City of Hope®

Southeastern Multidisciplinary Approaches to Cancer Symposium

Incorporating Radiopharmaceuticals in the Treatment of Prostate Cancer

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Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Discuss how to communicate radiopharmaceutical treatment to diverse populations.*
- *How do we improve access to radiopharmaceuticals and what barriers are there in Southern Georgia.*

Learning Objectives

By the end of this session, participants will be able to:

Objectives

- Describe the mechanism of PSMA-targeted radioligand therapy and bone-targeted alpha particle therapy
- Review use of PSMA PET to select appropriate patients with metastatic castration-resistant prostate cancer (mCRPC)
- Summarize the pivotal trial evidence (VISION, PSMAfore, ALSYMPCA) supporting radiopharmaceuticals
- Integrate NCCN and ASCO guideline recommendations into treatment sequencing
- Recognize key toxicities, radiation-safety practices, and barriers to equitable access

NCCN Guidelines, Prostate Cancer, v2026; ASCO, 2024

Foundations of Theranostics

PSMA as a target for imaging and therapy in prostate cancer

The Clinical Challenge of Advanced Prostate Cancer

Metastatic castration-resistant prostate cancer (mCRPC) remains lethal despite androgen receptor pathway inhibitors and taxane chemotherapy, driving the need for mechanistically distinct therapies.

~35,000
estimated U.S. prostate cancer deaths each year

>80%
of mCRPC tumors overexpress PSMA, enabling targeting

<35%
5-year relative survival once disease becomes castrate-resistant

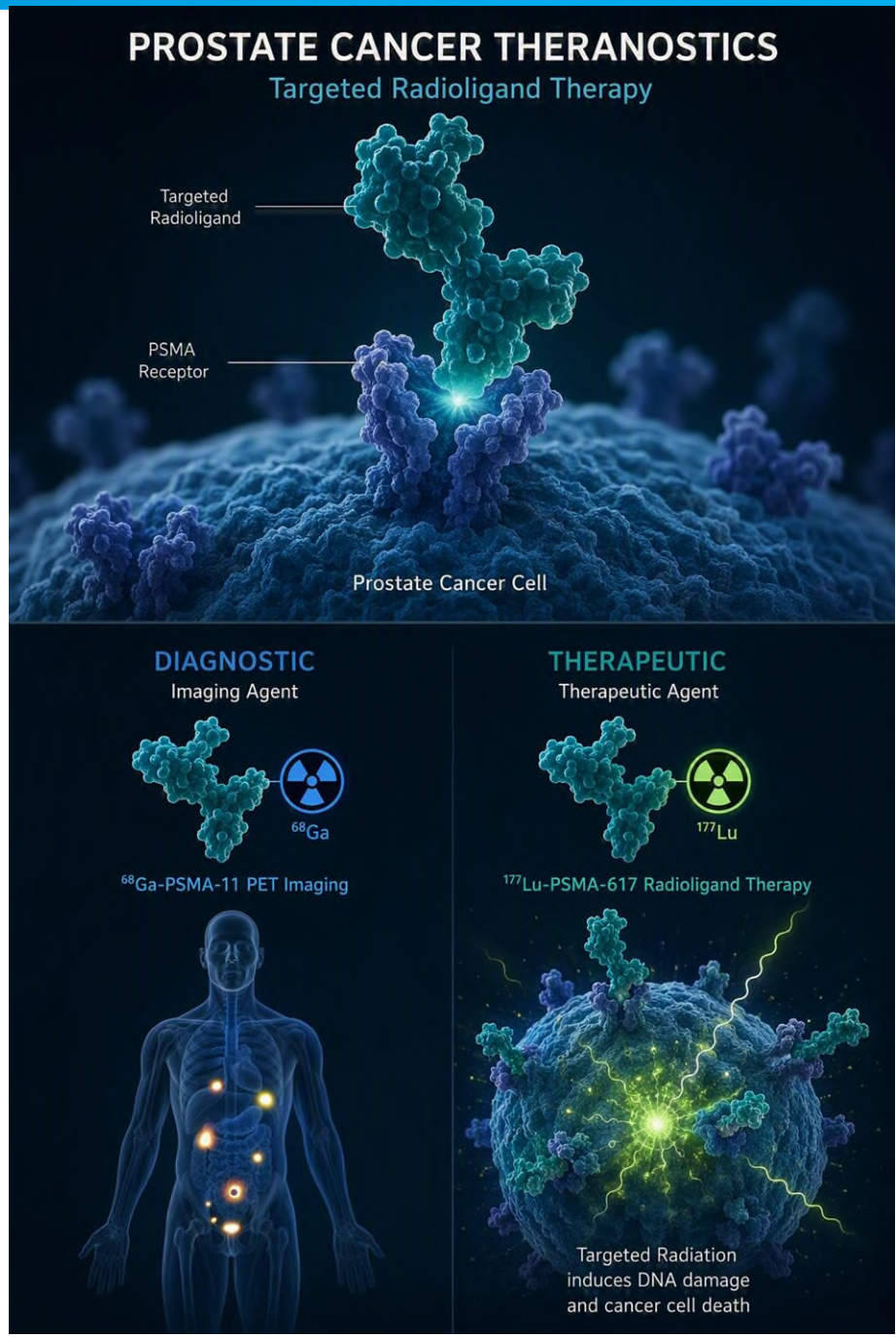
VISION, N Engl J Med. 2021; NCCN Guidelines, v2026

