

06.01.40 Pluvicto

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Summary

Description

Radiopharmaceuticals are composed of a radioisotope (i.e., a radioactive particle) bond to an organic molecule and are used for diagnostic and therapeutic purposes. The organic molecule acts as a targeting compound (ligand) that conveys the radioisotope to specific organs, tissues, or cells. Lutetium Lu 177 vipivotide tetraxetan (Pluvicto™), commonly abbreviated as Lu-177-PSMA-617, is a radioligand therapy that targets prostate-specific membrane antigen (PSMA), which is highly expressed on prostate cancer cells. Lu-177-PSMA-617 is indicated for use in adults with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have already been treated with other anticancer treatments, including androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

Summary of Evidence

For individuals with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have failed other anticancer therapies, including androgen receptor (AR) pathway inhibition and taxane-based chemotherapy, who receive Lu-177-PSMA-617, the evidence includes a systematic review and 2 randomized controlled trials (RCTs). Relevant outcomes are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and

morbidity. The systematic review, which included a heterogeneous population of patients with mCRPC, demonstrated a higher proportion of patients responding to PSMA-targeted radionucleotide therapy based on a prostate-specific antigen (PSA) decrease of 50% or more compared to controls; the review was also limited by the inclusion of mostly retrospective studies with small numbers of individuals. The VISION RCT compared Lu-177-PSMA-617 plus investigator-determined standard of care (SOC) therapy to SOC therapy alone in individuals with PSMA-positive mCRPC who had been treated with AR pathway inhibitors and taxane-based chemotherapy. Results demonstrated that Lu-177-PSMA-617 plus SOC significantly prolonged the median OS (15.3 vs. 11.3 months) and radiographic progression-free survival (rPFS) (8.7 vs. 3.4 months). The incidence of Grade 3 or higher adverse events was greater with Lu-177-PSMA-617 than without (52.7% vs. 38.0%). The phase 2 TheraP RCT compared Lu-177-PSMA-617 to cabazitaxel. Unlike the VISION trial, in TheraP, previous treatment with AR pathway inhibitors was not necessary for participants. Also, the TheraP trial used 2 positron-emission tomographic computed tomography scans to identify PSMA-positive status and excluded individuals with discordant findings using gallium-68-labeled PSMA-11 and 2-fluorine-18[18F]fluoro-2-deoxy-D-glucose. The primary endpoint of PSA response, defined by a reduction of at least 50% from baseline, was achieved more often by patients who received Lu-177-PSMA-617 (66%) compared to cabazitaxel (37%). In this RCT, the incidence of Grade 3 or higher adverse events were greater with cabazitaxel (53%) compared to Lu-177-PSMA-617 (33%). In a subsequent publication of this study with a median follow-up of 35.7 months, the OS did not differ between treatment groups (19.1 vs. 19.6 months). Additional evidence has been published that supports the use of Lu-177-PSMA-617 in patients who are taxane-naïve (and without advanced illness warranting consideration of taxane therapy a taxane) and have progressed on AR pathway inhibition. The PSMAfore trial demonstrated that treatment with Lu-177-PSMA-617 prolonged rPFS compared to switching to a different AR pathway inhibitor. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

None

OBJECTIVE

The objective of this evidence review is to determine whether the use of radiopharmaceuticals in adults with prostate cancer improves the net health outcomes.

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary

- Therapeutic radiopharmaceuticals for prostate cancer using Lu-177-PSMA-617 (Pluvicto™), may be considered **medically necessary** for the treatment of adults with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) **and one or more of the following:** 1 or more PSMA-positive lesion(s); and/or
- Metastatic disease that is predominately PSMA-positive with no dominant PSMA-negative metastatic lesions

And:

- Have been treated with androgen receptor-directed therapy **and** one of the following:
 - A taxane-based chemotherapy **or**
 - Are considered appropriate to delay taxane-based chemotherapy

Investigational

Therapeutic radiopharmaceuticals for prostate cancer using Lu-177-PSMA-617 (Pluvicto™) is considered **investigational** for the treatment of prostate cancer when the above criteria have not been met because the evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

POLICY GUIDELINES

Lutetium Lu 177 vipivotide tetraxetan

- Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) is a radiopharmaceutical and should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.
- The recommended dose of Lu-177-PSMA-617 (Pluvicto™) is 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses.
- Individuals should be well-hydrated during treatment.
- Refer to the [prescribing information](#) for Lu-177-PSMA-617 for recommended dosage modifications for adverse reactions. The management of adverse reactions may require temporary dose interruption (extending the dosing interval from every 6 weeks up to every 10 weeks), dose reduction, or permanent discontinuation of treatment with Lu-177-PSMA-617. The dose of Lu-177-PSMA-617 may be reduced by 20% to 5.9 GBq (160 mCi) once; the dose should not be re-escalated.
- Lu-177-PSMA-617 should be discontinued permanently if the individual develops any of the following:
 - Recurrent Grade 3 or higher myelosuppression after one dose reduction
 - Grade 3 or higher renal toxicity
 - Recurrent renal toxicity after 1 dose reduction
 - Recurrent Grade 3 dry mouth after 1 dose reduction
 - Recurrent Grade 3 or higher gastrointestinal toxicity after one dose reduction
 - Aspartate aminotransferase or alanine aminotransferase greater than 5 times the upper limit of normal in the absence of liver metastases
 - Any unacceptable toxicity
 - Any serious adverse reaction that requires treatment delay of greater than 4 weeks
 - Any recurrent Grade 3 or 4 or persistent and intolerable Grade 2 adverse reaction after 1 dose reduction

Common Toxicity Criteria for Adverse Events

Table PG1 describes the grading of severity used in the Common Toxicity Criteria for Adverse Events (version 4.03).

