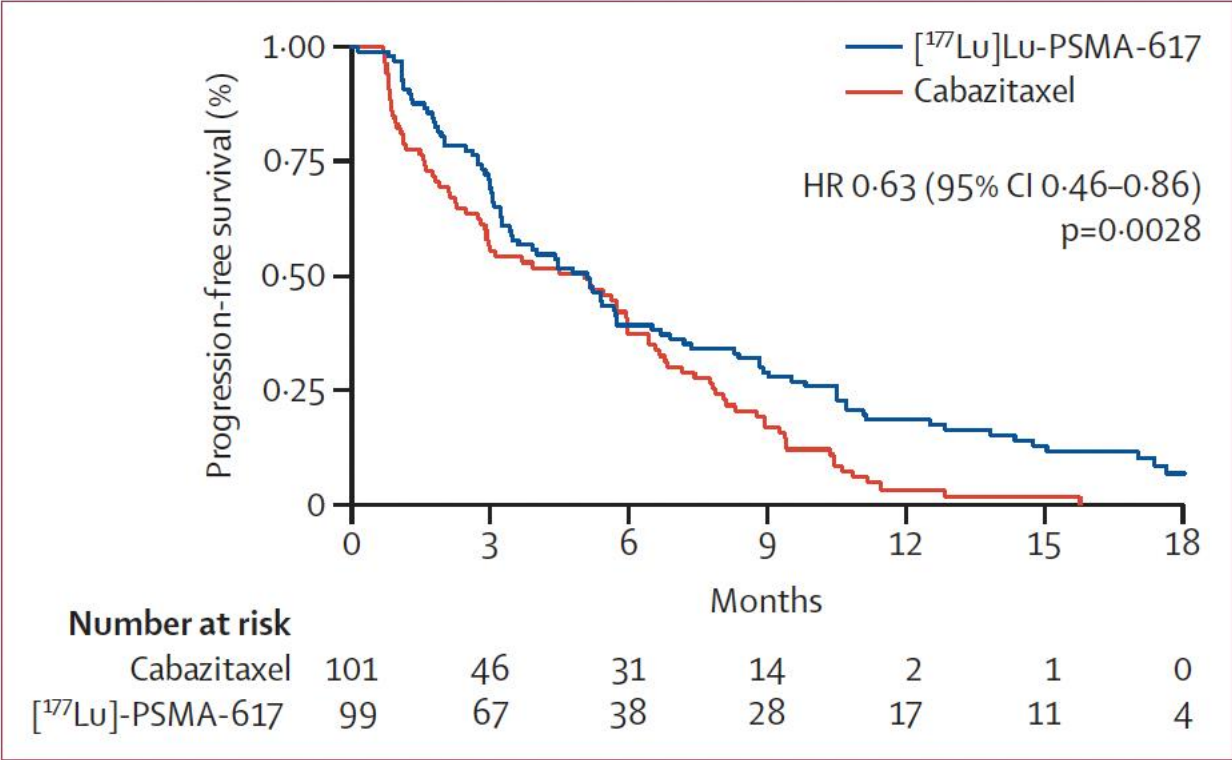


Excluded Patients with PSMA-low or FDG positive / PSMA discordant disease sites

Primary Endpoint: PSA50 Response



PFS and OS Outcomes

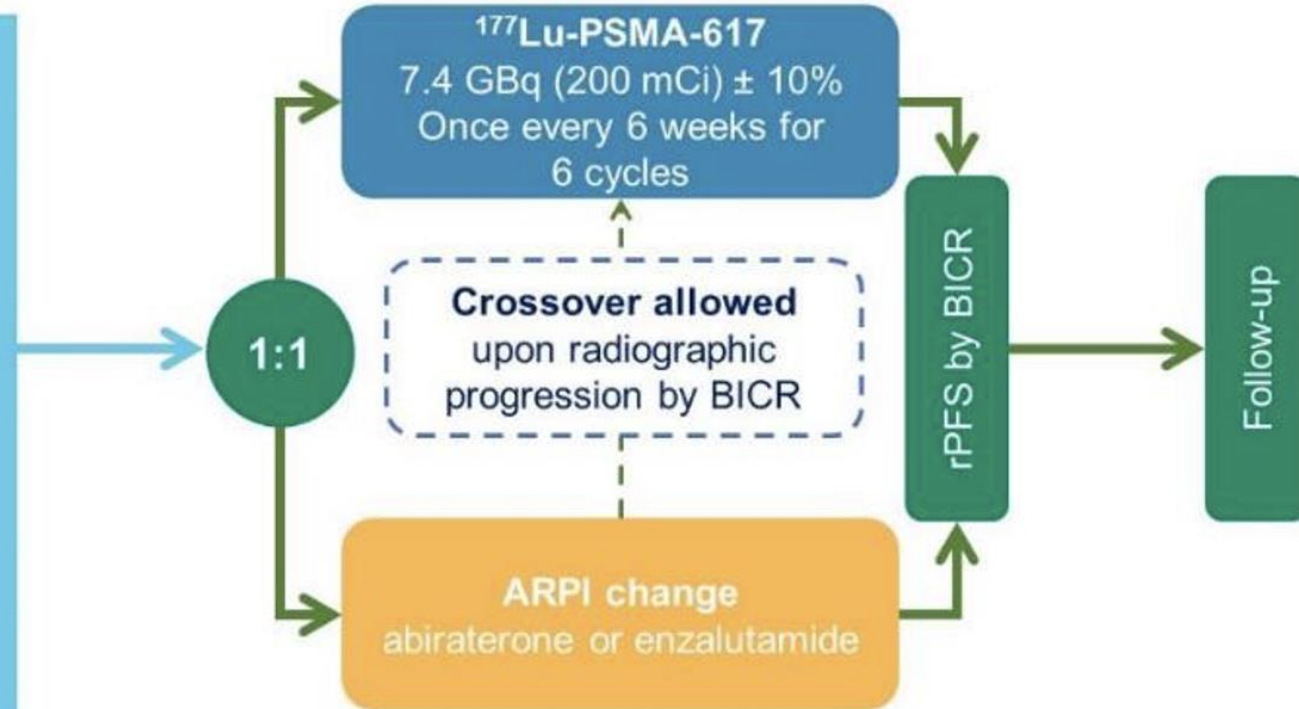


Post-ARPI and Pre-Docetaxel Setting

PSMAfore: a phase 3, randomized, open-label study

Eligible adults

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