The Theranostic Principle

Theranostics pairs a diagnostic radiotracer with a therapeutic radioligand that share the same molecular target: see what you treat, treat what you see.

How it works

- A targeting ligand binds prostate-specific membrane antigen (PSMA) on tumor cells
- A diagnostic isotope (gallium-68 or fluorine-18) confirms target expression on PET
- A therapeutic isotope (lutetium-177 beta or an alpha emitter) delivers cytotoxic radiation
- The same biology guides both patient selection and treatment



Representative illustration of PSMA theranostics; mechanism per Sartor O, et al. N Engl J Med. 2021

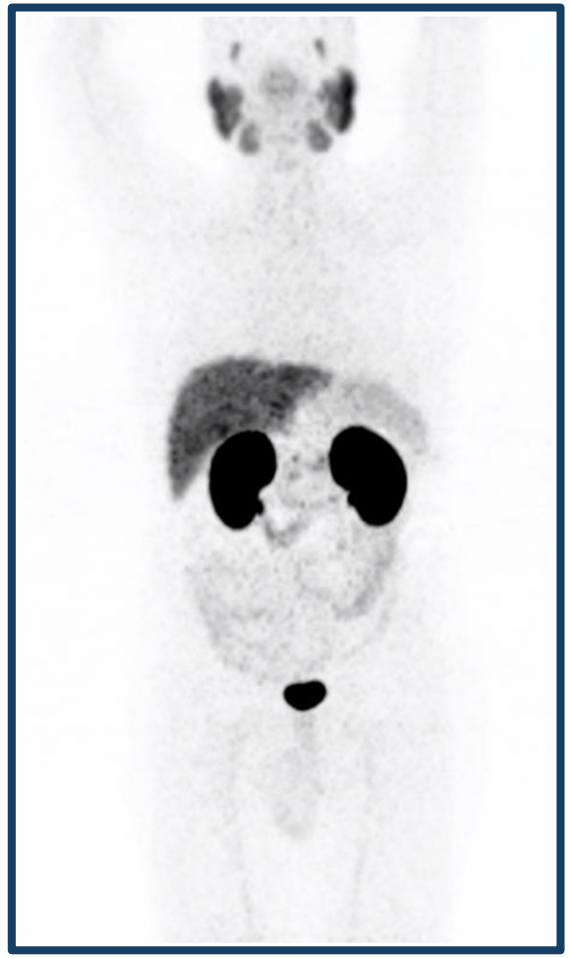
ASCO Rapid Recommendation Update, 2024

PSMA PET: Selecting the Right Patients

PSMA-targeted PET/CT identifies patients whose tumors express the target and are most likely to respond to radioligand therapy.

Approved imaging agents

- Ga-68 PSMA-11: Lometz
- Piflufolastat F-18: Pylarify
- Flotufolastat F-18: Posluma



Representative PSMA PET/CT MIP: Malan et al. Front Nucl Med. 2022

ASCO Rapid Recommendation Update, 2024

Radioligand Therapies in mCRPC

Beta and alpha emitters that extend survival

VISION, NEJM 2021; ALSYMPCA, NEJM 2013

Beta vs Alpha Emitters: Range and Energy

Beta emitter — Lutetium-177

Range ~0.5–2 mm — crossfire reaches many neighboring cells

- Lower energy, lower linear energy transfer (LET)
- Longer path treats bulkier, heterogeneous tumors via crossfire
- Greater exposure of nearby bone marrow