Table PG1. Common Toxicity Criteria for Adverse Events, Version 4.03

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living and refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living and refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

Coding

See the [Codes](#) table for details.

BACKGROUND

Prostate cancer is the second leading cause of cancer-related deaths among American XY individuals with 313,780 new cases and 35,770 disease-related deaths estimated for 2025. About 6 in 10 cases of prostate cancer are diagnosed in men who are 65 years of age or older, and the disease is rare in men under 40 years of age. Prostate cancer disproportionately affects African American and Caribbean XY individuals of African ancestry compared to XY individuals of other races. The disease is less common in Asian American, Hispanic, and Latino XY individuals than in non-Hispanic White XY individuals. The reasons for these racial and ethnic differences are not well understood. Typically, prostate cancer is suspected based on increased levels of prostate-specific antigen (PSA) upon screening.

Grading

Clinical staging is based on the digital rectal exam and biopsy results. T1 lesions are not palpable while T2 lesions are palpable but appear to be confined to the prostate. T3 lesions extend through the prostatic capsule, and T4 lesions are fixed to or invade adjacent structures. The most widely used grading scheme for a prostate biopsy is the Gleason system. It is an architectural grading system ranging from 1 (well-differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is a high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization. A crosswalk of these grading systems are shown in Table 1 below.

Table 1: Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well-differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

Treatment

Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose prostate cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In individuals with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. Androgen deprivation therapy (ADT) is generally the initial treatment for patients with advanced prostate cancer. Unfortunately, while ADT is effective at producing tumor response and improving quality of life, most patients' disease will eventually progress on ADT.

Castration-Resistant Prostate Cancer

Prostate cancer that progresses while the individual is on ADT is referred to as castration-resistant prostate cancer (CRPC). Androgen pathways are important in the progression of CRPC, therefore, even after progression, continued ADT is generally used in conjunction with other treatments. Several drugs have been developed that either inhibit enzymes involved in androgen production or inhibit the androgen receptor, such as abiraterone and enzalutamide. Taxane chemotherapy with docetaxel or cabazitaxel may also be used after progression. Immunotherapy (sipuleucel-T) or radium 223 are additional options for select XY individuals.

Prostate-Specific Membrane Antigen–Positive Metastatic Castration-Resistant Prostate Cancer

Prostate-specific membrane antigen (PSMA) is a transmembrane glutamate carboxypeptidase that is highly expressed on prostate cancer cells and high PSMA expression is an independent biomarker of poor prognosis. Metastatic lesions are PSMA-positive in most patients with metastatic CRPC (mCRPC) and high expression has been independently associated with reduced survival. More recently, radioligand therapies such as lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) have demonstrated the ability to selectively target prostate cancer cells in patients who have PSMA-positive mCRPC.

Radionuclide Therapy: Lutetium Lu 177 vipivotide tetraxetan

Lu-177-PSMA-617 is a radioligand therapeutic agent with 2 components: a drug that delivers the therapy to cancer cells and a radioactive particle. In the case of Lu-177-PSMA-617, the delivery vehicle is PSMA-617, and the radioactive component is lutetium-177. Upon binding of Lu-177-PSMA-617 to PSMA-expressing cells, the beta-minus emission from lutetium-177 delivers radiation to PSMA-expressing cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death. Patients should be selected for treatment with Lu-177-PSMA-617 using gallium Ga 68 gozetotide or an approved PSMA-11 imaging agent based on PSMA expression in tumors.

Regulatory Status

On March 23, 2022, Lu-177-PSMA-617 (Pluvicto™) was approved by the U.S. Food and Drug Administration (FDA) for use in adults with PSMA-positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. In March 2025, this indication was updated to also include individuals with PSMA-positive mCRPC who have been treated with AR pathway inhibition and are considered appropriate to delay taxane-based chemotherapy.

RATIONALE

This evidence review was created in March 2023 with a search of the PubMed database. The most recent literature update was performed through December 2025.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Prostate-Specific Membrane Antigen—Positive Metastatic Castration-Resistant Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) in individuals with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with PSMA-positive mCRPC who have failed other anticancer therapies, including androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

Interventions

The therapy being considered is Lu-177-PSMA-617.

Comparators

The following therapies are currently being used to make decisions about PSMA-positive mCRPC: androgen-deprivation therapy (ADT) with or without: abiraterone, apalutamide, chemotherapy, enzalutamide, external beam radiation; surgery; observation.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, quality of life (QOL), and treatment-related mortality and morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Table 2 summarizes the characteristics of a systematic review evaluating the efficacy of Lu-177-PSMA-617 in individuals with mCRPC.

