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Radiopharmaceutical Therapy (RPT) in Prostate Cancer

Safety, Toxicity, and Management of Side Effects

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Agenda

- Why radiopharmaceutical therapy (RPT) is now a core pillar of advanced prostate cancer care
- Where RPT fits in the prostate cancer treatment landscape
- Key trials and safety signals shaping current practice
- Toxicity “fingerprints” of prostate cancer radiopharmaceuticals
- Practical management playbooks for common toxicities
- What to check before each treatment cycle (labs and baseline risk factors)
- RPT with EBRT/SBRT: evidence, safety signals, and coordination
- Operationalizing radiation safety and multidisciplinary workflow

Xerostomia

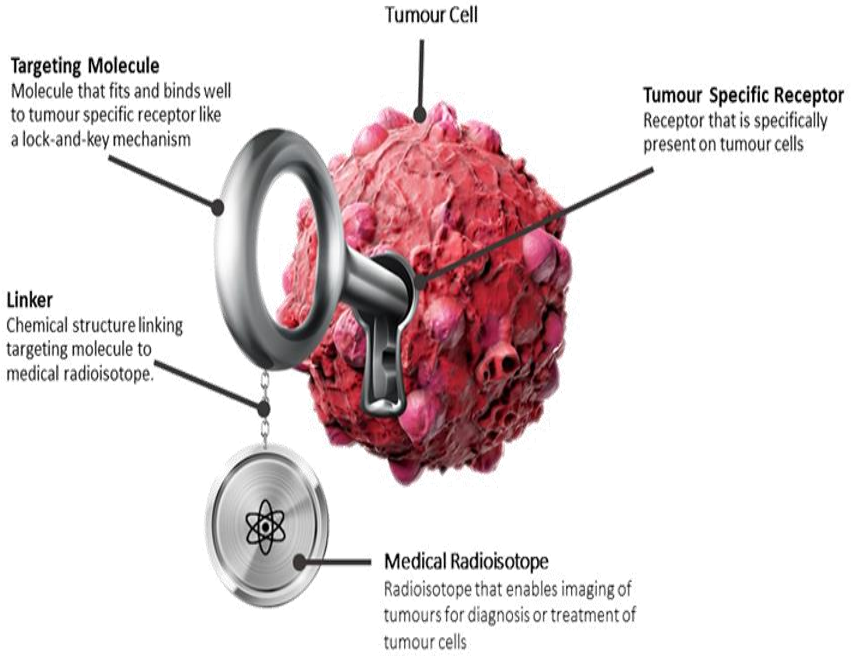
Myelosuppression

Renal monitoring

Bone health & fractures

What is Radiopharmaceutical Therapy? - Truly lock-and-key model

- Systemic therapy delivering radiation directly to tumor or tumor microenvironment.
- “Lock-and-key” model:
  - Targeting ligand (e.g., PSMA-binding molecule)
  - Linked to a radioactive isotope (e.g., 177Lu, 223Ra)
- Diagnostic/theranostic paradigm
  - Same target for imaging (e.g., PSMA PET) and therapy.
- Distinct from EBRT:
  - Prolonged low dose-rate radiation from *inside* the body.



Calais J et al. *J Nucl Med* 2024, EANM/SNMMI RLT Guidelines 2023, Hope TA et al. *Lancet Oncology* 2022

Radiopharmaceutical landscape in prostate cancer

Approved (U.S.)

- **177Lu-PSMA-617 (Pluvicto):**
--Indication: PSMA-positive metastatic disease (mCRPC)
--Targets PSMA-expressive sites of disease

- **Radium-223 dichloride (Ra-223):**
--Indication: Symptomatic bone metastases (no visceral disease)
– Targets areas of increased bone turnover (bone mets)

Investigational / emerging

- **^{225}Ac-PSMA (alpha emitter)**
- PSA50 response in ~60%+ in advanced mCRPC
- Xerostomia often dose-limiting
- Grade ≥3 anemia ~8–10% in pooled series

