ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 04 | April - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EVALUATING THE EFFICACY AND SAFETY OF [^{177}LU] LU-PSMA-617 RADIOLIGAND THERAPY IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC): A SYSTEMATIC REVIEW

Oncology

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ABSTRACT

Background: This systematic review evaluates clinical trials assessing LU-PSMA-617, a radioligand therapy targeting the prostate-specific membrane antigen (PSMA) overexpressed on prostate cancer cells. LU-PSMA-617 is a novel treatment for metastatic castrate-resistant prostate cancer (mCRPC) following progression on conventional therapies such as androgen receptor signaling inhibitors, taxanes, and PARP inhibitors. **Methods:** A comprehensive search was performed in PubMed, EMBASE, and Google Scholar to identify clinical trials published in the last four years. Seven key trials were identified, including VISION, TheraP, PSMAfore, UpFront PSMA, LuPSMA Trial (NCT03042312), RESIST PC, and ENZA-P. Data on imaging-based progression-free survival (rPFS), PSA progression-free survival, overall survival (OS), and PSA decline of 50% or more were extracted and compared. **Results:** The VISION and TheraP trials demonstrated significant improvements in overall survival (HR, 0.46; 95% CI: 0.35, 0.61) and PSA response, 29% difference vs. taxanes (95% CI 16–42; p<0.0001) in respective studies. The PSMAfore trial explored the benefit of earlier use in treatment-naïve patients, showing improvements in rPFS (9.30 vs. 5.50 months) and promising quality of life with minimal additional toxicities (HR 0.41 [95% CI 0.29–0.56]; p<0.0001). The LuPSMA Trial established the safety and efficacy profile of LU-PSMA-617, while the RESIST PC and ENZA-P studies provided further evidence of dose-related efficacy and potential synergistic effects when combined with hormonal therapy. **Conclusions:** LU-PSMA-617 benefits mCRPC patients by improving survival endpoints and PSA responses while maintaining a manageable safety profile. Ongoing trials are investigating its use in earlier-stage prostate cancer and in combination with other therapeutic modalities.

KEYWORDS

mCRPC, radioligand therapy, LU-PSMA-617, Pluvicto, clinical trials

INTRODUCTION

Prostate cancer remains one of the most common malignancies in men worldwide, and the development of metastatic castrate-resistant prostate cancer (mCRPC) marks a critical phase of disease progression with limited treatment options (1,2). Traditional therapeutic approaches—such as androgen receptor signaling inhibitors (i.e. enzalutamide (3), apalutamide and Abiraterone (4)), taxanes (i.e. docetaxel(5) and cabazitaxel (6)), PARP inhibitors (i.e. Olaparib (7)), immunotherapy (sipuleucel-T (8)), and bone-targeted radionuclide therapy (radium-223 (9))—have provided clinical benefit; however, a significant proportion of patients eventually progress despite these treatments.

ARPIs are initiated in the early phase of disease. If disease continues to progress despite ARPI treatment, taxanes are recommended second line therapy (10). On March 23, 2022, the FDA approved Pluvicto (lutetium Lu 177 vipivotide tetraxetan, also known as 177Lu-PSMA-617), a targeted radioligand therapy that binds to the prostate-specific membrane antigen (PSMA) expressed on prostate cancer cells (11). It was approved for treating patients with PSMA-positive, progressive metastatic castration-resistant prostate cancer who have previously undergone therapy with both androgen receptor pathway inhibitors and taxane-based chemotherapy. (12,13).

It represents a novel approach that exploits the overexpression of prostate-specific membrane antigen (PSMA) on prostate cancer cells. By conjugating a PSMA-targeting ligand with the beta-emitting radionuclide Lutetium-177, this therapy delivers localized radiation to tumor cells, thereby minimizing systemic toxicity while enhancing antitumor efficacy (14). However, kidneys and bone marrow remain at risk from this therapy. Kidney is affected since urinary excretion is the principal route of elimination and because PSMA is expressed in proximal tubular cells. Bone Marrow is affected by radiation-induced myelosuppression.