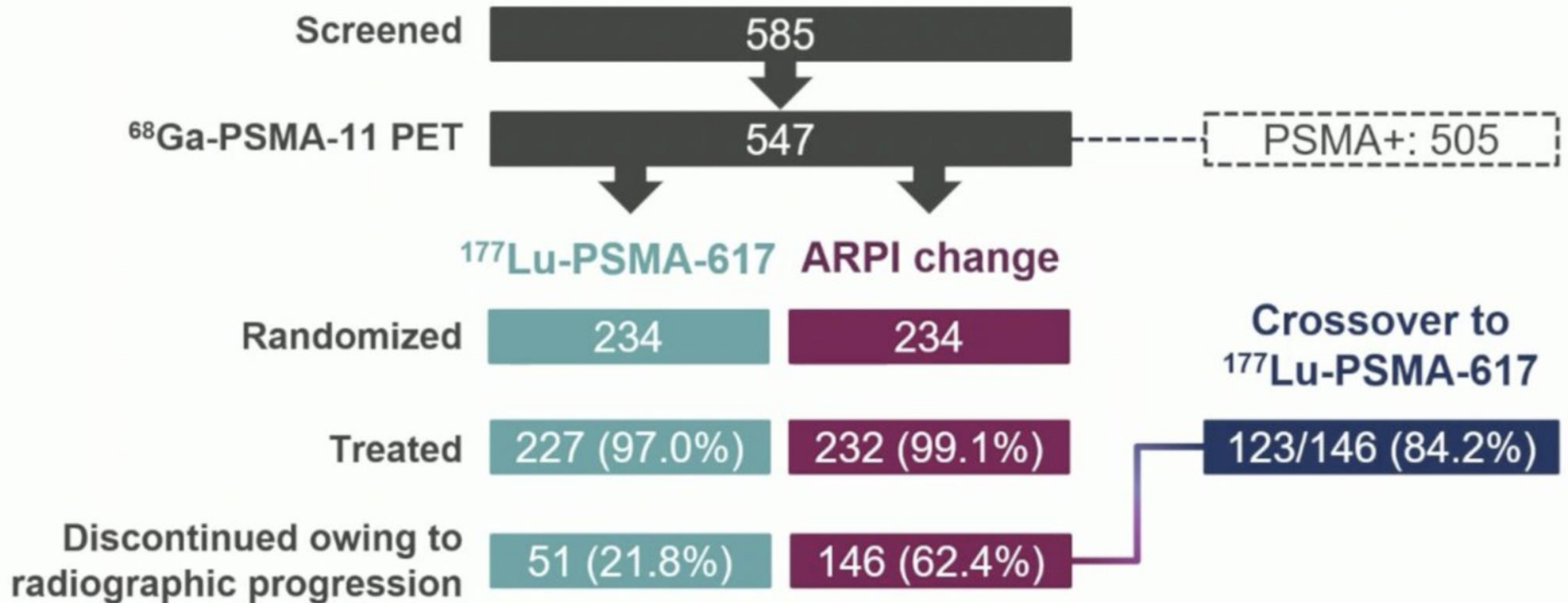
Stratification factors

- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

ARPI, androgen receptor pathway inhibitor; BICR, blinded independent central review; BPI-SF, brief pain inventory – short form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; PARPi, Poly (ADP-ribose) polymerase (PARP) inhibitor; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