- **^{161}Tb-PSMA (beta + Auger emitter)**
- Early phase I/II data (e.g., VIOLET)
- No dose-limiting toxicities (DLTs) reported
- AEs mainly grade 1–2: dry mouth, anemia, fatigue

FDA Pluvicto Label (updated 2025), ParkerC et al. *NEJM* 2013, Sathekge M et al.*Lancet Oncology* 2024 (225Ac-PSMA), Buteau JP et al. *Lancet Oncology*2025 (161Tb-PSMA, VIOLET)

PSMA Targeted Radioligand Therapy Overview

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PSMA-Targeted Radioligand Therapy for Prostate Cancer

- Landmark randomized phase III, multicenter open-label **VISION trial** (Sartor et al. 2021).
- Initially FDA-approved (Mar 23, 2022) for:
  - mCRPC previously treated with **ARPI** and **taxane-based chemotherapy**.
- Incorporated into **NCCN Guidelines** (May 10, 2022).
- **Label expansion (Mar 28, 2025):**
  - mCRPC previously treated with ARPI and considered **appropriate to delay taxane-based chemotherapy**.
- ^{177}Lu-PSMA-617 (Pluvicto™) is now a **core systemic option** in advanced mCRPC as part of a theranostic strategy

Sartor O et al. *NEJM* 2021 (VISION), FDA Approval Summary – *Clin Cancer Res* 2023, NCCN Guidelines 2024–2025

VISION Trial (Sartor et al. 2021)

- Design
  - mCRPC, post-ARPI and taxane.
  - 177Lu-PSMA-617 + best standard of care (SOC) vs SOC alone.
  - 7.4 GBq (200 mCi) every 6 weeks, up to 6 doses.
- Key efficacy outcomes:
  - Overall survival: **15.3 vs 11.3 months**
  - Radiographic PFS: **8.7 vs 3.4 months**
  - All key secondary endpoints favored Pluvicto™
- Impact:
  - Established Pluvicto™ as standard of care for eligible post-taxane mCRPC.

Sartor O et al. *NEJM* 2021, Fizazi K et al. *Lancet Oncology* 2023 (QoL analysis)

Pluvicto™ for the treatment of metastatic prostate cancer

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PSMAfore Trial (Morris et al. 2024)

- Design
  - Taxane-naïve mCRPC progressing on first ARPI.
  - Randomized 1:1: **Pluvicto™** vs **ARPI switch**.
- Treatment:
  - Pluvicto™ 7.4 GBq (200 mCi) every 6 weeks, up to 6 doses.
  - Patients on ARPI arm allowed **crossover** to Pluvicto™ upon progression (~60% crossed over).
- Key outcome:
  - Statistically significant improvement in **rPFS** with Pluvicto™ vs ARPI switch
  - Benefit observed **despite high crossover**
- Impact:
  - Confirms efficacy and tolerability earlier in mCRPC treatment sequence.

Morris MJ et al. *Lancet* 2024, Fizazi K et al. *Lancet Oncology* 2025 (HRQoL)

Pluvicto™ - Indication and Theranostics

- **Indications (as of 2025):**
  - PSMA-positive mCRPC post-ARPI and taxane (VISION).
  - PSMA-positive mCRPC post-ARPI and appropriate to delay taxane (PSMAfore).
- **Theranostic workflow:**
  - PSMA PET/CT for selection → 177Lu-PSMA-617 for therapy.
- **Why this matters**
  - Enables **targeted systemic radiation** with a generally favorable and predictable safety profile

