

#guardsymposium2026
X @GuardConsortium



GUARD INTERNATIONAL SYMPOSIUM

GU-Alliance for Research and Development

PRESENCIAL RETRANSMITIDO EN DIRECTO
FACE-TO-FACE AND LIVE STREAMING



16-18 SEPTIEMBRE 2026

Espacio Maldonado, Madrid

How to implement the use of RLTs in mCRPC

David Kersting

DISCLOSURES

ADVISORY AND CONSULTANCY ROLES

Novartis, GE Healthcare

HONORARIA

Alnylam, Novartis, Pfizer

RESEARCH FUNDING

Pfizer

TRAVEL SUPPORT

Life Molecular Imaging, Sanofi

PSMA – A TARGET FOR PC TUMOR VISUALISATION

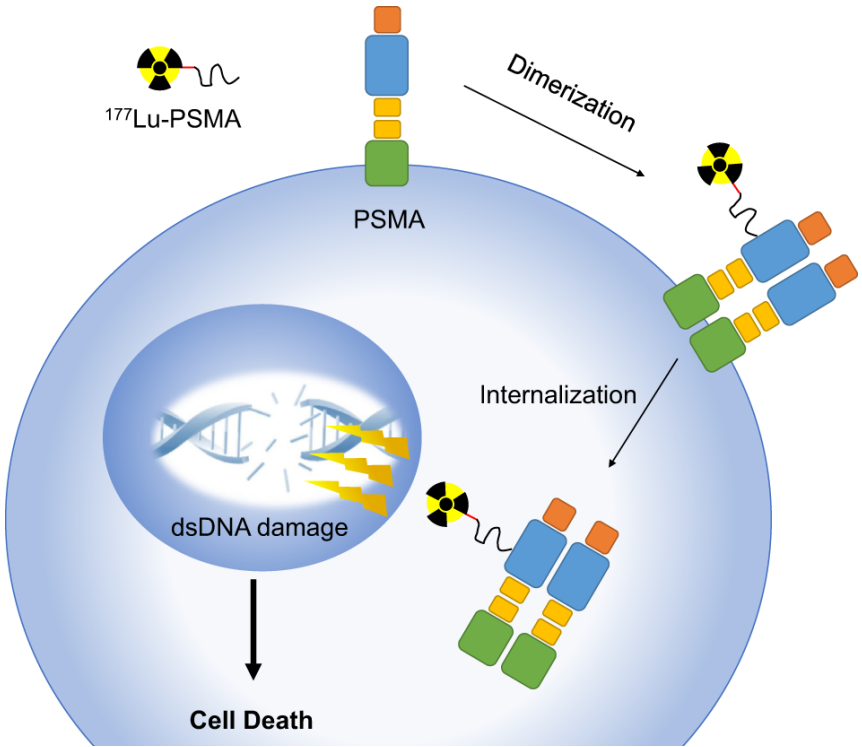
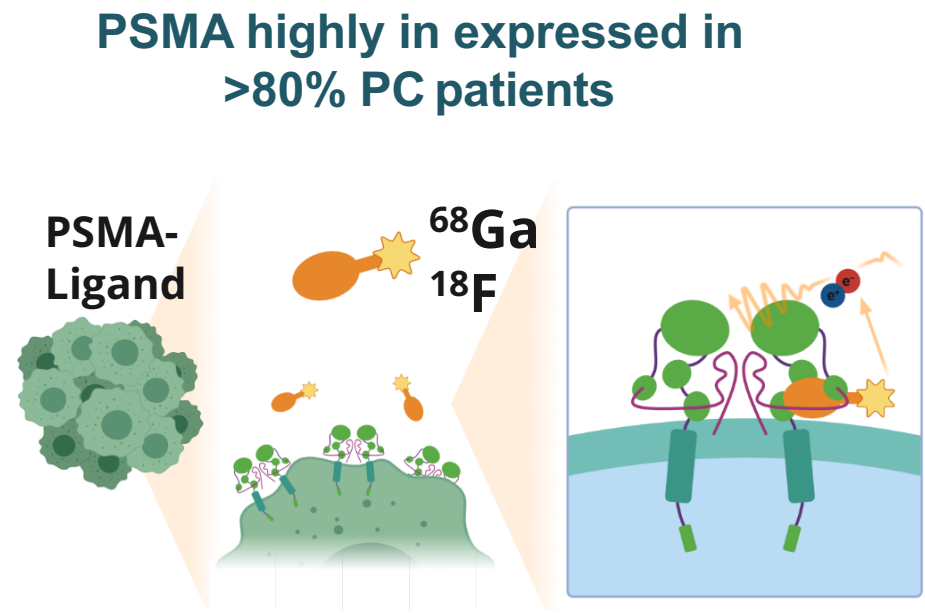
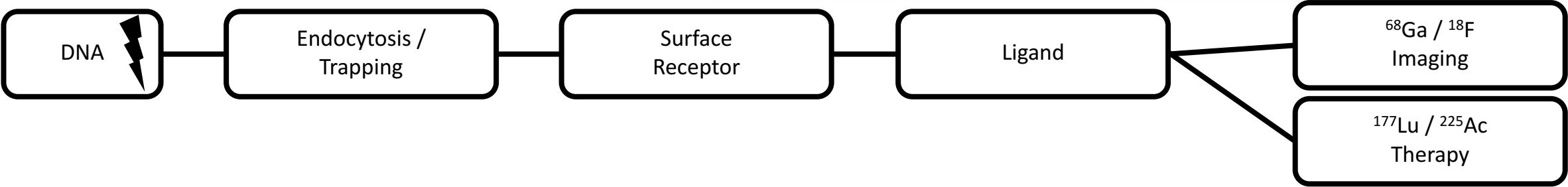


Figure made in BioRender.com

WHERE ARE WE NOW? THERANOSTIC PRINCIPLE

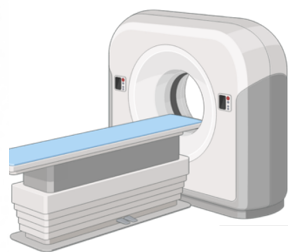
Diagnostics

See what you treat

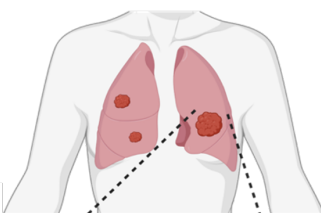
Therapy



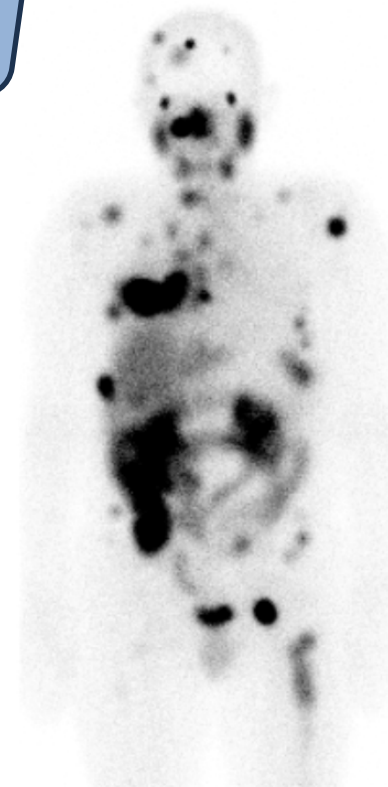
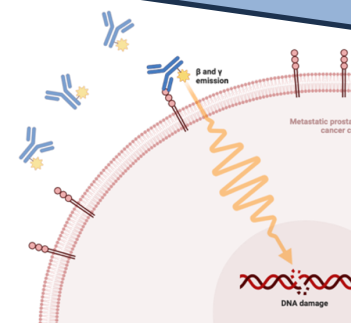
Pre-therapeutic
PET



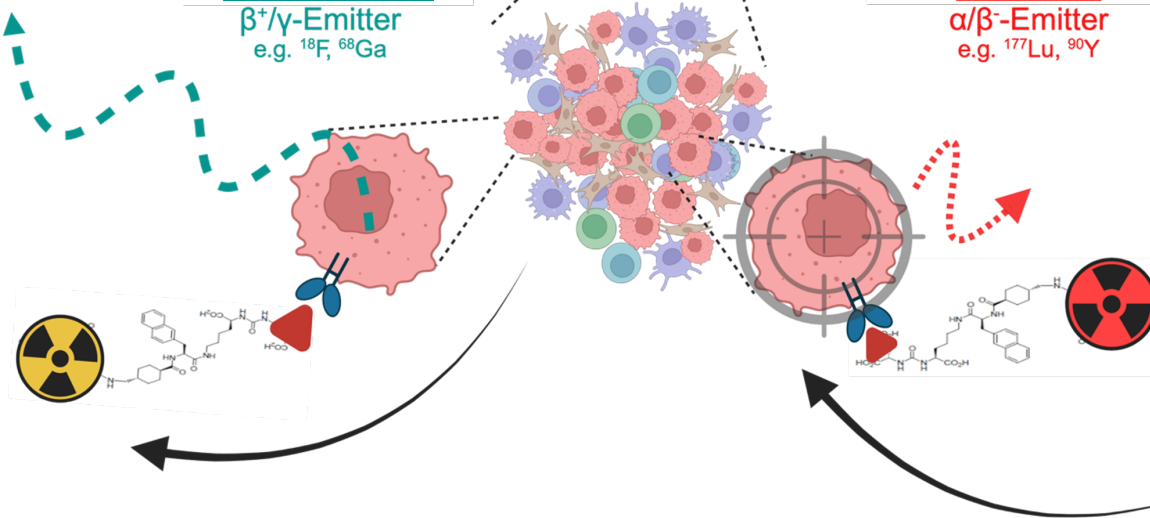
Diagnostics
 β^+/γ -Emitter
e.g. ^{18}F , ^{68}Ga



