PSMA-Targeted Therapy: Promising New Treatments for Men with Advanced Prostate Cancer

Karthryn Bylow, MD

GU Medical Oncology

Medical College of Wisconsin

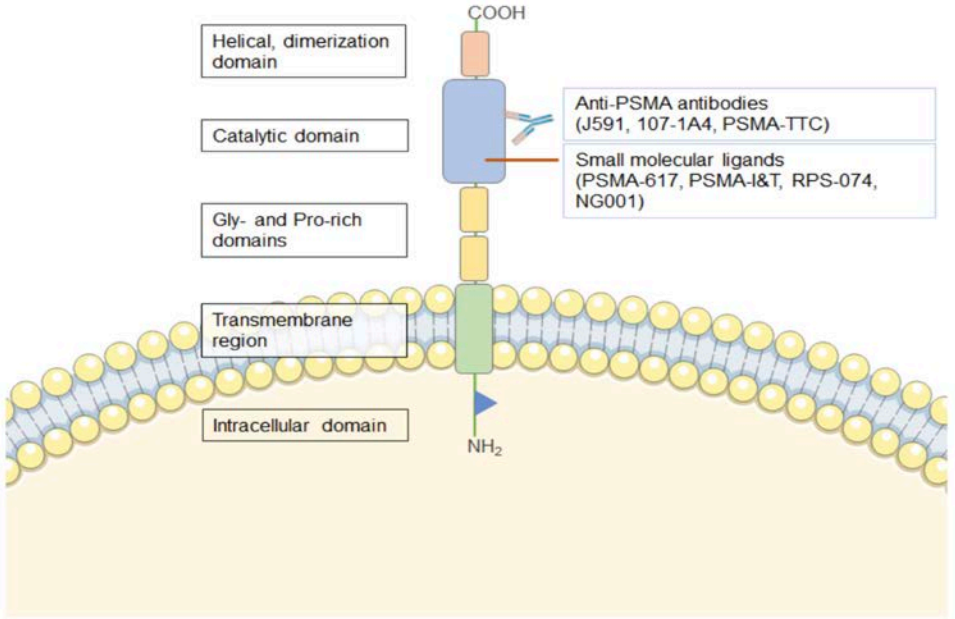
Objectives

To review and understand:

- The role of PSMA in prostate cancer
- Theragnostics
- The data on radiopharmaceuticals
- Other PSMA targeted therapies

Prostate-Specific Membrane Antigen (PSMA)

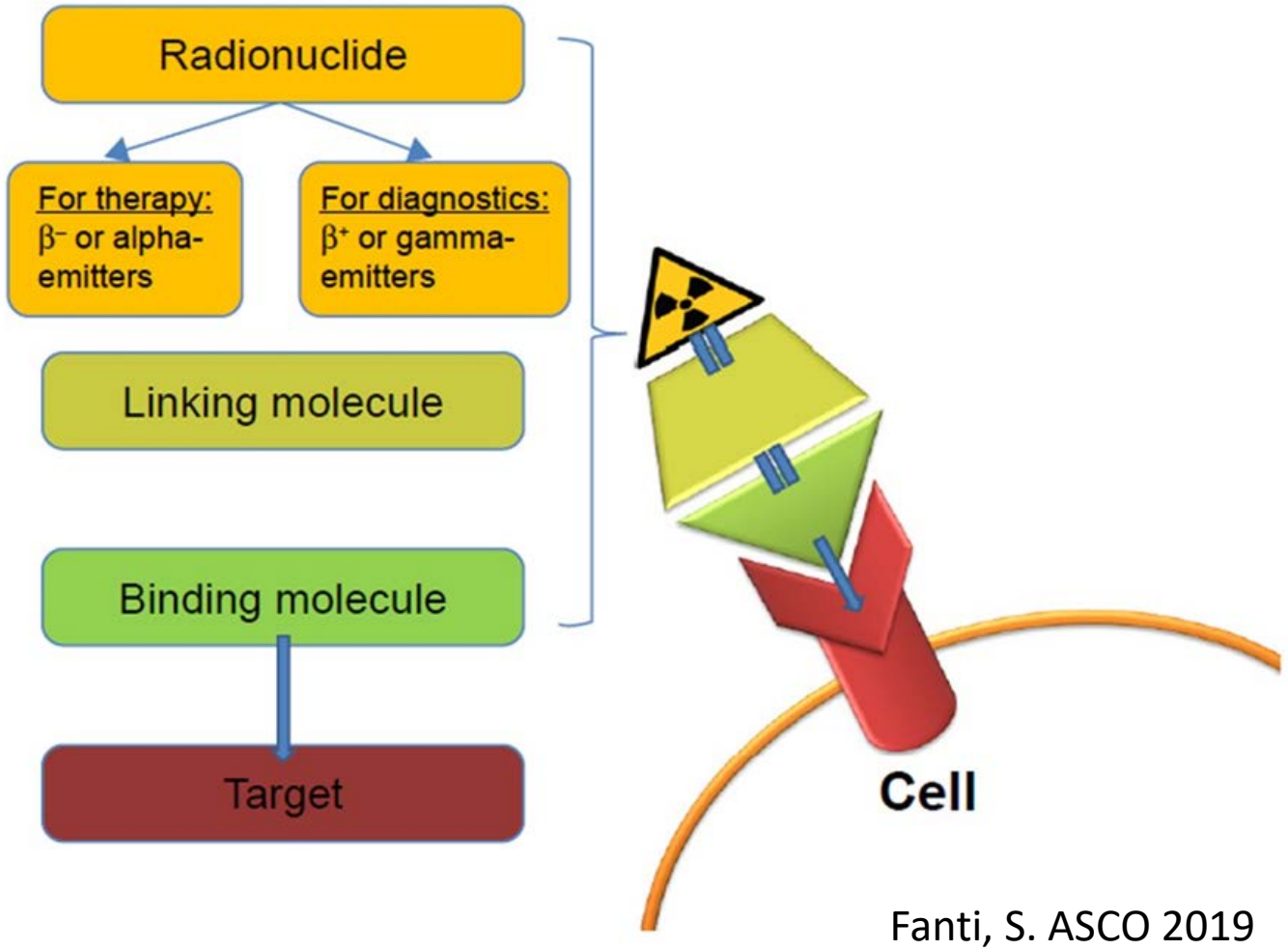
- Selectively overexpressed in prostate cancer
  - Limited expression in other organs
  - Renal tubules, small intestine, salivary/lacrimal glands
- PSMA may be targeted with antibodies (Ab) or small molecules
  - mAb: large, longer half life
    - More bone marrow exposure
    - Less exposure to organs with luminal PSMA expression
  - Small molecule: More on-target toxicity in tissues where PSMA is expressed
    - renal, salivary/lacrimal, small bowel



Tagawa, S et al. ASCO 2021

Theranostics

- Cancer cell is targeted using a ligand
- On top of ligand you put an isotope
- PET emitter: light to image disease
  - ^{18}F or ^{68}Ga
- Beta or alpha emitter: weapon to induce cytotoxic DNA damage
  - ^{177}Lu or ^{90}Y or ^{225}Ac