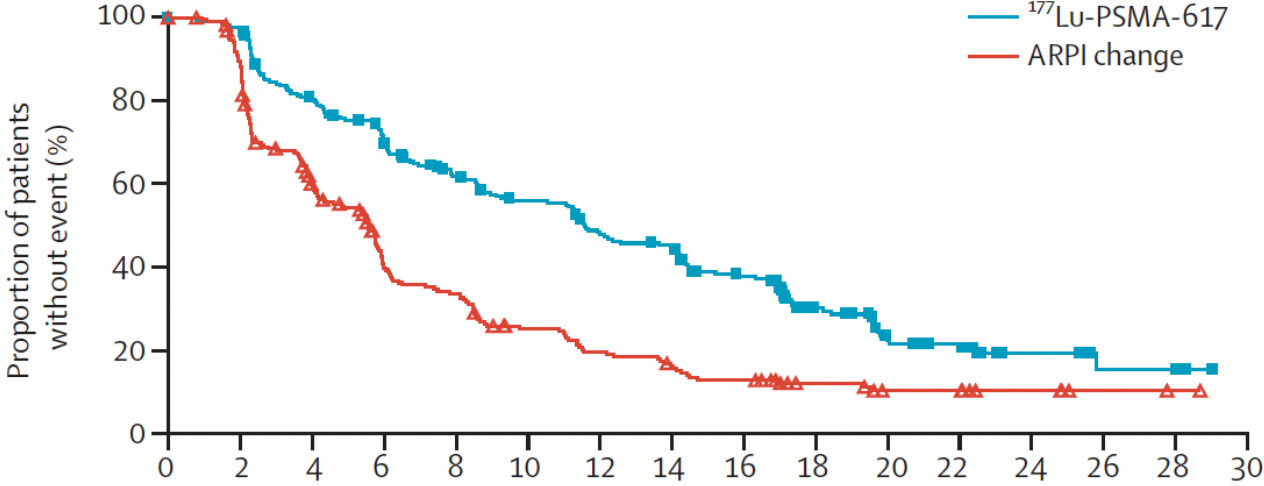
Baseline patient characteristics

	¹⁷⁷ Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Age, median (range), years	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)
Hemoglobin, median (range), g/L	128.0 (88–155)	129.0 (88–156)
Alkaline phosphatase, median (range), IU/L	100.0 (36–1727)	103.5 (28–1319)
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)