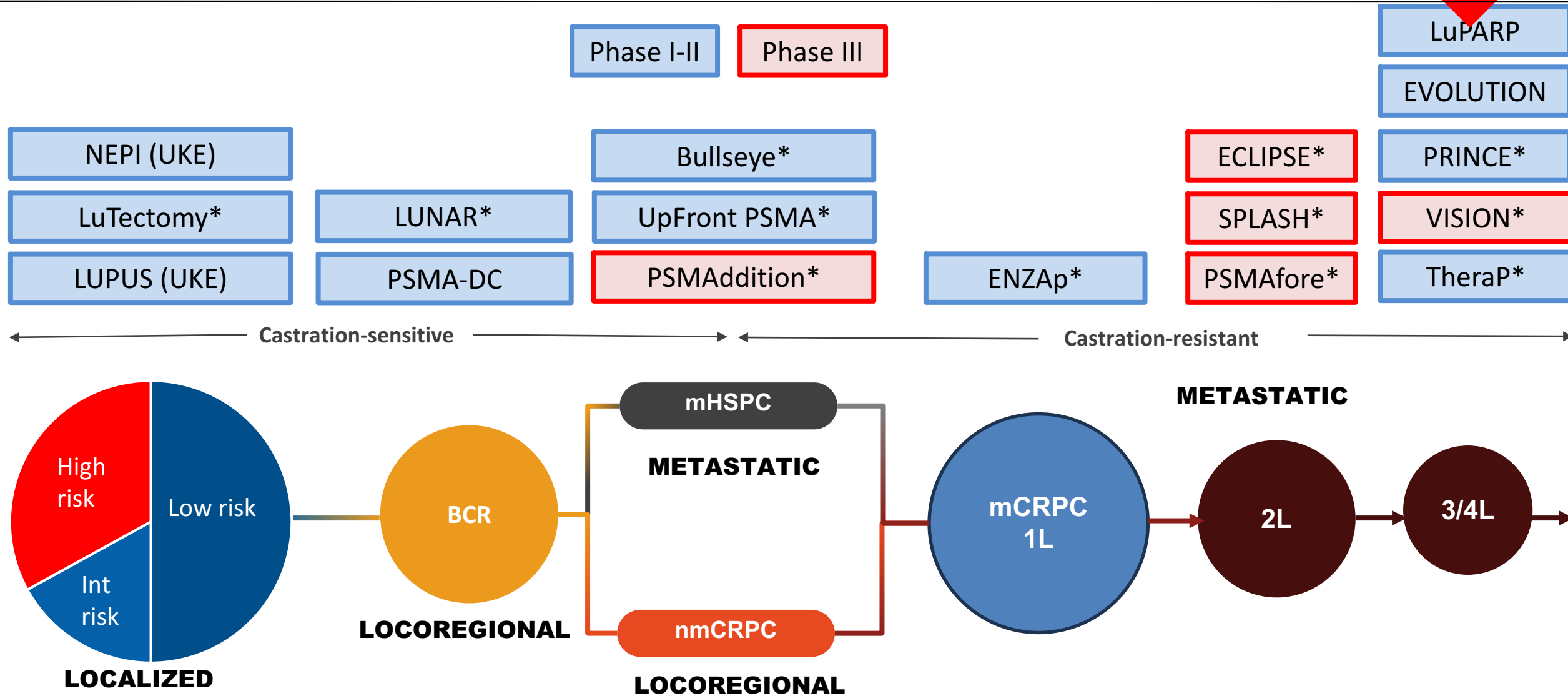
Therapy
 α/β -Emitter
e.g. ^{177}Lu , ^{90}Y



Intra-therapeutic
SPECT

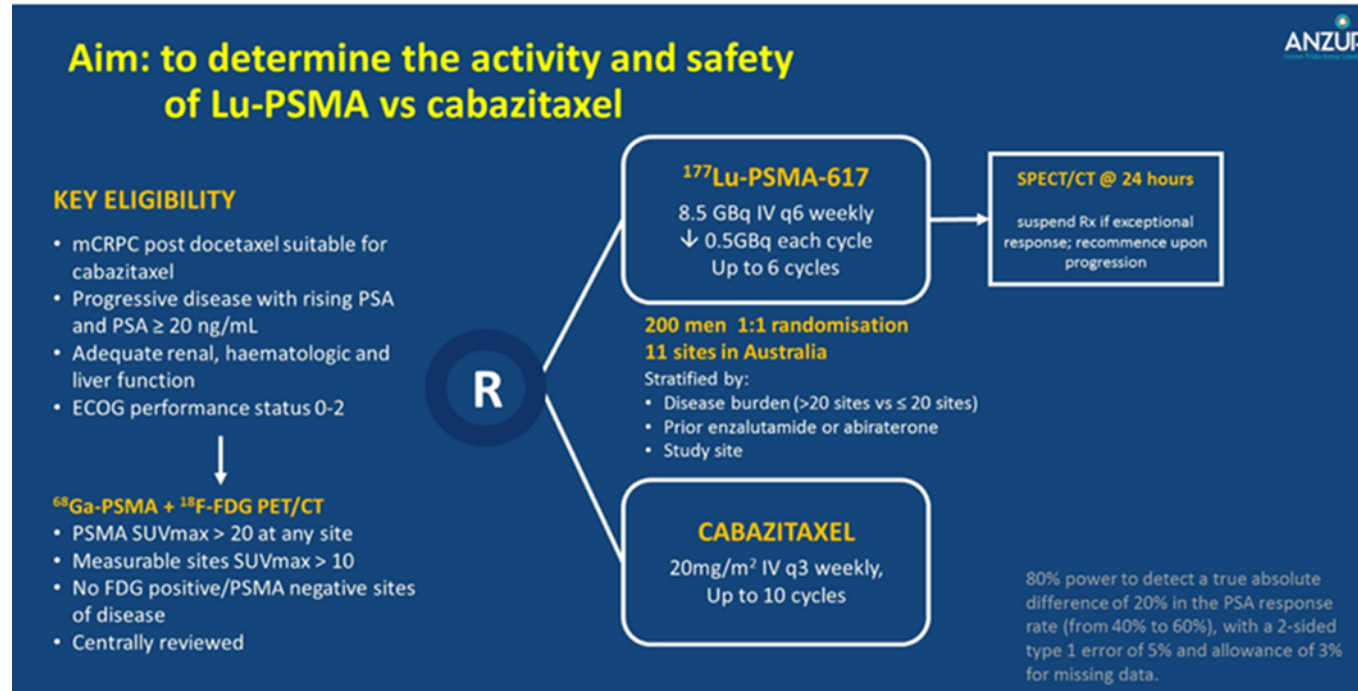


^{177}Lu -PSMA – KEY CLINICAL STUDIES



*primary endpoints published

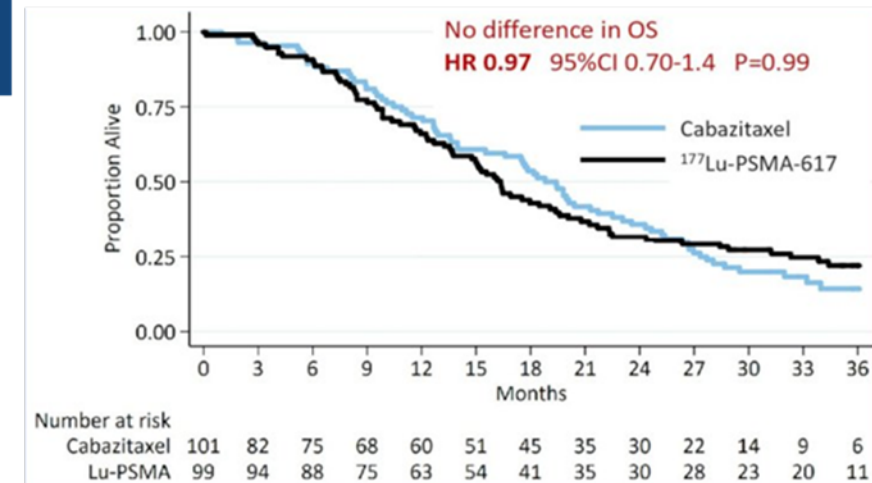
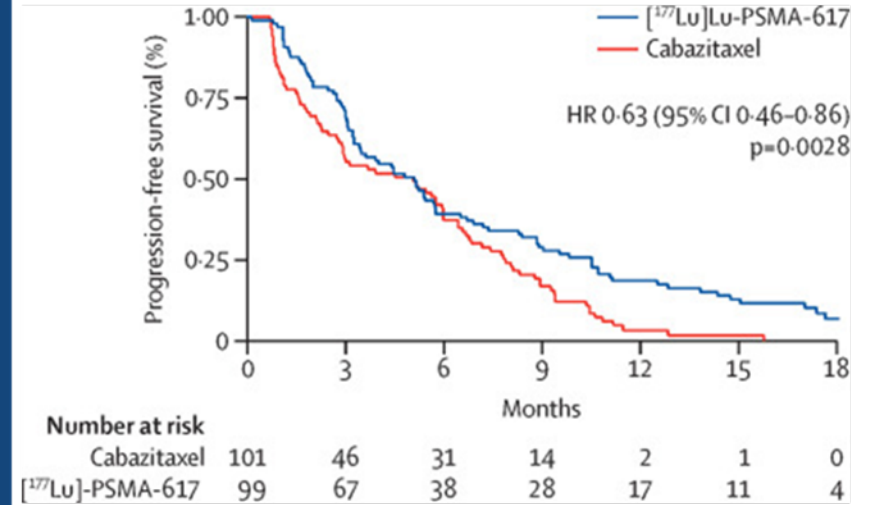
THERAP



PSA50-RR
66% (Lu-PSMA)
37% (Caba.)
($p < 0.0001$)

Total Grade 3-4 Events
35% (Lu-PSMA)
54% (Caba.)