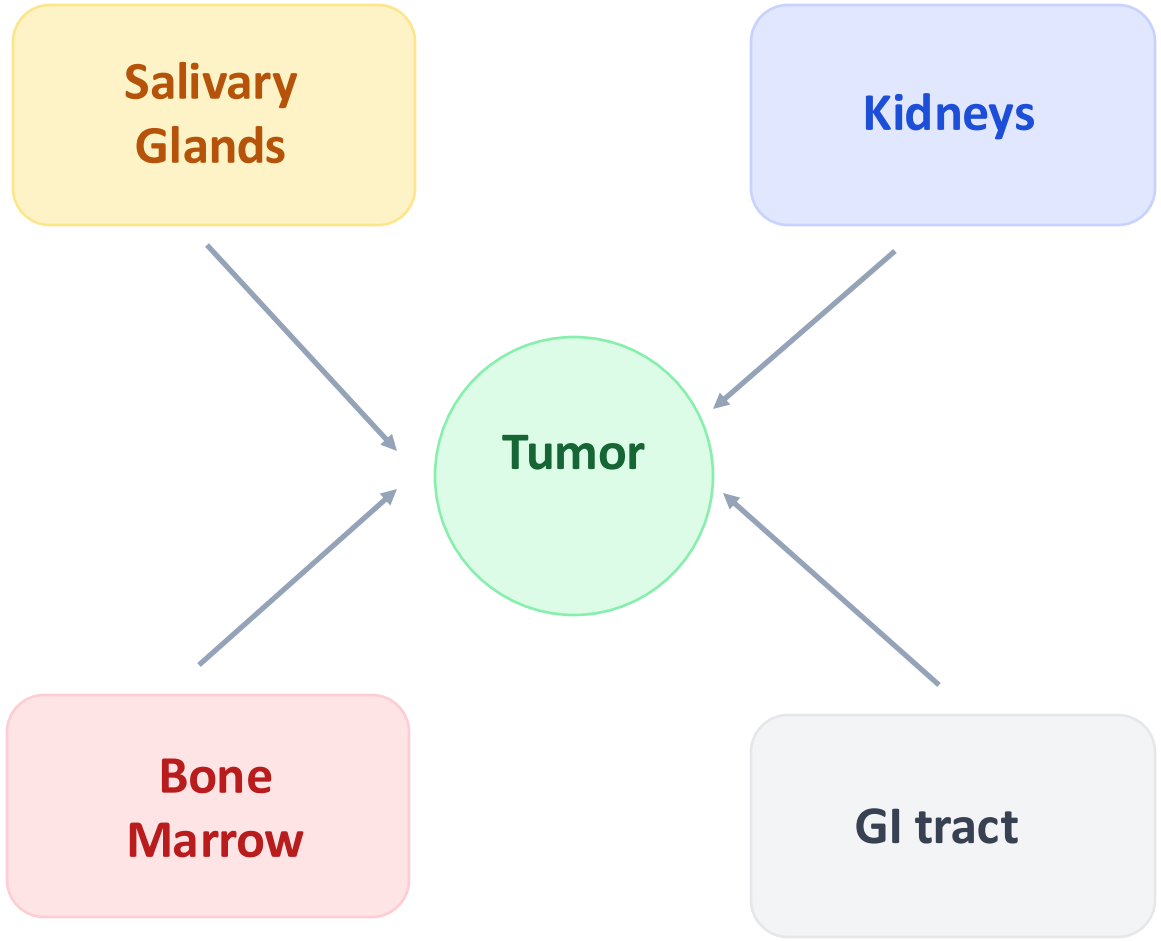
FDA Pluvicto Label (2025), NCCN Prostate Cancer Guidelines 2025, EANM/SNMMI Guidelines 2023

Pluvicto™ - Practical Use: Eligibility & Logistics

- **Patient Selection:**
  - PSMA PET/CT with PSMA-positive metastases.
  - Ideally no dominant PSMA-negative metastases.
- **Dosing schedule:**
  - 7.4 GBq (200 mCi) every 6 weeks.
  - Up to **6 total doses**.
- **Monitoring:**
  - Labs followed every ~3 weeks between cycles (CBC/CMP).
- **Clinical experience:**
  - Generally very well tolerated overall with predictable toxicity profile.

Calais J et al. *J Nucl Med* 2024, Kratochwil C et al. *EJNMMI* 2023

Radiopharmaceutical Activity in prostate cancer – where it goes?