This systematic review aims to collate and critically analyze the evidence from recent clinical trials to determine the efficacy and safety of LU-PSMA-617 in the treatment of PSMA-positive mCRPC.

MATERIALS AND METHODS

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards were followed to evaluate and describe an evidence-based minimum set of items for reporting in systematic reviews and meta-analysis (Fig 1).

A systematic literature search was conducted in PubMed, EMBASE, and Google Scholar for clinical trials published over the past four years. The following search strategy was used: ("Prostatic Neoplasms"[Mesh] OR "prostate cancer"[tiab] OR "prostatic carcinoma"[tiab]) AND ("Castration-Resistant"[tiab] OR "metastatic castration-resistant"[tiab] OR "mCRPC"[tiab] OR "hormone-refractory"[tiab]) AND ("radioligand therapy"[tiab] OR "PSMA-targeted therapy"[tiab] OR "177Lu-PSMA"[tiab] OR "lutetium-177"[tiab] OR "Pluvicto"[tiab]). Reference lists of key articles were also reviewed for additional studies.

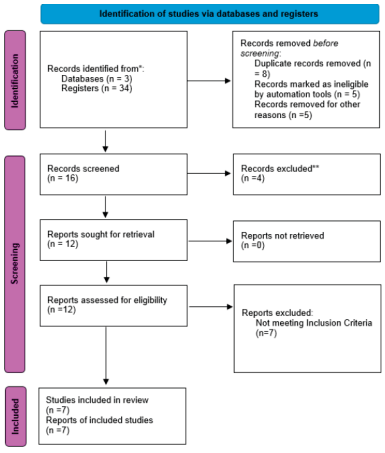

Fig. 1: PRISMA 2020 Flow Diagram for Systematic Reviews and Meta Analysis.

Inclusion and Exclusion Criteria

- **Inclusion Criteria:** Clinical trials (phase II or III) evaluating LU-PSMA-617 in mCRPC patients with confirmed PSMA positivity. PET proven metastatic disease. Studies reporting primary and secondary outcomes such as imaging-based progression-free survival (rPFS), PSA progression-free survival, overall survival (OS), or PSA decline of ≥50%. Trials published within the last four years. Papers published in English language.
- **Exclusion Criteria:** Preclinical studies, reviews, and case reports. Non-English language publications.

Study Selection and Data Extraction

After screening titles and abstracts, seven clinical trials were selected: VISION, TheraP, PSMAfore, UpFront PSMA, LuPSMA Trial (NCT03042312), RESIST PC, and ENZA-P. Data on study design, comparator arms, primary endpoints, and key outcomes were extracted. A PRISMA flow diagram was used to document the study selection process.

Two reviewers (HT and FV) evaluated the following details from finalized papers into a predefined Microsoft Excel sheet; trial name, first author, publication year and country, number of patients, type of study, intervention group and patients in them, comparison group and patients in them, objective imaging response, overall survival (OS), progression-free survival (PFS), toxicity, and number of deaths.

Quality Assessment

Using the Joanna Briggs Institute (JBI) critical appraisal tools, each study was systematically evaluated for potential sources of bias across multiple domains including participant selection, measurement of outcomes, confounding factors, and data analysis. Discrepancies in ratings between reviewers were resolved by consensus.