Hofman et al., Lancet Oncol 2020; Hofman et al., ASCO 2022



Eligibility

- Previous treatment with both
 - ≥ 1 androgen receptor pathway inhibitor
 - 1 or 2 taxane regimens
- SOC planned before randomization
 - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga -PSMA-11

2:1

SOC + ^{177}Lu -PSMA-617

7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6 cycles

SOC alone

Treatment

Follow-up

Final analysis

Randomization stratified by

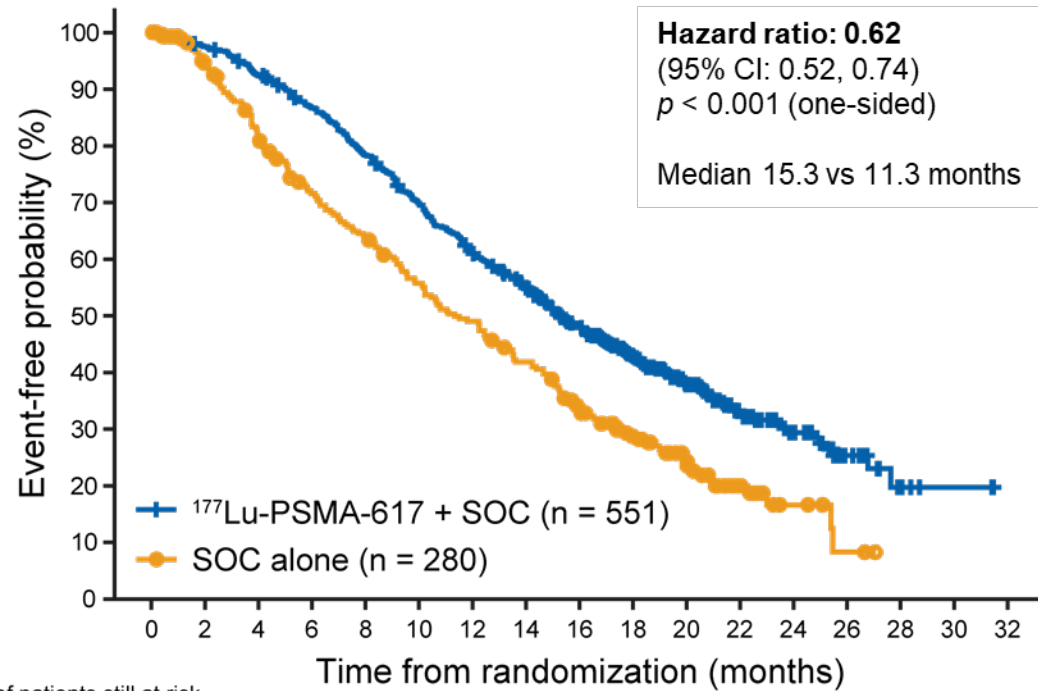
- ECOG performance status (0–1 or 2)
- LDH (high or low)
- Liver metastases (yes or no)
- Androgen receptor pathway inhibitors in SOC (yes or no)

CT/MRI/bone scans

- Every 8 weeks (treatment)
- Every 12 weeks (follow-up)
- Blinded independent central review

¹⁷⁷Lu-PSMA-617 prolonged overall survival

All randomized patients (N = 831)

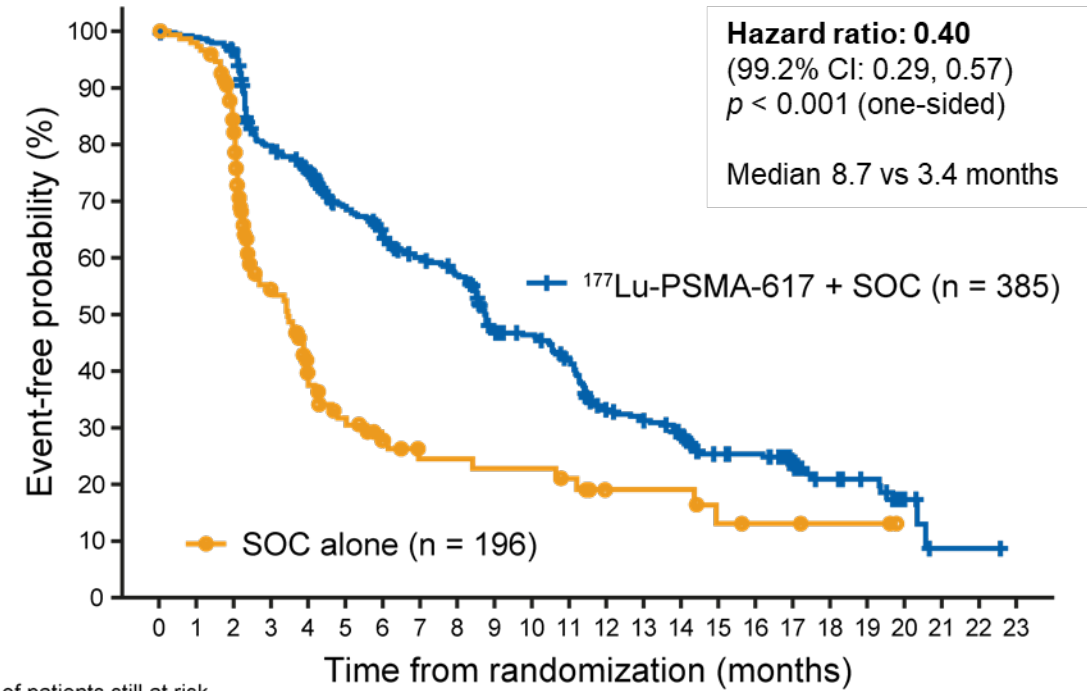


Number of patients still at risk

¹⁷⁷ Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

¹⁷⁷Lu-PSMA-617 improved rPFS

rPFS analysis set (n = 581)



Number of patients still at risk

¹⁷⁷ Lu-PSMA-617 + SOC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
SOC alone	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

VISION TOXICITY

Patients, n (%)			SOC alone ^{[L] [SEP]} (n = 205)	
	All grades	Grade 3–5	All grades	Grade 3–5
Any drug-related TEAE	451 (85.3)	150 (28.4)	59 (28.8)	8 (3.9)
Serious	49 (9.3)	43 (8.1)	5 (2.4)	5 (2.4)
Grade 5 ^a	5 (0.9)	5 (0.9)	0 (0.0)	0 (0.0)
TEAEs grouped by topics of interest				
Fatigue	260 (49.1)	37 (7.0)	60 (29.3)	5 (2.4)
Bone marrow suppression	251 (47.4)	124 (23.4)	36 (17.6)	14 (6.8)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Anaemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Dry mouth	208 (39.3)	0 (0.0)	2 (1.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	8 (1.5)	35 (17.1)	1 (0.5)
Renal effects	46 (8.7)	18 (3.4)	12 (5.9)	6 (2.9)
Second primary malignancies	11 (2.1)	4 (0.8)	2 (1.0)	1 (0.5)
Intracranial haemorrhage	7 (1.3)	5 (0.9)	3 (1.5)	2 (1.0)

^aThere were five drug-related treatment-emergent adverse events leading to death in the 177Lu-PSMA-617 arm: pancytopenia, n = 2; bone-marrow failure, n = 1; subdural hematoma, n = 1; intracranial haemorrhage, n = 1.

PSMA, prostate-specific membrane antigen; SOC, protocol-permitted standard of care; TEAE, treatment-emergent adverse event

PSMA RLT ACCORDING TO GUIDELINES (EAU AND ASCO)

Recommendations	Strength rating
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer ¹⁷⁷ Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

1.1

The panel recommends the use of ¹⁷⁷Lu-PSMA-617 intravenously once every 6 weeks for 4–6 cycles as a treatment option in patients with PSMA PET/CT positive mCRPC who have progressed on one prior line of androgen receptor pathway inhibitor and at least one line of prior chemotherapy.

1.2.1

The panel recommends that patients should be selected using PSMA PET.

1.2.2

The panel recommends that either Ga-68 PSMA-11 or F-18 piflufolastat be used as radiotracers to determine eligibility currently

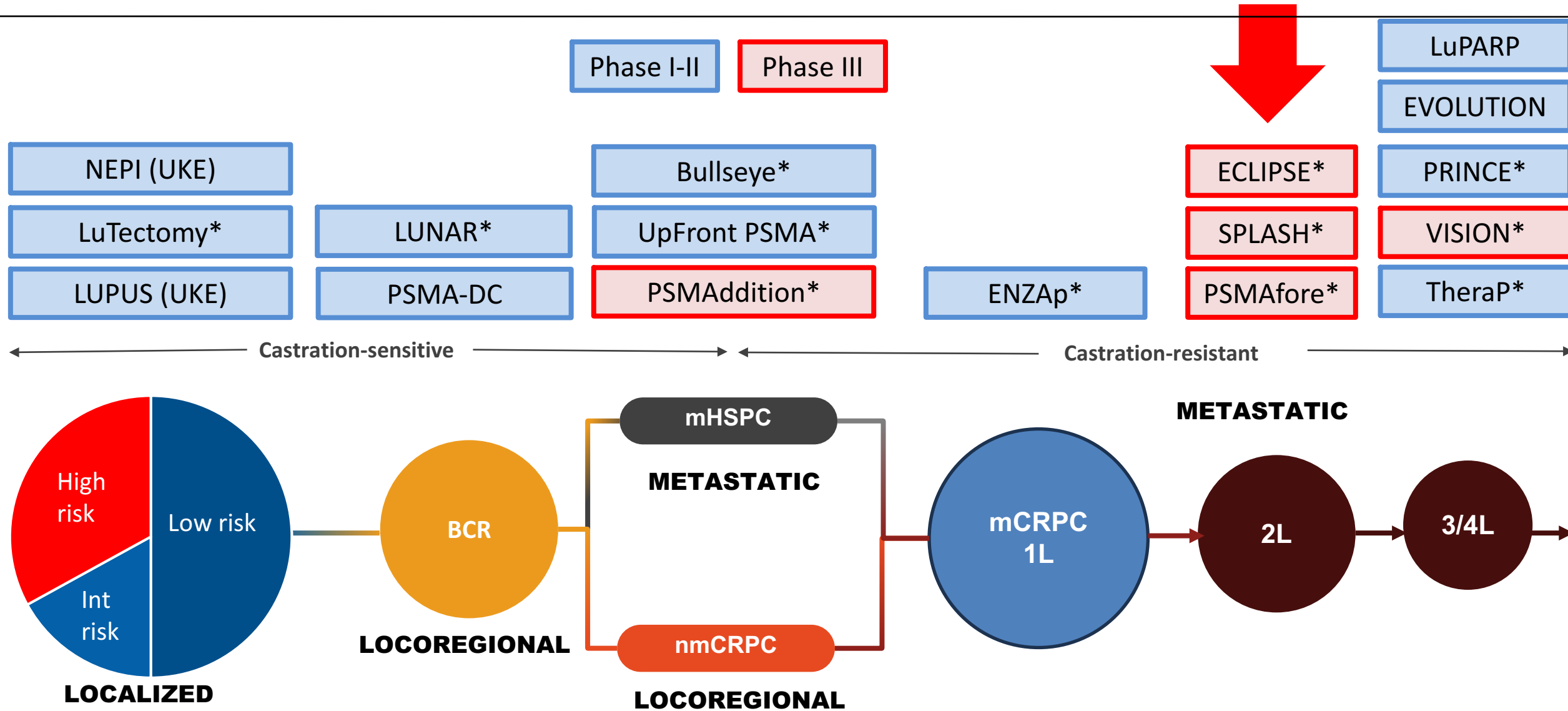
RLT FOR mCRPC APPROVED AND IN DEVELOPMENT