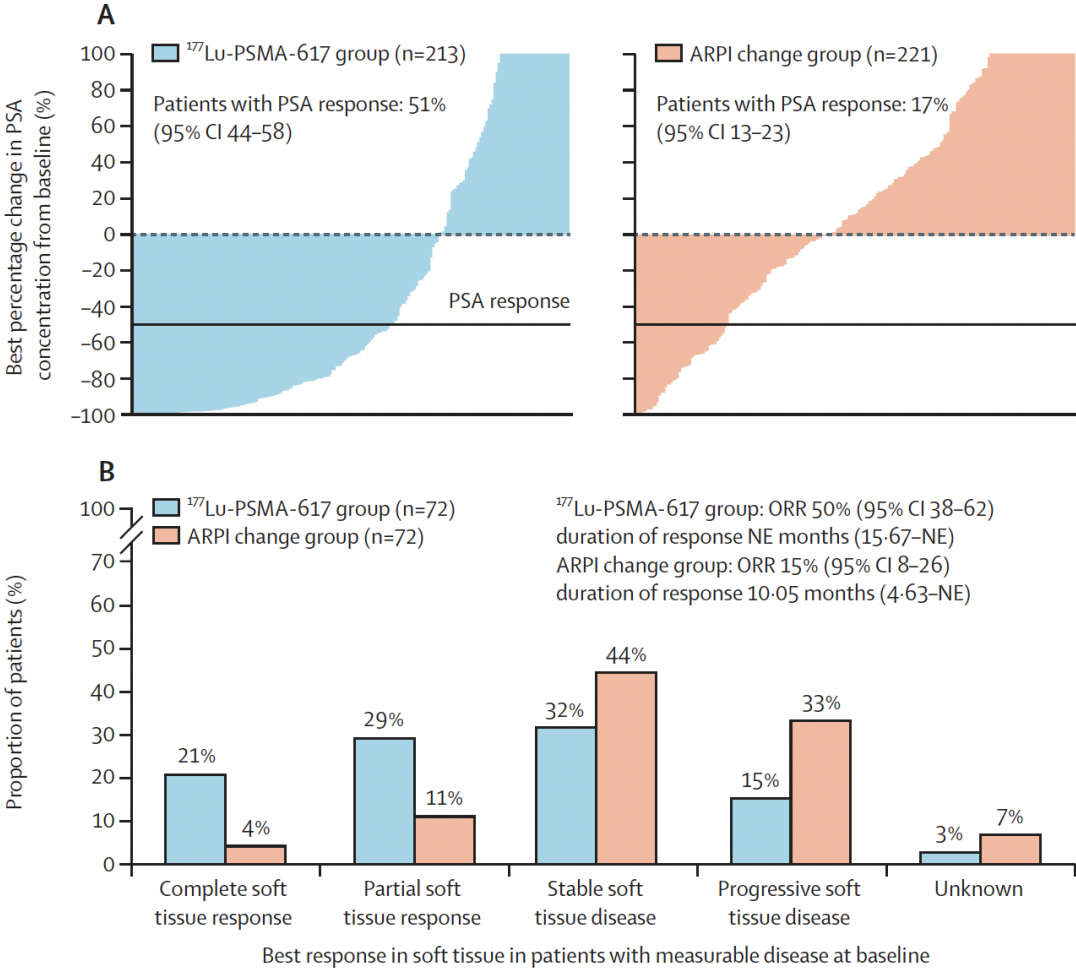
A Radiographic progression-free survival

¹⁷⁷Lu-PSMA-617 group: median 11·60 months (95% CI 9·30–14·19), 154 events
ARPI change group: median 5·59 months (95% CI 4·21–5·95), 180 events
HR 0·49 (95% CI 0·39–0·61)