RESULTS

The seven identified trials collectively enrolled 2,302 patients with mCRPC, evaluating LU PSMA 617 across diverse clinical settings. Key findings are summarized below:

VISION Trial

This Phase III RCT (n=581) compared LU PSMA 617 plus standard of care (SoC) vs SoC alone in heavily pretreated patients. LU PSMA 617 significantly improved imaging-based progression-free survival (median 8.7 vs. 3.4 months; HR 0.40, 99.2% CI 0.29–0.57, p<0.001) and overall survival (median 15.3 vs. 11.3 months; HR 0.62, 95% CI 0.52–0.74, p<0.001). Secondary endpoints, including time to symptomatic skeletal events (HR 0.49–0.50) and quality-of-life metrics, favored the intervention group. Grade ≥3 adverse events (AEs) were more frequent with LU PSMA 617 (52.7% vs. 38.0%), primarily hematologic (thrombocytopenia, anemia) and renal toxicity, though quality of life remained preserved.

TheraP Trial

In this Phase II RCT (n=200), LU PSMA 617 was compared to cabazitaxel. LU PSMA 617 demonstrated superior PSA response rates (66% vs. 37%, p<0.0001) and radiographic/PSA-PFS (HR 0·63; 95% CI 0·46–0·86 p=0·0028) compared to cabazitaxel. Restricted mean survival time (RMST) was comparable (19.1 vs. 19.6 months). Overall grade 3-4 adverse events were seen less in LUPSMA group (33% vs 53%). Individually speaking, grade 3-4 thrombocytopenia was higher in LU PSMA 617 (11% vs. 0%), while cabazitaxel showed more neutropenia (13% vs. 4%) and febrile neutropenia (0% vs 8). Deterioration-free survival for global health status at 6 months was better for men randomly assigned to [^{177}Lu] Lu-PSMA-617 (29% [95% CI 21–38] vs 13% [7–21].

PSMAfore Trial

This Phase III trial (n=468) evaluated LU PSMA 617 versus androgen receptor pathway inhibitor (ARPI) switch in taxane-naïve patients. LU PSMA 617 doubled median rPFS (12.02 vs. 5.59 months; HR 0.41, 95% CI 0.29–0.56, p<0.0001) and delayed PSA progression, though OS data were comparable and not statistically significant. Incidence of grade 3–5 adverse events was lower in the Lu-PSMA-617 group (36% vs 48%). According to this study, patients with PSMA-positive mCRPC who have progressed on a prior ARPI, transitioning to ^{177}Lu-PSMA-617 may offer a promising alternative treatment option.

RESIST PC Trial

This Phase III study (n=831) compared 177Lu-PSMA-617 plus protocol-permitted standard care versus standard care alone. 177Lu-PSMA-617 plus standard care extended imaging-based PFS (median 8.7 vs. 3.4 months; HR 0.40 [99.2% CI, 0.29–0.57; P<0.001]) and overall survival (median 15.3 vs. 11.3 months; HR 0.62 [95% CI, 0.52–0.74; P<0.001]) versus standard care alone, with all key secondary endpoints favoring 177Lu-PSMA-617; despite more grade ≥3 adverse events (52.7% vs. 38.0%), quality of life was maintained.

LuPSMA Trial

An early Phase II single-arm study (n=30) established LU PSMA. Among 30 patients—87% with prior chemotherapy (80% docetaxel, 47% cabazitaxel) and 83% with prior abiraterone/ enzalutamide—administered a mean of 7.5 GBq per cycle, 57% achieved a ≥50% PSA decline (95% CI 37–75) with no treatment-related deaths. Common toxicities included grade 1 dry mouth (87%), grade 1–2 nausea (50%) and fatigue (50%), with 13% experiencing grade 3–4 thrombocytopenia.

ENZA-P Trial

This Phase II RCT (n=162) combined LU PSMA 617 in combination with enzalutamide versus enzalutamide alone. Median PSA progression-free survival was 13.0 months (95% CI 11.0–17.0) in the combination arm versus 7.8 months (95% CI 4.3–11.0) with enzalutamide alone (HR 0.43, 95% CI 0.29–0.63, p<0.0001). Common all-grade adverse events in the combination group were fatigue (75%), nausea (47%), and dry mouth (40%), compared to fatigue (70%), nausea (27%), and constipation (23%) with enzalutamide alone. Grade 3–5 events occurred in 40% versus 41% of patients, with only the combination arm reporting grade 3 anemia (4%) and decreased platelets (1%); no treatment-related grade 4 or 5 events were observed.