Alpha emitter — Radium-223 / Actinium-225

Range <0.1 mm — energy deposited within ~1–3 cells

- Very high energy, high LET
- Dense DNA double-strand breaks; potent, localized cell kill
- Short range spares surrounding marrow

Schematic illustration, not to scale; Sartor O, et al. NEJM 2021; NCCN Guidelines, Prostate Cancer, v2026

Lutetium-177 PSMA-617: A Beta-Emitting Radioligand

Indication and administration

- Recommended within NCCN Guidelines for mCRPC
- Initially FDA-approved for PSMA+ mCRPC after progression on AR-directed therapy and taxane-based chemotherapy
- In March 2025 the indication expanded to taxane-naive patients following an ARPI
- Patient selection requires PSMA-positive disease on PET imaging and adequate organ function
    - Bone marrow reserve: • ANC ≥ 1.5 x 10^9/L • Platelets ≥100 x 10^9/L • Hemoglobin ≥ 9 g/dL
    - Hepatic: • Tbili < 2xULN • Albumin >2.5 g/dL
    - Renal: eGFR> 50 mL/min
- Standard regimen: 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 cycles

VISION, N Engl J Med. 2021; NCCN Guidelines, v2026

VISION Trial: Post-Taxane mCRPC

Phase 3 trial establishing lutetium-177 PSMA-617 plus standard of care in previously treated mCRPC (Sartor et al., NEJM 2021).

Design

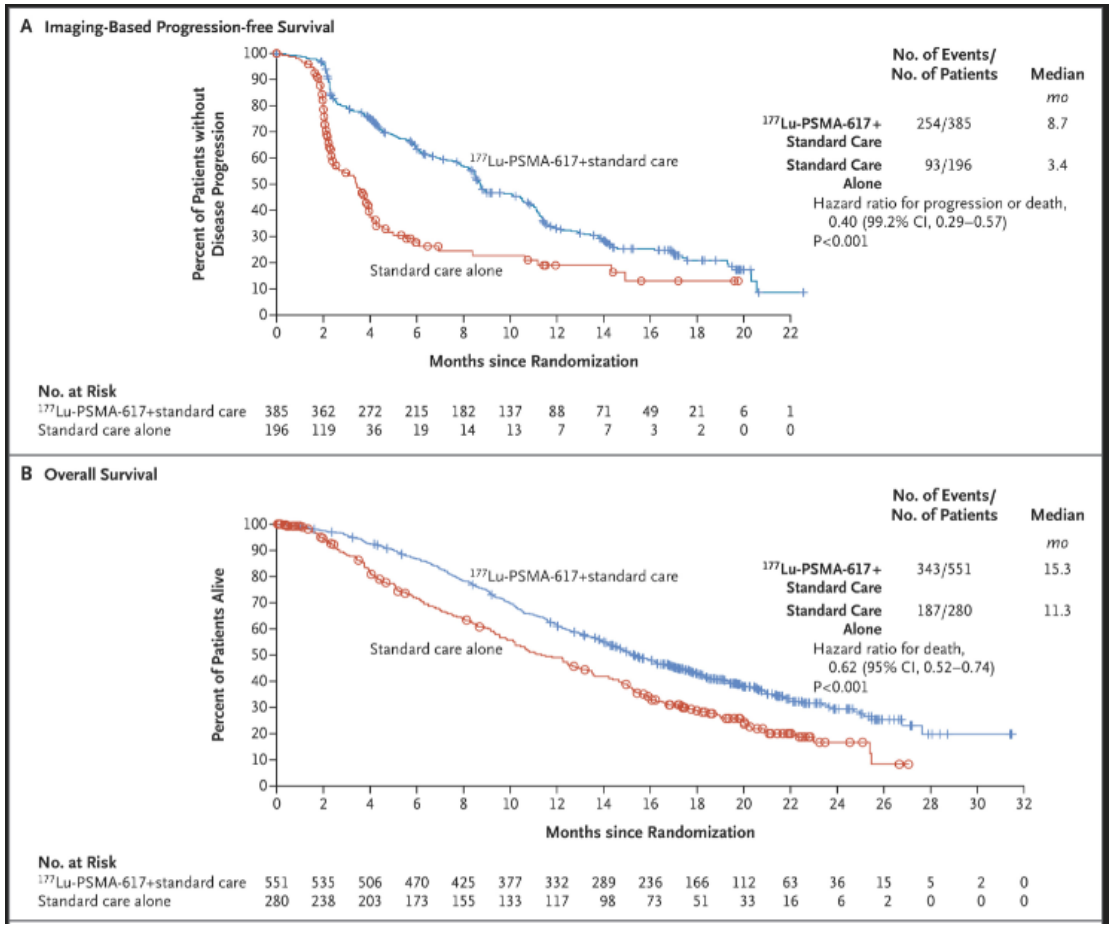
- 831 (of 1179 screened) patients with PSMA-positive mCRPC
- Prior ARPI and one to two taxane regimens
- ECOG 0-2 with adequate marrow, renal, and hepatic function
- Randomized 2:1 to radioligand therapy plus SOC vs SOC

