III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

Radioligandos. Cáncer de próstata

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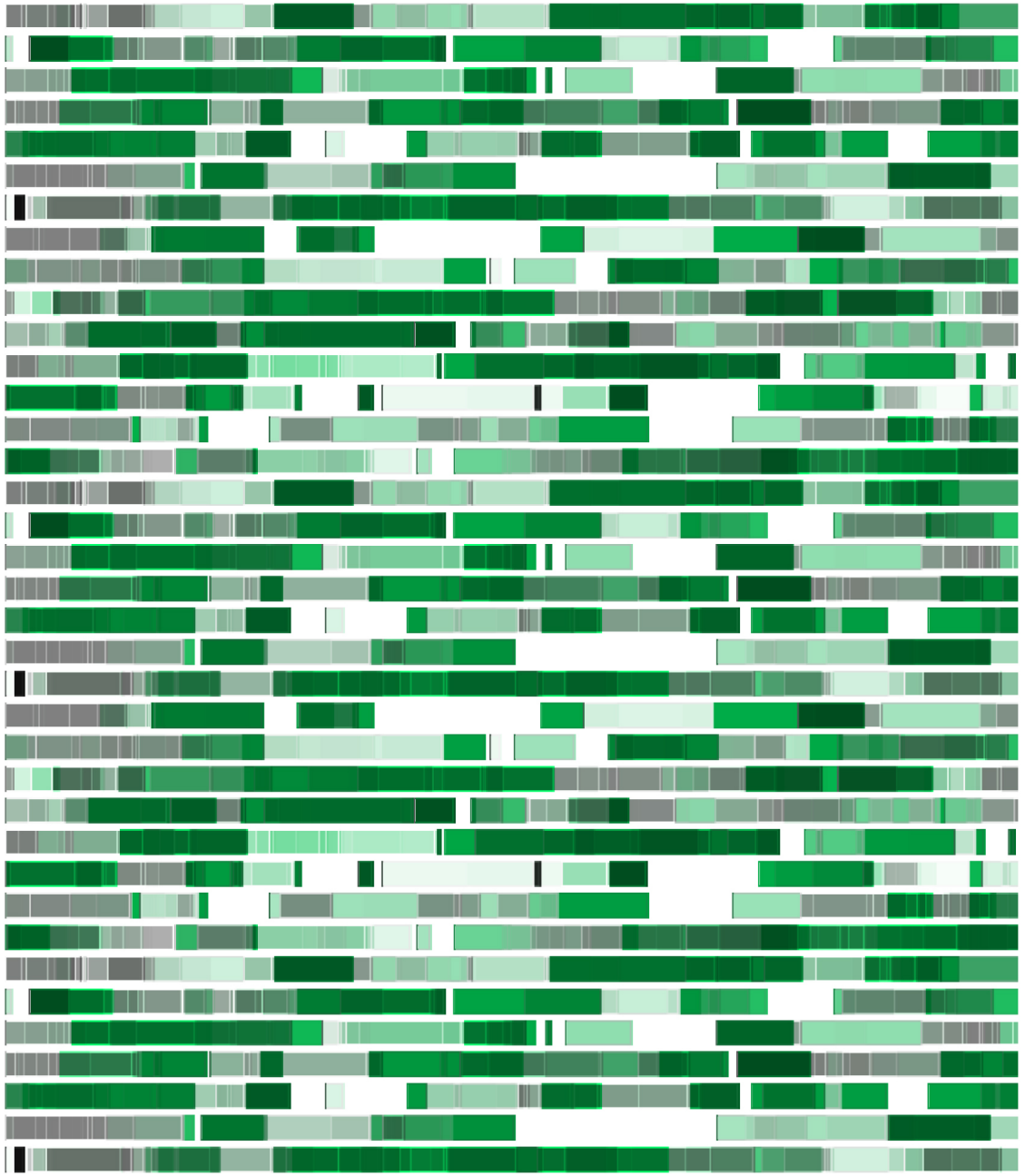
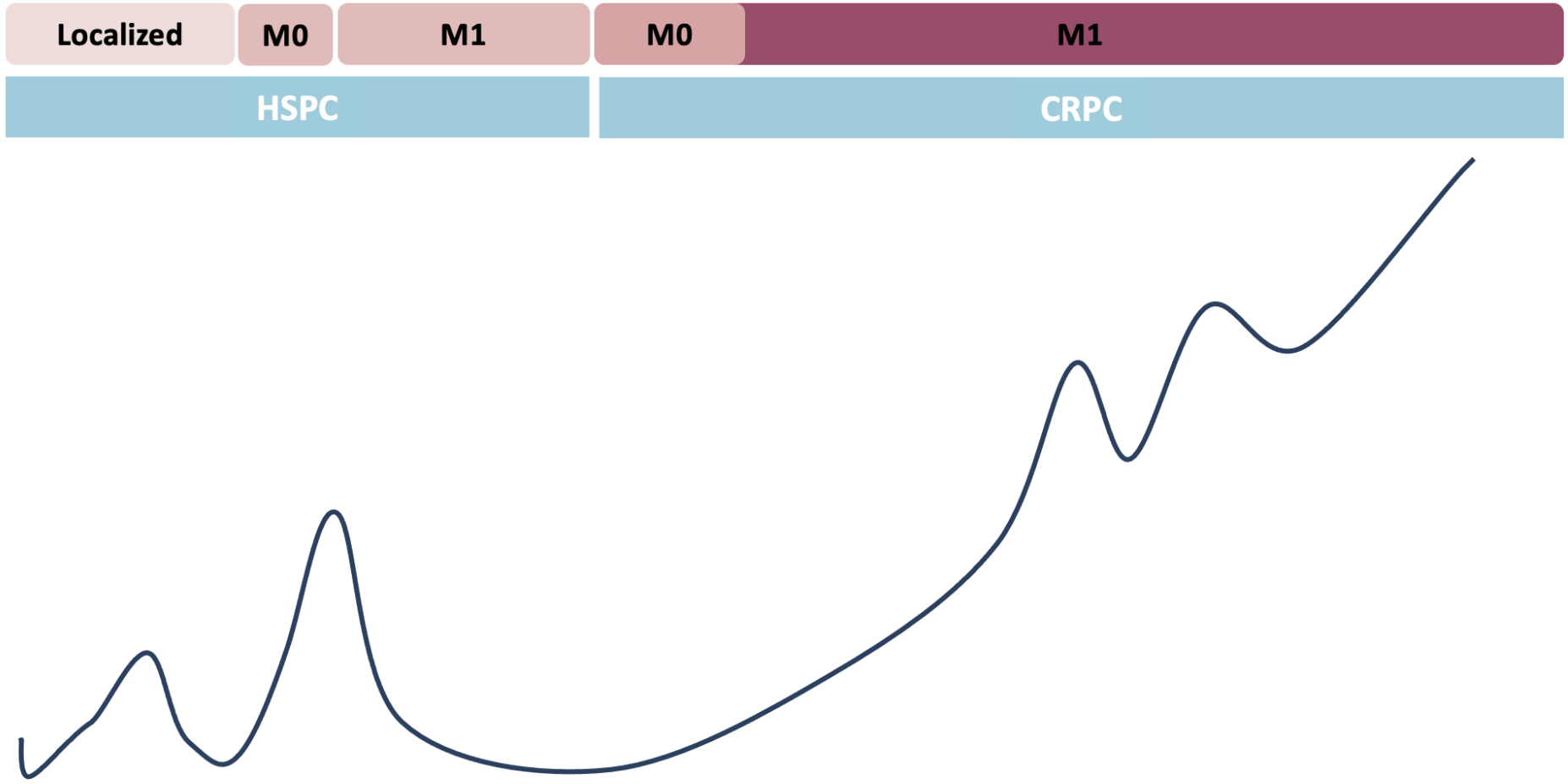
Organizador por:
HENDERE HEALTHCARE



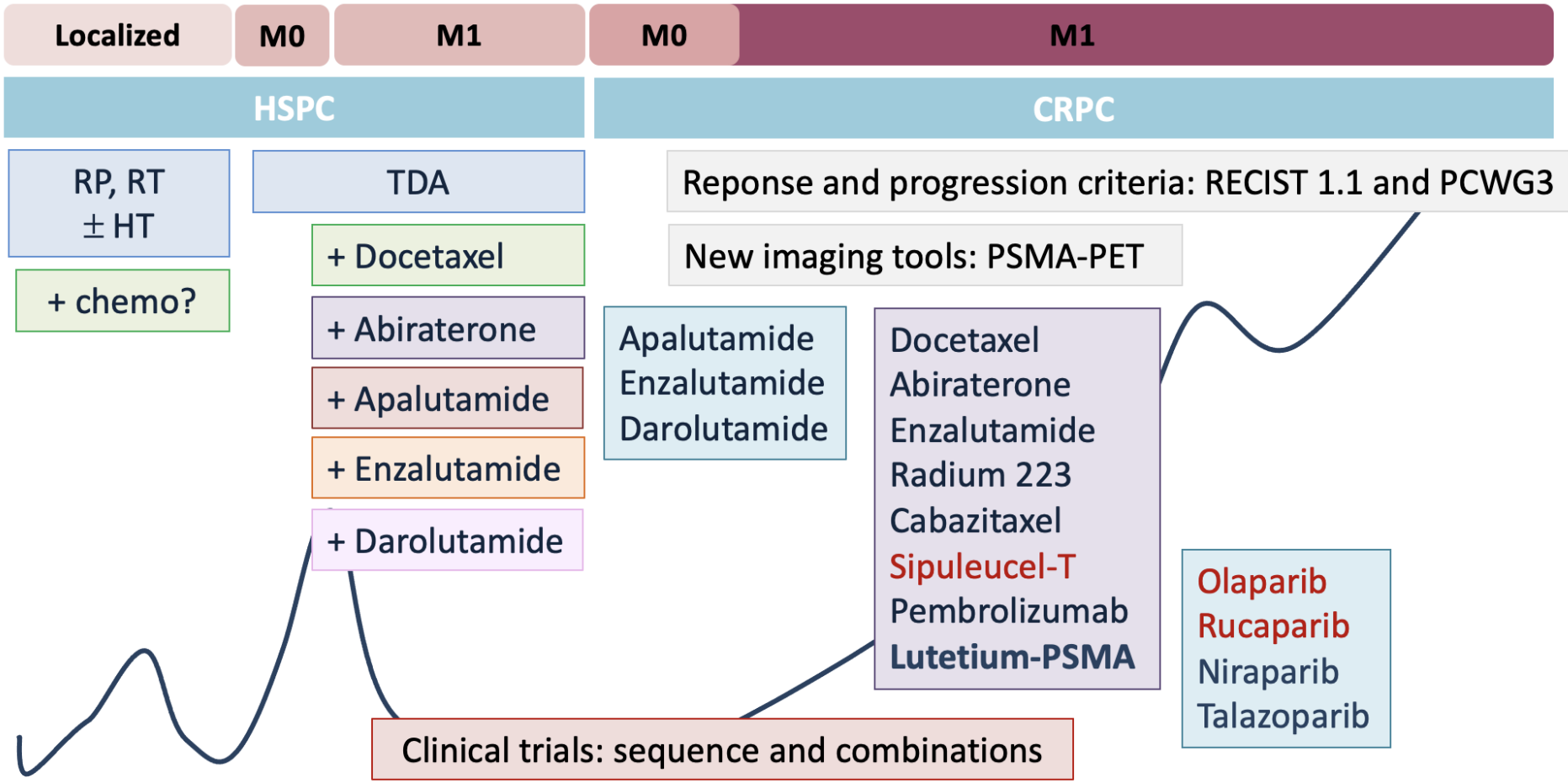
- **CONFLICTOS DE INTERÉS**

  - ✓ *Employment: none*
  - ✓ *Consultant or Advisory Role: Astellas Pharma, Roche, Novartis AAA, Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Recordati, Ipsen, Merck, Pfizer, MSD, Janssen*
  - ✓ *Stock Ownership: none*
  - ✓ *Research Funding: none*
  - ✓ *Speaking honoraria: Novartis AAA, Almirall Pharma, Astellas Pharma, Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Merck, MSD, Roche, Pfizer; Janssen*
  - ✓ *Travel/Accommodations: Bristol-Myers-Squibb, Pfizer, Roche, Astellas Pharma, MSD, Merck*