	Probe	Ligand type	Company	Status
	¹⁷⁷Lu-PSMA-617	Small molecule	AAA, academic centers	FDA and EMA approved
¹⁷⁷ Lu	¹⁷⁷ Lu-PSMA-I&T / ¹⁷⁷ Lu-PSMA-PNT2002	Small molecule	Curium Pharma / Point Biopharma	Phase 3 ongoing
	¹⁷⁷ Lu-DOTA-rosopatamab	Antibody (human)	Telix Pharmaceuticals Ltd	Phase 3 ongoing
	¹⁷⁷ Lu-J591	Antibody (murine; deimmunised)	Academic centers (Weill Cornell)	Phase 2 ongoing
	¹⁷⁷ Lu-EB-PSMA-617	Small molecule	Academic centers	Phase 1
²²⁵ Ac	²²⁵ Ac-PSMA-617	Small molecule	AAA	Phase 2 ongoing
	²²⁵ Ac-J591	Antibody (murine)	Academic centers (Weill Cornell)	Phase 2 ongoing
Other	¹³¹ I-PSMA-1095	Small molecule	Progenics Pharmaceuticals	Phase 2 ongoing
	²²⁷ Th-PSMA-TTC	Antibody (human)	Bayer	Phase 1

mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

<https://www.clinicaltrials.gov/ct2/results?cond=prostate+cancer&term=radioligand+therapy+&cntry=&state=&city=&dist=> (last accessed 15 July 2022).

¹⁷⁷Lu-PSMA – KEY CLINICAL STUDIES

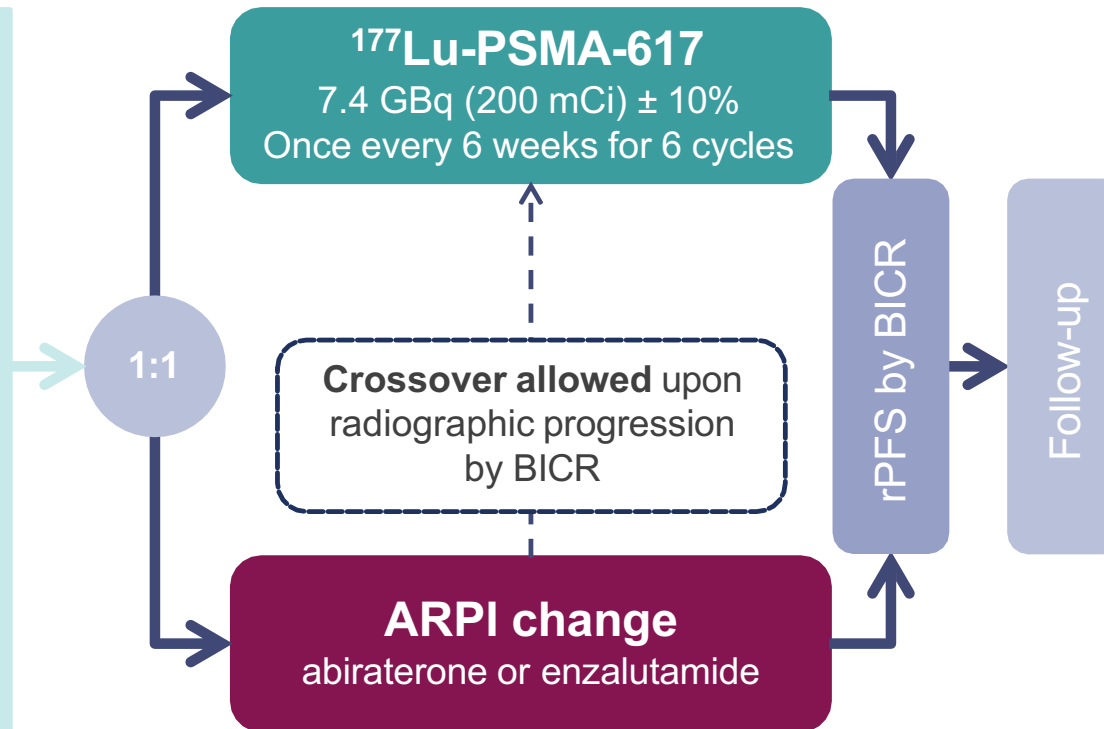


*primary endpoints published

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 prior 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