Fanti, S. ASCO 2019

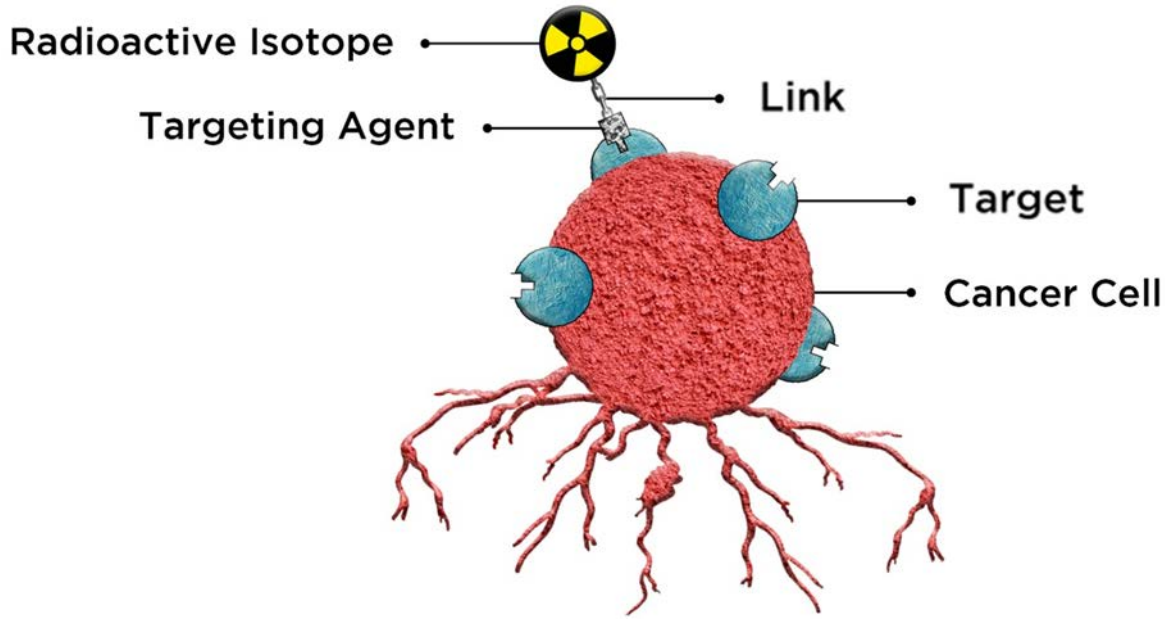
PSMA-targeted Radiotracers

- Dec 2020: ^{68}Ga-PSMA-11 became the first PSMA-targeted radiopharmaceutical approved for PET imaging purposes
  - Indication→ Rising PSA
  - UCLA, UCSF only

- May 2021 Piflufolastat F 18 was approved for the same indications

Radiopharmaceuticals

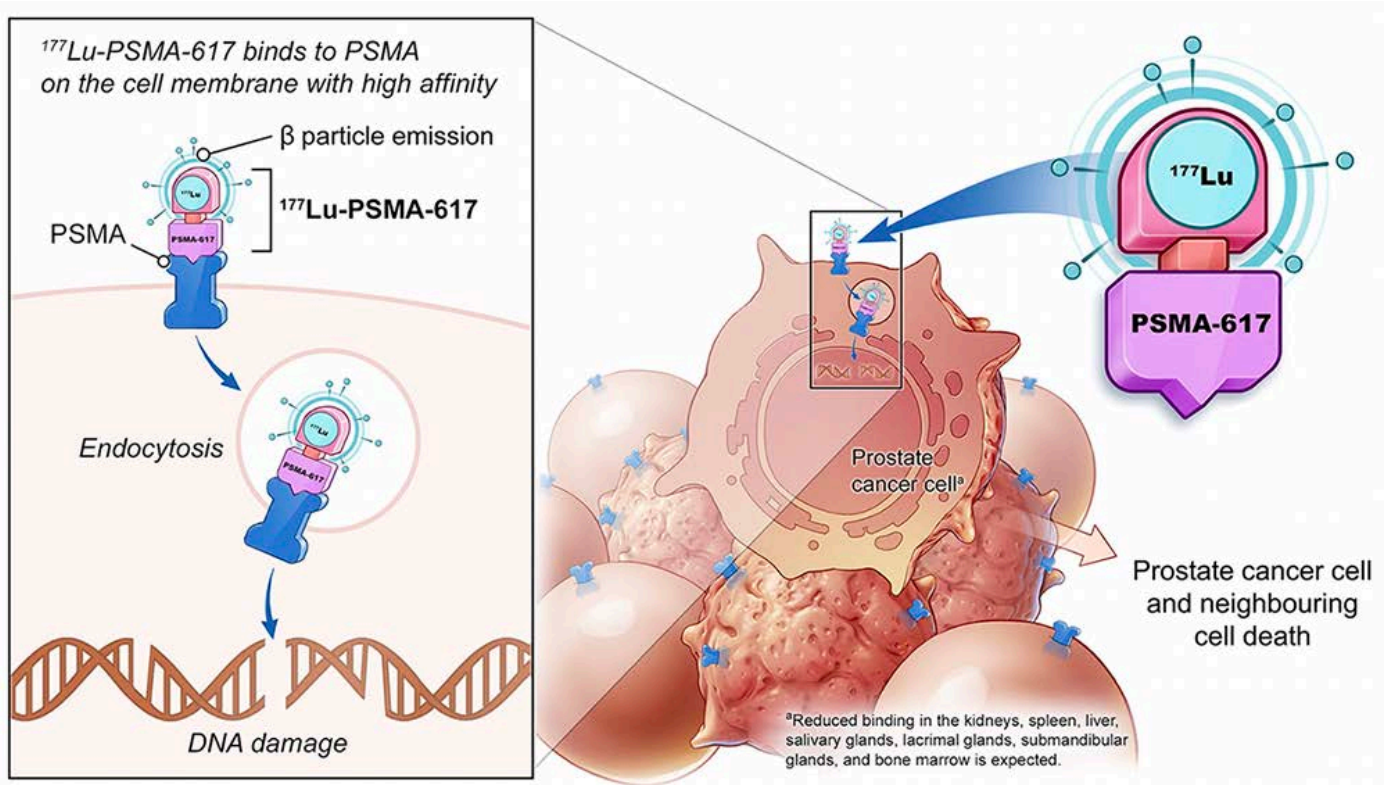
- Systemically delivered radioactive isotopes or compounds
- Localize to tumors while sparing normal tissues
- Can be used as tracers → tumor detection (PSMA PET)
- Can be used as weapons → induce cytotoxic DNA damage



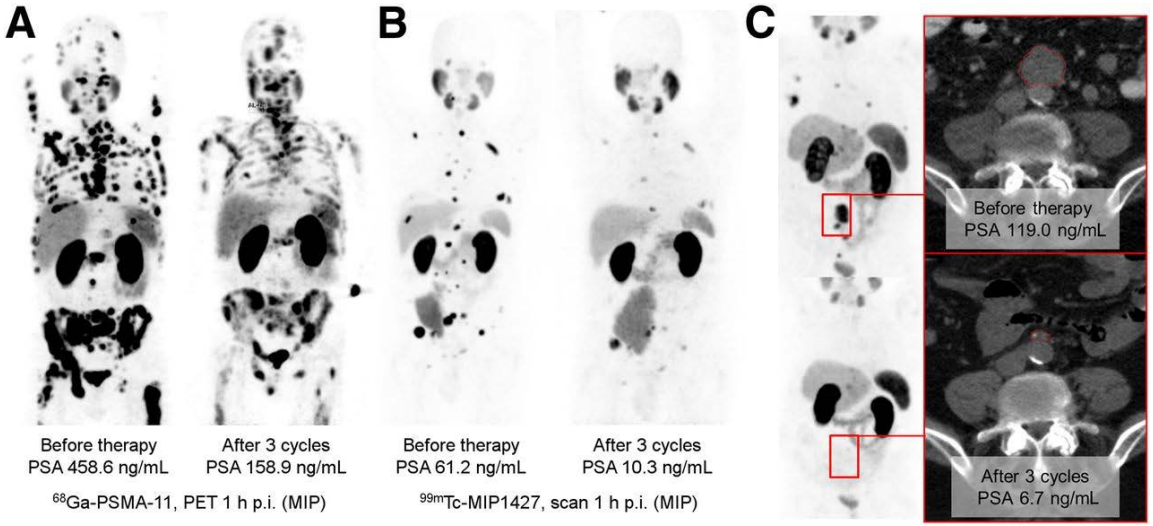
Fanti, S. ASCO 2019

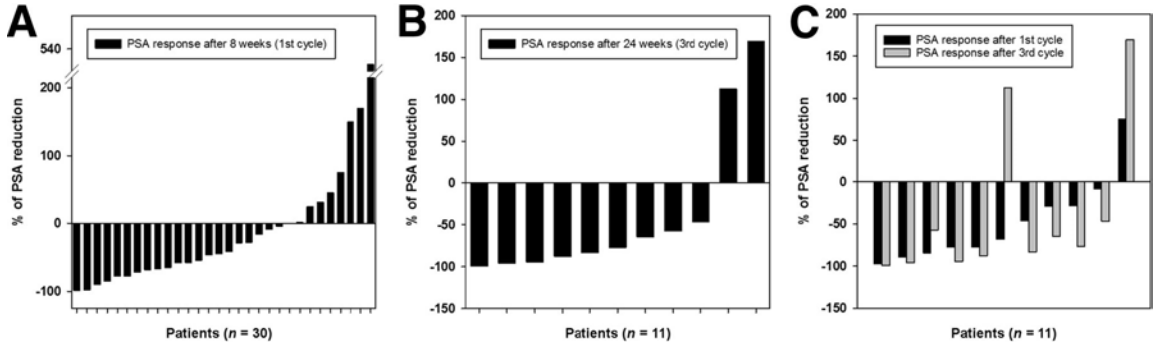
^{177}Lu-PSMA-617

- Small molecule
- Targets PSMA with high affinity
- Delivers a payload of beta particle-emitting Lutetium-177 via receptor-mediated endocytosis