- **HISTORIA NATURAL**



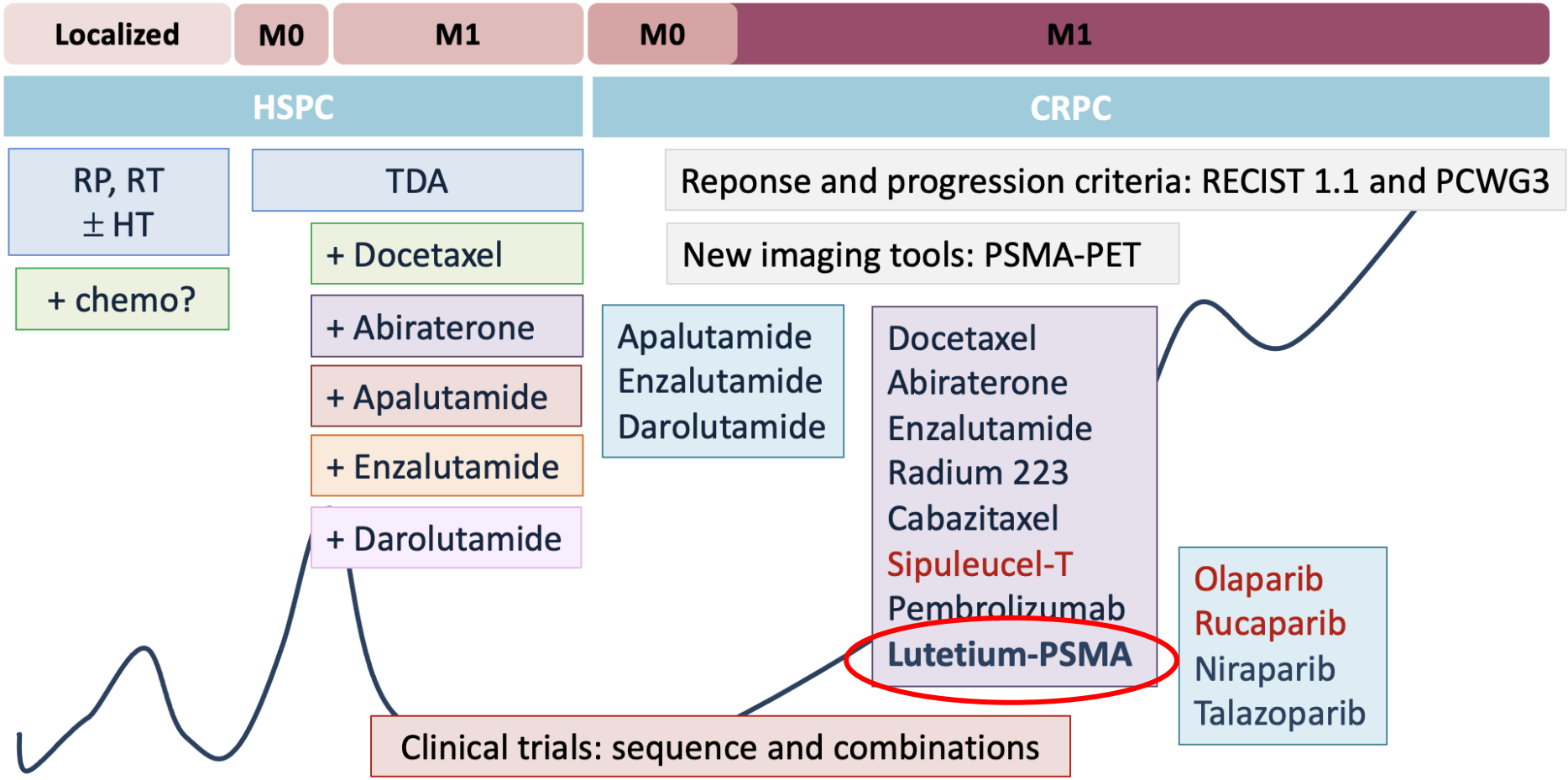
- **EVOLUCIÓN FARMACOLÓGICA**



- **CÁNCER DE PRÓSTATA: REALIDADES**

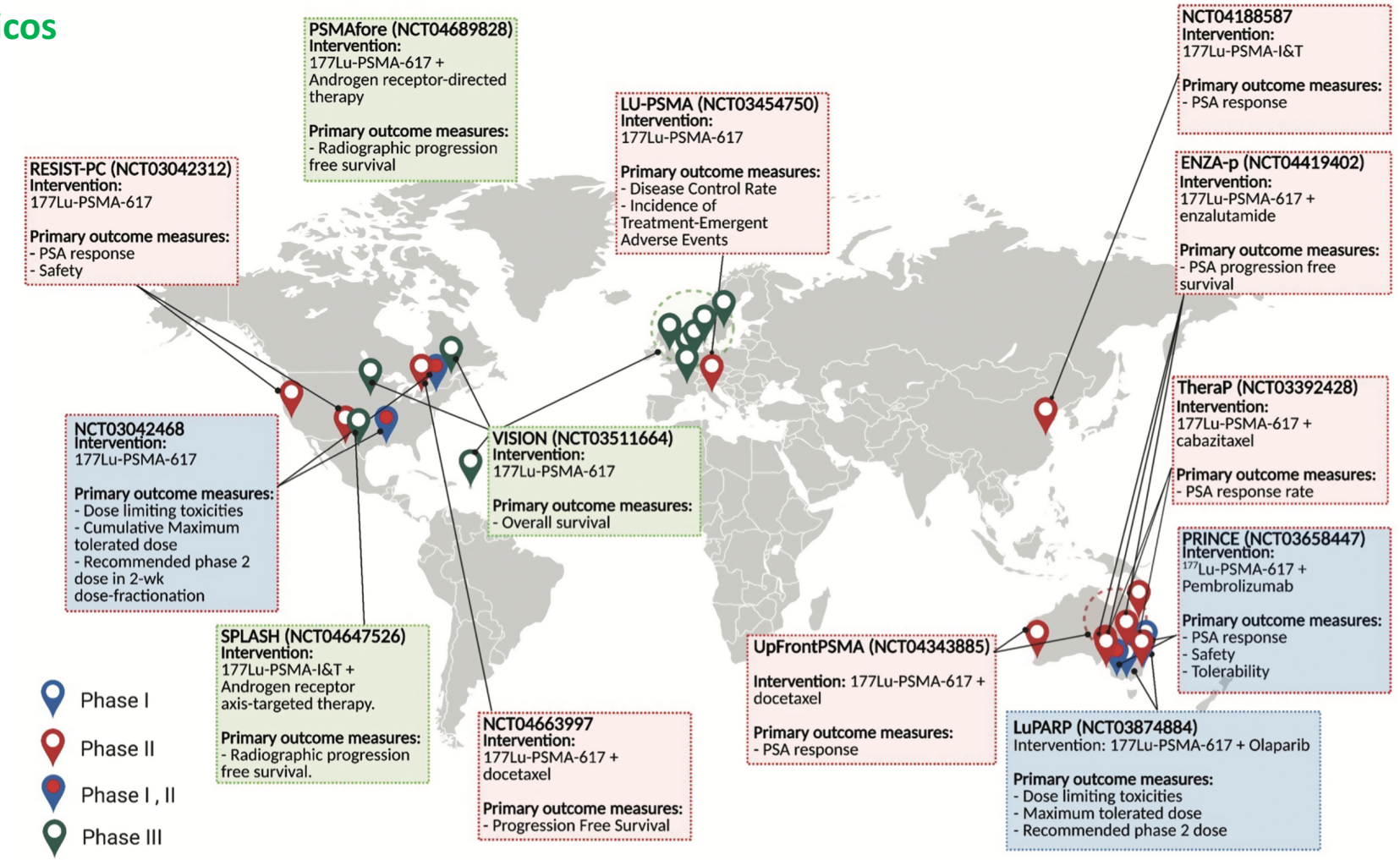
  - ✓ Tumor complejo desde el punto de vista clínico (además de molecular): PSA + imagen (convencional frente moderna)
  - ✓ Dos escenarios claros: CPHSm y CPRCm
  - ✓ Dentro del CPHSm: alto y bajo volumen /síncrono o metacrónico
  - ✓ Paciente con mutaciones BRCA1/2: peor pronóstico pero beneficios claros con iPARP
  - ✓ Fármacos que hemos ido aprobando en líneas tardías han pasado a tratamientos iniciales
  - ✓ Ensayos clínicos desarrollados en paralelo: difícil extrapolar conclusiones
  - ✓ Frecuentemente los brazos control no son estándares de tratamiento
  - ✓ Dificultad en demostrar SG a lo largo de la secuencia de la enfermedad
  - ✓ **Todo ello complica posicionar fármacos que sabemos son eficaces, pero no sabemos dónde utilizarlos exactamente**
  - ✓ Clave: control de síntomas y calidad de vida

- **EVOLUCIÓN FARMACOLÓGICA**



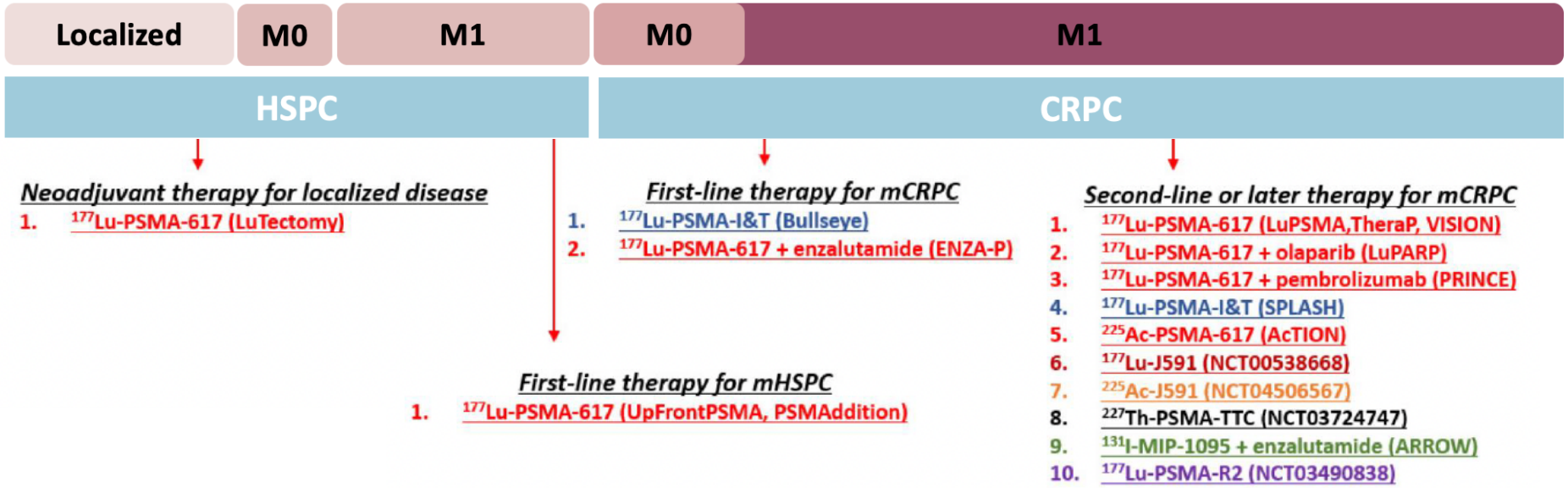
- # DESARROLLO DE ^{177}Lu-PSMA-617

Ensayos Clínicos



AlSadi R, et al. Oncologist 2022;27:e957.

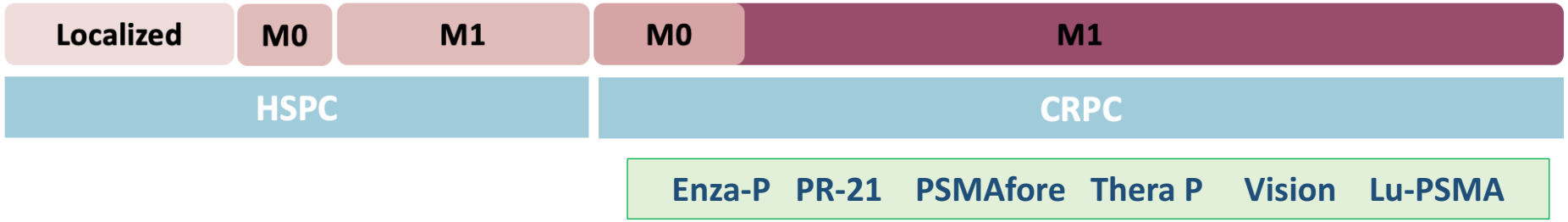
- **ENSAYOS CLÍNICOS**



EVIDENCIA CIENTÍFICA

Study	Scenario	Phase	N	Active Arm	Control Arm	Primary Endpoint	Sponsor	Ref.
LuPSMA	mCRPC post-ARPI and taxanes	Ph2	30	177-Lu-PSMA	NA	PSA response (PSA50) & Safety	Peter MacCallum CC (Melbourne, Australia).	Hofman, M. S. *Lancet Oncol* **19**, 825–833 (2018).
Vision	**mCRPC** post-ARPI and taxanes	Ph 3 (2:1)	831	177-Lu-PSMA + SOC	SOC (excl. Chemo & Rad 223)	rPFS / OS (alternate)	Novartis	Sartor, O. *N Engl J Med* (2021)
Therap-P	**mCPRC** post-ARPI and docetaxel	Ph 2 rand (1:1)	200	177-Lu-PSMA	Cabazitaxel	PSA response (PSA50)	ANZUP	Hofman MS. *The Lancet* **397**, 797–804 (2021). Buteau, J. P. *et al. Lancet Oncol* **23**, 1389–1397 (2022).
Enza P	**mCPRC** 1st line (>50% doce & 14% AAP mHSPC)	Ph 2 rand (1:1)	162	177-Lu-PSMA + Enzalutamide	Enzalutamide	PSA-PFS	ANZUP	Emmett, L. *Lancet Oncol.* **25**, 563–571 (2024). Emmett, L. *Lancet Oncol.* **26**, 1168–1177 (2025).
PSMA-FORE	**mCPRC** post-ARPI pre-docetaxel	Ph 3 (1:1)	468	177-Lu-PSMA	Docetaxel	rPFS (central)	Novartis	Morris, M. J. *Lancet* **404**, 1227–1239 (2024). Fizazi, K. *et al. Lancet Oncol.* **26**, 948–959 (2025). Fizazi, K. *et al. Ann. Oncol.* (2025
PSMA Addition	mHSPC	Ph 3 (1:1)	1144	177-Lu-PSMA + ARPI	ARPI	rPFS (central)	Novartis	Tagawa S, et al. ESMO 2025

- **EVIDENCIA CIENTÍFICA: CPRCm**



• EVIDENCIA CIENTÍFICA: CPRCm

Lu-PSMA

N=43

- mCRPC post docetaxel and post Abi - Enza
- Radiographic or clinical progression
- ECOG 0-2

→ ^{177}Lu-PSMA-617
6 GBq iv q6 weekly
Up to 4 cycles

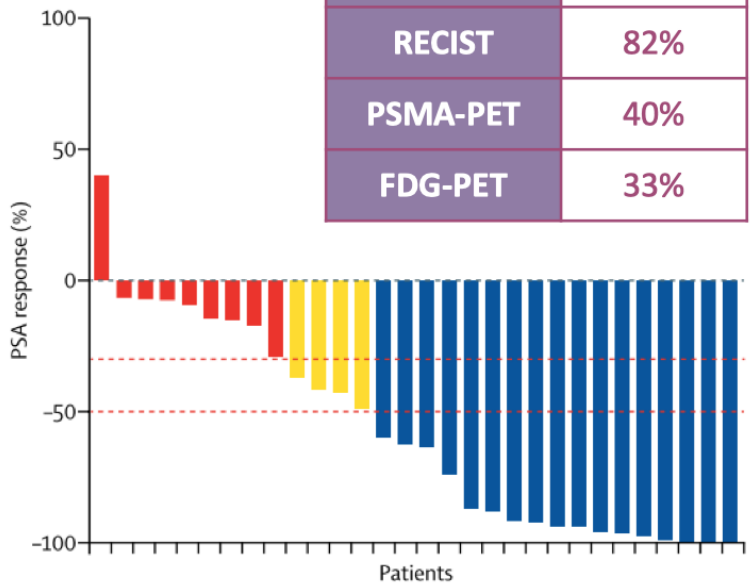
Primary endpoint: 50% PSA response rate

Selection based on ^{68}Ga-PSMA y ^{18}F-FDG PET-CT

- High PSMA expression: at least one location with SUV > 1.5 times normal liver SUV
- Those with discordant uptake (locations with PET-FDG uptake & no PET-PSMA uptake) were excluded

Response rate

PSA (50%)	57%
RECIST	82%
PSMA-PET	40%
FDG-PET	33%



Toxicity

	G1-2	G3	G4
Dry mouth	87%	0	0
Thrombopenia	27%	10%	3%
Anemia	13%	13%	
Dry eyes	17%	0	0
Asthenia	50%	0	0

Hofman MS, et al. Lancet Oncol 2018 ;19(6):825.