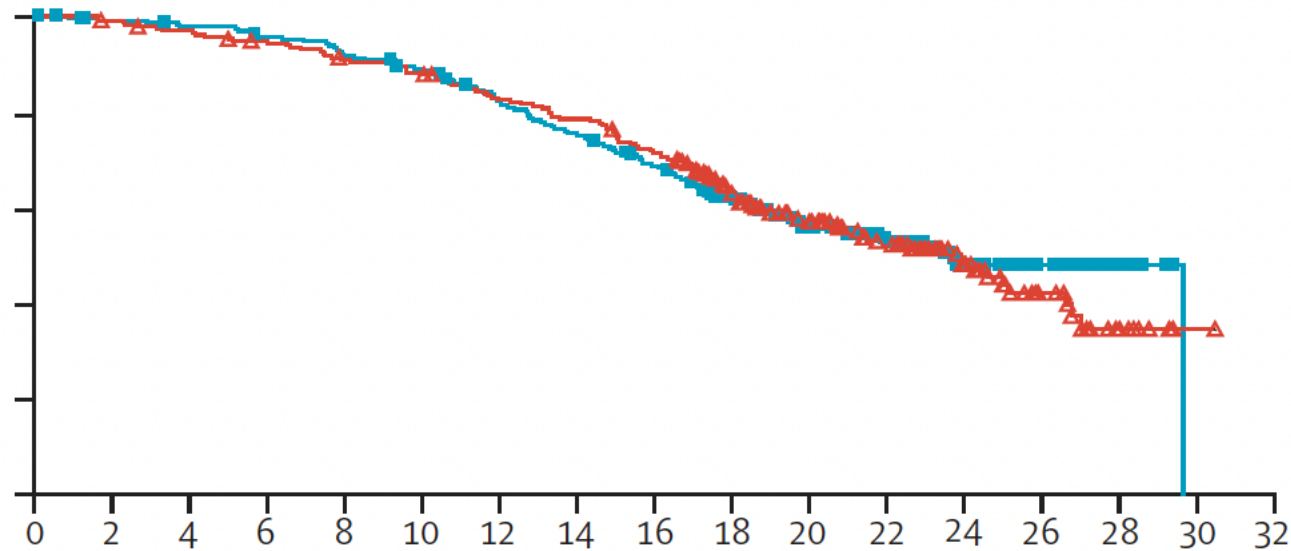
**Number at risk
(number censored)**

¹⁷⁷ Lu-PSMA-617 group	234	217	175	152	126	111	94	86	67	39	25	20	8	4	4	0
	(0)	(12)	(5)	(3)	(6)	(3)	(2)	(1)	(6)	(16)	(6)	(3)	(10)	(3)	(0)	(4)
ARPI change group	234	197	126	79	65	45	35	28	22	14	9	9	5	2	1	0
	(0)	(14)	(7)	(9)	(0)	(4)	(0)	(1)	(0)	(7)	(3)	(0)	(4)	(3)	(1)	(1)



B Overall survival (intention-to-treat analysis)

¹⁷⁷Lu-PSMA-617 group: median 23.66 months (95% CI 19.75–NE), 104 events
 ARPI change group: 23.85 months (20.60–26.55), 112 events
 HR 0.98 (95% CI 0.75–1.28), p=0.44



Crossover:

134/234 (57.3%) in ARPI change group
 134/173 (77.5%) eligible patients

RPSFT crossover-adjusted OS analysis

- HR: 0.98 (95% CI: 0.76, 1.27)
- No difference versus the ITT analysis because RPSFT cannot adjust for crossover confounding in the context of overlapping ITT curves

234	228	224	218	209	200	181	167	150	116	81	65	33	21	11	0	0
(0)	(4)	(1)	(1)	(0)	(2)	(3)	(0)	(3)	(19)	(25)	(12)	(28)	(12)	(10)	(10)	(0)
234	231	225	217	208	200	187	178	161	126	95	71	40	20	7	1	0
(0)	(1)	(1)	(2)	(1)	(1)	(1)	(0)	(1)	(17)	(20)	(17)	(27)	(16)	(10)	(6)	(1)

Closing Thoughts

- ❑ After failure of AR pathway inhibitor, treatment sequencing is complex, with limited prospective data
- ❑ Although available treatment options, many are not utilized (likely due to a multitude of factors)
- ❑ In **post-ARPI / post-docetaxel** setting:
 - ❑ Cabazitaxel, LuPSMA-177 both have supportive prospective evidence
- ❑ In **post-ARPI / pre-docetaxel** setting, potential use of PSMA TRT
- ❑ Importance of **early/adequate molecular testing** to best inform treatment options/sequencing

ACS ECHO Session 4 CRPC Treatment

March 6, 2025

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Prostate Cancer: Case 1

- 57-year-old man, Mr. Jones
- Presented in July 2021 with back pain, urinary complaints to 1st visit with PCP
 - PMHX : Mild HTN, GERD
 - FmHX : Grandfather prostate cancer
 - SocHx: Married, 2 grown children, works as contractor
- PSA 950 (no prior levels) : referred to Urology
- Prostate cancer diagnosed by TRUS biopsy as Adenocarcinoma
 - Gleason 9 (8/12 cores)

Prostate Cancer: Case 1

- Imaging showed high volume disease with 6 spinal lesions, one scapula lesion, several pelvic bone mets, a few calvarial mets, multiple 1-2 cm pelvic and RP LN
- Palliative RT to spine improved pain symptoms
- Referred to medical oncology for multi-disciplinary management
- Tumor NGS and genetic testing negative