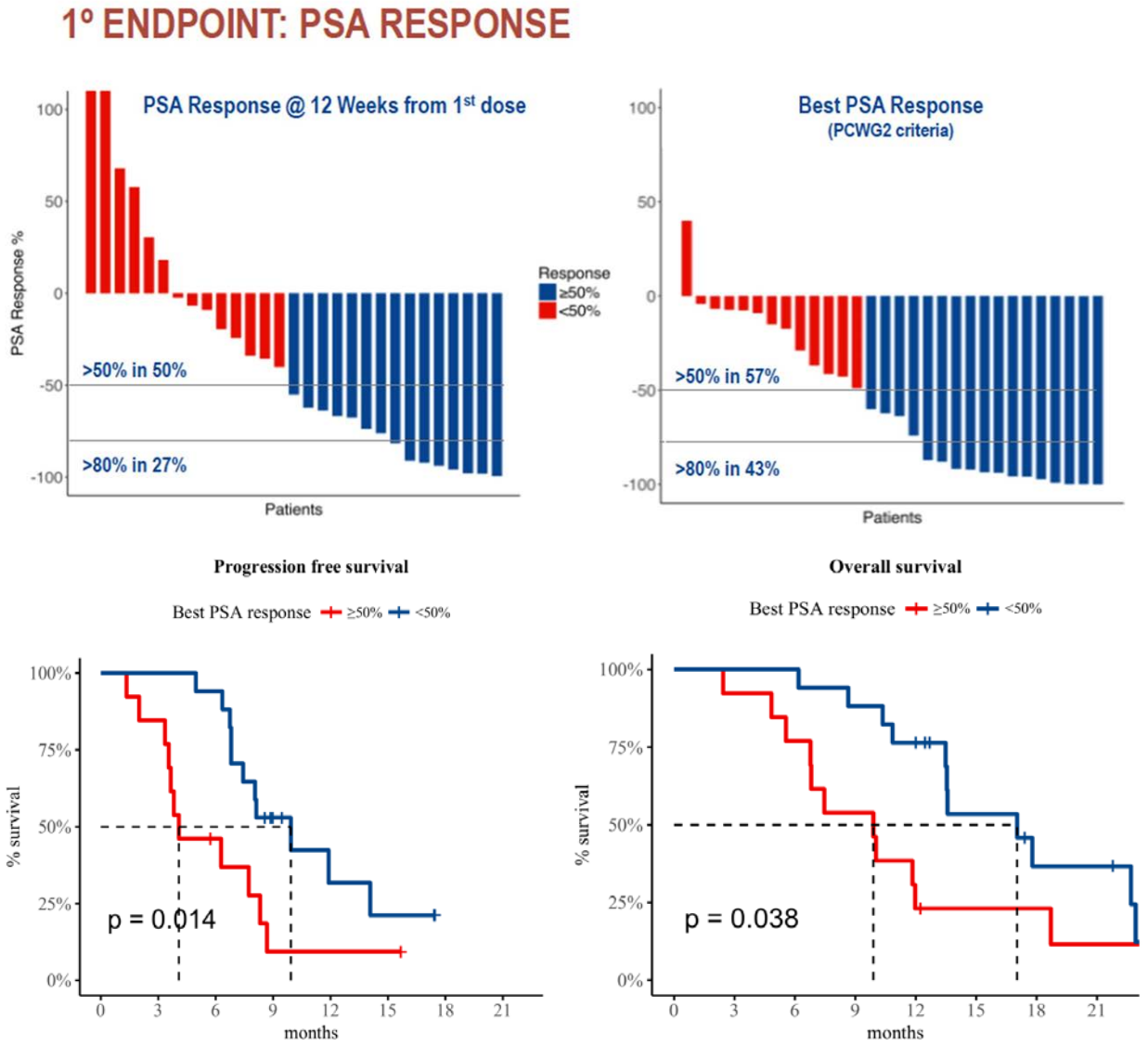
^{177}Lu-PSMA-617: Early Experience





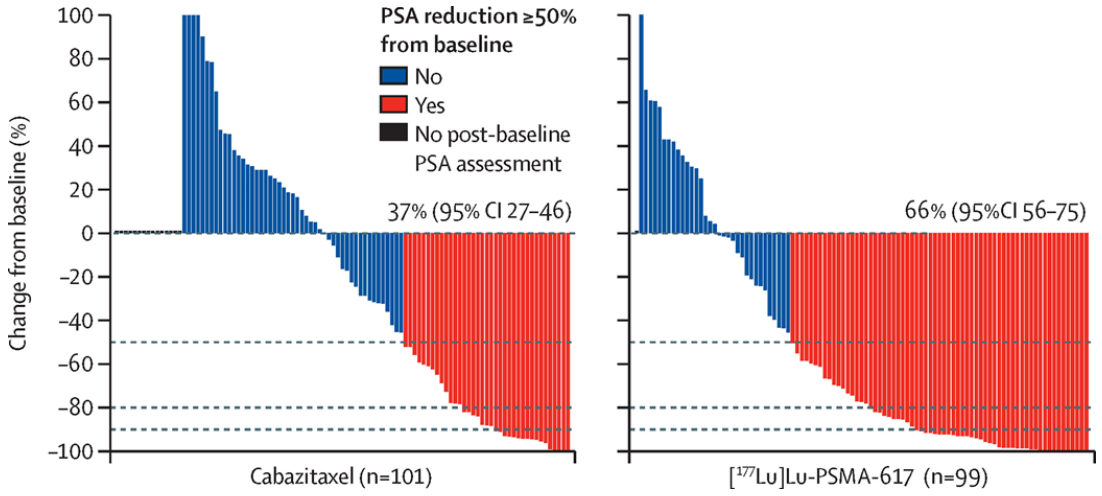
Kratochwi, C et al. J of Nuc Med 2016, 57(8):1170-76

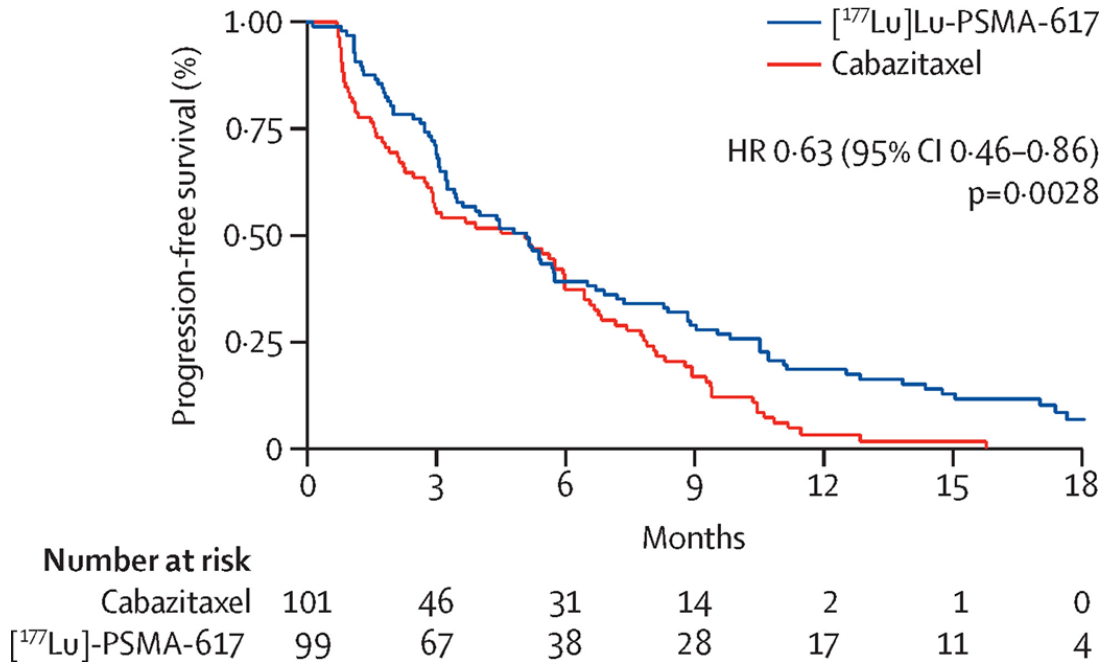
LuPSMA: First Prospective Trial of ^{177}Lu-PSMA-617