• EVIDENCIA CIENTÍFICA: CPRCm

VISION

N=831

- mCRPC post docetaxel
- Previous treatment with both:
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- PSMA-positive on ^{68}Ga-PSMA-11*

Randomization 2:1

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7.4 GBq iv q6 weekly
4 cycles, increasable to 6

Protocol-permitted SOC alone

Primary endpoint: OS and rPFS

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
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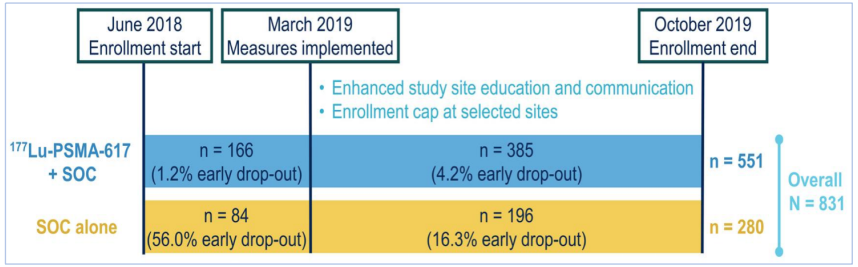

Baseline characteristics

Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N=581)		All Patients Who Underwent Randomization (N=831)	
	^{177}Lu-PSMA-617 plus Standard Care (N=385)	Standard Care Alone (N=196)	^{177}Lu-PSMA-617 plus Standard Care (N=551)	Standard Care Alone (N=280)
Median age (range) — yr	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG performance-status score of 0 or 1 — no. (%)†	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
Site of disease — no. (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range) — ng/ml	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)
Median alkaline phosphatase level (range) — IU/liter‡	108.0 (26–2524)	96.0 (34–1355)	105.0 (17–2524)	94.5 (28–1355)
Median LDH (range) — IU/liter‡	230.5 (119–5387)	232.0 (105–2693)	221.0 (88–5387)	224.0 (105–2693)
Median time since diagnosis (range) — yr	7.3 (0.9–28.9)	7.0 (0.7–26.2)	7.4 (0.9–28.9)	7.4 (0.7–26.2)
Gleason score at diagnosis — no. (%)§				
8–10	226 (58.7)	118 (60.2)	324 (58.8)	170 (60.7)
Unknown	28 (7.3)	19 (9.7)	42 (7.6)	24 (8.6)
Previous prostatectomy — no. (%)¶	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous androgen-receptor–pathway inhibitor — no. (%)‖				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%)**				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

Sartor O, et al. N Engl J Med 2021;385(12):1091.

• EVIDENCIA CIENTÍFICA: CPRCm

VISION

N=831

- mCRPC post docetaxel
- Previous treatment with both:
  - ≥ 1 ARi
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- Protocol-permitted SOC planned before randomization
- Excluding chemo, IO, Ra-223, investigational drugs
- ECOG 0-2
- PSMA-positive on ^{68}Ga-PSMA-11*

Randomization 2:1

^{177}Lu-PSMA-617 + protocol-permitted SOC
7.4 GBq iv q6 weekly
4 cycles, increasable to 6

Protocol-permitted SOC alone

Primary endpoint: OS and rPFS

Selection based on PET-CT ^{68}Ga-PSMA
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Treatment*	^{177}Lu-PSMA-617 plus standard care (n=529)	Standard care alone (n=205)	Overall (n=734)
Medication – no. (%)	529 (100.0)	205 (100.0)	734 (100.0)
Radiotherapy – no. (%)	79 (14.9)	34 (16.6)	113 (15.4)
Other interventions – no. (%)	24 (4.5)	5 (2.4)	29 (4.0)
Standard-care anti-cancer medications† received by ≥1% of patients – no. (%)‡			
Gonadotropin-releasing hormone analogues	468 (88.5)	172 (83.9)	640 (87.2)
Glucocorticoids	335 (63.3)	134 (65.4)	469 (63.9)
Androgen receptor pathway inhibitors	278 (52.6)	139 (67.8)	417 (56.8)
Enzalutamide	157 (29.7)	87 (42.4)	244 (33.2)
Abiraterone	132 (25.0)	72 (35.1)	204 (27.8)
Apalutamide	10 (1.9)	1 (0.5)	11 (1.5)
Darolutamide	2 (0.4)	1 (0.5)	3 (0.4)
Denosumab	184 (34.8)	80 (39.0)	264 (36.0)
Bisphosphonates	45 (8.5)	28 (13.7)	73 (9.9)
Testosterone 5α reductase inhibitors	16 (3.0)	11 (5.4)	27 (3.7)
Degarelix acetate	12 (2.3)	1 (0.5)	13 (1.8)
Degarelix	6 (1.1)	5 (2.4)	11 (1.5)
Estrogens	12 (2.3)	1 (0.5)	13 (1.8)

AR pathway inhibitors	64%
Glucocorticoids	57%
Denosumab	36%
Bisphosphonates	10%

Sartor O, et al. N Engl J Med 2021;385(12):1091.

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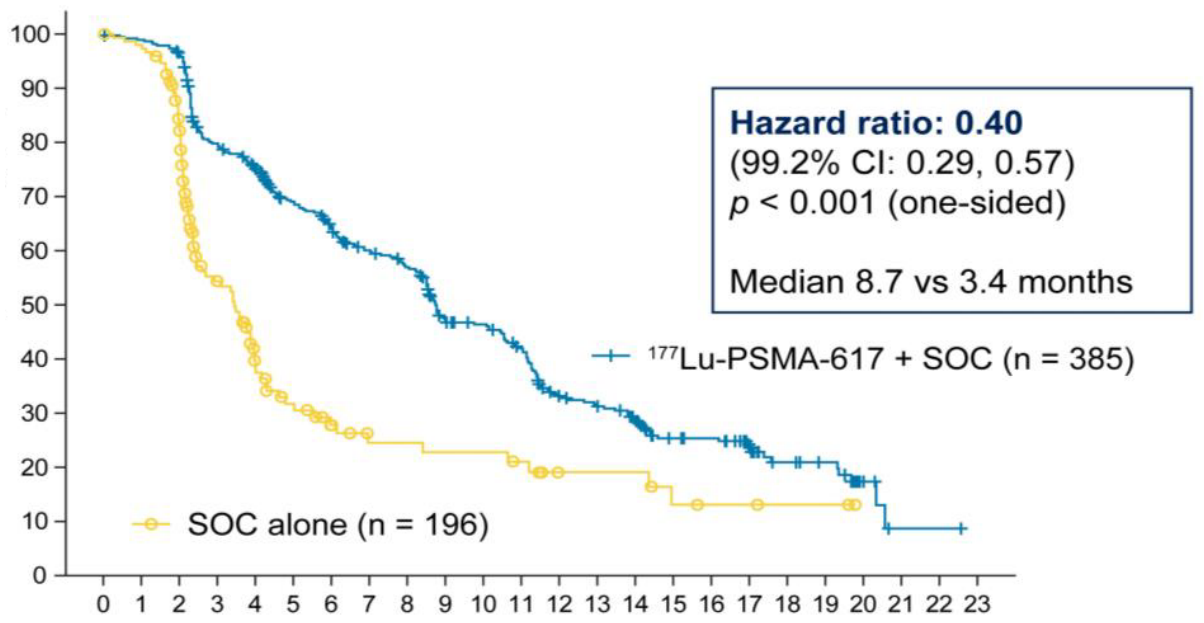
rPFS



Sartor O, et al. N Engl J Med 2021;385(12):1091.

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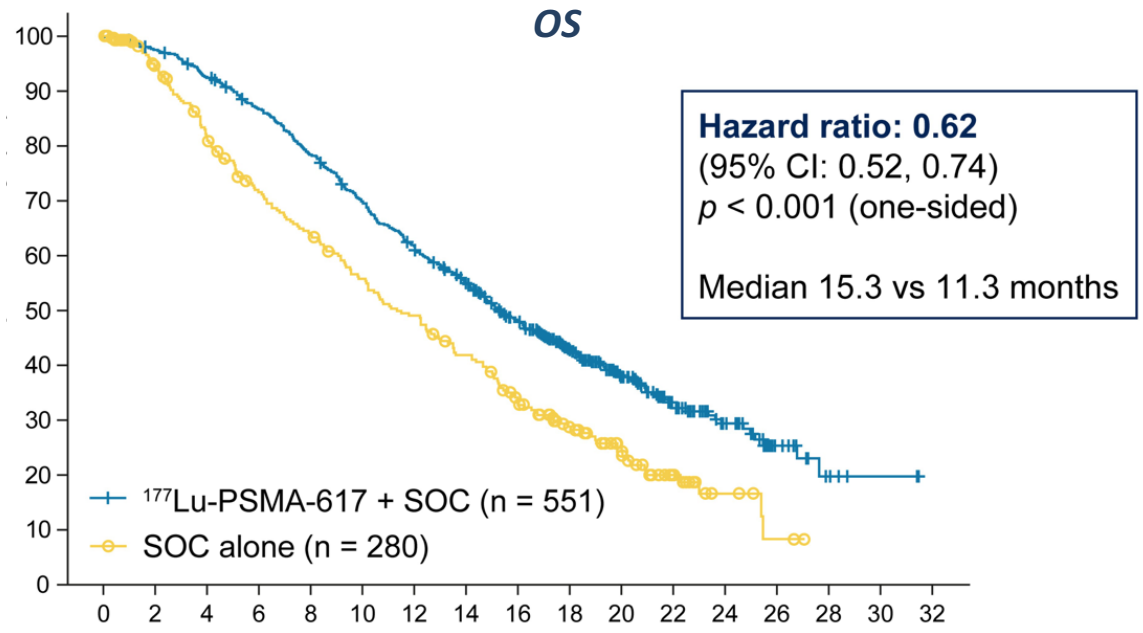

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	243	146	0.54 (0.41, 0.70)
No	308	134	0.68 (0.53, 0.87)
LDH			
≤ 260 IU/L	368	182	0.63 (0.50, 0.80)
> 260 IU/L	182	97	0.63 (0.48, 0.84)
Liver metastases			
Yes	48	34	0.87 (0.53, 1.43)
No	503	246	0.62 (0.51, 0.76)
ECOG score			
0 or 1	510	258	0.61 (0.50, 0.74)
2	41	22	0.63 (0.35, 1.13)
Age			
< 65 years	145	60	0.73 (0.49, 1.10)
≥ 65 years	406	220	0.59 (0.48, 0.73)
Race			
White	486	235	0.63 (0.52, 0.77)
African American or Black	34	21	0.60 (0.29, 1.24)
Asian	9	11	1.04 (0.38, 2.81)
All patients	551	280	0.62 (0.52, 0.74)

Sartor O, et al. N Engl J Med 2021;385(12):1091
De Bono J, et al. J Clin Oncol 2021;39(suppl 15;LBA4)

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AR pathway inhibitors	64%
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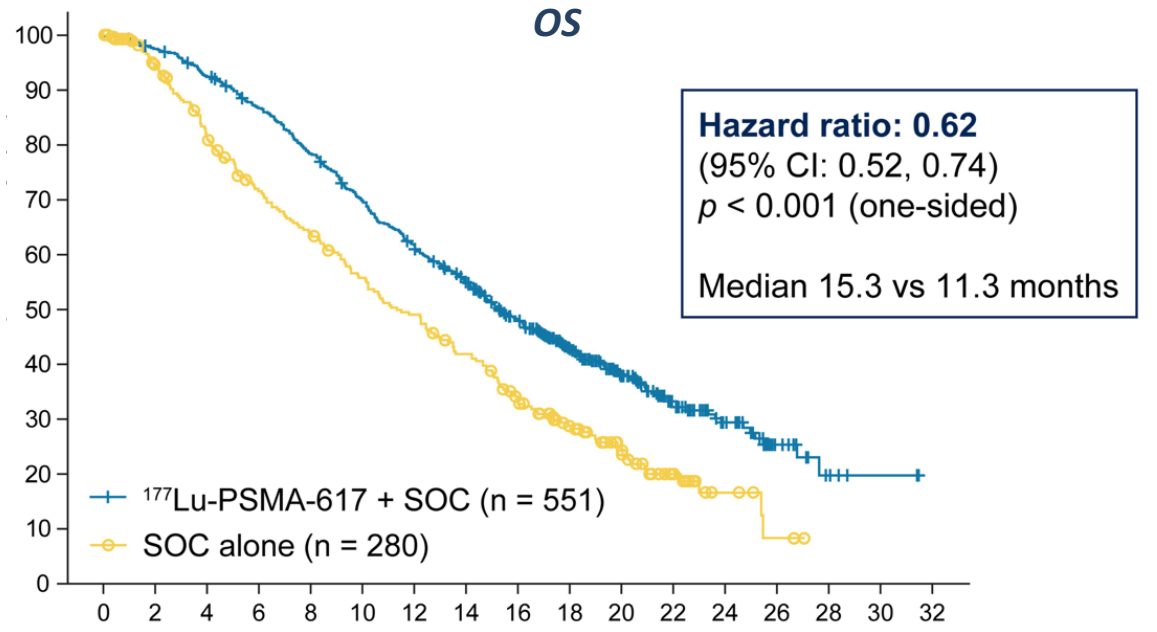

		^{177}Lu-PSMA-617 + SoC (n = 551) n/N (%)	SoC alone (n = 280) n/N (%)	HR (95% CI)
ARPIs	1	182/296 (61.5)	83/130 (63.8)	0.74 (0.57, 0.97)
	≥ 2	161/255 (63.1)	104/150 (69.3)	0.52 (0.41, 0.67)
Taxane regimens	1	206/342 (60.2)	108/165 (65.5)	0.59 (0.46, 0.75)
	≥ 2	113/170 (66.5)	70/99 (70.7)	0.73 (0.53, 0.99)
Non-taxane regimens	0	299/485 (61.6)	167/252 (66.3)	0.61 (0.50, 0.74)
	≥ 1	44/66 (66.7)	20/28 (71.4)	0.71 (0.42, 1.23)
Immunotherapies	0	255/414 (61.6)	134/200 (67.0)	0.58 (0.47, 0.73)
	≥ 1	88/137 (64.2)	53/80 (66.3)	0.72 (0.51, 1.01)
Bone health agents	Yes	66/99 (66.7)	43/57 (75.4)	0.54 (0.36, 0.80)
	No	277/452 (61.3)	144/223 (64.6)	0.64 (0.52, 0.79)
^{223}Ra	Yes	59/97 (60.8)	31/48 (64.6)	0.73 (0.47, 1.13)
	No	284/454 (62.6)	156/232 (67.2)	0.60 (0.49, 0.73)
PARP inhibitors	Yes	22/30 (73.3)	11/16 (68.8)	0.60 (0.28, 1.28)
	No	321/521 (61.6)	176/264 (66.7)	0.62 (0.51, 0.75)
All patients		**343/551 (62.3)**	**187/280 (66.8)**	**0.62 (0.52, 0.74)**

Favors ^{177}Lu-PSMA-617 | Favors SoC
0.05 0.2 0.8 3.2

Sartor O, et al. N Engl J Med 2021;385(12):1091
Vaishampayan N, et al. J Clin Oncol 2022;40(suppl 16;abstr 5001)

EVIDENCIA CIENTÍFICA: CPRCm

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- **mCRPC post docetaxel**
- **Previous treatment with both:**
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- **ECOG 0-2**
- **PSMA-positive on ^{68}Ga-PSMA-11***