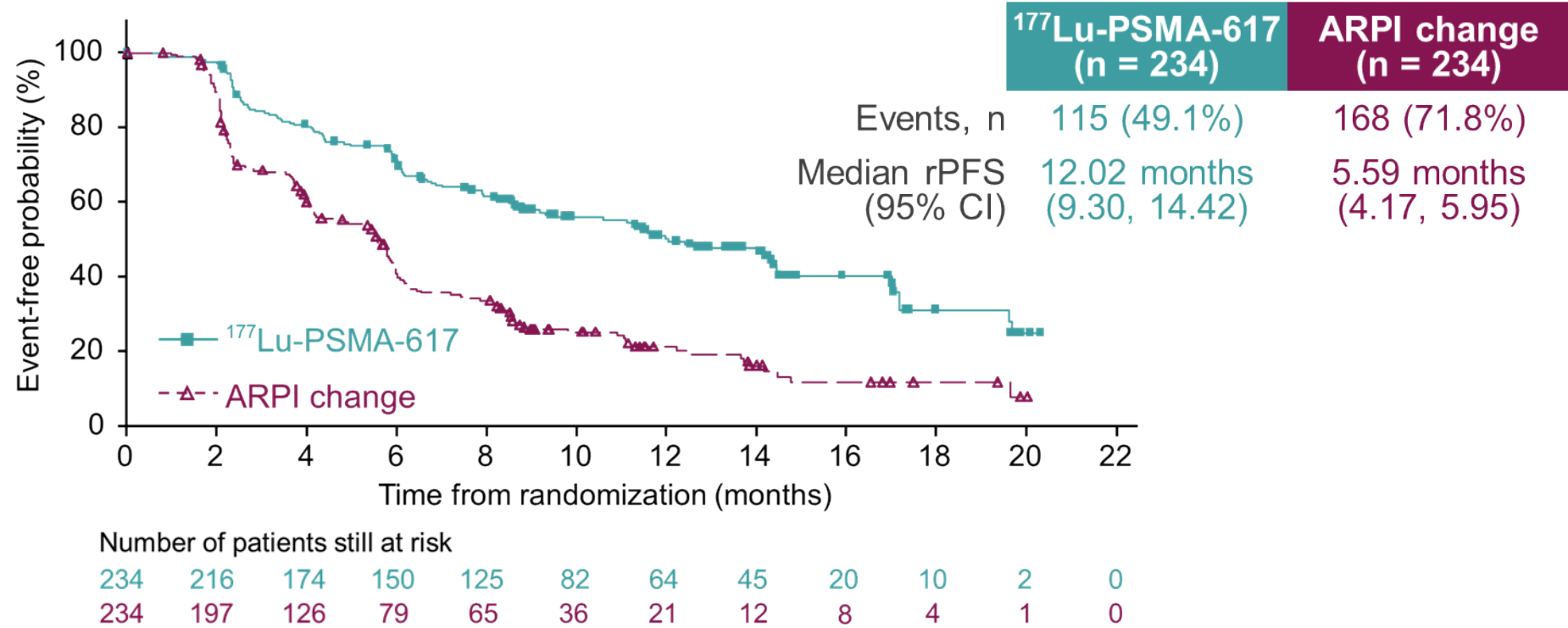
Stratification factors

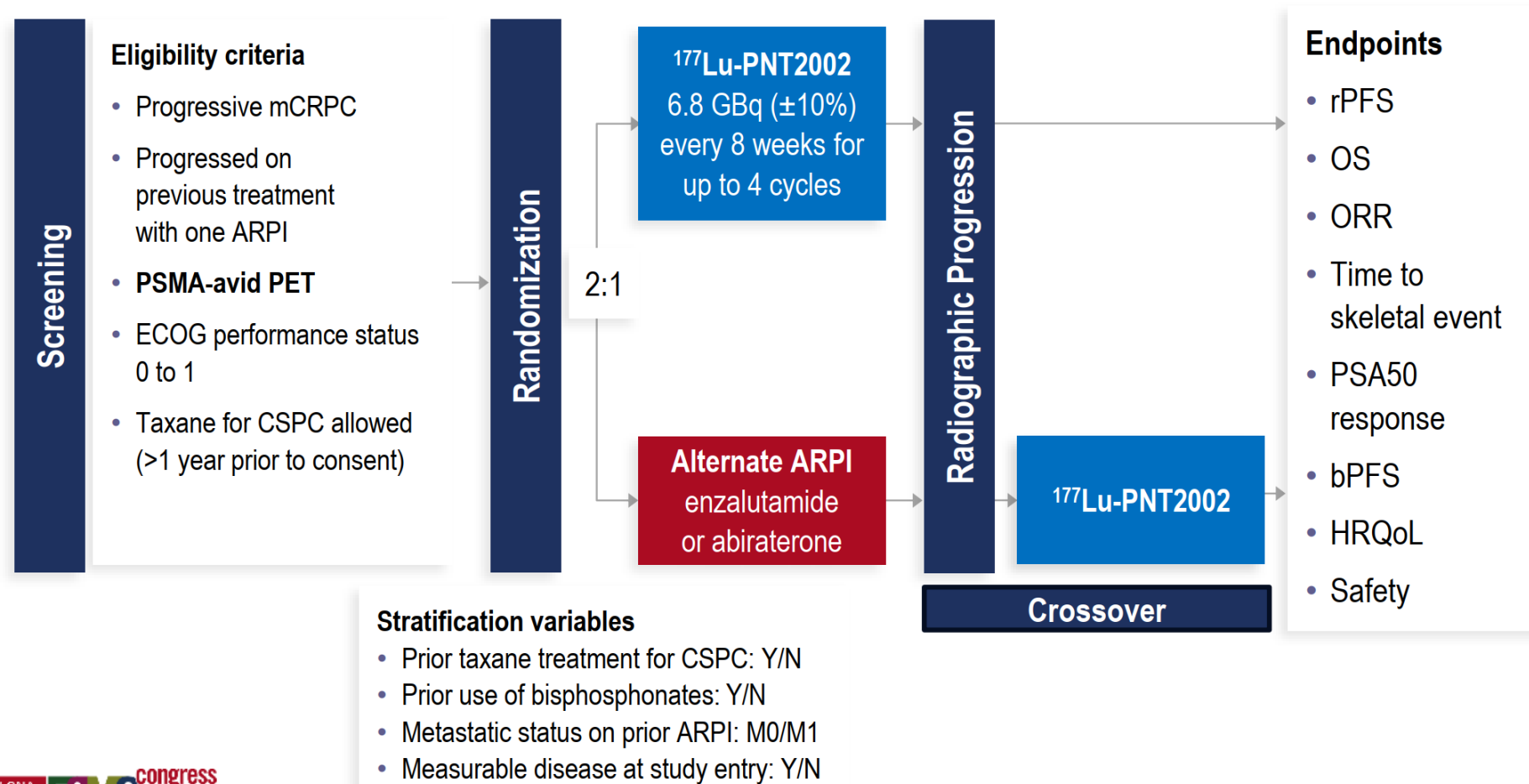
- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

rPFS: primary endpoint was met

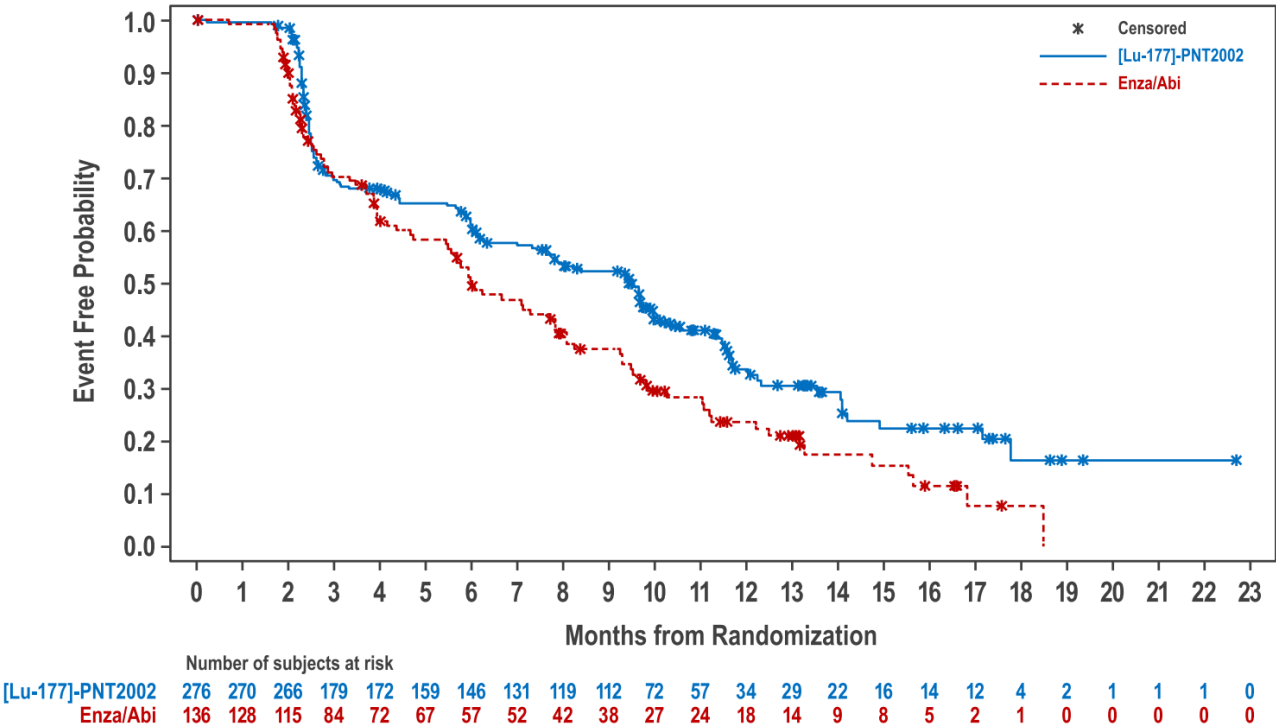
Primary HR: 0.41 (95% CI: 0.29, 0.56); $p < 0.0001$

Updated HR: 0.43 (95% CI: 0.33, 0.54)





Primary Endpoint - rPFS: Primary Analysis



	¹⁷⁷Lu-PNT2002 (n = 276)	Alternate ARPI (n = 136)
Events, n	162 (58.7%)	96 (70.6%)
Median rPFS (95% CI)	9.5 months (7.4, 10.0)	6.0 months (4.7, 7.9)
Median follow-up (95% CI)	11.1 months (10.1, 11.6)	12.9 months (10.2, 15.9)
HR: 0.71 (95% CI: 0.55, 0.92) p = 0.0088		

Data Cutoff: 01/NOV/2023

Summary 2nd line mCRPC



Search

Global | en ▼

Menu

[Home](#) > [News](#) > FDA approves Novartis radioligand therapy Pluvicto® for earlier use before chemotherapy in PSMA-positive metastatic castration-resistant prostate cancer

FDA approves Novartis radioligand therapy Pluvicto® for earlier use before chemotherapy in PSMA-positive metastatic castration-resistant prostate cancer

Mar 28, 2025

Ad hoc announcement pursuant to Art. 53 LR

- *New indication approximately triples eligible patient population, allowing Pluvicto® to be used after one androgen receptor pathway inhibitor (ARPI) and now before chemotherapy*
- *Pluvicto significantly reduced risk of progression or death by 59% and more than doubled median radiographic progression-free survival (rPFS) vs. change in ARPI in Phase III PSMAfore trial**

Summary 2nd line mCRPC



Novartis withdraws EMA application for adding new indication for Pluvicto®

Apr 24, 2026

Novartis has withdrawn a European Medical Agency type II variation application for Pluvicto to treat adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC)¹ pre-chemotherapy, following CHMP feedback. The CHMP indicated that they would not support the application based on the control arm used in the PSMAfore study. The withdrawal is not related to the quality, efficacy or safety of Pluvicto and does not impact ongoing clinical trials, approved indications or pending regulatory submissions inside or outside the EU.

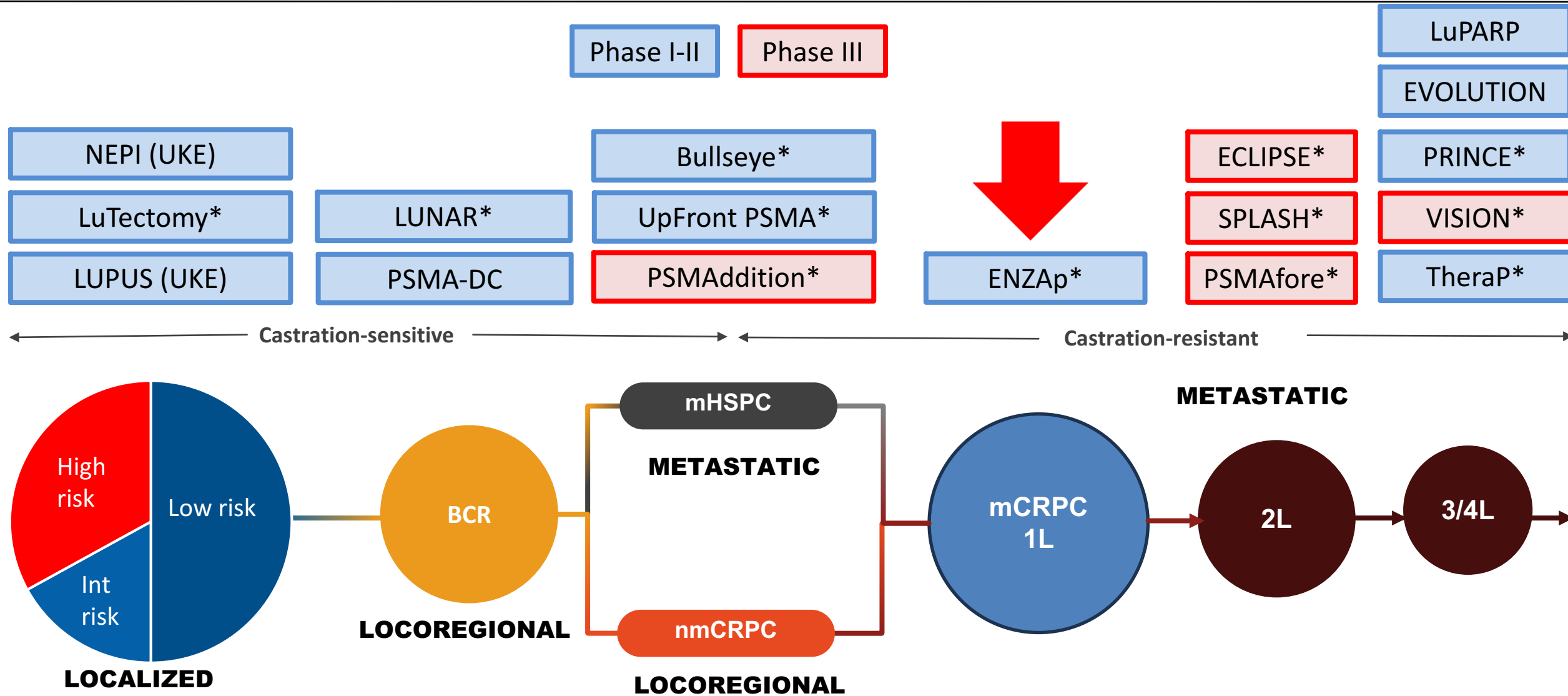
Importantly, the PSMAfore study that supported the application, was the basis for successful approval of Pluvicto in pre-chemotherapy mCRPC patients in the United States, Japan, and China. The value of Pluvicto in this population is also reflected in evidence-based recommendations from leading professional guidelines, including ESMO, EAU, ASCO and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)².