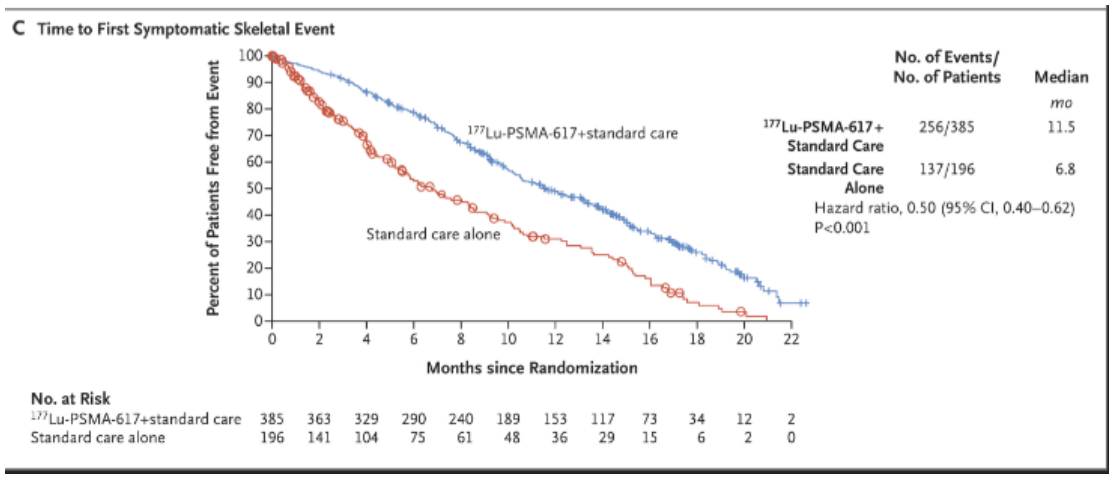
Key outcomes

- Overall survival 15.3 vs 11.3 months (HR 0.62)
- Radiographic PFS 8.7 vs 3.4 months (HR 0.40)
- Higher PSA response and improved quality of life
- Grade 3-4 events more frequent, mainly marrow suppression

Sartor O, et al. N Engl J Med. 2021 (VISION)

VISION Trial: Post-Taxane mCRPC





Sartor O, et al. N Engl J Med. 2021 (VISION)

PSMAfore Trial: Taxane-Naive mCRPC

A phase 3 trial evaluating lutetium-177 PSMA-617 before chemotherapy in patients who progressed on one ARPI (Lancet 2024).