Prostate Cancer Case 1

- Treated with Triplet therapy in 2021: ADT/Docetaxel x6 and Abiraterone/P
- PSA nadir of <0.1
- Imaging revealed substantial improvement in bone lesions and resolve of LN
- PSA remains zero until January of 2025 when it rises to PSA 5
- Imaging February 2025 reveals new bone lesions in spine, increase in old bone lesions and new pelvic LN
- Asymptomatic now

Prostate Cancer Case 2

- 75-year-old man, Mr. Smith
- Diagnosed with prostate cancer Gleason 4 +3 =7, PSA 12
- Treated with Robotic prostatectomy in 7/2015
- pT2N0, but positive apical and posterior margin positive
 - PSA Nadir 0 at 3 months from surgery, followed every 3 months
- PSA detectable at 1.0 about 18 months from surgery indicating biochemical relapse.
 - Imaging negative
- He received RT to prostate bed and ADT x 1 year completing in 12/2017

Prostate Cancer Case 2

- PMHX : HTN, HLD , DM (well controlled)
- FMHX:
 - Father and Paternal uncle prostate cancer
 - Paternal GM with breast cancer
- SocHX: Retired, married, several GK, Active with golf and gardening
- PSA 0 after Radiotherapy/ADT
- Testosterone normalizes 6 months after completed ADT
- PSA remains undetectable for 3 years

Prostate Cancer Case 2

- Patient was moved to yearly PSA monitoring PSA (missed a year due to Covid)
 - Most recent PSA rose to 10
- Imaging with PSMA PET now reveals 3 bone lesions and 4 small pelvic LN
- Testosterone is 345
- Asymptomatic
- Genetic Testing reveals BRCA2 mutation
- Now patient is 79 years old with low volume metachronous metastatic disease

Prostate Cancer Case 2

- ADT and Apalutamide started Feb 2021 for HSPC
 - Chemo deferred
- PSA returns to 0 after 3 months and imaging at 6 months (8/2021) shows improved bone lesions and resolved LN
- PSA undetectable until January 2025 when shown to be 3
- Imaging shows increased bone lesions and new pelvic LAD

Thank You

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Schedule Your Case Presentation Now



We will work to ensure your experience is **easy** and **valuable**.

Session	Date 11:00 AM – 12:00 PM EST	Day	Didactic Topic	Case Presenter 3-5 Minutes
5	April 11, 2025	Friday	Treatment of Small Cell/Neuroendocrine Prostate Cancer	AVAILABLE
6	May 8, 2025	Thursday	Treatment Choice in Somatic and Germline Genetic Testing for Advanced Prostate Cancer	AVAILABLE
7	June 6, 2025	Friday	Novel Imaging in Advanced Prostate Cancer	St Joseph/Candler & Mississippi Baptist Medical Center
8	July 10, 2025	Thursday	Radiopharmaceuticals for Metastatic Prostate Cancer	North MS Health Services
9	August 8, 2025	Friday	Quality of Life and Shared Decision Making: Sexual Dysfunction and Side Effects of Androgen Deprivation Therapy	Nancy N. and J.C. Lewis Cancer & Research Pavilion at St Joseph's/Candler
10	September 11, 2025	Thursday	TBD	AVAILABLE

Survey Time!

Participants Only

Post-Session 4 Survey



How to Use a QR Code



1. **Turn on** your phone camera
2. **Aim** the camera at the code
3. A link will show up
4. **Tap** the link to go to the survey

Take it now! Survey closes next Thursday, March 13th

Reminders

Session 4 Slides, Recordings, & Resources will be made available within one week on the [ACS ECHO Website](#).



Is **Session 5** on your calendar?

Friday, April 11, 2025

11:00 AM – 12:00 PM EST

Topic: *Treatment of Small Cell/Neuroendocrine Prostate Cancer*

Presenter: William K. Oh, MD, Professor of Medicine, Yale School of Medicine
Director of Precision Medicine, Yale Cancer Center and Smilow Cancer Hospital

Improving Treatment in Advanced Prostate Cancer ECHO



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Questions?

Post-Session 4 Survey



ECHO Resources

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