Where activity goes

Salivary glands
PSMA expression → xerostomia

Kidneys
Physiologic uptake/clearance → renal monitoring

Bone marrow
Baseline reserve + osseous tumor burden → cytopenias

Bone turnover
Ra-223 localizes to bone mets → marrow + fracture considerations

Ells Z et al. *J Nucl Med* 2024 (dosimetry meta-analysis), Schuchardt C et al. *J Nucl Med* 2022

Typical toxicity “fingerprints” (quick mental model)

PSMA – targeted beta therapy (177Lu-PSMA-617)

Xerostomia
Usually grade 1–2; start prophylaxis before cycle 1

Myelosuppression
Dose-dependent; risk rises with high bone tumor burden or prior myelotoxic therapy

Renal Toxicity (rare)
Hydration + renal monitoring

Non-hematologic AEs

Nausea, constipation, fatigue, bone pain flare,

Bone – targeted alpha therapy (Ra-223)

Marrow reserve matters
Monitor CBC before each dose; transfuse/support as needed

Fracture risk signal
Higher when combined with some ARPIs without bone health agents → co-prescribe BMA + Ca/Vit D

Non-hematologic AEs

Often mild: GI upset, fatigue, bone pain flare
Focus on bone health + fall-risk mitigation

- Sartor O et al. *NEJM* 2021, Calais J et al. *J Nucl Med* 2024

177Lu-PSMA-617: common adverse effects in VISION (mCRPC)

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Most common (usually grade 1–2)

- Fatigue
- Xerostomia (dry mouth)
- Nausea ± constipation
- Decreased appetite
- Transient pain flare

Less common (grade 3–4)

- Fatigue
- Back pain

Practical Tips

Set expectations early: dry mouth + fatigue are common. Give a symptom kit (saliva substitutes, antiemetic plan, constipation regimen) before cycle 1.

177Lu-PSMA-617: labs & marrow toxicity in VISION (mCRPC)

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Key safety domain: marrow

- Anemia, thrombocytopenia, leukopenia/lymphopenia
- Risk rises with extensive bone involvement and prior myelotoxic therapy
- Dose holds/reduction are driven by labs + symptoms

Common lab abnormalities (monitor each cycle)

- ↓ Lymphocytes, ↓ hemoglobin, ↓ platelets, ↓ neutrophils
- Electrolytes can shift (e.g., calcium, sodium); monitor CMP
- Renal function: eGFR/creatinine clearance—important for safety and eligibility

Before you treat: per-cycle safety checklist

Per-cycle “go / no-go” essentials

- Confirm indication and imaging criteria
  - PSMA PET for ^{177}Lu-PSMA
- Symptom check
  - Hydration, nausea/constipation, pain, fatigue
- CBC with differential (trend vs baseline)
- CMP
  - Creatinine/eGFR (± CrCl), electrolytes
- Medication review
  - Anticoagulants/antiplatelets, nephrotoxins (e.g., NSAIDs, contrast)
- Prior RT/chemo
  - Anticipate cumulative marrow toxicity
- If Ra-223
  - Bone health plan: bone-modifying agent + Ca/Vit D + fall-risk mitigation

Higher-risk features (plan ahead)

- Extensive bone metastases / high bone tumor volume
- Baseline cytopenias or prior myelotoxic therapy
- Renal impairment or dehydration risk
- Severe baseline xerostomia / poor dentition

Management playbook: xerostomia (dry mouth)

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Goal: maintain oral intake, sleep, and dental health across cycles

Stepwise approach

1) Start before cycle 1: hydration plan + oral hygiene; consider baseline dental review
2) First-line: saliva substitutes/lubricants; alcohol-free mouth rinse
3) Stimulation: sugar-free gum/lozenges (xylitol) if dentition allows
4) Rx options (select patients): pilocarpine or cevimeline (watch contraindications)
5) Dental protection: fluoride strategies + caries surveillance
6) If severe/persistent: consider hold and one 20% dose reduction per label

Muniz M et al. *Cancer Treatment Reviews* 2024
Mercadante V et al. *JCO* 2021 (ISOO/MASCC guideline)
Rathke H et al. *EJNMMI* 2018

30-second counseling script

"Dry mouth is common and usually mild. Start saliva substitutes now, sip water often, and call us if eating or sleeping becomes difficult or you get oral sores."