Design

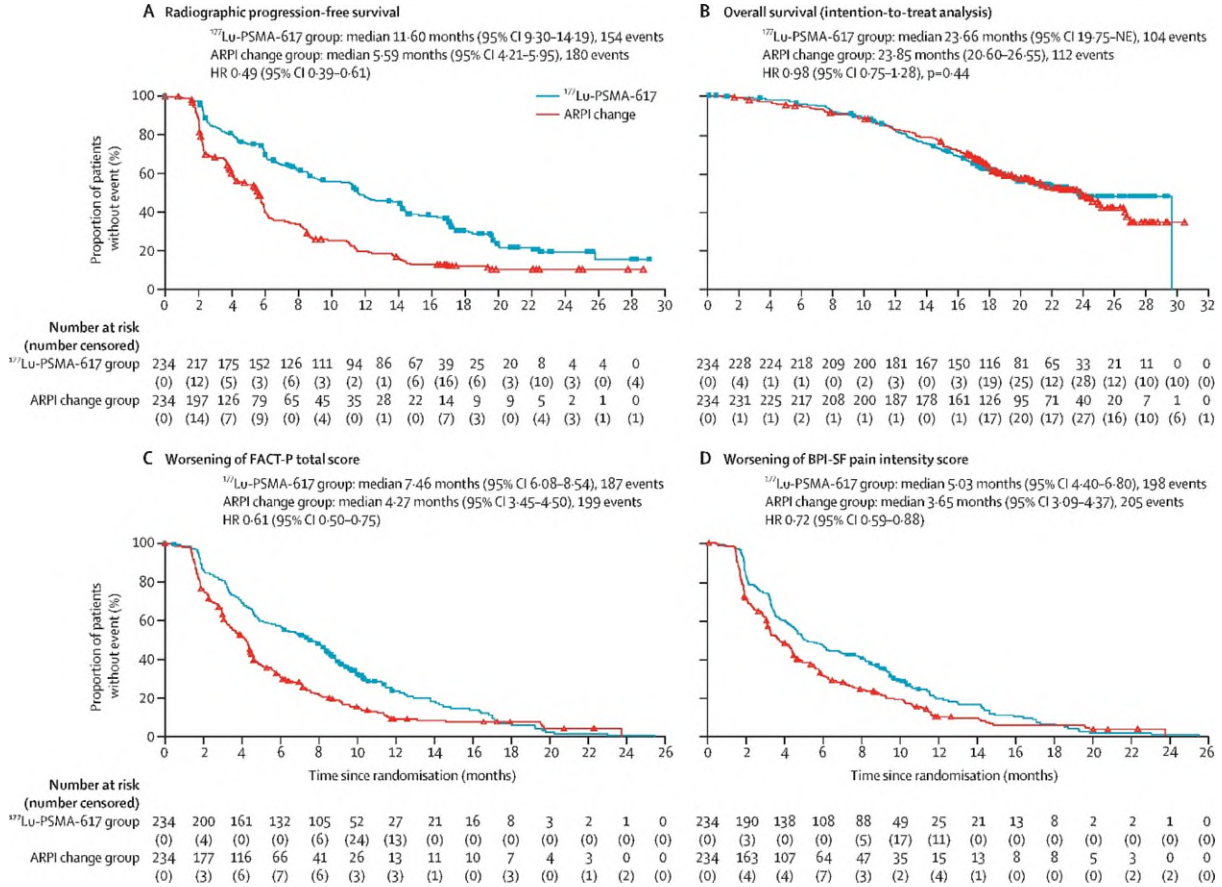
- 468 (of 585 screened) patients with taxane-naive mCRPC
- PSMA PET-selected; progression on one prior ARPI
- Randomized to radioligand therapy vs a second ARPI
- Crossover to radioligand therapy permitted at progression