Lancet Oncol 2018: 19:825-33

TheraP Trial: ^{177}Lu-PSMA-617 vs Cabazitaxel



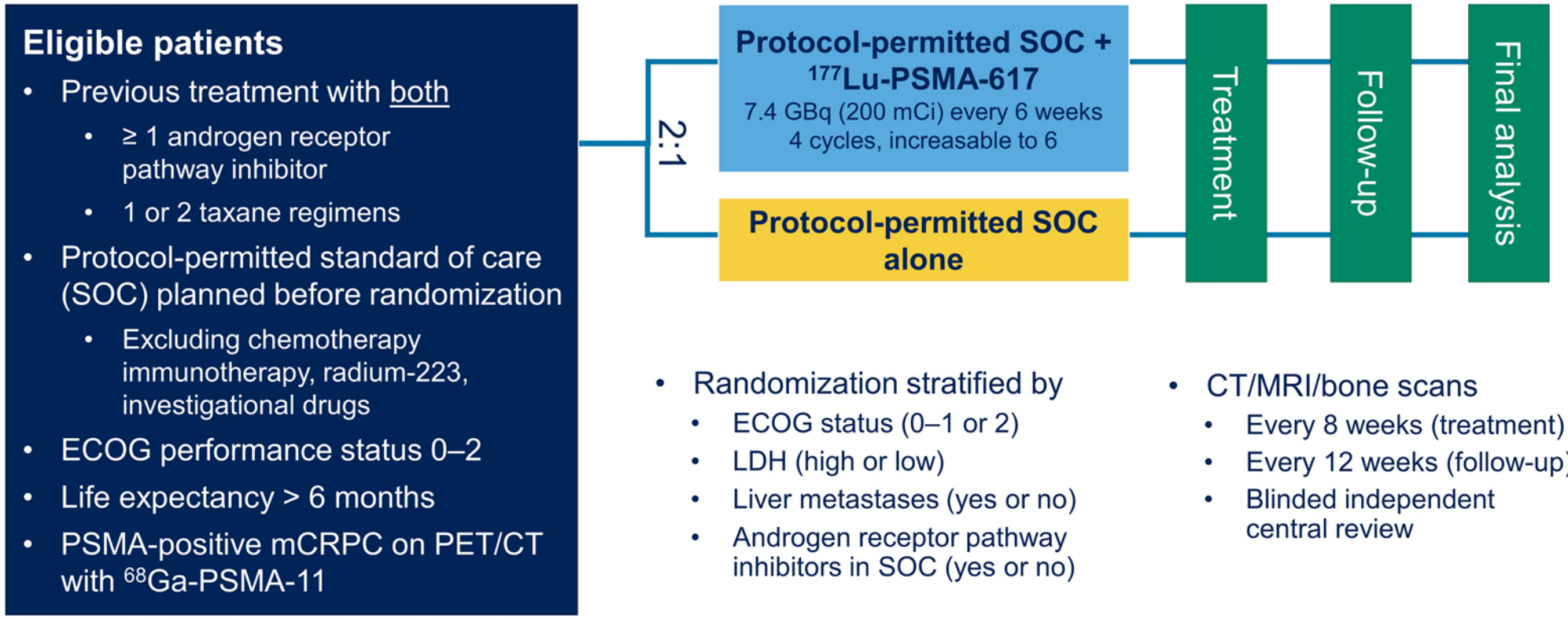


Number at risk

Cabazitaxel	101	46	31	14	2	1	0
[^{177}Lu]-PSMA-617	99	67	38	28	17	11	4

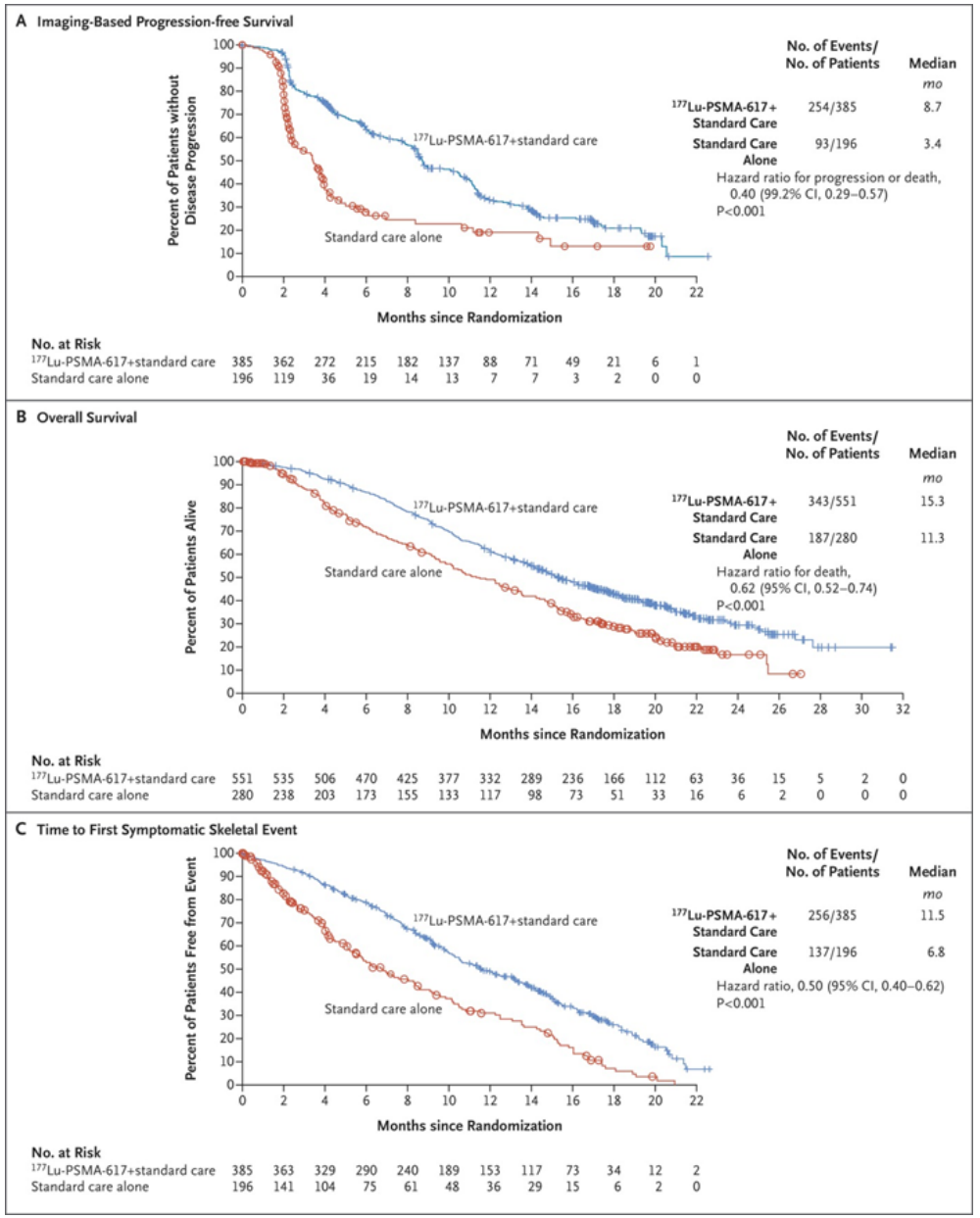
Hofman, M et al. Lancet 2021; 397:797-804