UpFront PSMA Trial

An ongoing Phase II study (n=130) is evaluating LU PSMA 617 with docetaxel versus docetaxel alone. PSMA-617 plus docetaxel group had undetectable PSA at 48 weeks compared with 16% in the docetaxel alone group (OR 3·88, 95% CI 1·61–9·38; p=0·0020). In patients treated with [^{177}Lu] Lu-PSMA-617 plus docetaxel, grade 3–4 events were febrile neutropenia (11%) and diarrhoea (6%), versus 10% and none, respectively, in the docetaxel group. Serious events occurred in 25% of both groups, with no treatment-related deaths. In de novo high-volume metastatic hormone-sensitive prostate cancer, sequential [^{177}Lu] Lu-PSMA-617 and docetaxel yielded superior antitumor activity versus docetaxel alone without extra toxicity.

Table 1: Study Baseline Characteristics

Study Title	First Author	Year Pubished	Duration of Study	Country of Study	No. of Patients
VISION	Fizazi et al.	June 1st, 2024	June 4, 2018 - October 23, 2019	University of Paris Saclay, Villejuif, France	581
TheraP	Hofman et al	Feruary 11th, 2021	Feb 6, 2018, and Sept 3, 2019	Australia	200
PSMAfore	Morris et al.	September 15th, 2024	June 15, 2021 and Oct 7, 2022	Europe 80% and North America 20%	468
UpFront PSMA	Azad et al.	September 15th, 2024	May 5, 2020, and April 18, 2023	Australian	130
RESIST PC –	Sartor et al.	September 16th, 2024	June 2018 to mid-October 2019	North America and Europe	831
Lu PSMA	Hofman et al.	May 8th, 2018	Aug 26, 2015, and Dec 8, 2016	Australia	30
ENZA-P	Emmett et al.	April 12th, 2024	Aug 17, 2020, and July 26, 2022	Australia	162

Table 2: Overview of Study Type, Intervention and Comparison Group

Study Title	Intervention Group	Comparison Group/ Control Group	Type of Study	Primary Endpoint	Cycles of Treatment
VISION	177Lu-PSMA-617 7·4 GBq (200 mCi) plus SoC (385)	Standard Care Alone (196)	Phase III, RCT	Imaging-based PFS; Overall survival	Q 6 weeks for 4 cycles.
TheraP	[^{177}Lu] Lu-PSMA-617	Cabazitaxel	Phase II, RCT	PSA response rate; Radiographic or PSA progression-free survival	Q6 weeks for 5 cycles
PSMA fore	^{177}Lu-PSMA-617 (234)	Androgen receptor pathway inhibitors (ARPI) (234)	Phase III, RCT	rPFS: 12.02 vs. 5.59 months; 59% risk reduction in radiographic progression or death	Q6 weekly for Six cycles
Up-Front PSMA	^{177}Lu-PSMA-617 + Docetaxel (63)	Docetaxel alone (67)	Phase II, RCT	Ongoing – endpoints include PSA response and PFS. Undetectable PSA (<0.2 ng/mL) at 48 weeks after treatment initiation	Two cycles of [^{177}Lu] Lu-PSMA-617 (7.5 GBq every 6 weeks), followed by six cycles of docetaxel (75 mg/m² every 3 weeks).
RESIST PC –	177Lu-PSMA-617 plus protocol-permitted standard care	Standard care alone	Phase III, Prospective	Imaging-Based Progression-Free Survival (PFS), Overall Survival(OS)	4 to 6 cycles Q6 weekly
Lu PSMA	[^{177}Lu]-PSMA-617	N/A	Phase II, Single arm	57% of patients showed a decline in PSA of ≥50%	4 cycles of intravenous [^{177}Lu]-PSMA-617 Q6 weekly intervals.
ENZA-P	enzalutamide plus [177Lu] Lu-PSMA-617 group	Enzalutamide alone	Phase II, RCT	Prostate-Specific Antigen (PSA) Progression-Free Survival (PFS)	Lu-PSMA-617: Intravenous 7.5 GBq doses Q6 weekly + Enzalutamide: 160 mg orally daily