Escalate urgently

- Inability to maintain oral intake / dehydration
- Oral candidiasis or painful mucositis
- New dental pain or rapidly worsening caries risk
- Dry mouth severe enough to require dose hold/reduction per label

Management playbook: cytopenias (anemia / platelets / neutrophils)

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Core idea: trend counts over time + treat symptoms early

Clinic-ready actions

- CBC before each cycle (consider mid-cycle CBC if high risk)
- Separate disease-related vs treatment-related anemia; assess bleeding
- Hold/resume per label; consider one 20% dose reduction after recovery
- Transfusion support per institutional thresholds (symptoms matter)
- Platelets: bleeding precautions; review anticoagulants/antiplatelets
- Neutropenia: fever protocol; growth factor case-by-case
- Optimize reversible causes (iron/B12/folate, bleeding, renal disease)

When to involve hematology / inpatient care

- Rapidly falling platelets or active bleeding
- Febrile neutropenia / sepsis concern
- Transfusion-refractory cytopenias
- Concern for marrow failure / MDS after heavy prior therapy

High-risk signal

Extensive PSMA-avid bone involvement → lower threshold for holds, mid-cycle labs, and transfusion planning.

Calais J et al. *J Nucl Med* 2024
Ghodsi A et al. *JCO* 2024

Management playbook: GI symptoms, fatigue, and renal protection

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GI symptoms

- Prophylaxis: antiemetic plan (pre + PRN)
- Start constipation regimen up front
- Hydration + small frequent meals
- Escalate for persistent grade ≥3 symptoms → hold/reduce per label

Fatigue

- Screen for anemia, sleep issues, depression, pain
- Activity pacing + light exercise as tolerated
- Optimize bowel regimen and analgesia
- Hold for grade ≥3 fatigue per label

Renal safety

- Check SCr/eGFR (± CrCl) before each cycle
- Encourage hydration; treat vomiting/diarrhea promptly
- Avoid nephrotoxins when feasible (NSAIDs, contrast timing)
- Grade ≥3 renal toxicity → discontinue per label

Give patients a simple “when to call” card: fever, bleeding/bruising, uncontrolled vomiting, no urine output, severe dizziness/dehydration

Hartrampf P et al. *Cancers* 2022, Lawhn-Heath C et al. *Lancet Oncology* 2022

Long term safety of RPTs

Long-term follow-up studies of PSMA-targeted RPT show that **clinically significant late renal or hepatic toxicity is uncommon**.

Cumulative marrow toxicity can become relevant in patients receiving many cycles or multiple lines of marrow-affecting therapy.

Radium-223 evidence

ALSYMPCA (Pivotal Phase III)

- Population: mCRPC with **symptomatic bone-predominant metastases**, no visceral disease
- Intervention: **Radium-223 vs placebo** (both with best standard of care)
- Key outcomes:
  - **Overall survival benefit** (14.9 vs 11.3 months)
  - **Delayed time to first symptomatic skeletal event**
  - Favorable safety profile vs placebo
- Result: **FDA approval of Radium-223** for symptomatic bone-metastatic mCRPC

ERA-223 (Practice-Changing Safety Signal)

- Population: **Asymptomatic or mildly symptomatic mCRPC**
- Intervention: **Radium-223 + abiraterone/prednisone vs abiraterone alone**
- Key findings:
  - **No improvement in OS or skeletal outcomes**
  - **Significantly increased fracture risk** with combination therapy
- Critical insight:
  - Majority of patients **were not receiving bone-protective agents**

Clinical takeaway

- Ra-223 is effective and relatively safe **when used in the right patients with bone-modifying agents**
- Avoid Ra-223 + ARPI combinations **without** bone health agents

- Parker C et al. **ALSYMPCA Trial.** *N Engl J Med.* 2013
- Smith M et al. **ERA-223 Trial.** *Lancet Oncol.* 2019
- NCCN Prostate Cancer Guidelines, 2024–2025