VISION Trial: Phase 3 ^{177}Lu-PSMA-617 in mCRCP



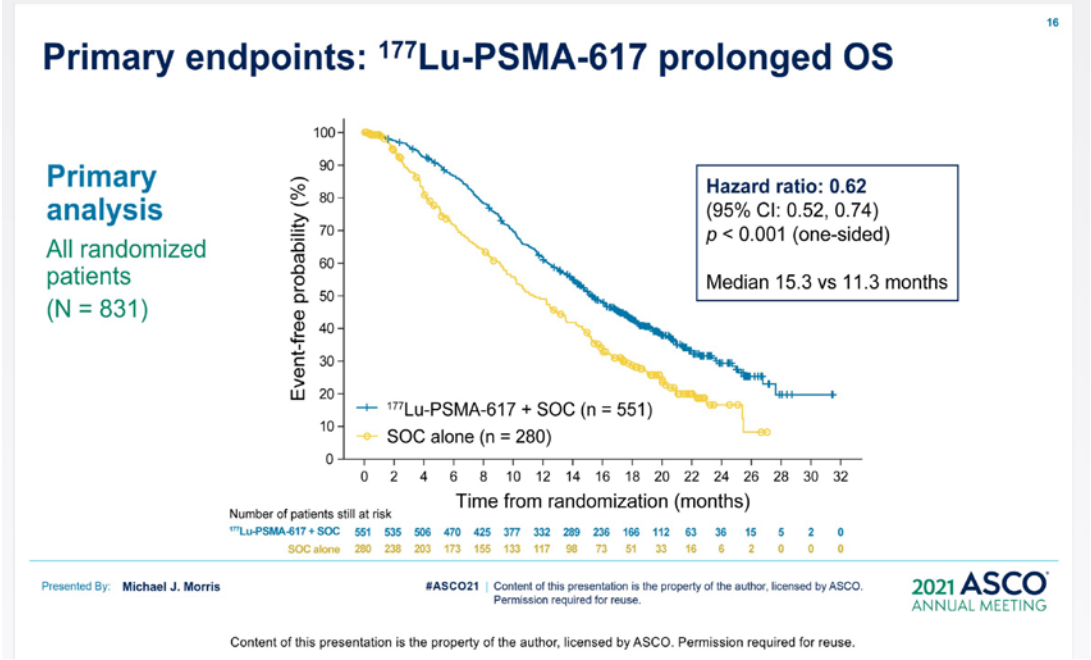
Morris, M ASCO 2021

VISION Trial: PFS, OS, SRE



^{177}Lu-PSMA-617

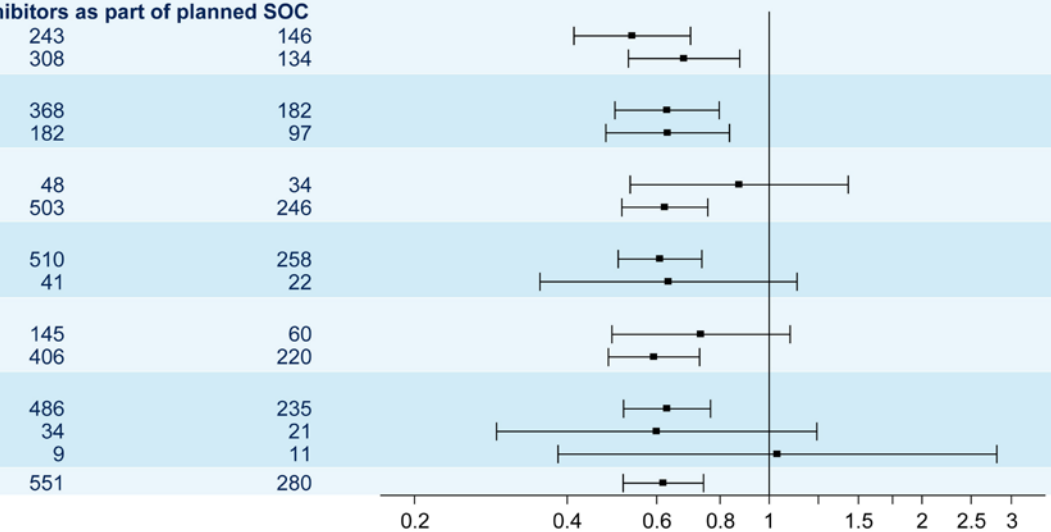
- VISION trial
  - Phase 3 trial of ^{177}Lu-PSMA-617
    - Met CRPC
      - Prior therapy: 1+androgen receptor pathway inhibitor, 1or 2 taxane chemotherapies or chemo inappropriate
      - PSMA+ cancer on Gallium-68 PSMA PET-CT scans (12.6% excluded for this)



Morris, M ASCO 2021

Overall survival was generally consistent across prespecified stratification factor subgroups

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)



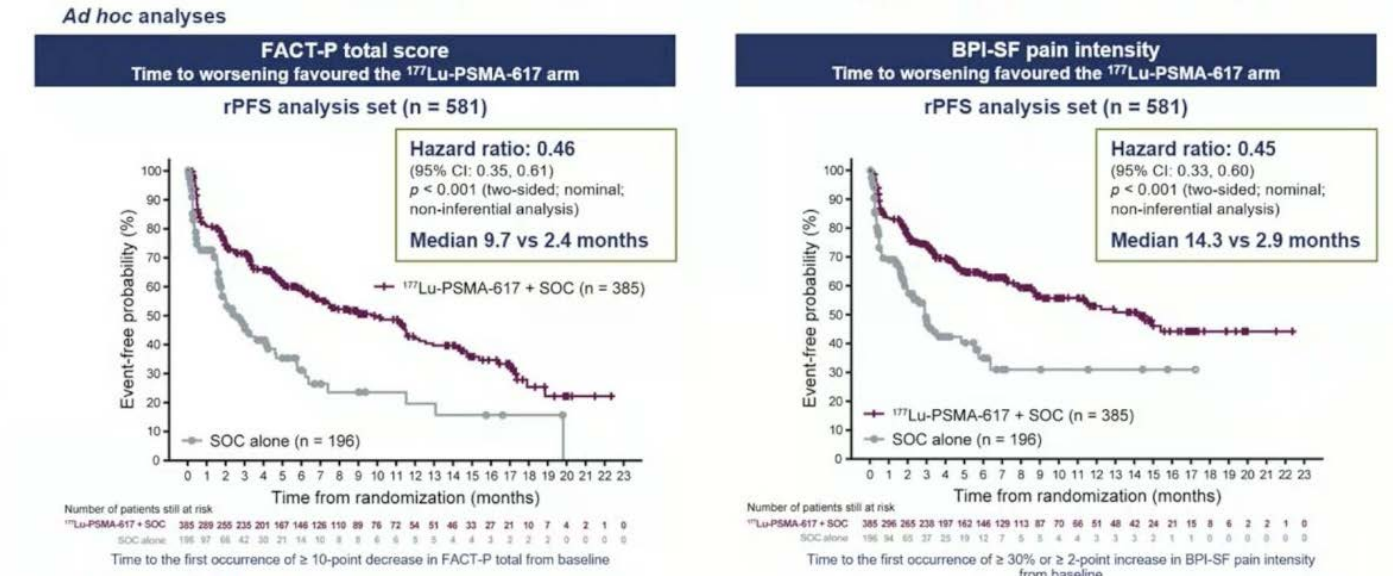
Post-protocol therapies: slightly higher rates of chemotherapy and radiotherapy in the control arm

Received by > 5% of patients, n (%)	All randomized (N = 831)	
	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)
Taxane	99 (18.0)	61 (21.8)
Cabazitaxel	82 (14.9)	53 (18.9)
Docetaxel	27 (4.9)	10 (3.6)
Paclitaxel	4 (0.7)	2 (0.7)
Platinum compound	40 (7.3)	27 (9.6)
Radiopharmaceutical	16 (2.9)	23 (8.2)
^{223}Ra	14 (2.5)	15 (5.4)
^{177}Lu-PSMA-617	2 (0.4)	3 (1.1)
^{225}Ac-PSMA-617	1 (0.2)	0 (0.0)
Other/various	0 (0.0)	5 (1.8)
Immune checkpoint/VEGF mAb	16 (2.9)	22 (7.9)

VISION study conclusions

- Adding ^{177}Lu-PSMA-617 to safely combinable standard of care in patients with mCRPC after androgen receptor pathway inhibition and chemotherapy
    - Extended overall survival
    - Delayed radiographic disease progression
- ^{177}Lu-PSMA-617 was well tolerated
- These findings warrant adoption of ^{177}Lu-PSMA-617 as a new treatment option in patients with mCRPC

VISION Trial: Quality of Life



Fizazi, ESMO 2021

VISION Trial: Adverse Events

Patients, n (%)	^{177}Lu-PSMA-617 + SOC (n = 529)		SOC alone (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)