We are disappointed by this outcome and remain committed to advancing treatment options for people with prostate cancer.

References:

1. Submission was for adult patients with mCRPC who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI) and for whom chemotherapy is not yet clinically indicated.
2. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

^{177}Lu -PSMA – KEY CLINICAL STUDIES



*primary endpoints published

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 risk features for early enzalutamide failure
Positive ⁶⁸Ga PSMA PET/CT

Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone



1:1

Enzalutamide 160 mg

Enzalutamide 160 mg
+ [¹⁷⁷Lu]Lu- PSMA-617 7.5 GBq
2-4 doses

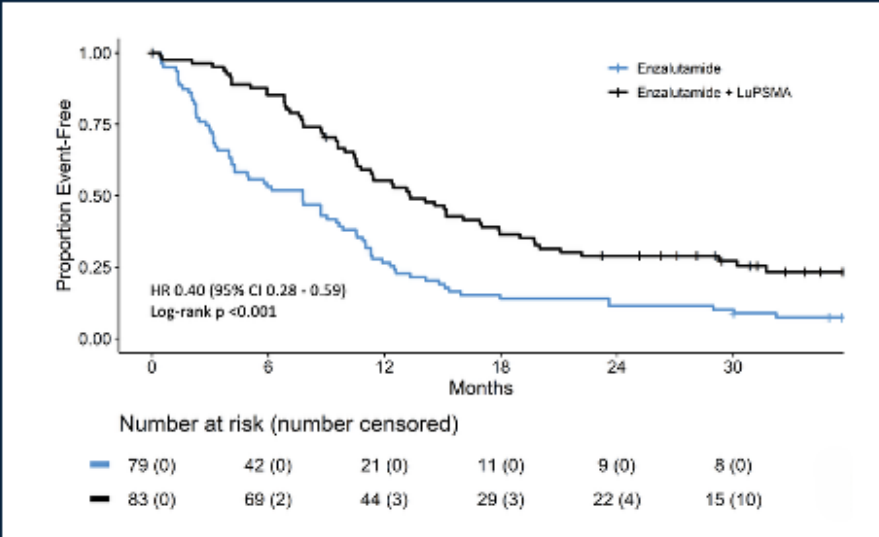
Objectives

PSA-PFS (primary endpoint)
Overall survival
Health-related Quality of Life
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
Adverse events
Health economic analyses
Translational/correlative

Progression Free Survival

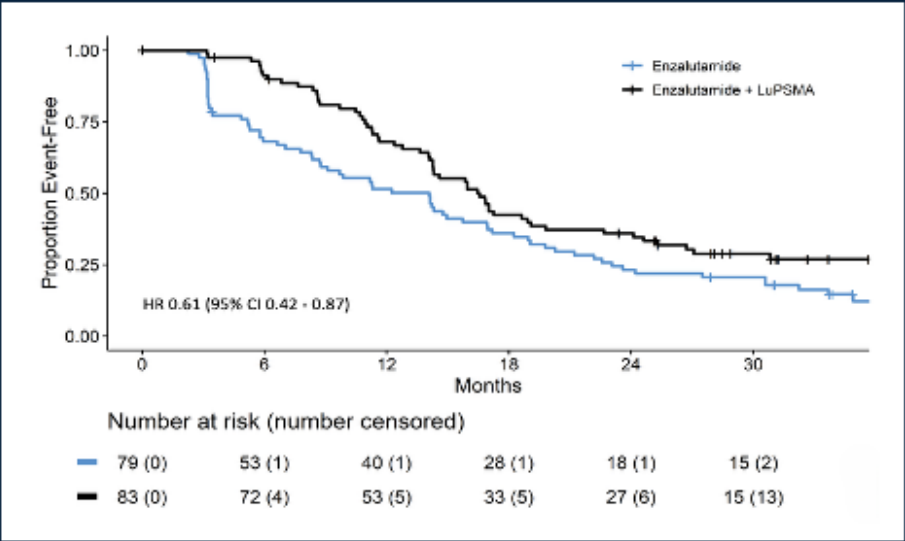
PSA-PFS

HR 0.40 (95%CI 0.28-0.59) p=0.000001



R-PFS

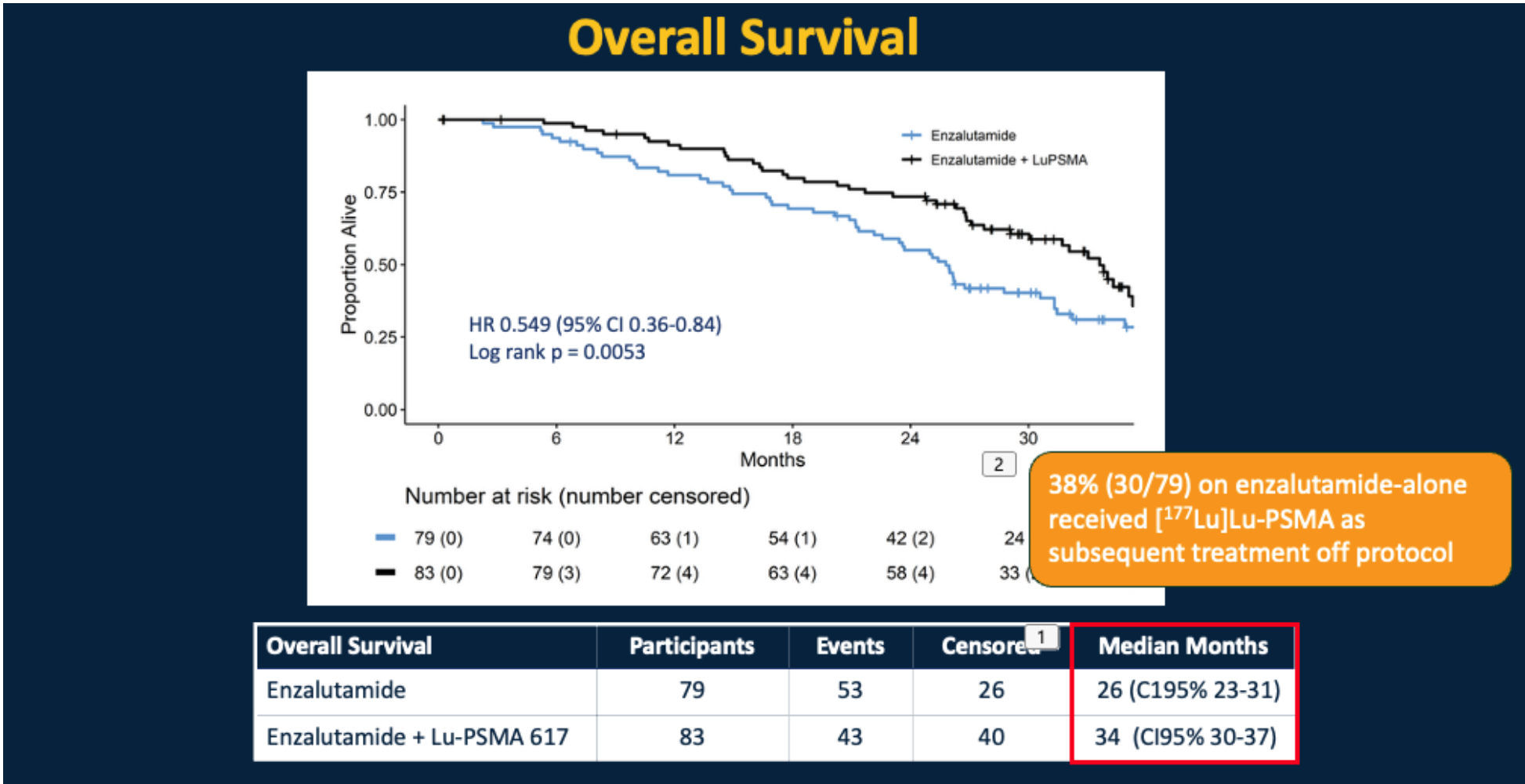
HR 0.61 (95% CI 0.42-0.87)