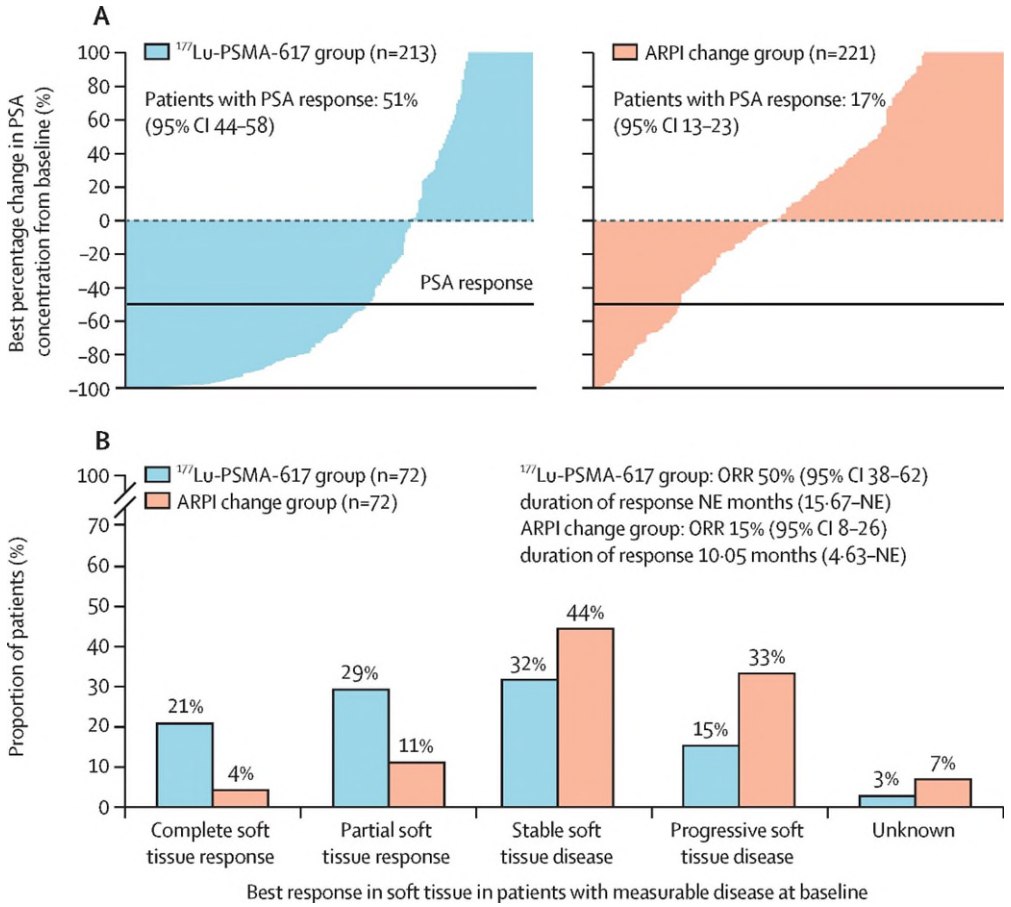
Key outcomes

- Radiographic PFS 9.3 vs 5.6 months (HR 0.41); updated to 11.6 vs 5.6 months
- About 59% reduction in risk of progression or death
- Overall survival not significantly different (HR 0.91), confounded by crossover
- Favorable safety; supported FDA expansion in March 2025

Morris MJ, et al. Lancet. 2024 (PSMAfore)

PSMAfore Trial: Taxane-Naive mCRPC





Morris MJ, et al. Lancet. 2024 (PSMAfore)

Radium-223: A Bone-Targeted Alpha Emitter

Radium Ra 223 dichloride (Xofigo) is an alpha-emitting calcium mimetic for mCRPC with symptomatic bone metastases and no known visceral disease (ALSYMPCA, NEJM 2013).

Mechanism and use

- Mimics calcium and deposits in areas of high bone turnover
- Short-range alpha particles limit marrow toxicity
- Six intravenous injections at 55 kBq/kg every 4 weeks
- For symptomatic bone-predominant disease without visceral metastases

Key outcomes

- 921 patients randomized 2:1 vs placebo
- Overall survival 14.9 vs 11.3 months (HR 0.70)
- Delayed symptomatic skeletal events

Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

* Only patients who had elevated total alkaline phosphatase levels at baseline are included.

Parker C, et al. N Engl J Med. 2013 (ALSYMPCA)

Comparing the Radiopharmaceutical Agents

Key distinctions across the pivotal trials to guide patient selection.

	Lu-177 PSMA-617 (VISION)	Lu-177 PSMA-617 (PSMAfore)	Radium-223 (ALSYMPCA)
Emitter	Beta	Beta	Alpha
Target	PSMA	PSMA	Bone (calcium mimetic)
Setting	Post-ARPI, post-taxane	Post-ARPI, taxane-naive	Symptomatic bone-predominant
Median OS	15.3 vs 11.3 mo (HR 0.62)	Not significant (HR 0.91)	14.9 vs 11.3 mo (HR 0.70)
Key efficacy	rPFS 8.7 vs 3.4 mo	rPFS 9.3 vs 5.6 mo	Delayed skeletal events
Notable toxicity	Marrow suppression, dry mouth	Marrow suppression, dry mouth	Low myelosuppression

VISION, NEJM 2021; PSMAfore, Lancet 2024; ALSYMPCA, NEJM 2013

Toxicities and Radiation Safety

Radiopharmaceuticals are generally well tolerated but require monitoring and adherence to radiation-safety practices.

Common toxicities

- Fatigue
- Dry mouth (xerostomia) with PSMA agents
- Nausea and reduced appetite

Monitoring

- Myelosuppression: monitor CBC each cycle
- Renal/liver function: monitor CMP each cycle
- Hold or dose-modify for grade 3-4 cytopenias

Radiation safety

- Counsel on excretion precautions and hygiene
- Limit prolonged close contact per local protocols
- Coordinate with nuclear medicine and radiation-safety staff

VISION, NEJM 2021; ALSYMPCA, NEJM 2013; FDA prescribing information

Integrating Radiopharmaceuticals into Treatment

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[g,aa,iii,jjj]