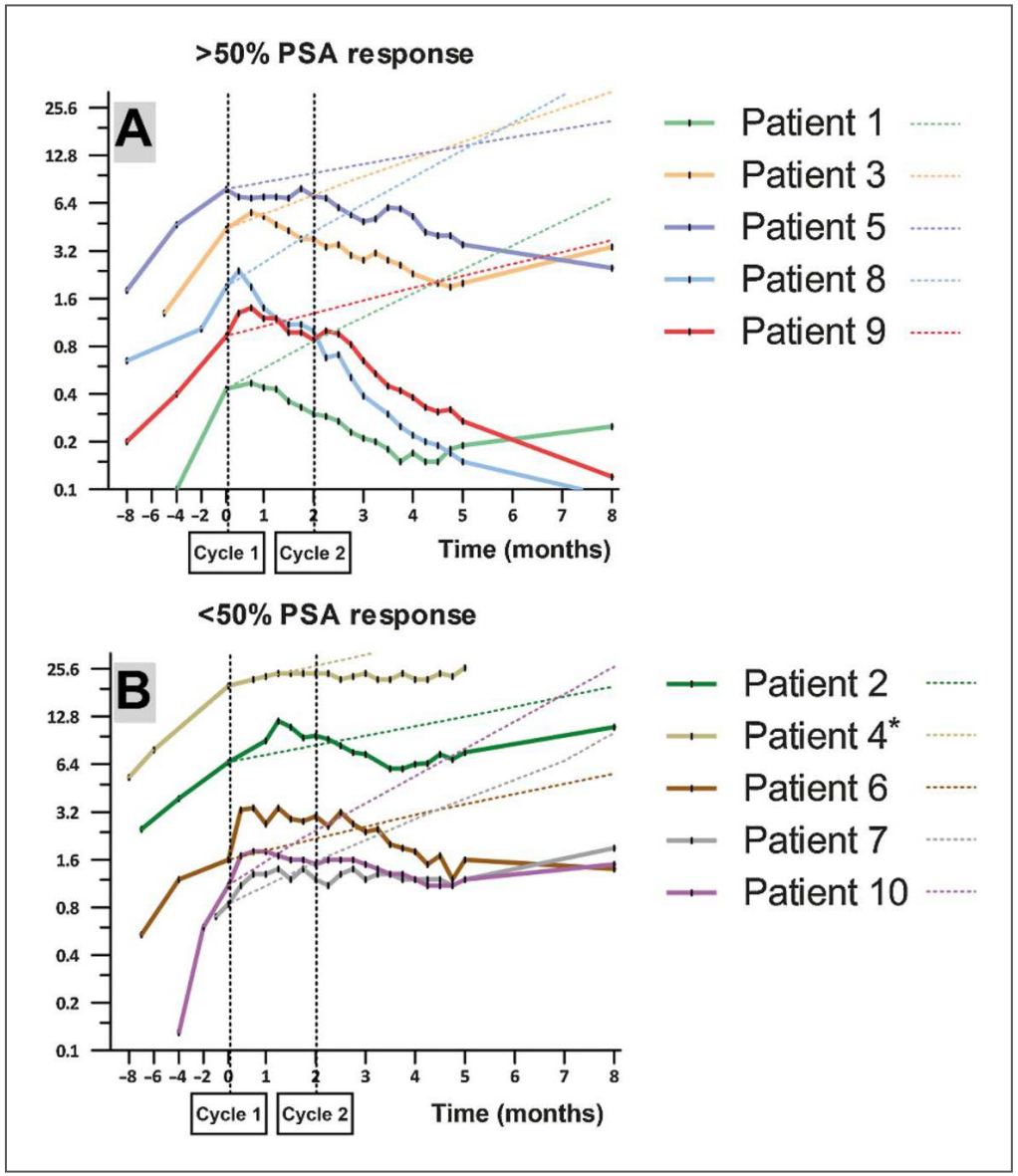
Fizazi, ESMO 2021

Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

^{177}Lu-PSMA-617 in Low Volume Hormone- Sensitive Metastatic Prostate Cancer

- 10 patients
- PD s/p local therapy
- Low volume disease
- 2 cycles of ^{177}Lu-PSMA-617

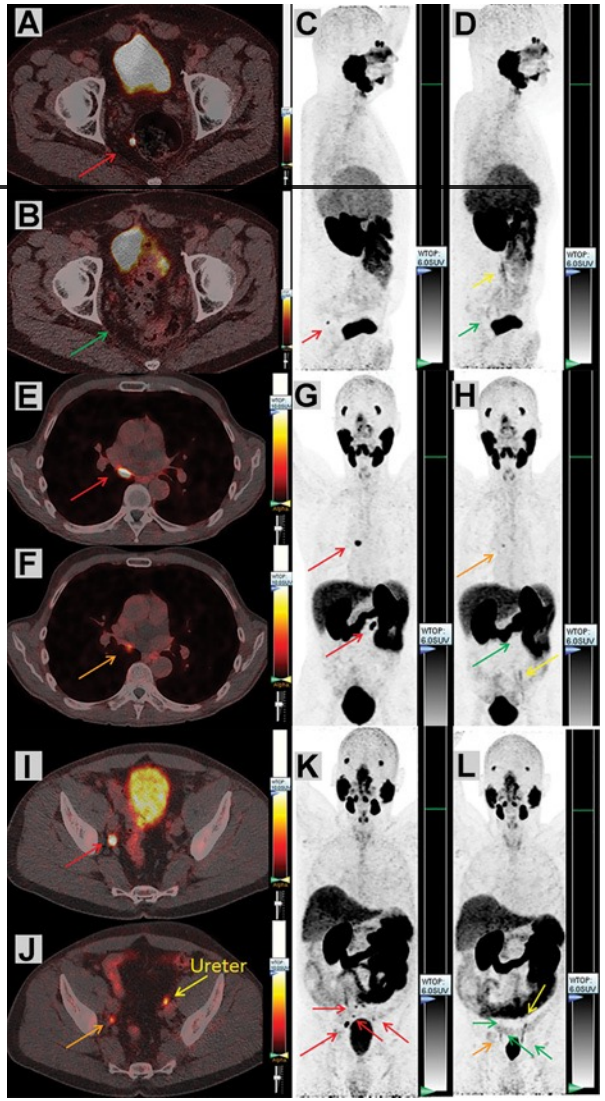


Prive, B et al. Clin Cancer Res 2021; 27(13):3595-3601

^{177}Lu-PSMA-617 in Low Volume Hormone- Sensitive Metastatic Prostate Cancer

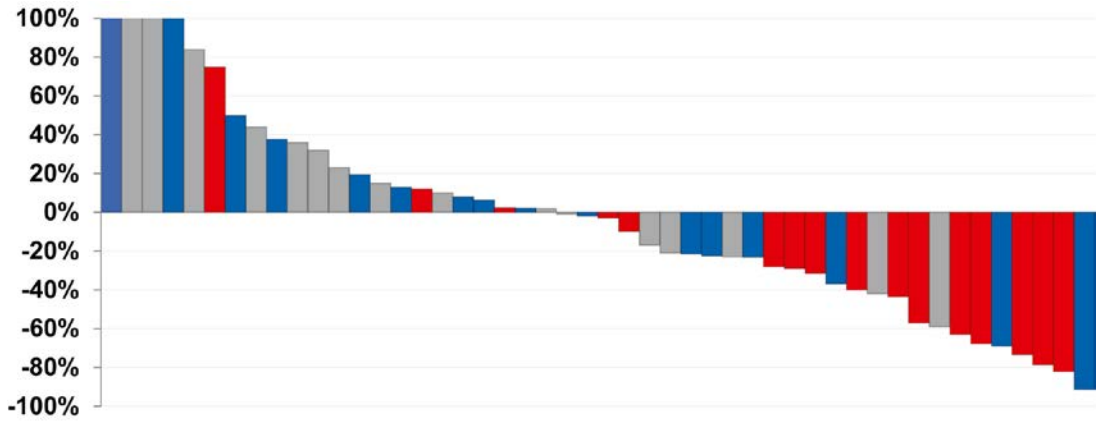
Table 2. Radiographic response.