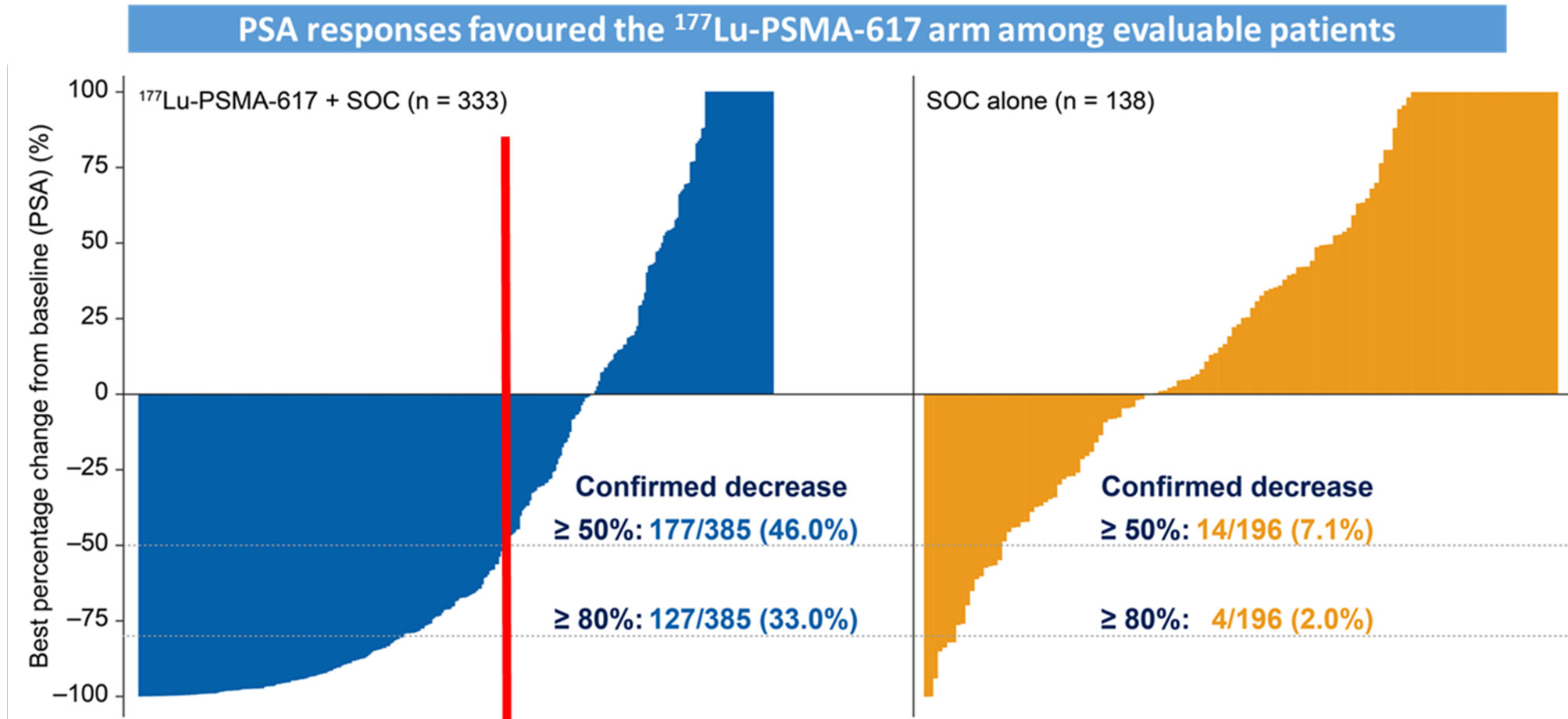
PSA-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	73	6	7.8
Enzalutamide+[¹⁷⁷ Lu]LuPSMA617	83	60	23	13

R-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	69	10	14
Enzalutamide+[¹⁷⁷ Lu]LuPSMA617	83	56	27	17

Lancet Oncol. 2024 May;25(5):563-571

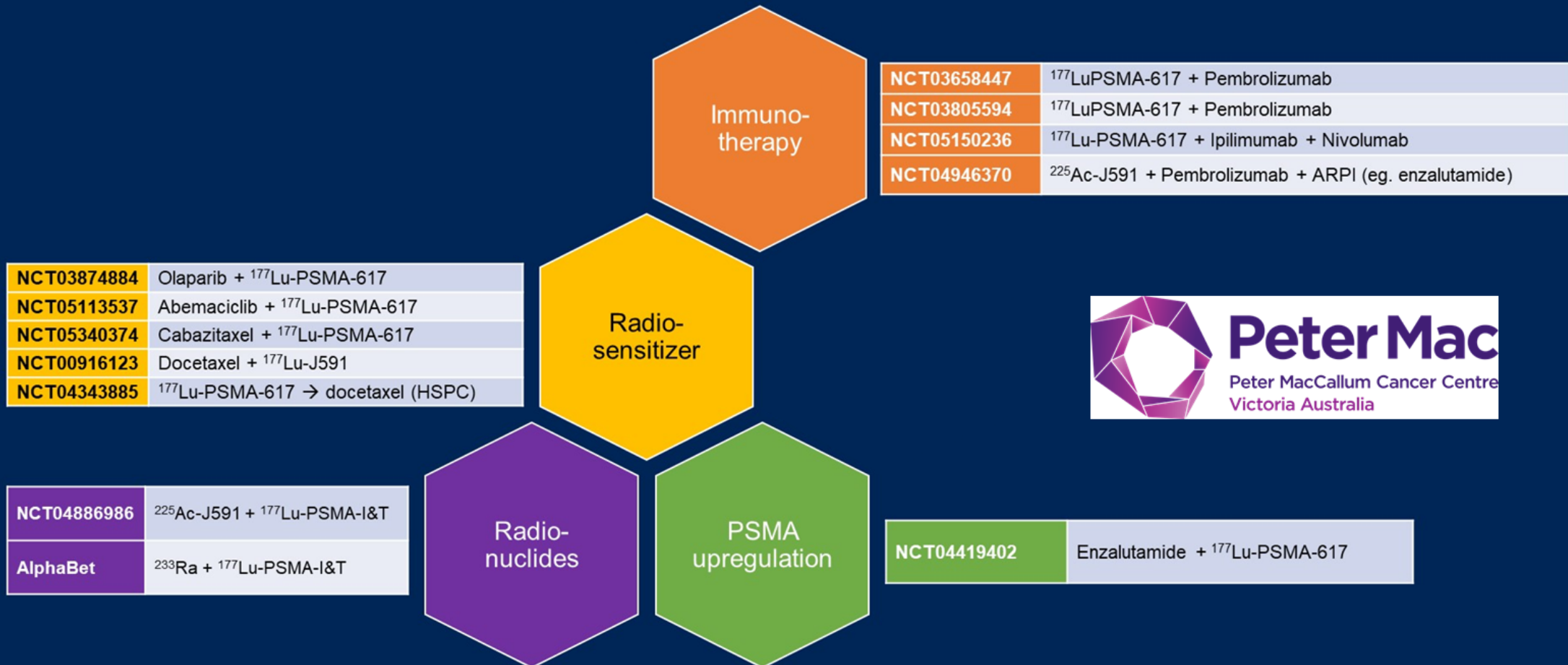


VISION: NEED FOR IMPROVEMENT

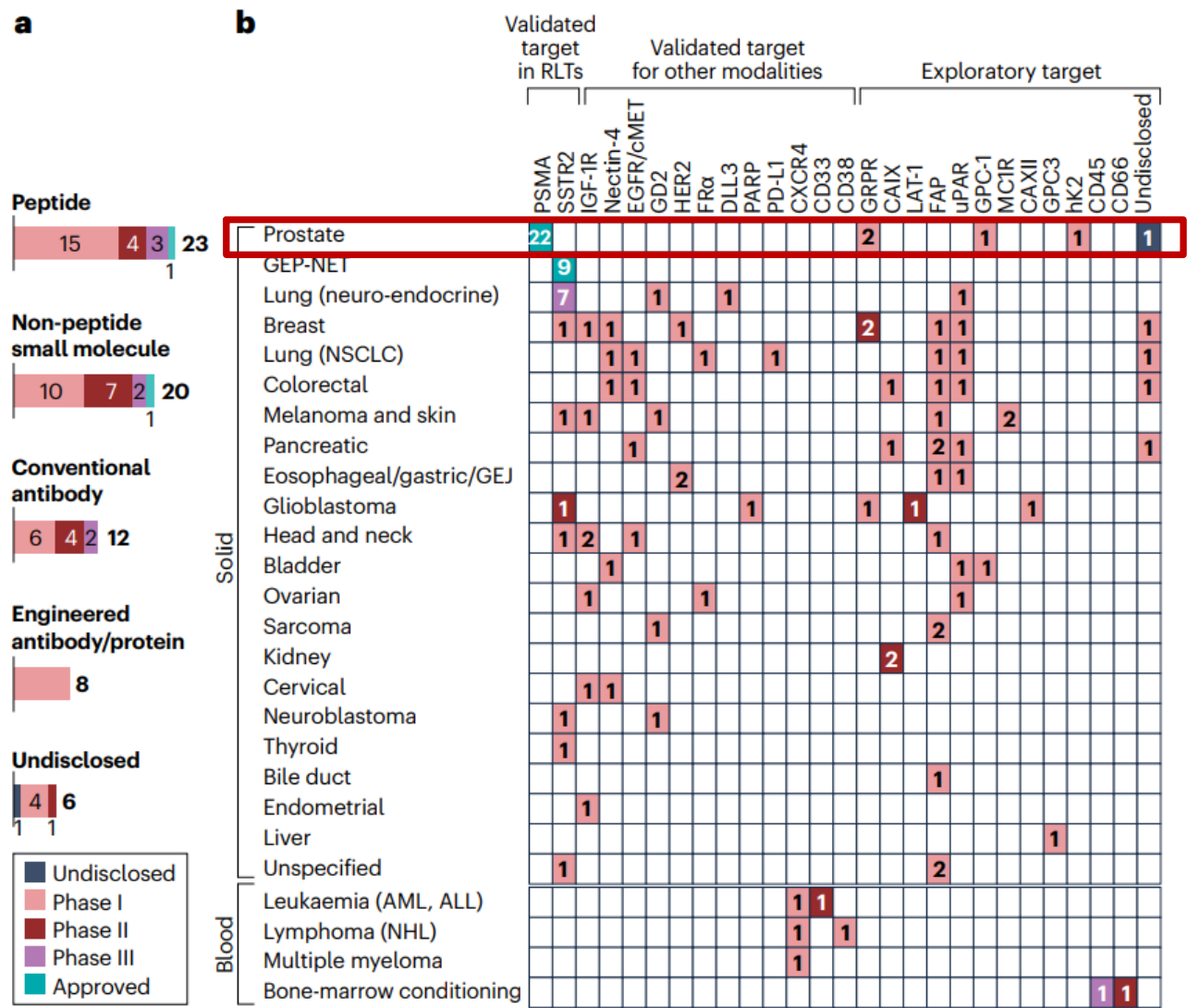


More than 50% of patients do NOT respond (PSA decrease $>50\%$).