Randomization 2:1

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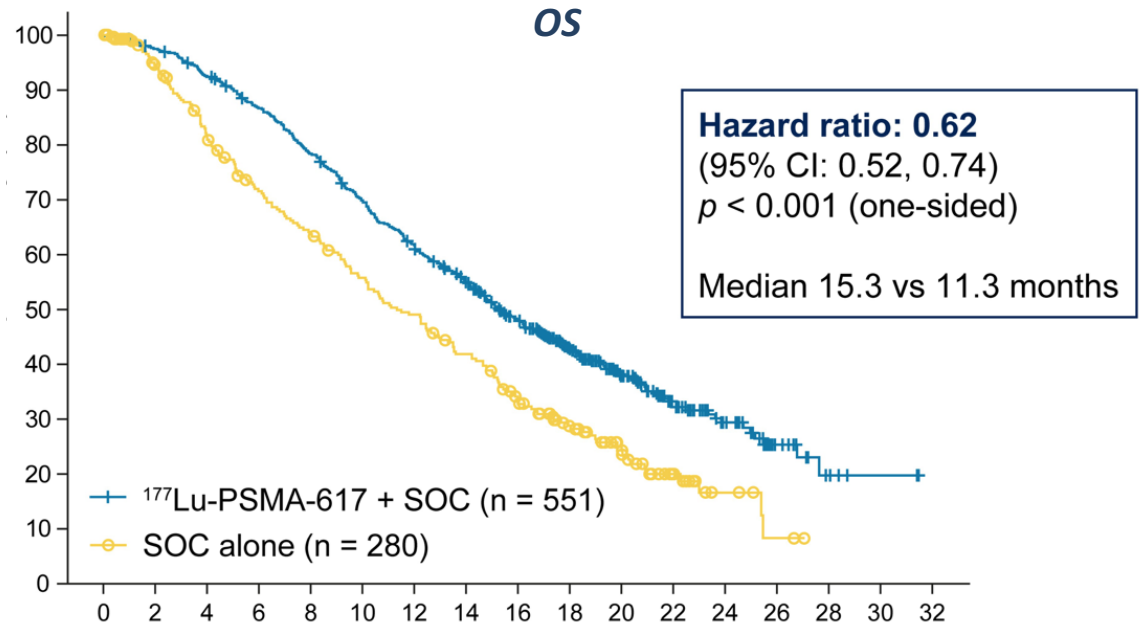
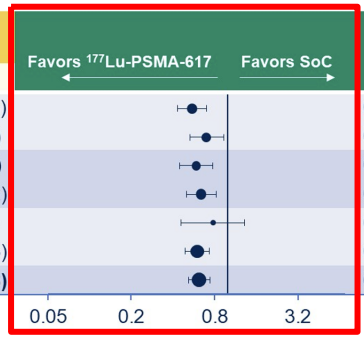


		^{177}Lu-PSMA-617 + SoC (n = 551) n/N (%)	SoC alone (n = 280) n/N (%)	HR (95% CI)
ARPIs	Yes	166/289 (57.4)	110/166 (66.3)	0.55 (0.43, 0.70)
	No	177/262 (67.6)	77/114 (67.5)	0.70 (0.53, 0.93)
Bone health agents	Yes	152/240 (63.3)	86/125 (68.8)	0.59 (0.45, 0.78)
	No	191/311 (61.4)	101/155 (65.2)	0.64 (0.50, 0.82)
Radiation therapy	Yes	51/75 (68.0)	22/31 (71.0)	0.78 (0.46, 1.32)
	No	292/476 (61.3)	165/249 (66.3)	0.60 (0.49, 0.73)
All patients		**343/551 (62.3)**	**187/280 (66.8)**	**0.62 (0.52, 0.74)**



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  - 1 or 2 taxane regimens
- Protocol-permitted SOC planned before randomization
- Excluding chemo, IO, Ra-223, investigational drugs
- ECOG 0-2
- PSMA-positive on ^{68}Ga-PSMA-11*

Randomization 2:1

^{177}Lu-PSMA-617 + protocol-permitted SOC
7.4 GBq iv q6 weekly
4 cycles, increasable to 6

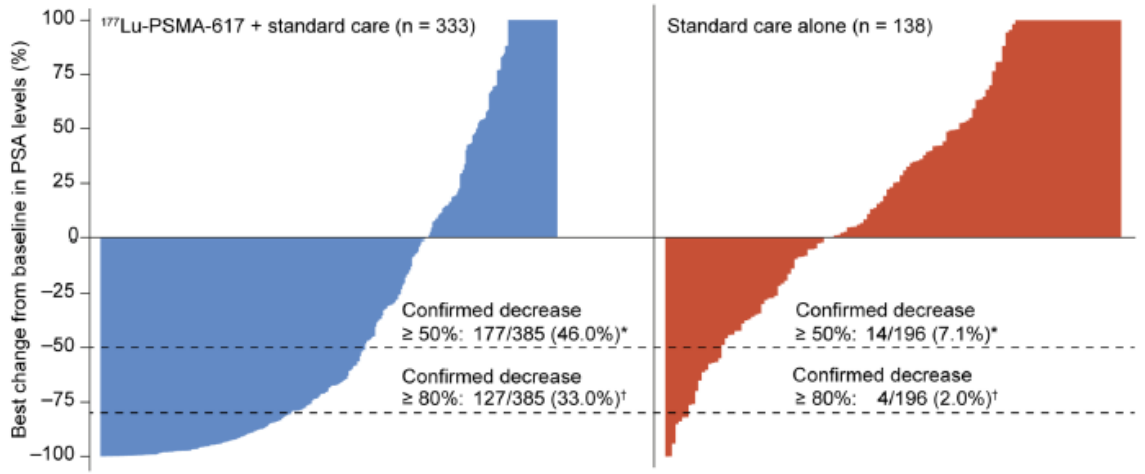
Protocol-permitted SOC alone

Primary endpoint: OS and rPFS

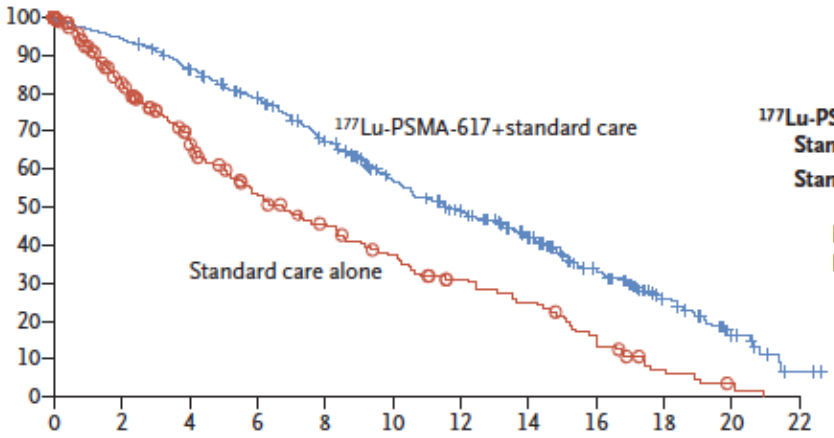
AR pathway inhibitors	64%
Glucocorticoids	57%
Denosumab	36%
Bisphosphonates	10%

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions: uptake ≤ liver uptake in lymph nodes > 25 mm (short axis) or solid > 10 mm

PSA-RR



Time to first symptomatic skeletal event



	No. of Events/ No. of Patients	Median (mo)
^{177}Lu-PSMA-617 + Standard Care	256/385	11.5
Standard Care Alone	137/196	6.8

Hazard ratio, 0.50 (95% CI, 0.40–0.62)
P<0.001

Sartor O, et al. N Engl J Med 2021;385(12):1091.

EVIDENCIA CIENTÍFICA: CPRCm

VISION

N=831

- mCRPC post docetaxel
- Previous treatment with both:
  - ≥ 1 ARi
  - 1 or 2 taxane regimens
- Protocol-permitted SOC planned before randomization
- Excluding chemo, IO, Ra-223, investigational drugs
- ECOG 0-2
- PSMA-positive on ^{68}Ga-PSMA-11*

Randomization 2:1

^{177}Lu-PSMA-617 + protocol-permitted SOC
7.4 GBq iv q6 weekly
4 cycles, increasable to 6

Protocol-permitted SOC alone

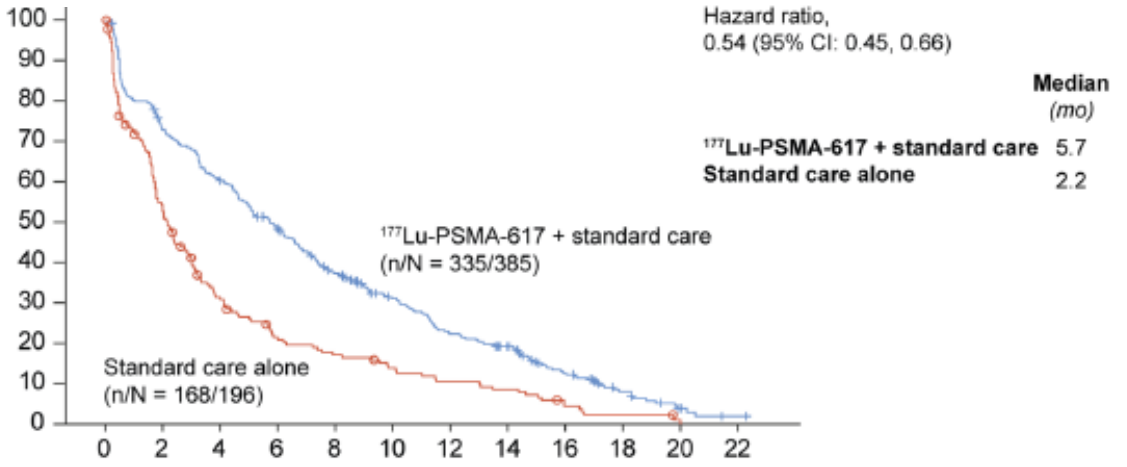
Primary endpoint: OS and rPFS

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions: uptake ≤ liver uptake in lymph nodes > 25 mm (short axis) or solid > 10 mm

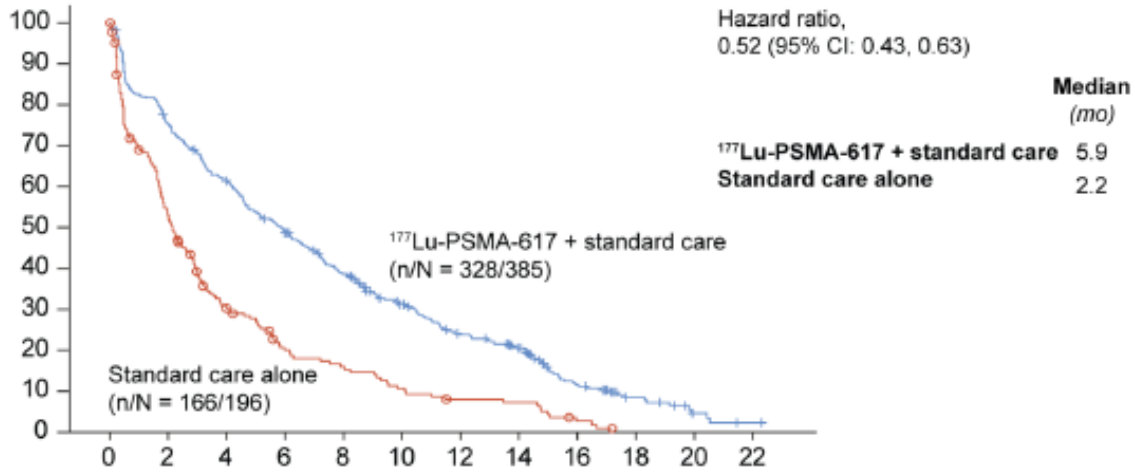
AR pathway inhibitors	64%
Glucocorticoids	57%
Denosumab	36%
Bisphosphonates	10%

QoL

FACT-P total score (n=581)



BPI-SF pain intensity (n=581)



Sartor O, et al. N Engl J Med 2021;385(12):1091.

• EVIDENCIA CIENTÍFICA: CPRCm

VISION

N=831

- mCRPC post docetaxel
- Previous treatment with both:
  - ≥ 1 ARi
  - 1 or 2 taxane regimens
- Protocol-permitted SOC planned before randomization
- Excluding chemo, IO, Ra-223, investigational drugs
- ECOG 0-2
- PSMA-positive on ^{68}Ga-PSMA-11*

Randomization 2:1

^{177}Lu-PSMA-617 + protocol-permitted SOC
7.4 GBq iv q6 weekly
4 cycles, increasable to 6

Protocol-permitted SOC alone

Primary endpoint: OS and rPFS

Selection based on PET-CT ^{68}Ga-PSMA
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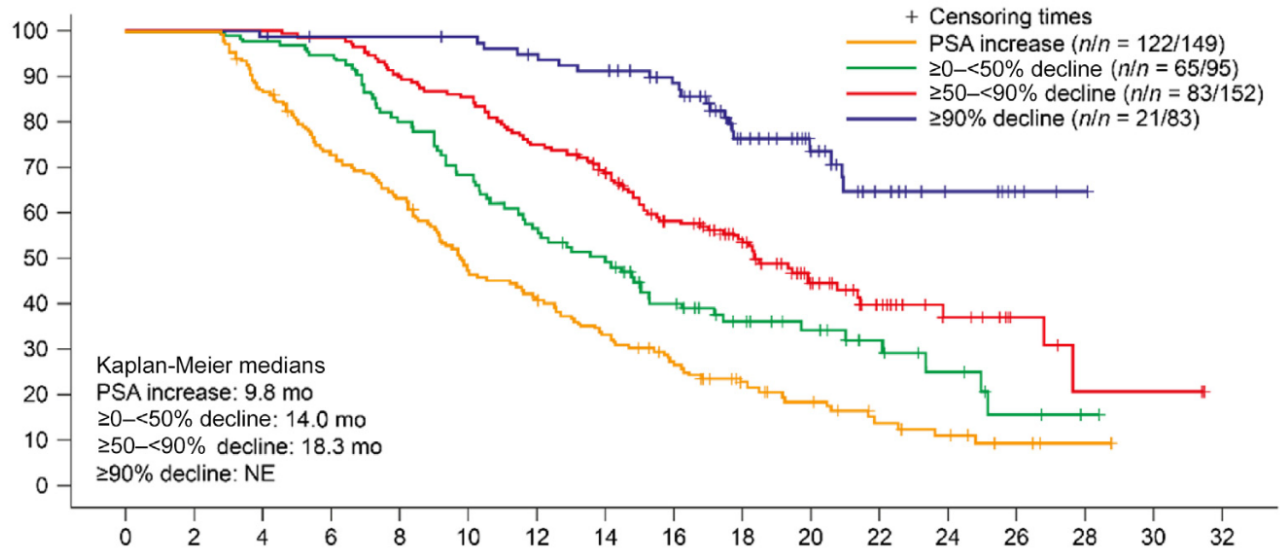
- No PSMA negative lesions: uptake ≤ liver uptake in lymph nodes > 25 mm (short axis) or solid > 10 mm