Table 3: Overview of PFS, OS, Reduction in PSA and Adverse Events Across 7 Studies

Study Title	Progression free survival	Overall Survival	PSA reduction of 50% or more	Adverse Events
VISION (15)	8.7 vs. 3.4 months	15.3 vs. 11.3 months	N/A	Grade ≥3 adverse events (AEs) more frequent with LU PSMA 617 (52.7% vs. 38.0%)
TheraP (16)	5.1 months [HR: 0.63 (95% CI 0.46–0.86), p=0.0028]	N/A	66% (experimental) vs. 37% (control), p<0.0001	Lu-PSMA-617 had lower rates of grade 3–4 adverse events 33% vs 53%
PSMA-fore (17)	12.02 vs. 5.59 months; HR 0.41, 95% CI 0.29–0.56, p<0.0001	23.36 months Not Significant; p 0.44	51% experimental group vs 17% in control group	Grade 3–5 adverse events was lower in the Lu-PSMA-617 group (36% vs 48%)
Up-Front PSMA (18)	31 months vs 20 months (95% CI 14–23) (HR 0.60; p=0.039)	N/S	41% (experimental) vs. 16% (control) (OR 3.88; p=0.002).	Febrile neutropenia: 11% (experimental) vs. 10% (control), Diarrhea: 6% (experimental) vs. 0% (control), Serious adverse events: 25% in both groups. No treatment-related deaths.
RESIST PC (19)	8.7 months vs 3.4 months [HR 0.40 (p < 0.001)]	15.3 months vs 11.3 months [HR 0.62 (p < 0.001)]	Higher in the LuPSMA group (Number not stated)	Grade ≥3 Adverse Events: Fatigue (5.9%); Anemia (12.9%); Thrombocytopenia (7.9%)
Lu PSMA (20)	7.6 months	13.5 months	57% (experimental); No control	Serious (Grade 3-4): Thrombocytopenia: 13%; Anemia: 13%; Neutropenia: 7%; Lymphocytopenia: 43%
ENZA-P (21)	13.0 months vs 7.8 months	N/A	93% (experimental) vs 68% (control)	Grade 3-5 adverse events: 40% versus 41%, with only the combination arm reporting grade 3 anemia (4%) and decreased platelets (1%)

DISCUSSION

The collective findings from recent clinical trials evaluating [^{177}Lu] Lu-PSMA-617 shows its transformative potential across diverse stages of prostate cancer, from metastatic castration-resistant prostate cancer (mCRPC) to hormone-sensitive disease. These studies highlight consistent improvements in progression-free survival (PFS), robust PSA responses, and a manageable safety profile, positioning [^{177}Lu] Lu-PSMA-617 as a cornerstone in the evolving therapeutic landscape.

In heavily pretreated mCRPC populations, the VISION (15) and RESIST-PC (19) trials demonstrated that [^{177}Lu]Lu-PSMA-617 plus standard of care (SoC) significantly extended imaging-based PFS (median 8.7 vs. 3.4 months; HR 0.40) and overall survival (OS; median 15.3 vs. 11.3 months; HR 0.62) (Table 3). These benefits were accompanied by delayed symptomatic skeletal events and preserved quality of life (QoL), despite higher rates of grade ≥3 hematologic toxicities. Notably, the TheraP (16)trial further validated [^{177}Lu]Lu-PSMA-617's superiority over cabazitaxel in PSA response (66% vs. 37%) and radiographic/PSA-PFS (HR 0.63), with fewer grade 3–4 adverse events (33% vs. 53%), emphasizing its role as a safer alternative in taxane-exposed patients.