Sadaghiani et al (2022) published a systematic review with meta-analysis that included a total of 69 mostly retrospective studies and a total of 4157 participants; a crosswalk of the 56 studies that specifically evaluated Lu-177-PSMA-617 is found in Table A1 in the Appendix. There were 3 RCTs among the included studies. The first trial, VISION, evaluated Lu-177-PSMA-617 in a population of patients with PSMA-positive mCRPC who failed other anticancer therapies (including AR pathway inhibition and taxane-based chemotherapy) and were not suitable for additional chemotherapy. Details of the VISION trial are summarized in the section below. The second RCT, TheraP (also summarized below), evaluated Lu-177-PSMA-617 as an alternative to cabazitaxel in patients with mCRPC, regardless of prior use of AR pathway inhibitors. The third RCT (RESIST-PC) compared 2 dosing strategies of Lu-177-PSMA-617 in patients with mCRPC; safety outcomes from this trial are summarized in the following section.

Belabaci et al (2025) published a systematic review with meta-analysis that included 6 RCTs (N=2113) of participants with mCRPC to assess the safety and efficacy of Lu-177-PSMA-617. Table A1 in the Appendix provides a crosswalk of the included RCTs. VISION and TheraP were both included, along with the ENZA-p trial, an open-label RCT phase 2 trial conducted in Australia in patients with mCRPC that investigated enzalutamide plus Lu-177-PSMA-617 versus enzalutamide alone as first-line therapy, Satapathy et al (2022 and 2023), a phase 2, open-label RCT non-inferiority trial comparing Lu-177-PSMA-617 to docetaxel in chemotherapy-naïve mCRPC patients, PSMAfore trial, a phase 3 RCT comparing Lu-177-PSMA-617 to AR pathway inhibition in taxane-naïve patients with mCRPC who had progressed on a previous AR pathway inhibition agent, and the SPLASH trial, a RCT in patients with mCRPC who had progressed while on AR pathway inhibition (not yet published). Details on the PSMAfore trial is summarized in the following sections.

Table 2: SR & MA Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Sadaghiani et al (2022)	Through June 2020	69	Participants with mCRPC treated with Lu-177-PSMA-617, Lu-177-	4157 (5 to 393)	3 RCTs; 13 non-randomized prospective;	NR

			PSMA-I&T*, or Lu-177-EB- PSMA-617*		56 retrospective	
Belabaci et al (2025)	Through February 2025	6 (10 publications)	Patients with mCRPC treated with Lu-177-PSMA-617	2113 (40 to 831)	RCTs	Range, 12 to 35.7 months

Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; MA: meta-analysis; mCRPC: metastatic castration-resistant prostate cancer; NR: not reported; RCT: randomized controlled trial; SR: systematic review.

*Product is not available in the US.

Table 3 summarizes the results of the systematic review evaluating the efficacy of Lu-177-PSMA-617 in individuals with mCRPC.

Sadaghiani et al (2022) demonstrated that PSMA-targeted radionucleotide therapy in mCRPC results in a higher proportion of patients responding to therapy based on a prostate-specific antigen (PSA) decrease of 50% or more compared to controls. Furthermore, any PSA decrease demonstrated a statistically significant prolongation of survival. Analyses were limited by the inclusion of mostly retrospective studies with small numbers of patients, and heterogeneity with regard to dosing, number of cycles, prior therapies, and extent of the disease. Importantly, the authors did not identify the number of studies that specifically included patients with PSMA-positive mCRPC who failed other anticancer therapies, including AR pathway inhibition and taxane-based chemotherapy, nor were there subgroup analyses done for this relevant population.

In Belabaci et al (2025), patients treated with Lu-177-PSMA-617 had a significantly higher PSA response (defined as $\geq 50\%$ PSA decrease) compared to controls. Additionally, Lu-177-PSMA-617 also reduced the relative risk of radiographic progression-free survival (rPFS) by 43%, although no significant impact on OS was observed. There were no differences in Grade ≥ 3 adverse events between groups. The authors did not differentiate between patients who had previously failed other anticancer therapies, and there were no subgroup analyses conducted for these patients.

Table 3: SR & MA Results

Study	PSA decrease ^a $\geq 50\%$	OS according to pooled HRs for any PSA decline ^b	OS according to pooled HRs for $\geq 50\%$ PSA decline ^c
Sadaghiani et al (2022)			
Total N	483	353	590
Pooled effect (95% CI)	OR, 5.33 (1.24 to 22.90)	HR, 0.26 (0.18 to 0.37)	HR, 0.52 (0.40 to 1.28)
I^2 (p)	92% (.0005)	21% (<.27)	0% (<.001)
Belabaci et al (2025)		rPFS	
Total N	1072	1072	1072

Pooled effect (95% CI)	OR, 4.27 (2.59 to 7.06)	HR, 0.57 (0.46 to 0.70)	HR, 0.81 (0.62 to 1.06)
I ² (p)	72% (.003)	59% (.05)	75% (.003)

CI: confidence interval; HR: hazard ratio; MA: meta-analysis;; NR: not reported; OR: odds ratio; OS: overall survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; SR: systematic review.

aOutcomes pooled data from the VISION and TheraP RCTs.

bOutcomes pooled data from 6 observational studies.

cOutcomes pooled data from 10 observational studies.