Current Lu-PSMA combination trials



TARGETS BEYOND PSMA

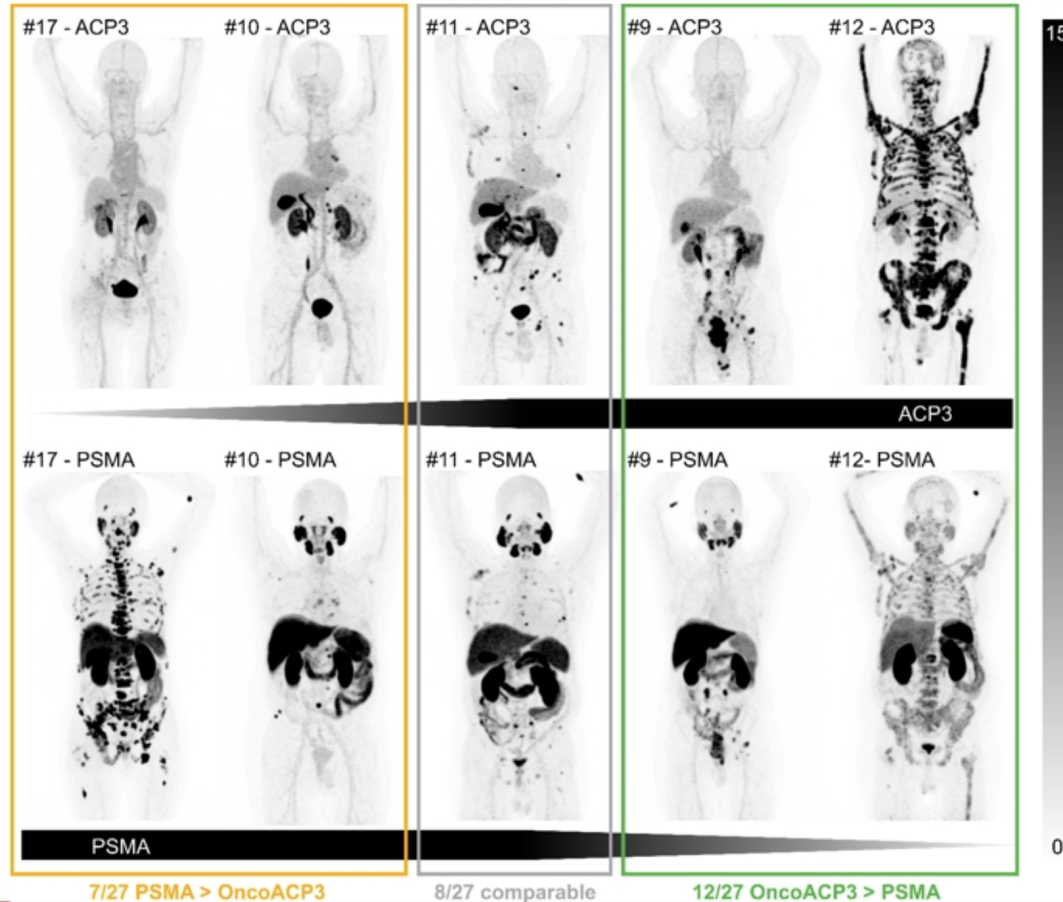


- Various targets investigated in different phase clinical trials

➤ Most trials focus on prostate cancer

TARGETS BEYOND PSMA: PROSTATIC ACID PHOSPHATASE (ACP3)

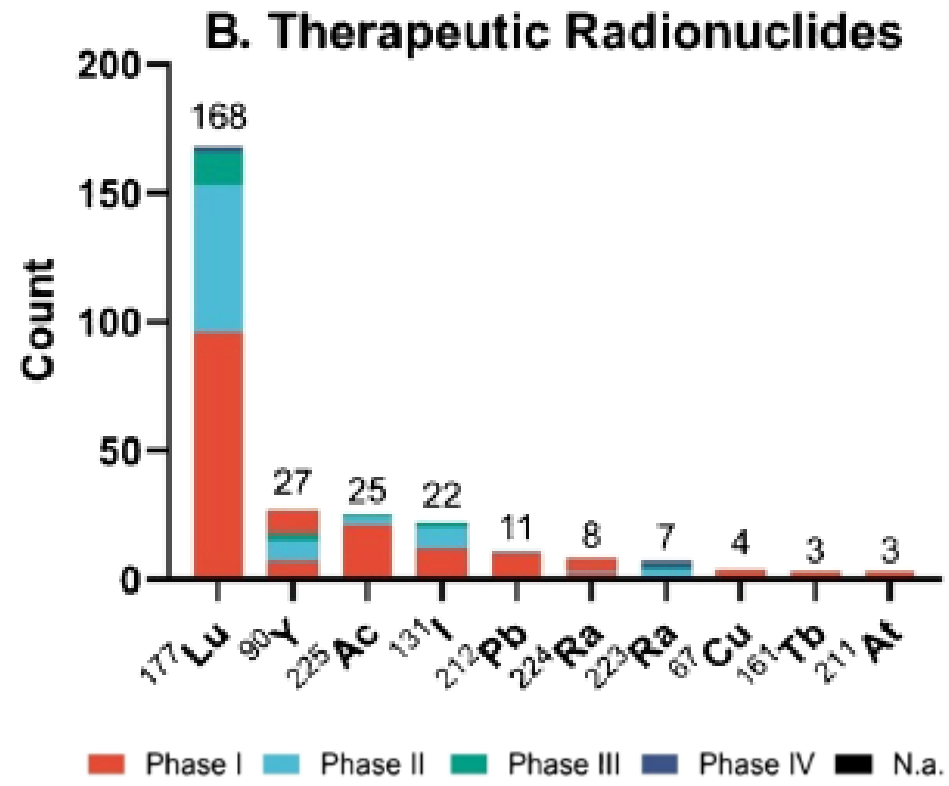
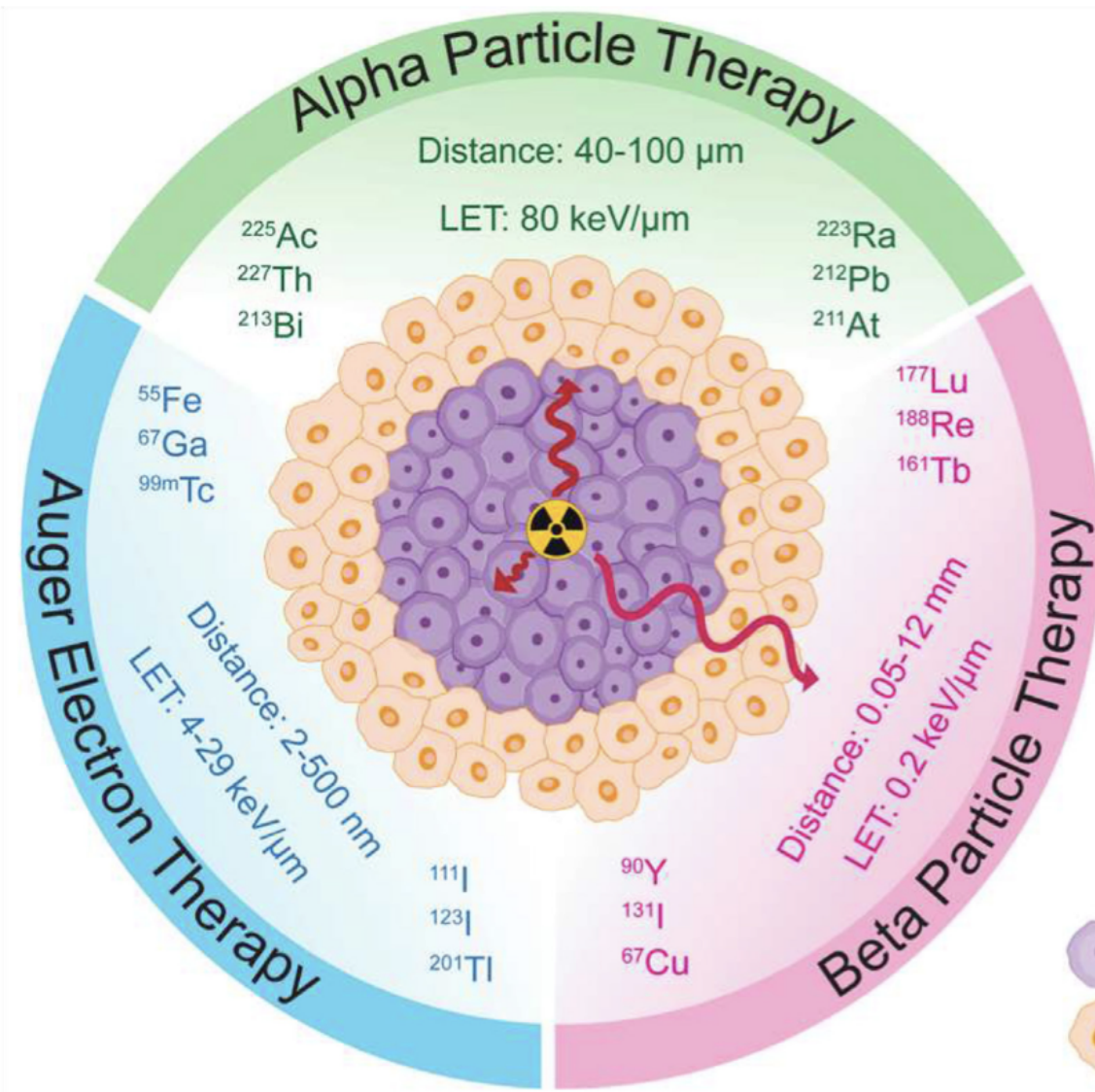
Results – biodistribution and tumor uptake



- No association with Gleason or # of prior therapies
- Complementary uptake, but overall superior performance of OncoACP3



WHERE ARE WE GOING? NEW RADIONUCLIDES



Summary

- PSMA-Radiotheranostics is a success story
- PSMA-directed RLT in mCRPC as pacemaker for theranostics
 - Approved by EMA and FDA
 - Moving to earlier therapy lines (oligometastatic disease)
- Next wave of prostate cancer RLT
(new targets, radionuclides, and combination approaches)
 - ACP3, GRPR, HK2
 - Ac-225 and other alpha emitters, Terbium isotopes
 - PSMA-Upregulation, Radiosensitizer, Immunotherapy

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Thank you for your kind attention!
Questions?



¡Gràcias!