Radium-223: safety profile + fracture risk mitigation

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What to expect

- Generally low rates of severe myelosuppression, but monitor marrow reserve
- Grade 3–4 hematologic toxicities reported include anemia and thrombocytopenia
- Caution with heavy marrow involvement or prior chemotherapy
- LT follow-up not reveal new major safety signals

Marrow monitoring & management

- CBC prior to each injection; hold if counts below protocol thresholds
- Transfusion support for symptomatic cytopenias
- Caution in patients with heavy marrow involvement or prior chemo

Fracture risk signal: combination matters

ERA-223 signal: Radium-223 + lincreased fractures vs control, no survival benefit

Avoid: Ra-223 + certain ARPIs without bone health agents

Do: build a bone health plan

- Denosumab or zoledronic acid
- Calcium + vitamin D
- Fall-risk assessment + PT as needed

Parker C et al. *NEJM* 2013, Smith M et al. *Lancet Oncology* 2019, Fizazi K et al. *Lancet Oncology* 2019 (PEACE-III context)

RPT with EBRT/SBRT: safety notes for coordination

If EBRT/SBRT is delivered within ~3 months of 177Lu-PSMA therapy, watch platelets closely
Higher thrombocytopenia rates reported, especially with pelvic/spine fields

Pepin et al

Lu-PSMA + EBRT/SBRT (retrospective experience)

- Multiple institutional series confirm feasibility of combining Lu-PSMA with EBRT/SBRT
- **Metastasis-directed EBRT** during or around Lu-PSMA commonly used for
  - pain control
  - oligoprogression
- Toxicity profile generally resembles each modality alone

Key safety signal

- **Higher thrombocytopenia** when EBRT is delivered **within ~3 months** of ^{177}Lu-PSMA
- Risk greatest with **pelvic/spine fields** and high baseline bone marrow involvement

- **No consistent overall survival penalty**
- No clear OS disadvantage observed for patients receiving combined therapy
- **Clinical implication**
  - Combination is feasible, but **marrow dose, field selection, and timing** matter

- Pepin A et al. *J Nucl Med* 2025
- Teunissen F et al. *J Nucl Med* 2025

Prospective Lu-PSMA + RT Trials (Safety-Focused)

LUNAR (Phase II, randomized)

- Population: Oligorecurrent hormone-sensitive prostate cancer
- Arms: SBRT alone vs **2 cycles neoadjuvant Lu-PSMA → SBRT**
- Result: Improved PFS with combination
- Safety: No major increase in grade ≥3 toxicity; lymphopenia most notable

PROQURE-I (Phase I)

- Population: N1M0, curative-intent
- Design: EBRT + ADT with **single-dose Lu-PSMA (dose escalation)**
- Early findings: Feasible, no unexpected dose-limiting toxicities

PSMA-DC (Phase III, ongoing)

- SBRT to all PSMA-positive lesions → Lu-PSMA vs observation
- Goal: Delay systemic ADT
- Safety data maturing; no new signals to date

Kishan AU et al. *JCO* 2025 (LUNAR), van der Sar E et al. *BMC Cancer* 2023 (PROQURE-I), Sartor O et al. *JCO* 2025 (PSMA-DC)

Radium-223 + RT — What We Know

Beyond ALSYMPCA

- Small series evaluating **concurrent or sequential Ra-223 + EBRT** for painful bone metastases
- Appears **feasible with careful field selection and marrow monitoring**

Key considerations

- Marrow reserve remains the dominant safety constraint
- Overlapping marrow-rich fields increase cytopenia risk
- EBRT can provide focal palliation while Ra-223 addresses diffuse bone disease

Take-home

- Ra-223 + EBRT can be delivered safely in select patients with careful coordination

Operational essentials: radiation safety + clinic workflow

Radiation safety (clinic + patient)

Clinic:

- Trained staff; shielding/contamination precautions
- Handling/disposal + extravasation/spill protocol
- Room monitoring after administration
- Special planning for urinary incontinence

Patient:

- Written instructions: hygiene + bathroom precautions
- Hydration + frequent voiding; laundry/fluids guidance
- Sexual/close contact guidance per institutional policy
- Handling of bodily fluids and laundry for a defined period
- Clear “who to call” pathway for AEs 24/7