Randomized Controlled Trials

Characteristics of RCTs evaluating Lu-177-PSMA-617 in patients with PSMA-positive mCRPC are summarized in the table below.

The multinational, randomized, open-label, VISION trial (N=831) compared the efficacy and safety of Lu-177-PSMA-617 plus investigator-chosen standard of care (SOC) versus SOC alone. The SOC treatments could not include chemotherapy or radium-223 (a radioisotope specifically used to treat bone metastases). PSMA-positive status was determined with the use of gallium-68-labeled PSMA-11 positron-emission tomographic (PET)-computed tomography (CT) imaging at baseline. Radiographic progression-free survival (PFS) and OS were alternate primary outcomes, which meant that the trial would be deemed to be positive if the results with respect to either or both of these primary outcomes were significant at the allocated significance level of $p=.025$ for OS and $p=.004$ for rPFS. Of note, rPFS was added as an alternate primary endpoint in January 2019 (ie, after the trial had started) on the basis of discussions with the Food and Drug Administration (FDA). The analysis of OS was based on all randomized patients, while the analysis of rPFS was based on patients randomized on or after March 5th, 2019. The median follow-up was 20.9 months.

In a subsequent publication of the VISION trial, after a median follow-up of 7.8 months (interquartile range [IQR] 4.4 to 10.6), the incidence of any-grade treatment-emergent adverse events among patients receiving Lu-177-PSMA-617 was similar between cycles 1 to 4 (98%) and cycles 5 to 6 (99%). The incidence of serious treatment-emergent adverse events was 42% during cycles 1 to 4, compared to 32% during cycles 5 and 6. No additional safety concerns were reported for patients who received more than 4 cycles of Lu-177-PSMA-617.

The phase 2 TheraP trial compared Lu-177-PSMA-617 (n=99) to cabazitaxel (n=101). Unlike the VISION trial, in TheraP, previous treatment with AR pathway inhibitors was not necessary for participants, and 9.9% of those randomized to the cabazitaxel group and 8.1% of those randomized to Lu-177-PSMA-617 were not previously treated with these therapies. Also, the TheraP trial used 2 PET/CT scans to identify PSMA-positive status and excluded patients with discordant findings using gallium-68-labeled PSMA-11 and 2-fluorine-18[18F] fluoro-2-deoxy-D-glucose (FDG). The primary endpoint of PSA response, defined by a reduction of at least 50% from baseline, was achieved more often by patients who received Lu-177-PSMA-617 (66%) versus cabazitaxel (37%), resulting in a between-group difference of 29% (95% confidence interval [CI], 16 to 42; $p<.0001$). Lu-177-PSMA-617 also delayed rPFS and PSA PFS (defined as the interval from randomization to first evidence of PSA progression; defined by an increase of $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks).

In a subsequent publication of the TheraP trial, after a median follow-up of 35.7 months (IQR, 31.1 to 39.2), 77 (78%) participants in the Lu-177-PSMA-617 group and 70 (69%) in the cabazitaxel group had

died. The OS was similar between groups (restricted mean survival time [RMST] 19.1 vs. 19.6 months; difference, -0.5 months; 95% CI, -3.7 to 2.7; p=.77). No new safety signals were identified.

Table 4: Summary of Key RCT Characteristics

Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Sartor (2021); VISION	North America and EU	84 (52 in North America and 32 in EU)	June 2018 to October 2019	PSMA-positive mCRPC (≥ 1 metastatic lesion) previously treated with ≥ 1 AR pathway inhibitor and ≤ 2 taxane regimens (mean age, 71 years; $\geq 88\%$ White men)	n=551; Lu-177-PSMA-617 (7.4 GBq) administered by IV infusion every 6 weeks for a max of 6 cycles) plus investigator-chosen SOC	n=280; investigator-chosen SOC
Hofman (2021); TheraP ¹	Australia	11	February 2018 to September 2019	PSMA-positive mCRPC previously treated with docetaxel and progressive disease defined by a rising PSA as per Prostate Cancer Working Group 3 criteria	n=99; Lu-177-PSMA-617 administered by IV infusion every 6 weeks for a max of 6 cycles); starting dose was 8.5 GBq, and was decreased by 0.5 GBq/cycle	n=101; cabazitaxel 20 mg/m ² IV, every 3 weeks for a max of 10 cycles

AR: androgen receptor; EU: European Union; IV: intravenous; mCRPC: metastatic castration-resistant prostate cancer; Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; RCT: randomized controlled trial; SOC: standard of care.

The results of these trials are summarized in the table below. Importantly, for the outcome of rPFS, similar results were found in an ad hoc analysis that included all the patients who had undergone randomization.