Pre-ARPI[aa,kkk]	Post-ARPI[kkk]/Pre-Docetaxel[aa]	Post-ARPI[kkk]/Post-Docetaxel[aa]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Niraparib/abiraterone[lll] (category 1) ◊ Olaparib/abiraterone[lll] (category 1) ◊ Talazoparib/enzalutamide[lll] (category 1) ▸ *HRRm* (other than BRCA1/2) ◊ Talazoparib/enzalutamide[lll] (category 1) • Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[nnn]/enzalutamide	**Preferred:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[lll] (category 1, preferred) ◊ Rucaparib[lll] (category 1, preferred) ◊ Niraparib/abiraterone[lll] (category 2B) ◊ Talazoparib/enzalutamide[lll] (category 2B) ▸ *HRRm* (other than BRCA1/2) ◊ Olaparib[lll] ◊ Talazoparib/enzalutamide[lll] (category 2B) • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[ppp] ▸ Aggressive variant[hhh] ◊ Cabazitaxel/Carboplatin[ggg]	**Preferred:** • Cabazitaxel[ggg] (category 1) • Docetaxel rechallenge[ggg] **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[lll] (category 1) ◊ Rucaparib[lll] ▸ *HRRm* (other than *BRCA1/2*) ◊ Olaparib[lll] ▸ Other FDA-approved agents for tissue agnostic indications[ggg] • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lu-177-PSMA-617[ppp] (category 1) ▸ Aggressive variant[hhh] ◊ Cabazitaxel/carboplatin[ggg] ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone[ggg]

Additional Options Irrespective of Prior ARPI or Prior Docetaxel (Useful in Certain Circumstances)	
• Disease State-Specific Therapy ▸ Asymptomatic without visceral metastases ◊ Sipuleucel-T[ggg,ooo] ▸ Oligometastatic[h]/Oligoprogressive disease ◊ Metastasis-directed therapy[mmm] with metastatic castration-resistant prostate cancer (mCRPC) systemic therapy ▸ Symptomatic bone-predominant metastases ◊ Radium-223[nnn] (category 1)	• Molecular Biomarker-Directed Therapy ▸ MSI-High (MSI-H)/dMMR ◊ Pembrolizumab[ggg] (category 2B)

NCCN Guidelines, Prostate Cancer, v2026;

Case 1: Progression After a Single ARPI

A taxane-naive patient with PSMA-positive mCRPC progressing on one prior ARPI.

Clinical scenario

- 72M, ECOG 0, mCRPC with rising PSA on enzalutamide; asymptomatic
- No prior chemotherapy; prefers to defer taxane
- PSMA PET/CT: multiple PSMA-avid nodal and bone lesions, no PSMA-negative disease
- Adequate marrow, renal, and hepatic function

Answer choices

- A. Switch to a second ARPI (darolutamide)
- B. Start docetaxel chemotherapy
- C. Lutetium-177 PSMA-617 radioligand therapy
- D. Radium-223

Question
Which next-line option is best supported by phase 3 evidence for this taxane-naive, PSMA-positive patient who progressed on one ARPI?

Illustrative de-identified case; PSMAfore, Lancet 2024; NCCN Guidelines, Prostate Cancer, v2026

Case 1 Answer: Lutetium-177 PSMA-617

Correct answer: C. Lutetium-177 PSMA-617, supported by the PSMAfore trial.

Why this choice

- PSMAfore randomized taxane-naive, post-one-ARPI patients to Lu-177 PSMA-617 vs a second ARPI
- Radiographic PFS 9.3 vs 5.6 months (HR 0.41); updated to 11.6 vs 5.6 months
- About a 59% reduction in risk of progression or death
- FDA expanded the indication to taxane-naive patients in March 2025

Teaching points

- Confirm PSMA-positive disease on PET with no dominant PSMA-negative lesions
- Verify marrow (ANC ≥1.5, Plt ≥100, Hgb ≥9), renal (eGFR >50), and hepatic reserve
- Dose 7.4 GBq IV every 6 weeks for up to 6 cycles
- Counsel on xerostomia, cytopenias, and radiation-safety precautions

Key evidence
PSMAfore: rPFS 11.6 vs 5.6 months (HR 0.41); overall survival not significant (HR 0.91), confounded by crossover. A second ARPI offers limited benefit after progression on the first.

Morris MJ, et al. Lancet. 2024 (PSMAfore); Sartor O, et al. N Engl J Med. 2021 (VISION); NCCN Guidelines, Prostate Cancer, v2026

Case 2: Rising PSA and Dry Mouth on Pluvicto

A patient on lutetium-177 PSMA-617 with an early PSA rise and significant xerostomia.