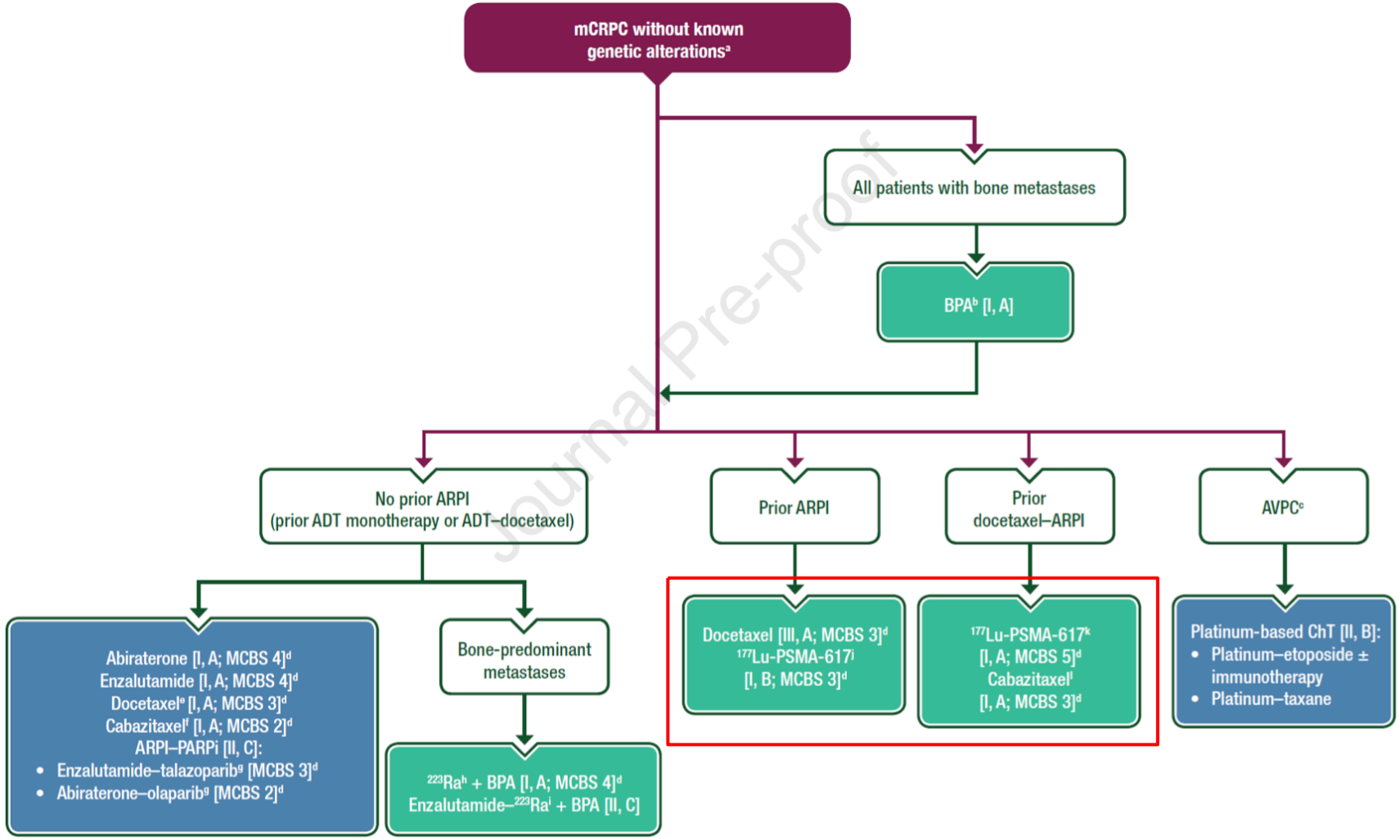
AR pathway inhibitors	64%
Glucocorticoids	57%
Denosumab	36%
Bisphosphonates	10%

OS by PSA-response



Armstrong AJ, et al. Eur Urol 2024;86(1):52.

- **GUÍAS ESMO 2026**



Fizazi K, et AL. Ann Oncol 2026;Feb 10:S0923-7534(26)00042-6.

- **APROBACIÓN ESPAÑA**

Indicación autorizada	Resolución expediente de financiación indicación
Pluvicto en combinación con terapia de deprivación androgénica (TDA) con o sin inhibidores de la vía del receptor androgénico (RA) está indicado para el tratamiento de pacientes adultos con cáncer de próstata metastásico progresivo resistente a la castración positivo al antígeno de membrana específico de la próstata (PSMA) que han recibido tratamiento con inhibidores de la vía del RA y quimioterapia con taxanos (ver sección 5.1)	Sí, con restricción a la indicación autorizada: Pacientes adultos con cáncer de próstata metastásico progresivo resistente a la castración, positivo al antígeno de membrana específico de la próstata (PSMA) que han recibido tratamiento con inhibidores de la vía del receptor androgénico (RA) y dos líneas de quimioterapia con taxanos, o bien en pacientes que no son elegibles para una segunda línea de quimioterapia con taxanos, en combinación con terapia de deprivación androgénica (TDA) con o sin inhibidores de la vía del RA. Los pacientes deben cumplir los siguientes criterios: - Expectativa de vida >6 meses. - ECOG 0-1. - Captación de PSMA en la mayoría de las lesiones, por PET/TC o PET/RM y ausencia de lesiones PSMA negativas relevantes. - Ausencia de metástasis hepáticas, cerebrales o características neuroendocrinas. - Haber recibido al menos un inhibidor de la vía del RA y dos tratamientos de quimioterapia basada en taxanos, habiendo progresado a cabazitaxel o haber recibido al menos un inhibidor de la vía del RA y no ser candidato a taxanos de segunda línea. - No haber recibido tratamiento previo con terapia de radioligandos (TRL) dirigida a PSMA. - Funciones medular, hepática y renal adecuadas: • Para la reserva medular: recuento de leucocitos ≥2,5 x 109 /L o neutrófilos ≥1,5 x 109 /L; plaquetas ≥100 x 109 /L; hemoglobina ≥9 g/dL • Para la función renal: creatinina sérica ≤1,5 x LSN o aclaramiento de creatinina ≥50 mL/min • Para la función hepática: bilirrubina total ≤1,5 x LSN; ALT o AST ≤3,0 x LSN. - No haber presentado toxicidad hematológica grave (grado ≥3) o mantenida con los tratamientos previos. - Los pacientes con antecedentes de metástasis en el sistema nervioso central deben haber recibido terapia y encontrarse neurológicamente estables. • Se realizará un análisis de PSA a las 12 semanas a todos los pacientes, coincidiendo con el tercer ciclo de Pluvicto. En caso de que el valor del PSA a las 12 semanas sea superior al valor basal, se procederá a la interrupción del tratamiento con Pluvicto. • Las dosis se podrán cancelar sin coste hasta 72 horas laborables antes de la hora programada de inyección.

https://www.sanidad.gob.es/profesionales/medicamentos.do?metodo=verDetalle&cn=759982.

• EVIDENCIA CIENTÍFICA: CPRCm

TheraP

N=200

- mCRPC post docetaxel suitable for cabazitaxel
- PD with rising PSA and PSA ≥ 20
- ECOG 0-2
- Previous ARi therapy
- PET eligibility criteria*

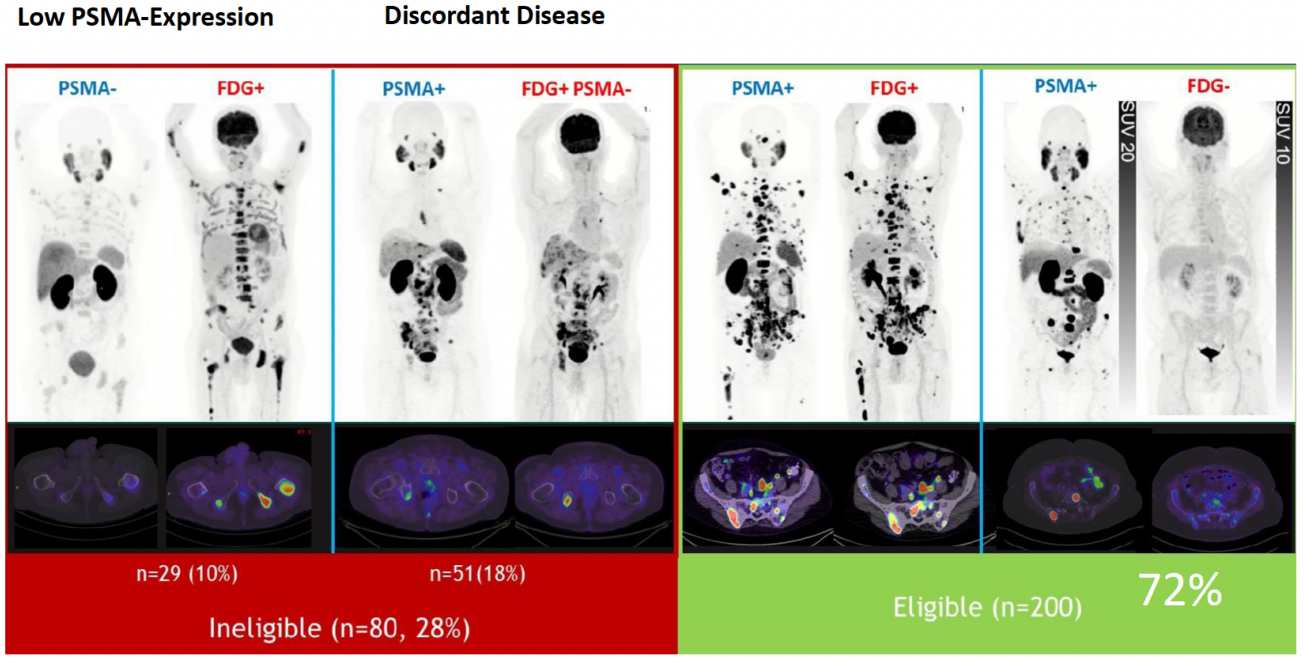
Randomization 1:1

^{177}Lu-PSMA-617
8.5 GBq iv q6 weekly
↓ 0.5 GBq each cycle
Up to 6 cycles

Cabazitaxel
20 mg/m2 iv q3 weekly
Up to 6 cycles

Primary endpoint: 50% PSA response rate

Selection based on PET-CT ^{68}Ga-PSMA & ^{18}F-FDG
- PSMA SUVmax > 20 at any location
- Measurable disease with SUVmax > 10
- No FDG positive / PSMA negative sites
- Central imaging review



Hofman MS, et al. Lancet 2021;397(10276):797.

• EVIDENCIA CIENTÍFICA: CPRCm

TheraP

N=200

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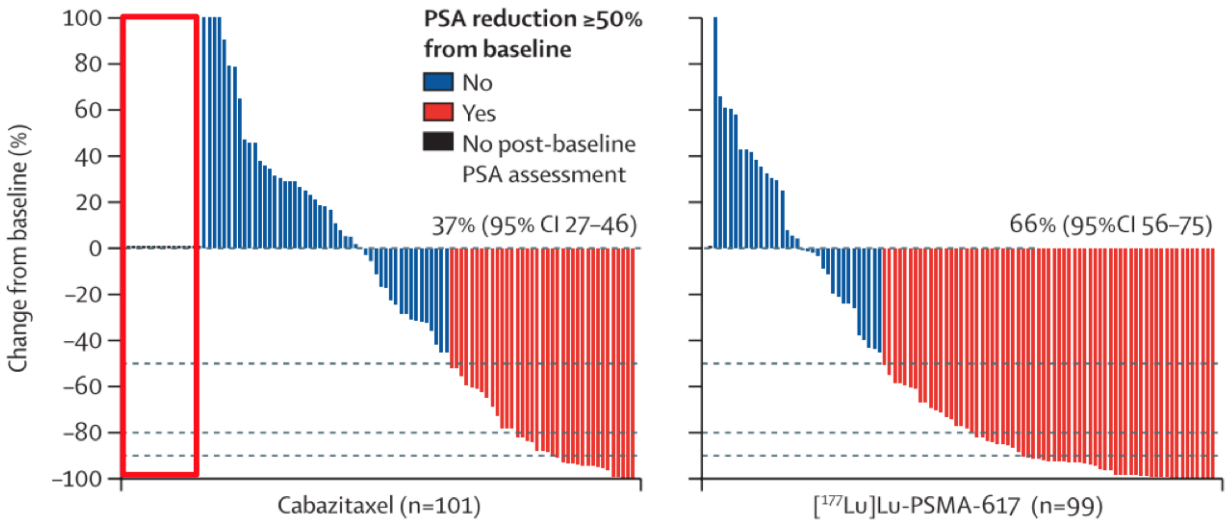
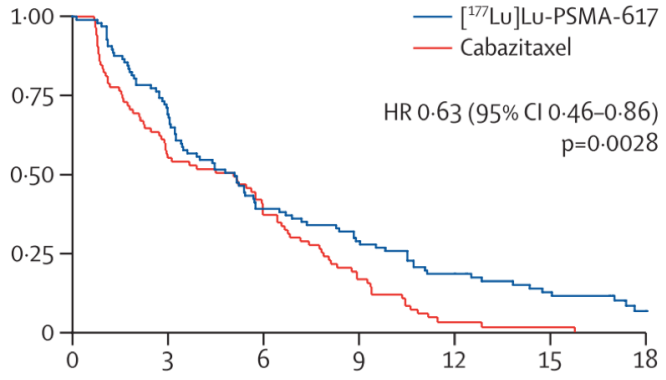
- PSMA SUVmax > 20 at any location
- Measurable disease with SUVmax > 10
- No FDG positive / PSMA negative sites
- Central imaging review

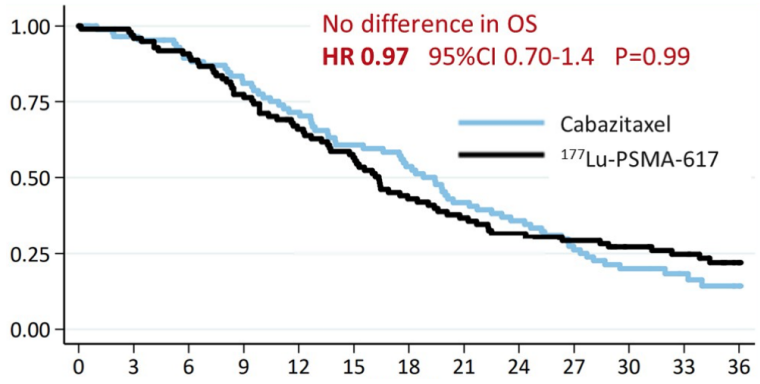
Primary Endpoint: PSA response rate: 66% vs 37% (p<0.001)



PFS



OS



Hofman MS, et al. Lancet 2021;397(10276):797.