Table 5: Summary of Key RCT Results

Study	OS (months)	rPFS^a (months)	PSA PFS^b	PSA response^c , %	Grade ≥3 adverse event, %
Sartor (2021); VISION	Lu-177-PSMA-617 plus SOC (n=551); SOC (n=280)	Lu-177-PSMA-617 plus SOC (n=385); SOC (n=196)			Lu-177-PSMA-617 plus SOC (n=529); SOC (n=205)
Lu-177-PSMA-617 plus SOC	15.3	8.7			52.7
SOC	11.3	3.4			38.0
HR (CI); p-value	0.62 (95% CI, 0.52 to 0.74); <.001	0.40 (99.2% CI, 0.29 to 0.57); <.001			NR
Hofman (2021); TheraP	Lu-177-PSMA-617 (n=99); cabazitaxel (n=101)				
Lu-177-PSMA-617				66	33
Cabazitaxel				37	53
Treatment difference (CI); p-value		HR, 0.64 (0.46 to 0.88); =.007	HR, 0.60 (0.44 to 0.83); =.0017	Difference, 29 (16 to 42); <.0001	NR

CI: confidence interval; HR: hazard ratio; Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; NR: not reported; OS: overall survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; RCT: randomized controlled trial; SOC: standard of care.

^aOnly includes data from patients randomized on or after March 5th, 2019, when rPFS was upgraded to an alternate primary outcome.

^bPSA PFS was defined as the interval from randomization to first evidence of PSA progression, defined by an increase of ≥25% and ≥2 ng/mL after 12 weeks.

^cPSA response was defined by a reduction of ≥50% from baseline.

The purpose of the study limitations tables is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 6: Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Sartor (2021); VISION	4. Majority (≥88%) White men	1. Non-standardized protocol for SOC therapies; SOC treatments could not include chemotherapy or radium-233 5. PSMA-positive status was determined using gallium Ga 68 gozetotide exclusively	1. Non-standardized protocol for SOC therapies; SOC treatments could not include chemotherapy or radium-233	7. rPFS was upgraded to an alternate primary outcome after the trial was already underway	
Hofman (2021); TheraP	3. Not all enrolled patients (9.9% in cabazitaxel group and 8.1% in Lu-177-PSMA-617 group) were not previously treated with AR pathway inhibitors	5. PSMA-positive status was determined using both gallium Ga 68 gozetotide and FDG		1. Primary outcome focused on PSA response	

AR: androgen receptor; FDG: 2-fluorine-18[18F]fluoro-2-deoxy-D-glucose; Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; PSA: prostate specific antigen; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SOC: standard of care.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 7: Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Sartor (2021); VISION		1, 2; Open-label		7; Adverse events were measured only up to 30 days after the last dose of treatment		

Hofman (2021); TheraP		1, 2; Open-label				
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The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

As previously noted, the RESIST-PC trial compared 2 Lu-177-PSMA-617 dosing regimens (6.0 GBq and 7.4 GBq) in patients with progressive mCRPC who previously received therapy with at least 1 AR pathway inhibitor and were either chemotherapy naïve or postchemotherapy. The study took place at a single site in the US and included 51 patients. After a median follow-up of 24.8 months, improvement in bone pain occurred in 12 of 18 patients (67%) in the overall cohort, 6 of 7 patients (86%) in the 6.0 GBq dosing group, and 6 of 11 patients (55%) in the 7.4 GBq dosing group ($p=.31$). Pain PFS was 8.2 months (95% CI, 3.9 to 12.5), 5.4 months (95% CI, not reached), and 8.2 months (95% CI, 2.3 to 14.1) in the overall study population, 6.0 GBq dosing group, and 7.4 GBq dosing group, respectively ($p=.94$).

Taxane-Naïve Patients The indication for Lu-177-PSMA-617 was expanded in 2025 to include individuals with PSMA-positive mCRPC who have been treated with AR pathway inhibition and are considered appropriate to delay taxane-based chemotherapy. Trials focused on that patient population are described below, with a summary of RCT characteristics in Table 8.

Randomized Controlled Trials

The PSMAfore trial, a phase 3 RCT comparing Lu-177-PSMA-617 to AR pathway inhibition in taxane-naïve patients with mCRPC who had progressed on a previous AR pathway inhibition agent, had primary and updated results published by Morris et al (2024). This open-label trial randomized patients 1:1 to Lu-177-PSMA-617 or a different AR pathway inhibitor. Crossover from the AR pathway inhibitor group to Lu-177-PSMA-617 was allowed after radiographic progression. Of the patients initially assigned to AR pathway inhibitor change, 134 (57%) eventually crossed over to receive Lu-177-PSMA-617. The primary endpoint was rPFS. The primary analysis was defined as the median time from randomization to first data cutoff of 7.26 months (IQR, 3.38 to 10.55). The updated analysis was defined as the median time from randomization to third data cutoff at 24.11 months (IQR, 20.24 to 27.40). In both the primary and updated analysis, treatment with Lu-177-PSMA-617 prolonged rPFS compared to change in AR pathway inhibitor. There was no significant difference in OS between groups at the updated analysis and grade ≥ 3 adverse events were similar between groups. The results of this trial are summarized in Table 9.

The final overall survival analysis of the PSMAfore trial was published by Fizazi et al (2025). The median OS was 24.48 months with Lu-177-PSMA-617 versus 23.13 months with AR pathway inhibitor change (hazard ratio [HR], 0.91; 95% CI, 0.72 to 1.14; $p=.20$). Notably, results were likely confounded due to high rate of crossover. Dry mouth and anemia were more common with Lu-177-PSMA-617 than with change in AR pathway inhibitor and no new safety signals were identified.