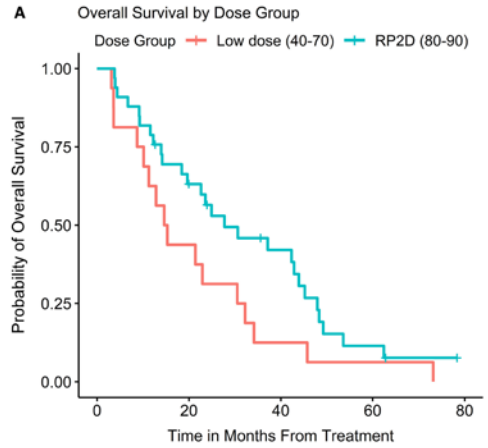
Patient #	C1W8	C2W12	C2W24
1	PR	CR	CR
2	PD	PD	PD
3	SD	SD	SD
4	SD	SD	PD[a]
5	SD	PR	PR
6	SD	PR	PR
7	SD	SD	PD
8	SD	PR	PR
9	SD	PR	PR
10	SD	SD	PD

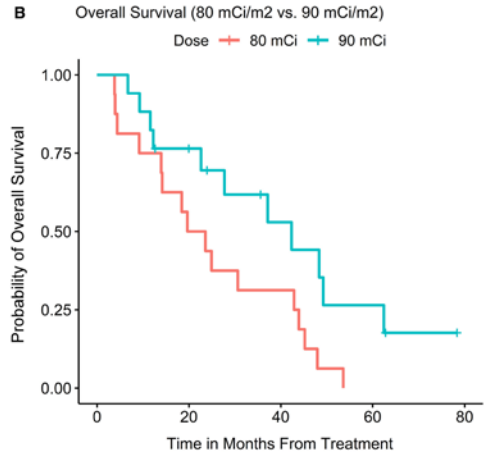


Prive, B et al. Clin Cancer Res 2021; 27(13):3595-3601

^{177}Lu-J591: Anti-PSMA Monoclonal Ab



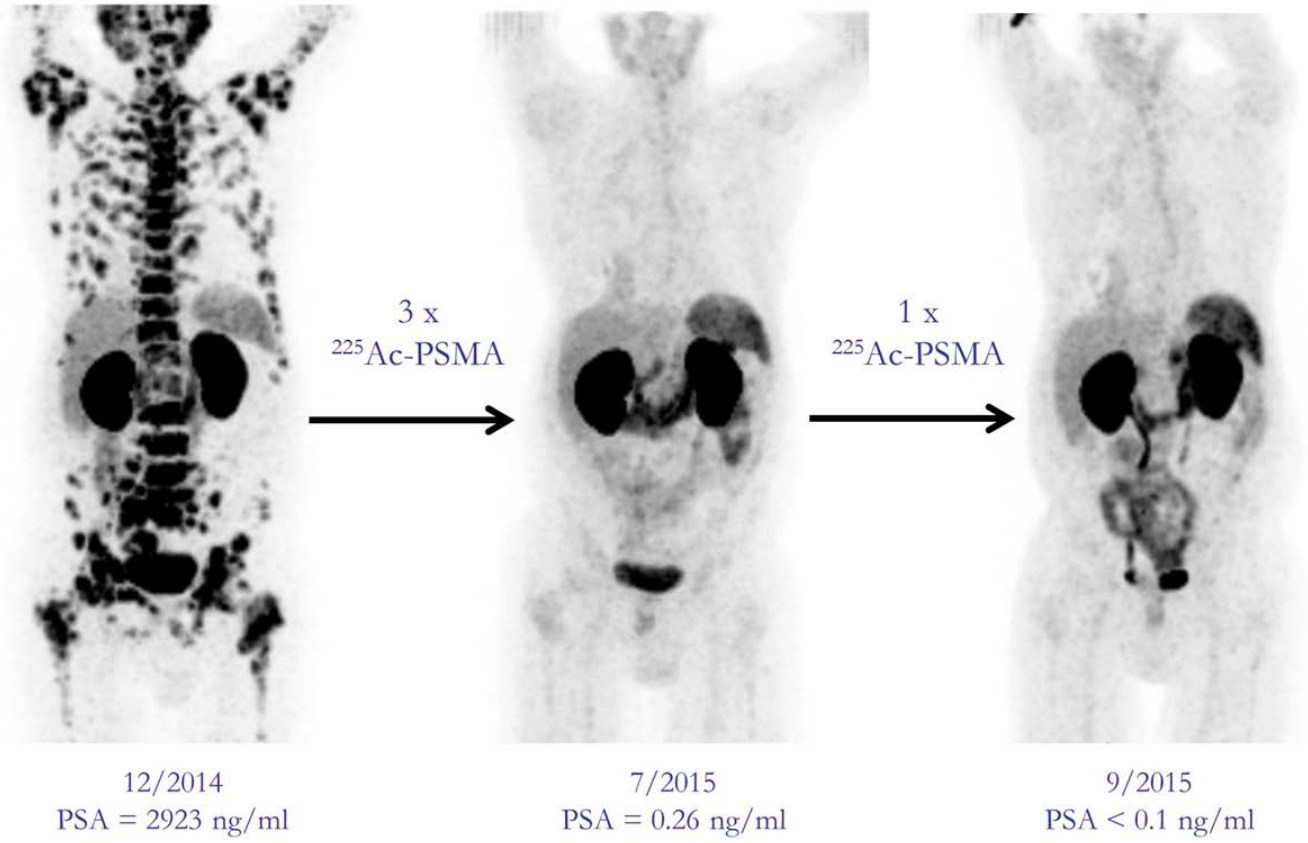




Tagawa, S et al. Cancer 2019;125:2561-2569

^{225}Ac-PSMA

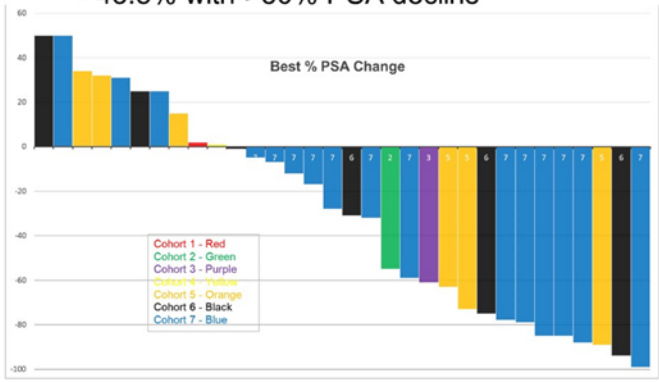
- Alpha emitters are 1000x more potent than beta emitters
- Can induce double-stranded DNA breaks
  - Tumor cells unable to repair
- Alpha emitters can overcome resistance to beta and gamma irradiation

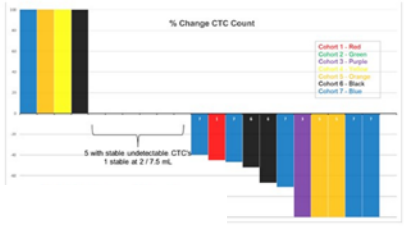


^{225}Ac-J591: Phase I Trial in mCRPC

PSA Response

- 68.8% experienced any PSA decline
- 43.8% with >50% PSA decline





Treatment Emergent Adverse Events (with at least 10% incidence)	Gr 1/2 n (%)	Gr 3 n (%)	Gr 4 n (%)
Fatigue	24 (75%)	4 (12.5%)	0
Thrombocytopenia	20 (62.5%)	2 (3.6%)	3 (9.4%)
Anemia	16 (50%)	3 (9.4%)	1 (3.1%)
Pain	14 (43.8%)	1 (3.1%)	0
Nausea	14 (43.8%)	0	0
Neutropenia	9 (28.1%)	2 (6.3%)	1 (3.1%)
Xerostomia*	12 (37.2%)	0	0
Transaminitis	3 (9.4%)	1 (3.1%)	0

*7 of 12 with xerostomia with prior ^{177}Lu-PSMA

Median PFS 5.1 months [95% CI 4.0 – 9.3]
Median OS 11.1 months [95% CI 7.6 – 27.1]*

*n=31 for OS analysis, censoring for subject enrolled in both dose-escalation and expansion cohorts

CTC count (CellSearch) assessment
n=22 with paired counts baseline – 12 weeks:
11 (50%) decreased (40-100% decline)
5 (27%) stably undetectable (1 stable at 2)
4 (18.2%) increased