• EVIDENCIA CIENTÍFICA: CPRCm

TheraP

N=200

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- PD with rising PSA and PSA ≥ 20
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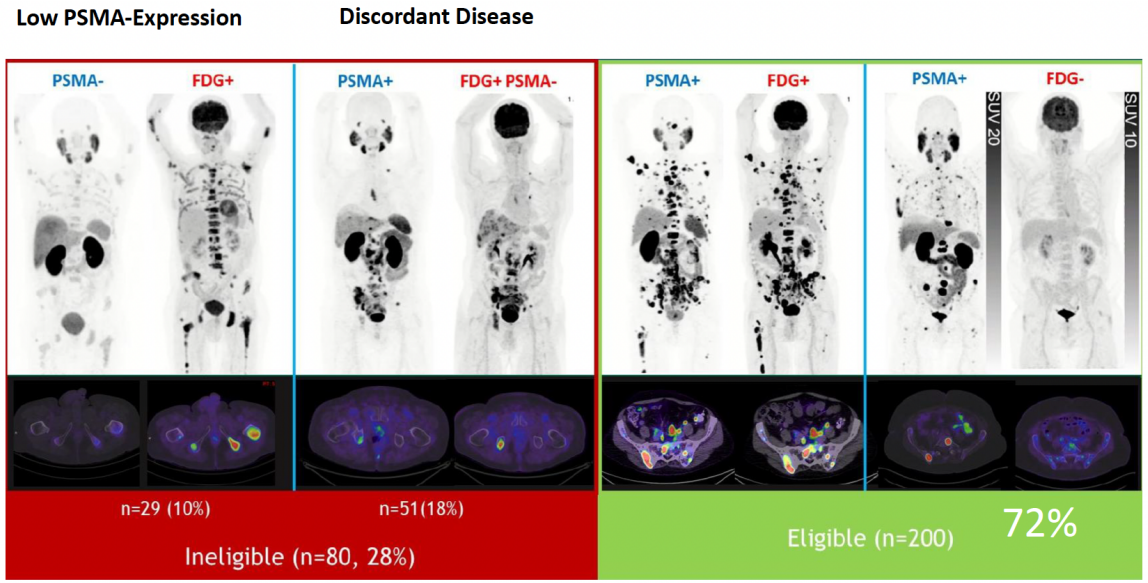
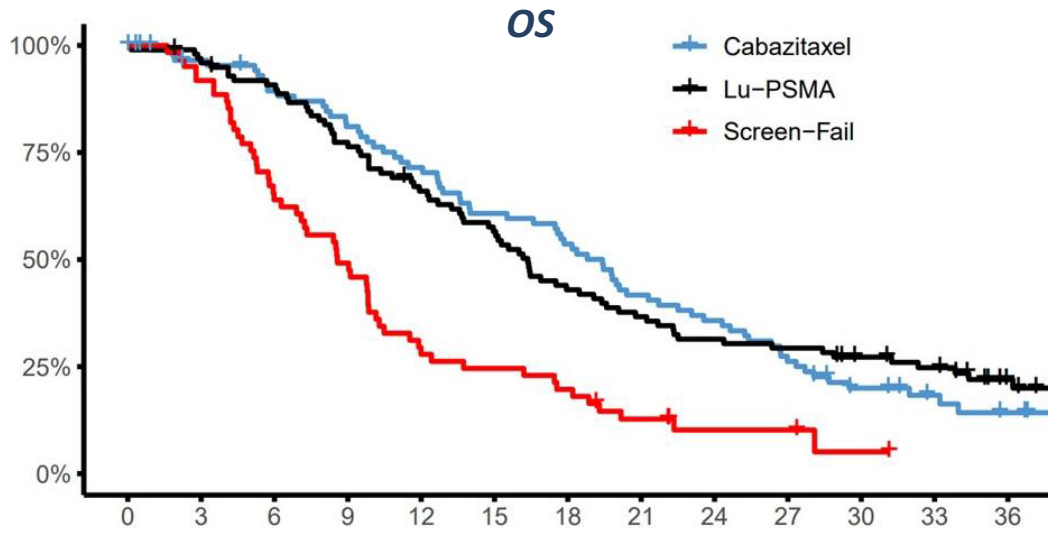




Hofman MS, et al. Lancet 2021;397(10276):797.

• EVIDENCIA CIENTÍFICA: CPRCm

PSMAfore

N=468

- mCRPC
- Previous ARi therapy
- ≥ 1 PSMA + lesion on ^{68}Ga-PSMA-11 PET/CT
- Candidates for change in ARi
- Taxane-naïve
- ECOG 0-1

Randomization 1:1

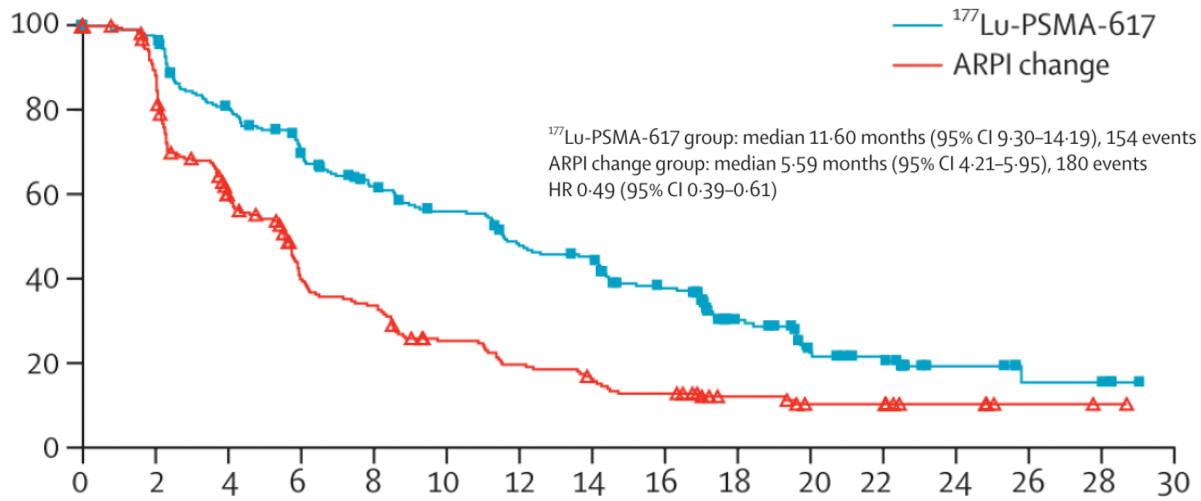
^{177}Lu-PSMA-617
7.4 GBq iv q6 weekly
Up to 6 cycles

ARi change:
Abiraterone or enzalutamide

Primary endpoint: rPFS

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions

rPFS



Morris MJ, et al. Lancet 2024;404:10459.

• EVIDENCIA CIENTÍFICA: CPRCm

PSMAfore

N=468

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- Previous ARi therapy
- ≥ 1 PSMA + lesion on ^{68}Ga-PSMA-11 PET/CT
- Candidates for change in ARi
- Taxane-naïve
- ECOG 0-1

Randomization 1:1

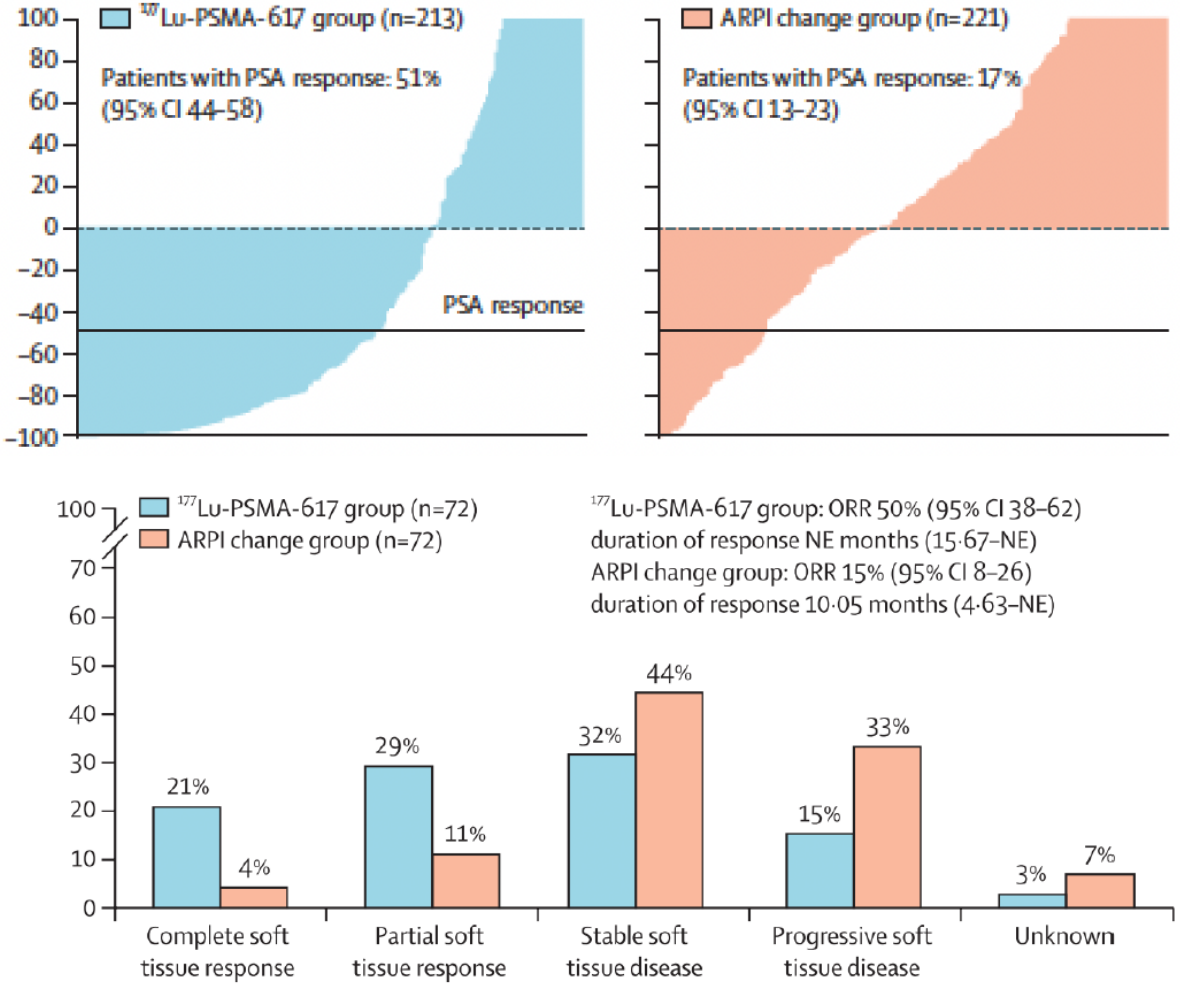
^{177}Lu-PSMA-617
7.4 GBq iv q6 weekly
Up to 6 cycles

ARi change:
Abiraterone or enzalutamide

Primary endpoint: rPFS

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions

Overall responses



Morris MJ, et al. Lancet 2024;404:10459.

- **EVIDENCIA CIENTÍFICA: CPRCm**

PSMAfore

N=468

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- **Previous ARi therapy**
- **≥ 1 PSMA + lesion on ^{68}Ga-PSMA-11 PET/CT**
- **Candidates for change in ARi**
- **Taxane-naïve**
- **ECOG 0-1**

Randomization 1:1

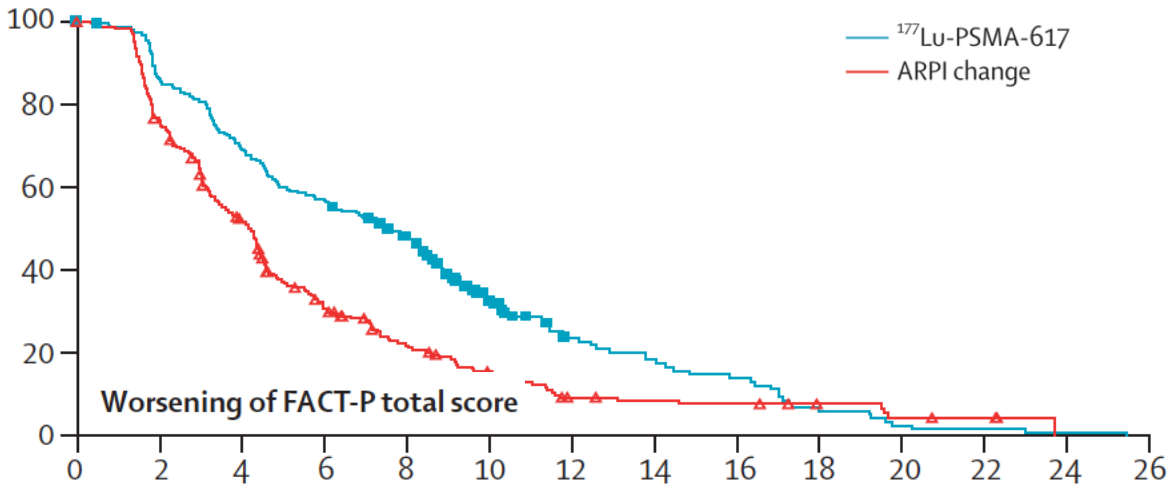
^{177}Lu-PSMA-617
7.4 GBq iv q6 weekly
Up to 6 cycles

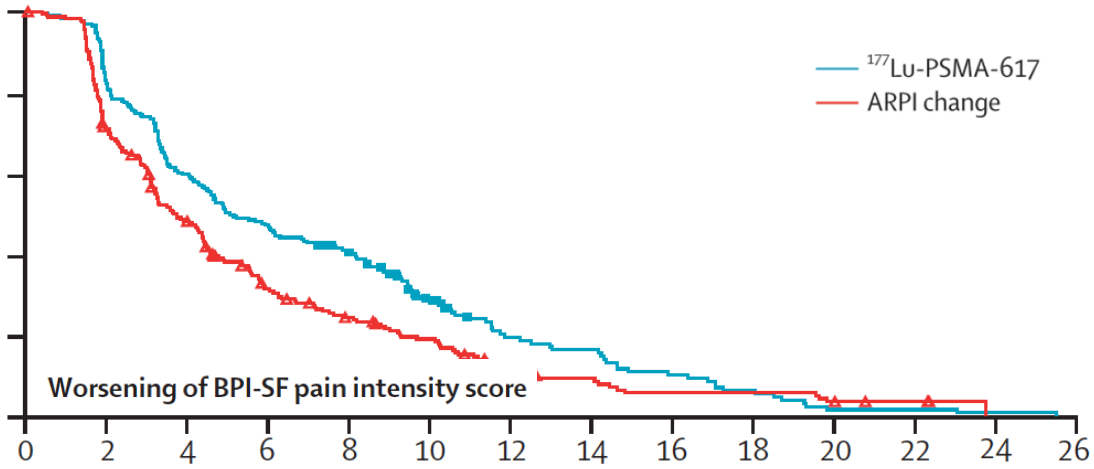
ARi change:
Abiraterone or enzalutamide

Primary endpoint: rPFS

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions

QoL





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- **EVIDENCIA CIENTÍFICA: CPRCm**

PSMAfore

N=468

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- ≥ 1 PSMA + lesion on ^{68}Ga-PSMA-11 PET/CT
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^{177}Lu-PSMA-617
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Abiraterone or enzalutamide

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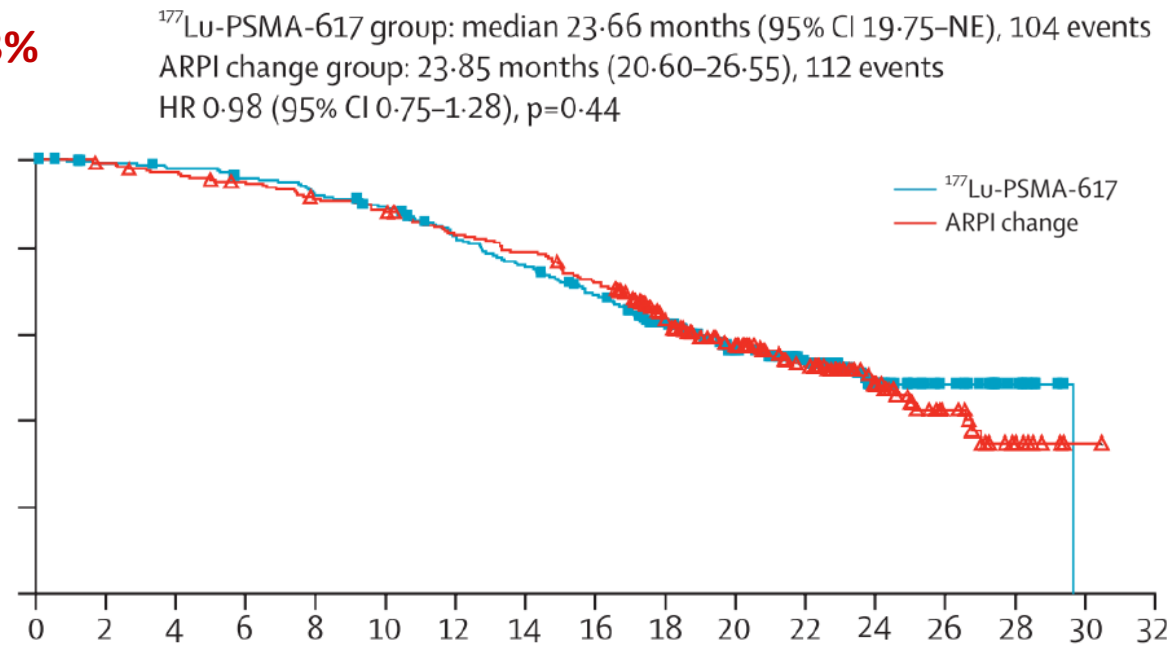
Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions

OS

60.3%



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PSMAfore

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- ≥ 1 PSMA + lesion on ^{68}Ga-PSMA-11 PET/CT
- Candidates for change in ARi
- Taxane-naïve
- ECOG 0-1

Randomization 1:1

^{177}Lu-PSMA-617
7.4 GBq iv q6 weekly
Up to 6 cycles

ARi change:
Abiraterone or enzalutamide

60.3%

Primary endpoint: rPFS

Selection based on PET-CT ^{68}Ga-PSMA
- At least one PSMA positive lesion: uptake > liver uptake (any size)
- No PSMA negative lesions

Table 1. Crossover-adjusted overall survival 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)	

Model 1 = rPD confirmed by BICR, ECOG performance status, and randomized treatment;

Fizazi , et al. Ann Oncol 2025;404:10459.