Table 8. Summary of Key RCT Characteristics in Taxane-Naïve Patients

Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Morris (2024); PSMAfore	EU and North America	74 (25 in North America and 49 in EU)	June 2021 to October 2022	PSMA-positive mCRPC (≥ 1 metastatic lesion) who were taxane-naive and had progressed on a previous AR pathway inhibitor (median age, 71 years; 91% White)	n=234; Lu-177-PSMA-617 (7.4 GBq administered by IV infusion every 6 weeks for a max of 6 cycles) plus investigator-chosen SOC	n=234; change of AR pathway inhibitor (to abiraterone or enzalutamide, administered orally on a continuous basis per product labeling) plus investigator-chosen SOC; 134 (57%) eventually crossed over to receive Lu-177-PSMA-617

AR: androgen receptor; EU: European Union; IV: intravenous; mCRPC: metastatic castration-resistant prostate cancer; Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; PSMA: prostate-specific membrane antigen; RCT: randomized controlled trial; SOC: standard of care.

Table 9. Summary of Key RCT Results in Taxane-Naive Patients

Study	rPFS (months)	OS (months)	PSA response ^a , %	Grade ≥ 3 adverse event, %
Morris (2024); PSMAfore				
Primary analysis (7.26 months)				
Lu-177-PSMA-617	9.3	NR	NR	NR
AR pathway inhibitor change	5.5	NR	NR	NR
HR (95% CI); p-value	0.41 (0.29 to 0.56); <.0001	NR	NR	NR
Updated analysis (24.11 months)				
Lu-177-PSMA-617	11.6	23.66	51% (110/217)	36% (at least 1 event in 81 of 227 patients); 4 (2%) grade 5 (none treatment related)
AR pathway inhibitor change	5.59	23.84	17% (39/225)	48% (112 of 232 patients); 5 (2%) grade 5 (1 treatment related)
HR (95% CI); p-value	0.49 (0.39 to 0.61)	0.98 (0.75 to 1.28); p=.44	NR	NR

CI: confidence interval; HR: hazard ratio; Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; NR: not reported; OS: overall survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; RCT: randomized controlled trial.
^aPSA response was defined by a reduction of $\geq 50\%$ from baseline.

The purpose of the study limitations tables (Tables 10 and 11) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 10. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Morris (2024); PSMAfore	4. Majority (91%) White 5. Results not generalizable to a population with a more aggressive disease for whom taxane-therapy would be most appropriate; did not assess efficacy in patients based on gene alterations	5. PSMA-positive status was determined using gallium Ga 68-PSMA-11 exclusively			

PSMA: prostate-specific membrane antigen.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 11. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Morris (2024); PSMAfore		1, 2. Open-label	4. Manufacturer involved in all aspects of study analysis	7. Adverse events were measured only up to 30 days after the last dose of treatment		5. Confounding likely due to high crossover

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Prostate-Specific Membrane Antigen–Positive Metastatic Castration-Resistant Prostate Cancer

For individuals with PSMA-positive mCRPC who have failed other anticancer therapies, including AR pathway inhibition and taxane-based chemotherapy, who receive Lu-177-PSMA-617, the evidence includes a systematic review and 2 RCTs. The systematic review, which included a heterogeneous population of patients with mCRPC, demonstrated a higher proportion of patients responding to PSMA-targeted radionucleotide therapy based on a PSA decrease of $\geq 50\%$ compared to controls; the review was also limited by the inclusion of mostly retrospective studies with small numbers of patients. The VISION RCT compared Lu-177-PSMA-617 plus investigator-determined SOC to SOC alone in patients with PSMA-positive mCRPC who had been treated with AR pathway inhibitors and taxane-based chemotherapy. Results demonstrated that Lu-177-PSMA-617 plus SOC significantly prolonged the median OS (15.3 vs. 11.3 months) and rPFS (8.7 vs. 3.4 months) compared to SOC alone. The incidence of Grade 3 or higher adverse events was greater with Lu-177-PSMA-617 than without (52.7% vs. 38.0%). The phase 2 TheraP trial compared Lu-177-PSMA-617 to cabazitaxel. Unlike the VISION trial, in TheraP, previous treatment with AR pathway inhibitors was not necessary for participants. Also, the TheraP trial used 2 PET/CT scans to identify PSMA-positive status and excluded patients with discordant findings using gallium-68-labeled PSMA-11 and FDG. The primary endpoint of PSA response, defined by a reduction of at least 50% from baseline, was achieved more often by patients who received Lu-177-PSMA-617 (66%) compared to cabazitaxel (37%). In this RCT, the incidence of Grade 3 or higher adverse events was greater with cabazitaxel (53%) compared to Lu-177-PSMA-617 (33%). In a subsequent publication of this trial with a median follow-up of 35.7 months, the OS did not differ between treatment groups (19.1 vs. 19.6 months). Additional evidence has been published that supports the use of Lu-177-PSMA-617 in patients who are taxane-naïve (and not yet with advanced enough illness to require a taxane) and have progressed on AR pathway inhibition. The PSMAfore trial demonstrated that treatment with Lu-177-PSMA-617 prolonged rPFS compared to switching to a different AR pathway inhibitor.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) guideline on systemic therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) was updated in May 2025. Relevant recommendations regarding lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617) are below:

"For patients previously treated with ADT [androgen-deprivation therapy], ARPI [androgen receptor pathway inhibition], and docetaxel, and have progressive mCRPC, the Panel recommends Lu-177-

PSMA-617 for PSMA [prostate-specific membrane antigen]-positive disease or chemotherapy using cabazitaxel (evidence quality: moderate; strength of recommendation: strong)."