Operational essentials: Multidisciplinary Workflow

Multidisciplinary team workflow

- Medical oncology:
  - Systemic treatment strategy
  - Transfusion thresholds
- Nuclear medicine/ Radiation Oncology :
  - RPT administration
  - Radiation precautions
- Radiation oncology:
  - Prior fields / marrow exposure context
- Nursing/pharmacy:
  - Symptom kits (antiemetics, bowel regimen, saliva aids)
  - Triage scripts and patient education materials

Pluvicto™ - Patient Resources

Stay hydrated
For 1 day drink a lot and urinate (pee) as much as you can

Stay more than 3 feet away from others
For 2 days from other adults
For 7 days from children under 18 or pregnant women

Sleep alone in a separate bedroom
For 3 days away from other adults
For 7 days away from children
For 15 days away from pregnant women

No sex at first, and then use effective birth control
For 7 days no sex
During your course of treatment and for 14 weeks after your last dose use effective birth control to avoid pregnancy

Use the bathroom carefully
Use a separate bathroom if possible, and wipe it down after you use it
For 2 days always sit while using the toilet
Use and flush toilet paper every time
For 3 days whenever anyone helps you in the bathroom, they should wear disposable gloves

Shower daily
For 7 days take at least one shower a day

Do separate laundry
During your course of treatment wash your laundry separately from others

Be aware that treatment may cause infertility

https://us.pluvicto.com/resources/helpful-materials

RPT: Toxicity Management Algorithm - (177Lu-PSMA-617)

General Dose Modification Rules

•Standard dose: 7.4 GBq
•Only one dose reduction permitted
→ 20% reduction to 5.9 GBq
•Any toxicity requiring further reduction → Permanent discontinuation

Permanent Discontinuation Criteria

•Treatment delay >4 weeks due to toxicity
•Any unacceptable toxicity
•Recurrent Grade 3–4 adverse reaction after one dose reduction
•Persistent, intolerable Grade 2 toxicity after one dose reduction

Dry Mouth (Xerostomia)

•Grade 2
  •Hold treatment until improvement
  •Consider dose reduction
•Grade 3
  •Hold treatment AND
  •Mandatory 20% dose reduction
•Recurrent Grade 3 after dose reduction
  •Permanent discontinuation

- **Renal Toxicity**

- Grade ≥2 serum creatinine increase OR ≥40% decrease in creatinine clearance
  - Hold treatment
  - Resume with 20% dose reduction
- Grade ≥3 renal toxicity OR Recurrent renal toxicity after dose reduction
  - Permanent discontinuation

RPT: Toxicity Management Algorithm - (177Lu-PSMA-617)

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Myelosuppression (Most Common Reason)

- Grade 2 (anemia, thrombocytopenia, leukopenia, neutropenia)
  - Hold treatment until improvement to Grade 1 or baseline
- Grade ≥3
  - Hold treatment until improvement AND
  - Resume with 20% dose reduction
- Recurrent Grade ≥3 after dose reduction
  - Permanent discontinuation

Other Non-Hematologic Toxicities

- Gastrointestinal toxicity (Grade ≥3, not medically manageable)
  - Hold until improvement
  - Dose reduction required
- Fatigue (Grade ≥3)
  - Hold until improvement
- Electrolyte/Metabolic abnormalities (Grade ≥2)
  - Hold until improvement

Take-home summary

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Predictable and manageable

Most RPT AEs are low-grade; success is preparation (symptom kit + labs + counseling).

177Lu-PSMA-617: focus on xerostomia + marrow

Follow label-based hold/reduce rules; plan transfusion support for high-risk patients.

Radium-223: bone health is not optional

Avoid unsafe combinations; use bone-modifying agent + Ca/Vit D + fall-risk mitigation.

RPT + EBRT/SBRT

Feasible, with higher thrombocytopenia risk when EBRT is close to Lu-PSMA; requires close lab monitoring, careful field planning and coordination.

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THANK YOU

QUESTIONS