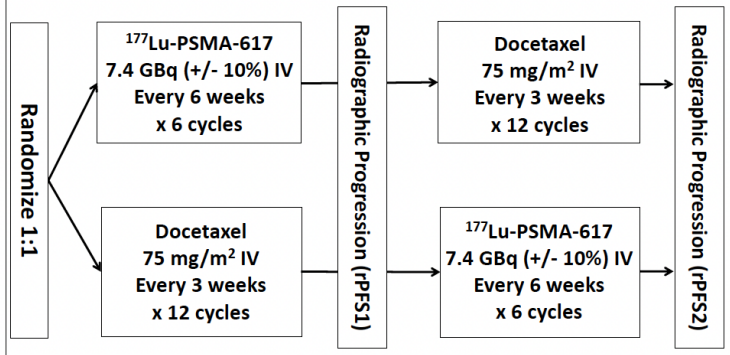
• EVIDENCIA CIENTÍFICA: CPRCm

PR.21

N=199

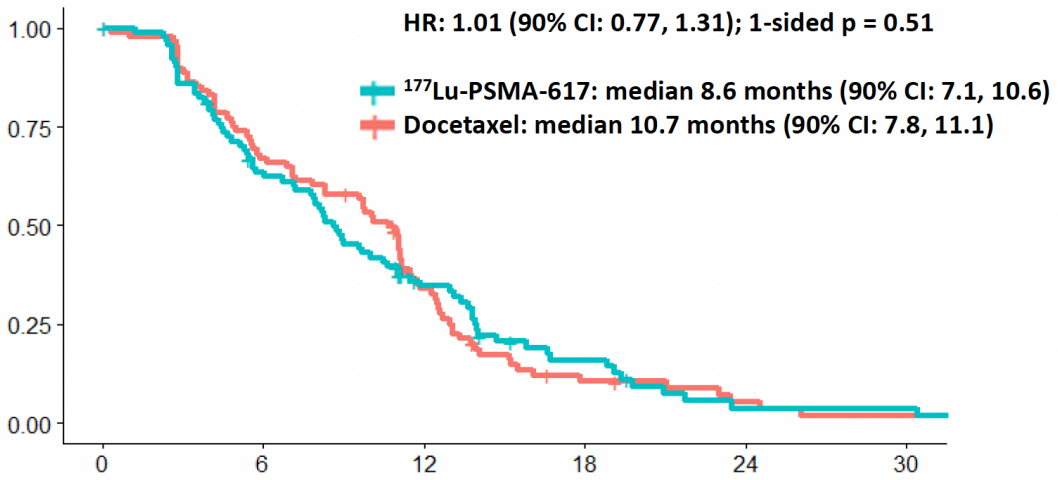
Key Eligibility

- Chemotherapy-naïve mCRPC progressing after ARPI
- PSMA PET positive (uptake >liver)
  - Excluded if >50% of extra-osseous lesions or >5 cm soft tissue lesion were PSMA negative
- ANC ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Hemoglobin ≥ 90 g/L
- CrCl ≥ 30 ml/min
- Bilirubin < 1.5 x ULN
- ALT < 3.5 x ULN (<5 x UN for liver metastases)
- ECOG PS of 0 - 2
- Prior docetaxel for mHSPC permitted if ≥12 months prior

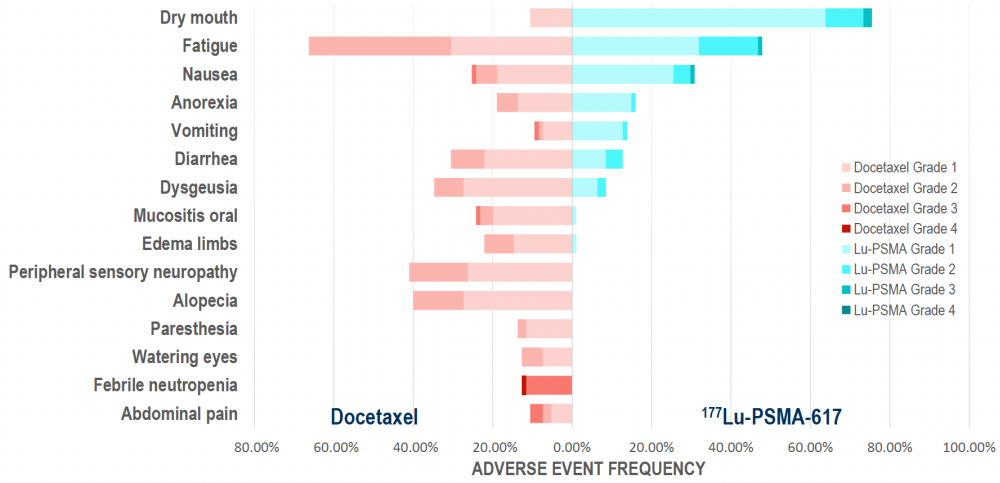


Primary endpoint: rPFS1

rPFS1



Adverse effects



- Grade 3-4 treatment related adverse events was 34% in the docetaxel arm and 13% in the ^{177}Lu-PSMA-617 arm

Chi KN, et al. ESMO 2025.

• EVIDENCIA CIENTÍFICA: CPRCm

Enza-P

N=162

- **mCRPC with PSA rising and > 5 ng/ml**
- **ECOG 0-2**
- **No prior chemotherapy or ARPi in mCRPC**
- **≥ 2 high risk features**

Randomization 1:1

^{177}Lu-PSMA-617
7.5 GBq iv q6-8w
x 2 or 4 doses
Enzalutamide 160 mg

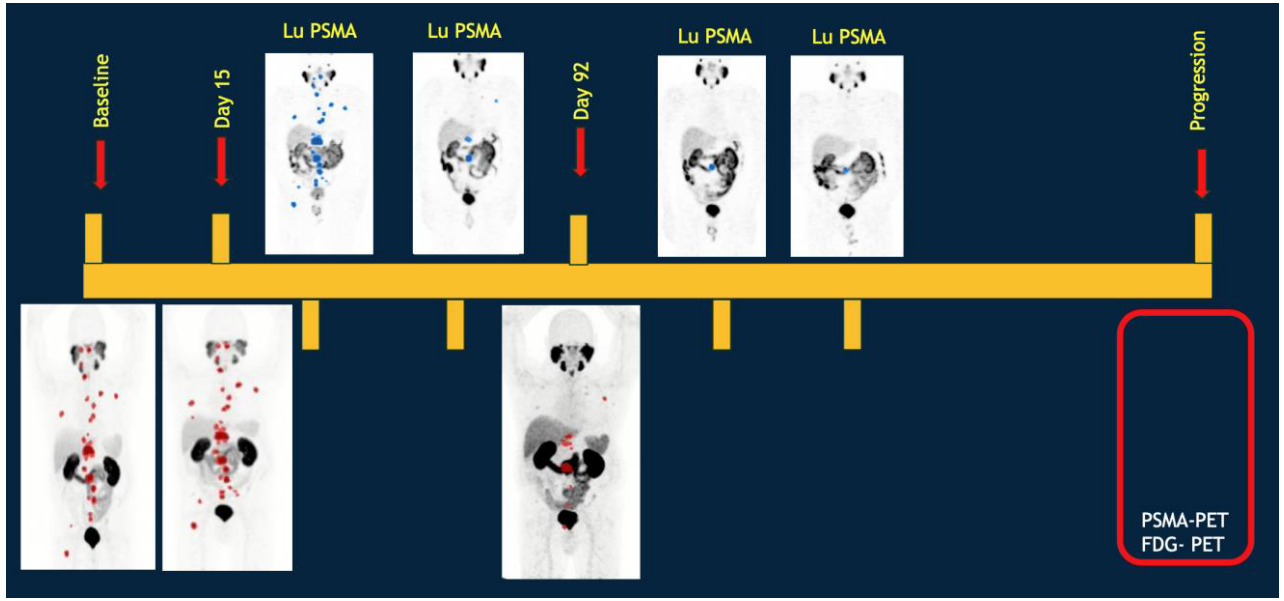
Enzalutamide 160 mg

Primary endpoint: PSA-PFS

High risk features (at least 2):
- LDH ≥ ULN
- ALP ≥ ULN
- Alb < 3.5 g/dL
- De novo metastatic
- <3yrs since diagnosis
- >5 bone mets
- Visceral mets
- PSADT < 84 days
- Opiates
- Prior abiraterone

^{68}Ga-PSMA
- SUVmax ≥15 at one site AND ≥10 at all measurable sites

Adaptative dosing scheme



Emmet L, et al. Lancet Oncol 2024;25(5):563.

• EVIDENCIA CIENTÍFICA: CPRCm

Enza-P

N=162

- **mCRPC with PSA rising and > 5 ng/ml**
- **ECOG 0-2**
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Randomization 1:1

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x 2 or 4 doses
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Enzalutamide 160 mg

Primary endpoint: PSA-PFS

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^{68}Ga-PSMA
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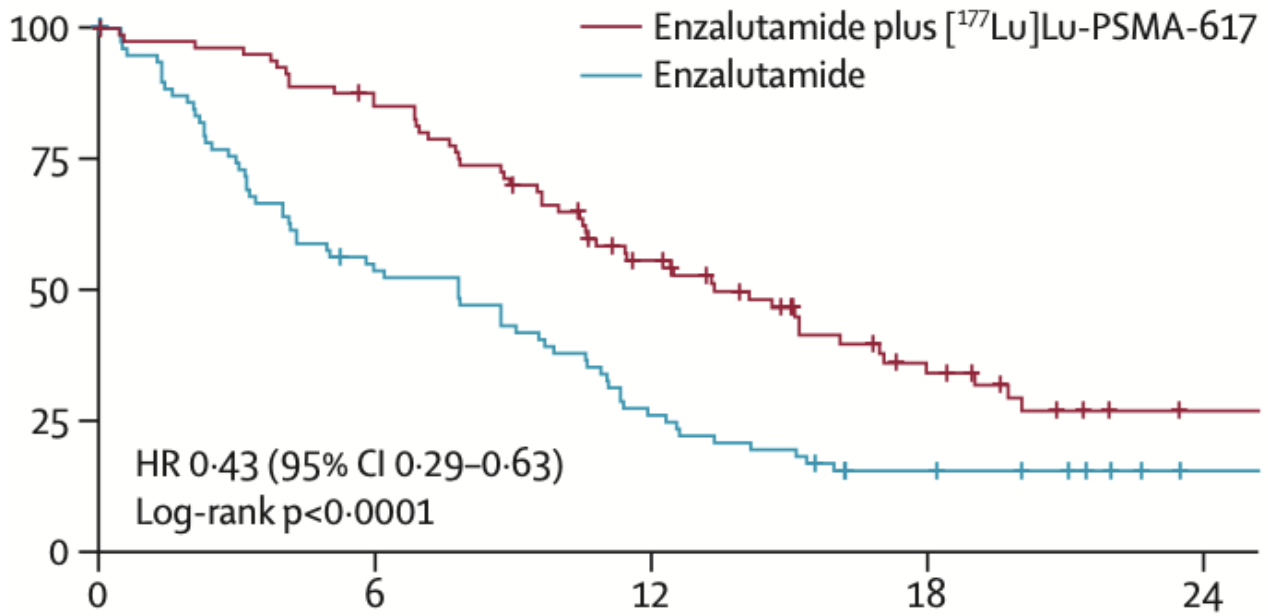
PSA-PFS



Emmet L, et al. Lancet Oncol 2024;25(5):563.