The Panel also states that "currently, the role of PSMA PET [positron emission tomography]-CT [computed tomography] is limited to identify PSMA-expressing tumors for patients who will benefit with Lu-177-PSMA-617. In selected patients, PSMA PET can be used to stage patients with a rising PSA [prostate-specific antigen] and concern for progression not visualized on conventional imaging. Prospective data on using PSMA PET scans for response assessment are still emerging, and at this time, the Panel does not recommend their routine use."

In 2023, ASCO published a rapid recommendation update related to Lu-177-PSMA-617 based on the Food and Drug Administration (FDA) approval of F-18 flutemetastat. Their updated recommendation stated:

"The panel recommends that either Ga-68 PSMA-11, F-18 piflumetastat, or F-18 flutemetastat be used as radiotracers to determine eligibility currently (type: informal consensus, benefits outweigh harms; evidence quality: low; strength of recommendation: weak)."

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) guideline for Prostate Cancer (v 3.2026) provides the following relevant recommendations with regard to the use of lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617):

" The NCCN Panel recommends Lu-177-PSMA-617 as a treatment option for patients with one or more PSMA-positive lesion and/or metastatic disease that is predominantly PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with an ARPI and a taxane-based chemotherapy (category 1) or who have prior ARPI therapy and are considered appropriate to delay taxane-based chemotherapy PSMA-negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components ≥ 1.0 cm, lymph nodes ≥ 2.5 cm in short axis, and solid organ metastases ≥ 1.0 cm in size. The Panel notes that Ga-68 PSMA-11, F-18 piflumetastat PSMA, or F-18 flutemetastat PSMA can be used to identify patients eligible for treatment with Lu-177-PSMA-617."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

REFERENCES

1. Prostate Cancer. American Cancer Society. <https://www.cancer.org/cancer/prostate-cancer.html> Accessed December 4, 2025.
2. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep. Mar 1966; 50(3): 125-8. PMID 5948714
3. SEER Inquiry System. SEER Database. <https://seer.cancer.gov/seerinqury/index.php?page=view&id=20170036&type=q> Accessed December 4, 2025.

4. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. Sep 16 2021; 385(12): 1091-1103. PMID 34161051
5. Pluvicto [package insert]. Advanced Accelerator Applications USA, Inc; 2025.
6. Locametz [package insert]. Advanced Accelerator Applications USA, Inc; 2025.
7. Pylarify [package insert]. Progenics Pharmaceuticals, Inc.; 2025.
8. Illuccix [package insert]. Telix Pharmaceuticals US, Inc.; 2024.
9. Sadaghiani MS, Sheikhabahei S, Werner RA, et al. 177 Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review and meta-analysis. *Prostate*. May 2022; 82(7): 826-835. PMID 35286735
10. Hofman MS, Emmett L, Sandhu S, et al. [177 Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*. Feb 27 2021; 397(10276): 797-804. PMID 33581798
11. Calais J, Gafita A, Eiber M, et al. Prospective phase 2 trial of PSMA-targeted molecular Radiotherapy with 177 Lu-PSMA-617 for metastatic castration-resistant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort. *J Nucl Med*. Oct 2021; 62(10): 1440-1446. PMID 34016732
12. Chi KN, Armstrong AJ, Krause BJ, et al. Safety Analyses of the Phase 3 VISION Trial of [177 Lu]Lu-PSMA-617 in Patients with Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. Apr 2024; 85(4): 382-391. PMID 38185538
13. Hofman MS, Emmett L, Sandhu S, et al. Overall survival with [177 Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. *Lancet Oncol*. Jan 2024; 25(1): 99-107. PMID 38043558
14. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer (version 3.2026). www.nccn.org/professionals/physician_gls/pdf/prostate.pdf NCCN. Accessed December 4, 2025.
15. Lowrance W, Dreicer R, Farrard DF, et al. Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). *Journal of Urology*. Volume 209, Issue 6. June 2023. Available at: www.auajournals.org/journal/juro .
16. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.
17. National Institute for Health and Care Excellence. Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone relapsed metastatic prostate cancer after 2 or more treatments. November 15, 2023. Available at: www.nice.org.uk/guidance/ta930 . Accessed December 4, 2025.
18. Garje R, Rumble BR, Parikh RA, et al. Systemic Therapy Update on 177Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer: ASCO Rapid Recommendation. *JCO* 40, 3664-3666(2022). DOI:10.1200/JCO.22.01865.
19. Hayes, a symplr company. Clinical Research Response. Lutetium Lu 177 Vipivotide Tetraxetan (Pluvicto; Novartis Pharmaceuticals Corp.) for Metastatic Castrate-Resistant Prostate Cancer. Hayes, Inc. January 29, 2024. Available at: www.hayesinc.com Accessed December 2, 2025.