In earlier disease settings, the PSMAfore (17) trial expanded indications to taxane-naïve mCRPC, where [^{177}Lu]Lu-PSMA-617 doubled median radiographic PFS (12.0 vs. 5.6 months; HR 0.41) compared to ARPI switching. While OS data were confounded by high crossover rates (57%), the marked delay in progression and PSA decline (51% vs. 17%) suggest [^{177}Lu] Lu-PSMA-617 could redefine second-line therapy, particularly for patients seeking to defer chemotherapy. Similarly, the ENZA-P (21) trial demonstrated synergy

with enzalutamide, nearly doubling median PSA-PFS (13.0 vs. 7.8 months; HR 0.43), supporting combinatorial strategies in ARPI-sensitive cohorts.

The UpFront PSMA (18) trial extended these benefits to metastatic hormone-sensitive prostate cancer (mHSPC), where sequential [^{177}Lu]Lu-PSMA-617 and docetaxel achieved undetectable PSA in 41% of patients at 48 weeks (vs. 16% with docetaxel alone), alongside improved PFS (31 vs. 20 months; HR 0.60). This suggests that early integration of radioligand therapy may enhance tumor debulking and delay castration resistance without additive toxicity, a paradigm shift supported by ongoing Phase III trials.

Despite hematologic toxicities (e.g., thrombocytopenia, anemia) being a class effect of [^{177}Lu] Lu-PSMA-617, its safety profile remains favorable compared to chemotherapy. The TheraP trial reported lower grade 3–4 adverse events (33% vs. 53% with cabazitaxel), while PSMAfore noted fewer severe events with [^{177}Lu] Lu-PSMA-617 than ARPI switching (36% vs. 48%). Notably, non-hematologic toxicities such as dry mouth and fatigue were predominantly low-grade and transient, with no treatment-related deaths reported in LuPSMA or ENZA-P. These findings underscore that [^{177}Lu] Lu-PSMA-617's toxicity burden is both predictable and manageable, particularly when weighed against its clinical benefits.

The consistent PFS and PSA response advantages across trials support [^{177}Lu] Lu-PSMA-617 as a first-choice therapy in PSMA-positive mCRPC, particularly after ARPI failure. However, key certain questions still need to be answered: While PSMAfore highlights efficacy in taxane-naïve patients, the OS impact of crossover and delayed taxane use requires further exploration. The LuPSMA trial's 57% PSA response rate in a heterogeneous population underscores the need for predictive biomarkers (e.g., PSMA expression thresholds, genomic alterations) to refine patient selection. The ENZA-P and UpFront PSMA trials suggest synergy with hormonal agents and chemotherapies, warranting Phase III validation to optimize multimodal regimens.

Limitations and Future Directions

While these trials are practice-changing, limitations include crossover effects (e.g., PSMAfore), heterogeneous PSMA imaging criteria, and immature OS data in earlier-line settings. Additionally, real-world studies are needed to assess long-term renal safety and therapy-related myeloid neoplasms. Future research should prioritize: Head-to-head comparisons with novel agents (e.g., PARP inhibitors, immunotherapy). Integration of artificial intelligence for PSMA PET quantification. Exploration of [^{177}Lu] Lu-PSMA-617 in oligometastatic or localized disease.

CONCLUSION

Collectively, these trials position [^{177}Lu] Lu-PSMA-617 as a versatile therapeutic agent with efficacy spanning mCRPC to mHSPC. Its ability to delay progression, improve QoL, and offer a favorable toxicity profile underscores its transformative role in precision oncology. As ongoing studies address sequencing and combination strategies, [^{177}Lu] Lu-PSMA-617 is poised to become a backbone therapy in prostate cancer, reshaping treatment paradigms for years to come.

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