Tagawa, S et al. ASCO 2021

Sequential Treatment is Possible

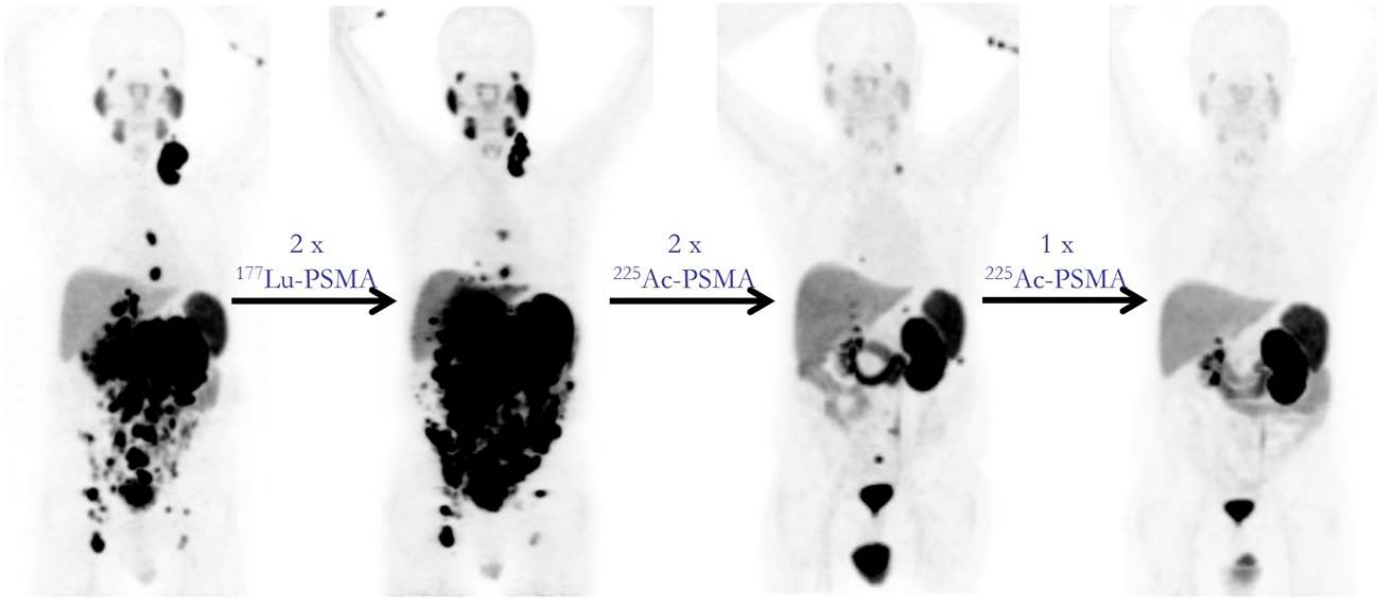
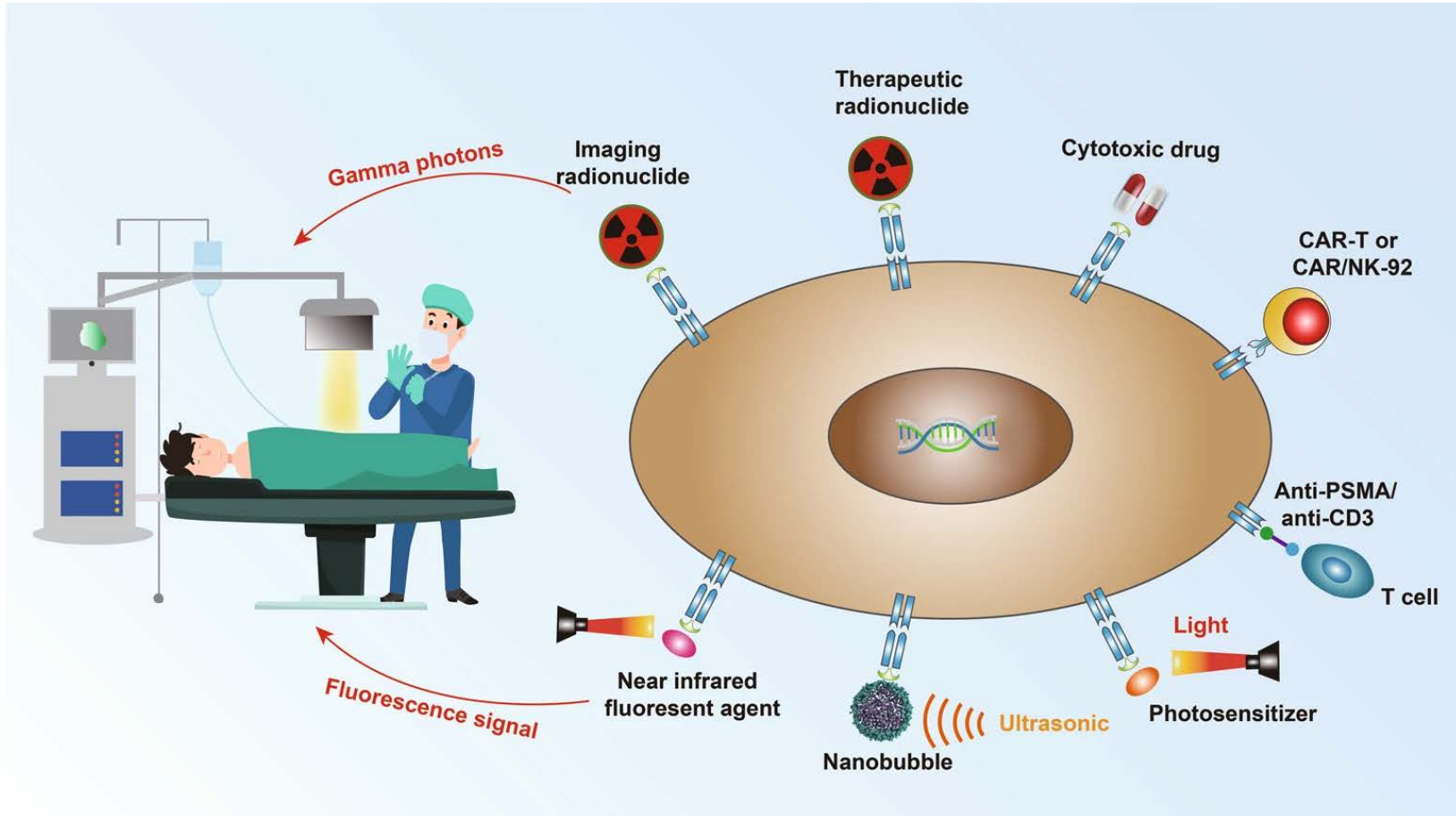


TABLE. Clinical Development of PSMA-Targeted Therapies

Therapy (manufacturer)	Clinical phase(s)	Clinical setting(s); trial name/ClinicalTrials.gov identifier
Radiolabeled small molecule inhibitors of PSMA		
^{177}Lu-PSMA-617 (Novartis)	3	**mCRPC:** VISION/NCT03511664[a] PSMAfore/NCT04689828 **Metastatic hormone-sensitive prostate cancer:** PSMAddition/NCT04720157
^{177}Lu-PSMA-I&T (PNT2002) (POINT Biopharma)	3	**mCRPC:** SPLASH/NCT04647526[a]
^{177}Lu-PSMA-R2 (Advanced Accelerator Applications)	1/2	**mCRPC:** PROter/NCT03490838
^{225}Ac-PSMA-617 (Novartis)	1	**mCRPC:** NCT04597411
^{177}Lu-DOTA-N3-CTT1403 (CTT1403) (Cancer Targeted Technology)	1	**mCRPC:** NCT03822871
I-131-1095 (Progenics Pharmaceuticals)	2	**mCRPC:** ARROW/NCT03939689
Radiolabeled mAbs targeting PSMA		
TLX591 (^{177}Lu-DOTA-rosopatamab) (Telix Pharmaceuticals)	3	**mCRPC:** ProstACT/NCT04876651[b]
TLX592 (Telix Pharmaceuticals)[c]	1	**Metastatic prostate cancer:** CUPID/NCT04726033
^{227}Th-PSMA-TTC (BAY 2315497) (Bayer)	1	**mCRPC:** NCT03724747
^{177}Lu-J591 (Weill Cornell)	2 1	**High-risk castrate biochemically relapsed prostate cancer:** NCT00859781 **Metastatic nonprostate solid tumors:** NCT00967577[a]
^{225}Ac-J591 (Weill Cornell)	1/2	**mCRPC:** NCT04506567 NCT04946370[b]

DOTA, dodecane tetraacetic acid; I-131, iodine 131; mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; ^{177}Lu, lutetium 177; PSMA, prostate-specific membrane antigen; ^{225}Ac, actinium 225; 227Th, thorium 227; ^{227}Th, thorium 227.

[a]Study is ongoing but not actively recruiting participants.
[b]Study is not yet recruiting participants.
[c]The agent also has been identified as ^{225}Ac-TLX592 and ^{64}Cu-DOTA-TLX592.


Gamma photons
Imaging radionuclide
Therapeutic radionuclide
Cytotoxic drug
CAR-T or CAR/NK-92
Anti-PSMA/ anti-CD3
T cell
Light
Photosensitizer
Ultrasonic
Nanobubble
Near infrared fluoresent agent
Fluorescence signal