20. UpToDate. Dawson NA, Leger P, Lee RW et al. Overview of the treatment of castration-resistant prostate cancer (CRPC). Review current through November 2025. Last updated July 17, 2025. Available at: www.uptodate.com . Accessed December 2025.
21. Belabaci Z, Sleiy M, Abdelshafi A, et al. Safety and Efficacy of Lutetium-177 PSMA Therapy for Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Genitourin Cancer. Oct 2025; 23(5): 102398. PMID 40737767
22. Emmett L, Subramaniam S, Crumbaker M, et al. Overall survival and quality of life with [177 Lu]Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. Mar 2025; 26(3): 291-299. PMID 39956124
23. Emmett L, Subramaniam S, Crumbaker M, et al. [177 Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. May 2024; 25(5): 563-571. PMID 38621400
24. Satapathy S, Mittal BR, Sood A, et al. 177 Lu-PSMA-617 versus docetaxel in chemotherapy-naïve metastatic castration-resistant prostate cancer: a randomized, controlled, phase 2 non-inferiority trial. Eur J Nucl Med Mol Imaging. Apr 2022; 49(5): 1754-1764. PMID 34842950
25. Satapathy S, Mittal BR, Sood A, et al. [177 Lu]Lu-PSMA-617 Versus Docetaxel in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer: Final Survival Analysis of a Phase 2 Randomized, Controlled Trial. J Nucl Med. Nov 2023; 64(11): 1726-1729. PMID 37709534
26. Morris MJ, Castellano D, Herrmann K, et al. 177 Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naïve patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. Lancet. Sep 28 2024; 404(10459): 1227-1239. PMID 39293462
27. Fizazi K, Chi KN, Shore ND, et al. Final overall survival and safety analyses of the phase III PSMAfore trial of [177 Lu]Lu-PSMA-617 versus change of androgen receptor pathway inhibitor in taxane-naïve patients with metastatic castration-resistant prostate cancer. Ann Oncol. Jul 17 2025. PMID 40680993
28. Garje R, Riaz IB, Naqvi SAA, et al. Systemic Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer: ASCO Guideline Update. J Clin Oncol. Jul 10 2025; 43(20): 2311-2334. PMID 40315400
29. Garje R, Rumble RB, Parikh RA. Systemic Therapy Update on 177 Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol. Nov 2024; 42(31): 3751-3752. PMID 37931186

CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	No code(s)	
HCPCS		
	A9607	Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 millicurie
Type of Service	Radiological	
Place of Service	Outpatient/ Inpatient	

POLICY HISTORY

Date	Reason	Action
December 2025	Annual Review	Policy Revised
December 2024	Annual Review	Policy Renewed
December 2023	Annual Review	Policy Renewed
March 2023		New Medical Policy

Appendix

Table A1. Comparison of Trials/Studies Included in SR & MA and Evaluating Lu-177-PSMA-617

Study	Sadaghiani et al (2022)	Belabaci et al (2025)
Aghdam, 2019	●	
Ahmadzadehfar, 2016	●	
Ahmadzadehfar, 2017	●	
Ahmadzadehfar, 2017	●	

Study	Sadaghiani et al (2022)	Belabaci et al (2025)
Ahmadzadehfar, 2017	●	
Ahmadzadehfar, 2021	●	
Assadi, 2020	●	
Bräuer, 2017	●	
Calais, 2021	●	
Derlin, 2020	●	
Derlin, 2020	●	
Emmet, 2019	●	
Emmet, 2024		●
Emmet, 2025		●
Fendler, 2016	●	
Ferdinandus, 2016	●	
Fizazi, 2023		●
Gado, 2020	●	
Gafita, 2020	●	
Grubmüller, 2018	●	
Gupta, 2019	●	
Gupta, 2020	●	
Heck, 2018	●	
Heinzel, 2019	●	
Hofman, 2018	●	
Hofman, 2021	●	●
Hofman, 2024		●
Kalmthout, 2019	●	
Kessel, 2019	●	
Khreish, 2021	●	
Khurshid, 2018	●	
Kratochwil, 2016	●	
Leibowitz, 2020	●	

Study	Sadaghiani et al (2022)	Belabaci et al (2025)
Maffey-Steffan, 2019	●	
Marinova, 2020	●	
McBean, 2019	●	
Michalski, 2021	●	
Morris, 2024		●
Paganelli, 2020	●	
Prasad , 2021	●	
Privé, 2021	●	
Rahbar, 2016	●	
Rahbar, 2016	●	
Rahbar, 2017	●	
Rahbar, 2017	●	
Rasul, 2020	●	
Rasul, 2021	●	
Rasul, 2021	●	
Rathke, 2017	●	
Rathke, 2020	●	
Rosasr, 2021	●	
Sartor, 2021	●	●
Sartor, 2024		●
Satapathy, 2022		●
Satapathy, 2023		●
Scarpa , 2017	●	
Seifert, 2020	●	
Suman, 2019	●	
Tatkovic, 2021	●	
Violet, 2020	●	
Völter, 2021	●	
Widjaja, 2021	●	

Study	Sadaghiani et al (2022)	Belabaci et al (2025)
Yadav, 2019	●	
Yordanova, 2019	●	
Yadav, 2021	●	

Lu-177-PSMA-617: lutetium Lu 177 vipivotide tetraxetan; MA: meta-analysis; SR: systematic review.

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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Medical Policy Analyst
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