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Enza-P

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x 2 or 4 doses
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- >5 bone mets
- Visceral mets
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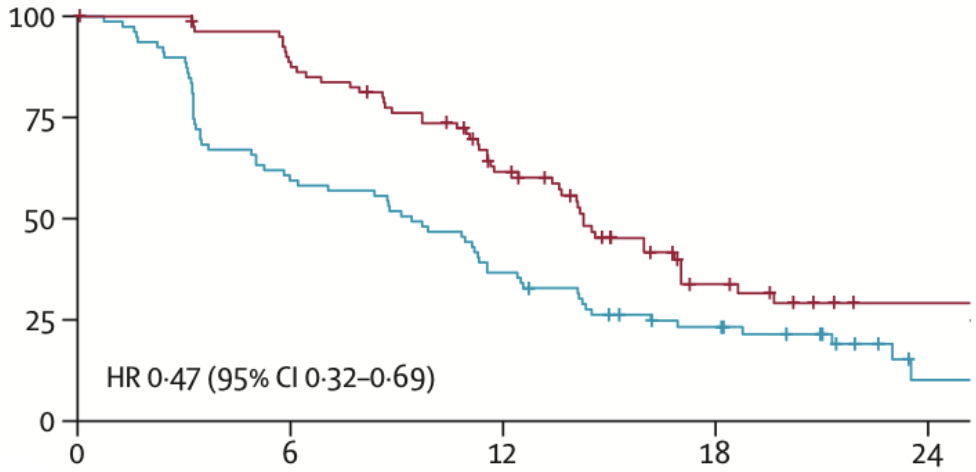
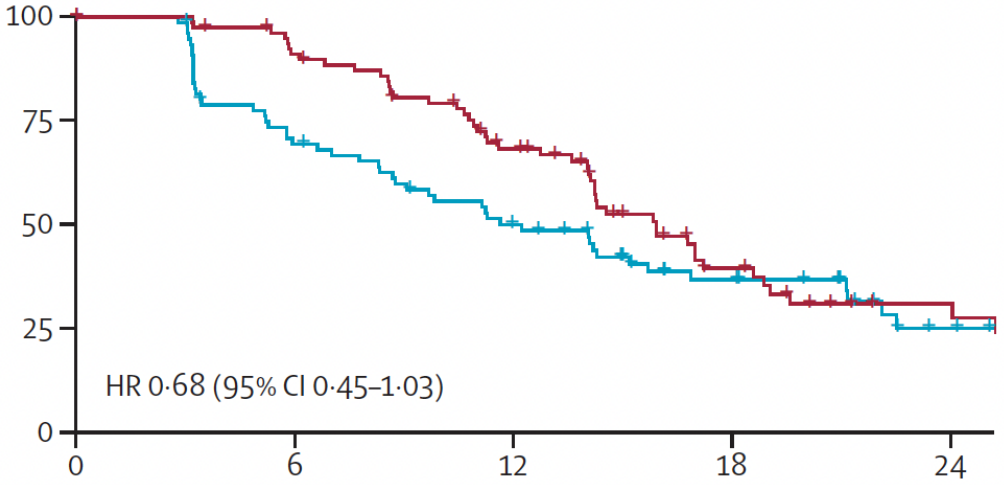
^{68}Ga-PSMA
- SUVmax ≥15 at one site AND ≥10 at all measurable sites

Clinical PFS

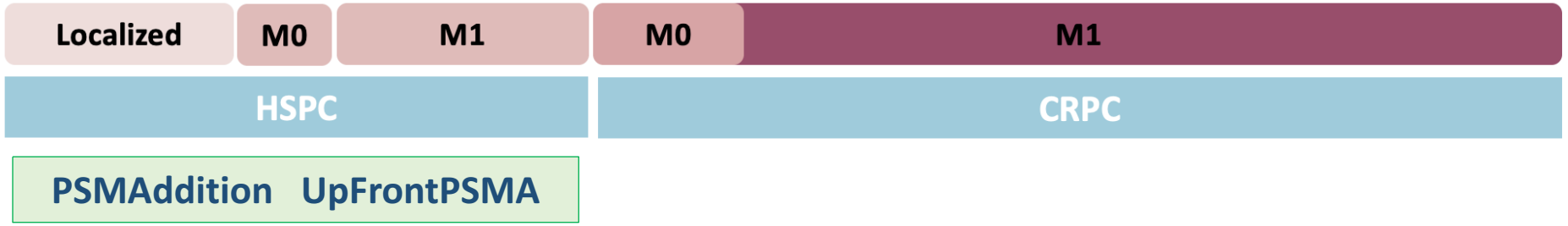


rPFS



Emmet L, et al. Lancet Oncol 2024;25(5):563.

- **EVIDENCIA CIENTÍFICA: CPHSm**



EVIDENCIA CIENTÍFICA: CPHSm

PSMAddition

N=1144

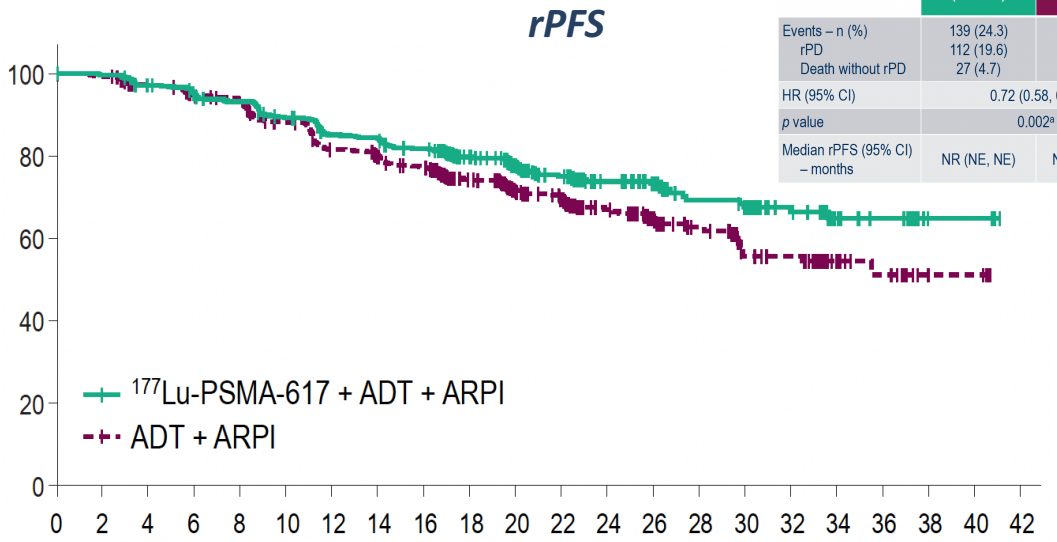
Eligible male patients

- Untreated or minimally treated[a] mHSPC
- ECOG PS 0–2
- ≥1 PSMA+ metastatic lesion on ^{68}Ga-PSMA-11 PET/CT
- Appropriate for ADT + ARPI

R 1:1

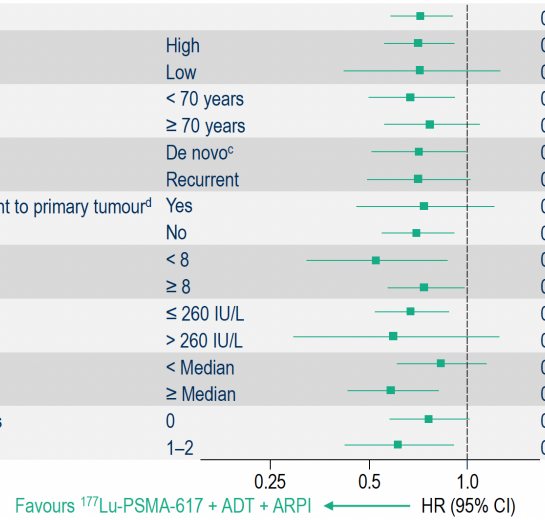
- **^{177}Lu-PSMA-617** (7.4 GBq ±10% 6 cycles q6w) **+ ADT + ARPI[b]**
- **ADT + ARPI[b]**

Primary endpoint: rPFS



	^{177}Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%)		
rPD	139 (24.3)	172 (30.1)
Death without rPD	112 (19.6)	152 (26.6)
	27 (4.7)	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)

		HR (95% CI)	^{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)



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EVIDENCIA CIENTÍFICA: CPHSm

PSMAddition

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Eligible male patients

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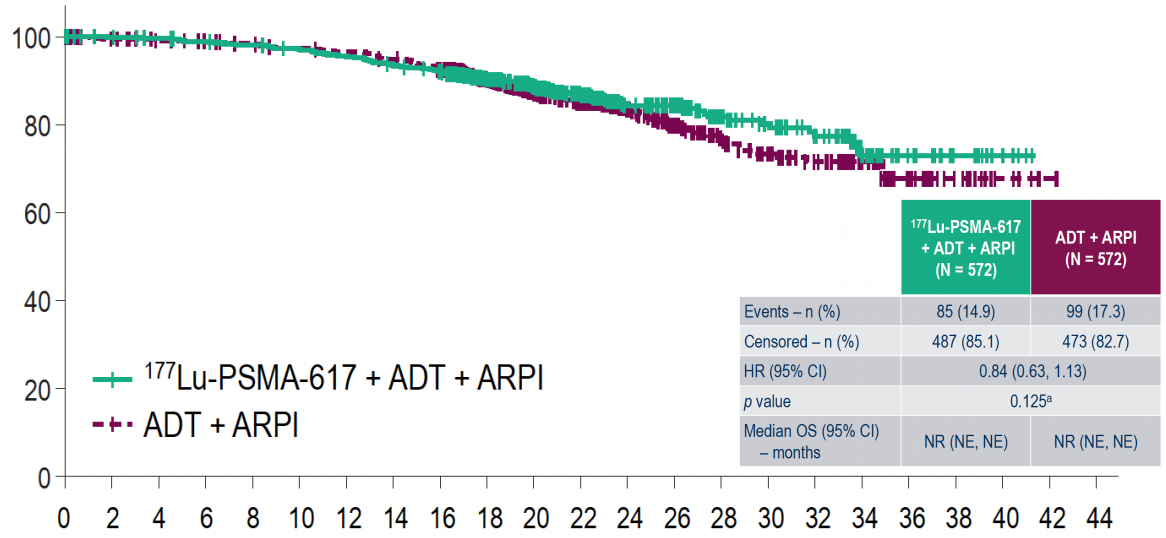
R 1:1

- **^{177}Lu-PSMA-617** (7.4 GBq ±10% 6 cycles q6w) **+ ADT + ARPI[b]**
- **ADT + ARPI[b]**

Primary endpoint: rPFS

OS



	^{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)

Emmet L, et al. Lancet Oncol 2024;25(5):563.

- **EVIDENCIA CIENTÍFICA: CPHSm**

UpFrontPSMA

N=130

Eligibility
De novo metastatic hormone-naïve prostate cancer suitable for docetaxel

R

1:1 Randomization
Stratified by:
- Disease volume
- Duration of ADT

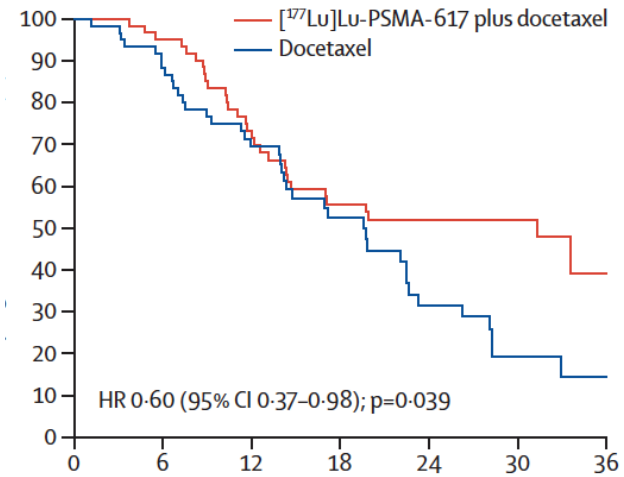
^{177}Lu-PSMA-617$_{(7.5GBq\ x2\ cycles)}$ Followed by Docetaxel$_{(75mg/m^2\ x6\ cycles)}$

Docetaxel$_{(75mg/m^2\ x6\ cycles)}$

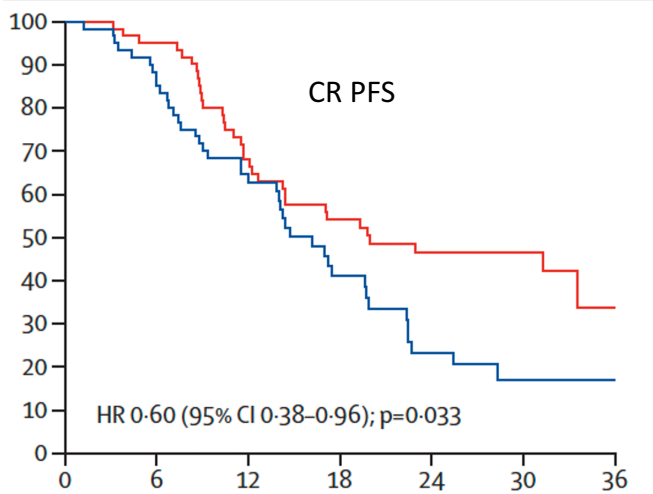
PSMA PET/CT & FDG PET/CT
- PSMA SUVmax >15
- High-volume metastatic disease
- FDG PET discordance < 5 sites or < 50% of total disease volume (PET scans centrally reviewed)

Primary endpoint: undetectable PSA (≤0.2 ng/mL) at 48 weeks

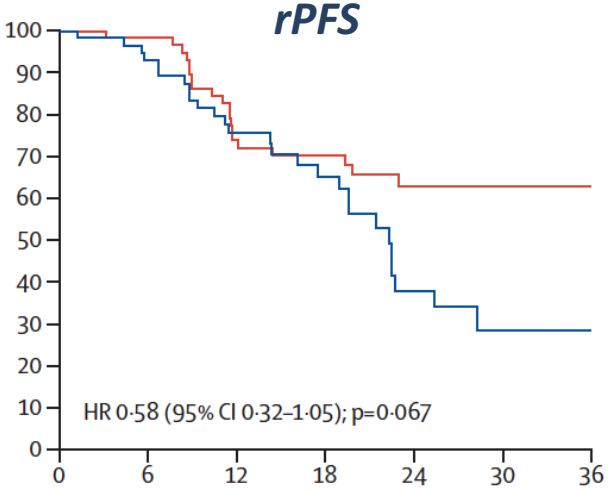
PSA PFS



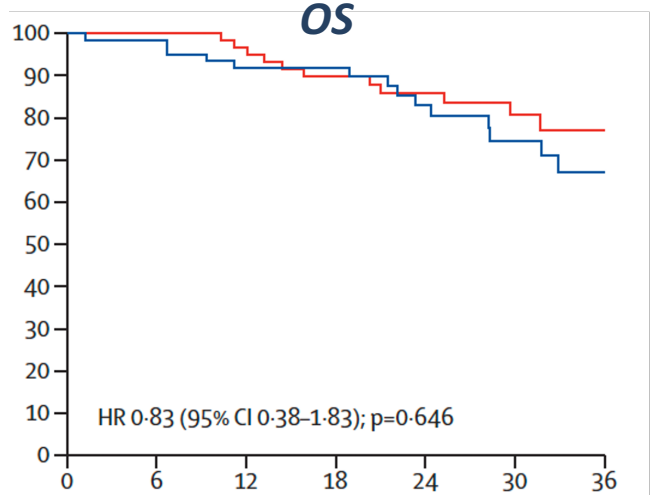
CR PFS



rPFS



OS



Azad AA, et al. Lancet Oncol 2024;25:1267..

- **TAKE-HOME MESSAGES**

✓ ^{177}Lu-PSMA en monoterapia demuestra beneficio clínicamente relevante en varios escenarios en CPRCm

- **Tras ARPi y docetaxel +/- cabazitaxel (VISION): beneficio claro en SG (contra un "SoC" impreciso)**
- Tras ARPi y docetaxel (Thera-P): mejora respuestas por PSA response y SLP (secundario), pero no SG
- **Tras ARPi (PSMAfore): beneficio significativo *vs.* 2º agente hormonal. No SG (diseño?)**
- Tras ARPi *vs.* docetaxel (PR.21): no beneficio en SLPr
- En primera línea combinado con enzalutamida *vs* enzalutamida (Enza-P): mejora SLP-PSA en mal pronóstico

✓ 177Lu-PSMA demuestra beneficio inicial in mHSPC

- **Combinado con ARPi *vs* ARPi solo (PSMAddition): beneficio significativo en SLPr. SG inmadura (negativa de momento).**
- Combinado con docetaxel *vs* docetaxel solo (UpFrontPSMA): beneficio significativo en PSA CR, no parece SLP ni SG
- Y frente a triplete ???

✓ ^{177}Lu-PSMA presenta un buen perfil de toxicidad

- Boca seca, toxicidad medular, astenia (grado 1-2)

✓ Es **ESENCIAL** un buen diseño de ensayos clínicos para entender la magnitud del beneficio de ^{177}Lu-PSMA, el momento de utilizarlo y ver una optima selección del paciente

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025