Clinical scenario

- 70M, ECOG 1, PSMA-positive mCRPC, completed 2 cycles of lutetium-177 PSMA-617
- PSA has risen ~20% from baseline after cycle 2
- Significant dry mouth (grade 2 xerostomia) affecting eating and sleep
- No new pain; performance status stable; good baseline PSMA PET before cycle 1

Answer choices

- A. Stop now — the rising PSA signals treatment failure
- B. Stop and switch to taxane chemotherapy
- C. Continue treatment and reassess with imaging and additional markers
- D. Continue but empirically reduce the dose

Question
After two cycles with a modest PSA rise and manageable xerostomia, should this patient continue lutetium-177 PSMA-617 or stop for progression?

Illustrative de-identified case; VISION, NEJM 2021; NCCN Guidelines, Prostate Cancer, v2026

Case 2 Answer: Don't Stop on PSA Alone

Correct answer: C. Continue therapy and reassess with imaging and markers; do not stop on PSA alone.

Why this choice

- PSA flare is common early: in a post-hoc VISION analysis, ~15% with a week-6 rise declined by week 12
- An isolated early PSA rise with stable symptoms is not reliable evidence of progression
- Confirm true progression with imaging (PSMA PET ± CT and bone scan) against baseline
- Discontinue only for radiographic or clear clinical progression, not PSA alone

Teaching points

- Alkaline phosphatase tracks bone-disease activity; LDH and CTC counts add prognostic information
- Watch for PSMA-negative or PSA-low disease and neuroendocrine dedifferentiation (consider FDG PET)
- Manage xerostomia: hydration, saliva substitutes, sugar-free lozenges; rarely requires stopping therapy
- Continue lutetium-177 PSMA-617 up to 6 cycles while benefit persists

When to reassess or stop therapy

- ✓ Rising PSA alone should not trigger stopping — early flare is common
- ✓ Image for large or accelerating PSA rise, or new symptoms
- ✓ Compare against a good pre-treatment baseline scan
- ✓ Stop for confirmed radiographic progression
- ✓ Stop for clear clinical progression or unacceptable toxicity
- ✓ Suspect PSMA-negative or neuroendocrine disease if PSA and imaging disagree (consider FDG PET)

Sartor O, et al. N Engl J Med. 2021 (VISION); NCCN Guidelines, Prostate Cancer, v2026; Pluvicto FDA prescribing information

Access, Equity, and Delivery Challenges

Radiopharmaceutical therapy requires specialized infrastructure, which can widen disparities in access to care.

Barriers

- Limited availability of licensed nuclear medicine facilities
- Isotope supply-chain and short half-life logistics
- Travel burden for repeated infusions

Advancing equity

- Expand referral networks and telemedicine consultation
- Address insurance and reimbursement gaps
- Ensure diverse enrollment in ongoing trials

Czernin J, Calais J. J Nucl Med. 2023;64(3):343; Pomykala KL, et al. J Nucl Med. 2023;64(3):347; Mehrens D, et al. J Natl Compr Canc Netw. 2023;21(1):43; NCCN Guidelines, Prostate Cancer, v2026

Future Directions

The radiopharmaceutical pipeline is expanding rapidly across isotopes, targets, and treatment settings.

On the horizon

- Actinium-225 PSMA-617 delivers high-energy, short-range alpha particles for greater tumor cell kill than lutetium-177 beta therapy (investigational, not FDA-approved)
- Actinium-225 shows activity in lutetium-refractory mCRPC; xerostomia is the key dose-limiting toxicity under study
- Earlier use in hormone-sensitive disease is under investigation
- Combinations with PARP inhibitors and immunotherapy are being evaluated (investigational)
- Novel PSMA ligands and dosimetry-guided dosing aim to improve the therapeutic index

ClinicalTrials.gov; investigational agents not FDA-approved

Key Takeaways

Radiopharmaceuticals are now a core component of mCRPC management.

- PSMA PET imaging enables precise patient selection
- Lutetium-177 PSMA-617 improves survival in post-taxane (VISION) and taxane-naive (PSMAfore) mCRPC
- Radium-223 extends survival in symptomatic bone-predominant disease (ALSYMPCA)
- Guideline-concordant sequencing and radiation safety optimize outcomes
- Equitable access to specialized care remains a priority and unmet need

VISION, NEJM 2021; PSMAfore, Lancet 2024; ALSYMPCA, NEJM 2013

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Thank You!

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