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Pluvicto™

(lutetium Lu 177 vipivotide tetraxetan)

The latest evidence on drug efficacy & recommendations.

InpharmD™

UPDATED AUGUST 2022

OVERVIEW

REGIMEN

Generic Name	Lutetium Lu 177 vipivotide tetraxetan
Trade Name	Pluvicto™
Manufacturer	Advanced Accelerator Applications USA, Inc (A Novartis company)
FDA Approval	Mar 23, 2022
Dosage	Administer 7.4 GBq (200 mCi) IV every 6 weeks for up to 6 doses
Therapeutic Class	Radiopharmaceutical

Indications

Prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

PHARMACOLOGY

Lutetium Lu 177 vipivotide tetraxetan is a radioligand therapeutic agent. The active moiety of lutetium Lu 177 vipivotide tetraxetan is the radionuclide lutetium-177 which is linked to a moiety that binds to PSMA, a transmembrane protein that is expressed in prostate cancer, including mCRPC. Upon binding of lutetium Lu 177 vipivotide tetraxetan 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.

PHARMACODYNAMICS

Lutetium Lu 177 vipivotide tetraxetan exposure-efficacy relationships and the time course of pharmacodynamic response have not been fully characterized.

PHARMACOKINETICS

Absorption

At the recommended dosage:

- AUC: 52.3 ng.h/mL
- Maximum blood concentration: 6.58 ng/mL
- Time to peak: within 2.5 hours of administration, lutetium Lu 177 vipivotide tetraxetan distributes to gastrointestinal tract, liver, lungs, kidneys, heart wall, bone marrow, and salivary glands.

Distribution

V_d:123 L

Plasma protein binding: 60% to 70% bound

Metabolism

Not provided

Excretion

Primarily renally eliminated; clearance (CL): 2.04 L/h

Half-Life

$t_{1/2}$: 41.6 hours

CLINICAL DATA OVERVIEW

n = 30 • Hofman MS, Violet J, Hicks RJ, et al. • Single-center, single-arm, phase 2 study

[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-center, single-arm, phase 2 study.

STUDY DESIGN

To investigate the safety, efficacy, and effect on the quality of life of [^{177}Lu]Lu-PSMA617 in men with metastatic castration-resistant prostate cancer who progressed after standard treatments

Study population (N= 30)

METHODS

Inclusion criteria: Men, age ≥ 18 years, confirmed metastatic castration-resistant prostate cancer with progressive disease after standard treatment, Eastern Cooperative Oncology Group (ECOG) performance status score 2 or less, life expectancy > 12 weeks

Intervention: Patients were given up to 4 cycles of [^{177}Lu]Lu-PSMA-617 on an every 6 week schedule, with radioactivity adjusted from 6 GBq based on tumor burden, patient weight, and renal function

Primary outcome: Prostate specific antigen (PSA) response rate (decline ≥ 50% from baseline), radiological response up to 3 months after completion of therapy, quality of life based on global health scores

Secondary/safety outcomes: Overall survival, progression-free survival, adverse events

RESULTS

Primary outcome: PSA response (decline ≥ 50% from baseline) was achieved in 17 (57%) of patients. Radiological response of nodal or visceral disease up to 3 months after completion of therapy was seen in 82% of patients who had measurable baseline disease on imaging. An improvement in global health scores of 10 points or more was experienced by 37% of patients by the second cycle of treatment

Secondary outcomes: Median overall survival was 13.5 months and median progress-free survival was 7.6 months

Safety outcomes: Most common adverse events were grade 1 dry mouth (87% of patients), grade 1 and 2 fatigue (50%), grade 1 and 2 transient nausea (50%), and grade 3/4 thrombocytopenia was observed in 13% of patients

CONCLUSIONS

Authors' conclusions: The authors showed in a prospective study that in men with metastatic castration-resistant PSMA-acid prostate cancer who have progressed after standard treatments, LuPSMA resulted in high responses, a low toxicity profile, and improves quality-of-life parameters, especially in men with pain.

Critique: This preliminary data was the basis for a larger, multicenter randomized trial comparing LuPSMA with cabazitaxel chemotherapy. Based on selection criteria, patients with an unfavorable diagnosis at baseline may have been excluded. Additionally, the lack of a comparator group limits a proper assessment of treatment effect with LuPSMA.

n = 200 • Hofman MS, Emmett L, Sandhu S, et al. • Multicenter, unblinded, randomized, phase 2 trial

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomized, open-label, phase 2 trial

STUDY DESIGN

To compare [^{177}Lu]Lu-PSMA-617 (Lu) with cabazitaxel in patients with metastatic castration-resistant prostate cancer

N= 200
Lu (n= 99)
Cabazitaxel (n= 101)

METHODS

Inclusion criteria: Patients with prostate cancer previously treated with docetaxel, progressive disease (defined by the Prostate Cancer Working Group 3 [PCWG3]), metastatic castration-resistant prostate cancer for whom cabazitaxel was considered the next appropriate treatment, adequate organ, and hematological function, ECOG score of 0 to 2, previous androgen receptor-directed therapy was allowed.

Intervention: Patients were randomized (1:1) to receive either cabazitaxel 20 mg/m^2 intravenously every 3 weeks for a max of 10 cycles or Lu at a radioactivity starting dose of 8.5 GBq, decreased by 0.5 GBq per cycle, administered intravenously every 6 weeks for a max of six cycles.

Primary outcome: PSA response rate (patients with PSA reduction of 50% or more from baseline)

Secondary/safety outcomes: Progression-free survival (interval from randomization to first evidence of PSA progression defined as an increase of at least 25% and at least 2 ng/mL after 12 weeks), delayed progression, radiographic progression

RESULTS

Primary outcome:

PSA responses were more frequent among men in the [^{177}Lu]Lu-PSMA-617 group than in the cabazitaxel group (65 vs 37 PSA responses; 66% vs 37% by intention to treat; difference 29% (95% CI 16-42; p< 0.0001; and 66% vs 44% by treatment received; difference 23% [9-37]; p= 0.0016).

Secondary outcomes (all values significant):

PSA progression-free survival defined as the HR versus cabazitaxel (95% CI) 0.60 (0.44 to 0.83)

Delayed progression HR: 0.63 (CI 0.46 to 0.86)

Radiographic progression HR: 0.64 (CI 0.46 to 0.88)

Safety outcomes:

Grade 3-4 adverse events occurred in 32 (33%) of 98 men in the [^{177}Lu]Lu-PSMA-617 group versus 45 (53%) of 85 men in the cabazitaxel group. No deaths were attributed to [177Lu]Lu-PSMA-617.

CONCLUSIONS

[^{177}Lu]Lu-PSMA-617 compared with cabazitaxel in men with metastatic castration-resistant prostate cancer led to a higher PSA response and fewer grade 3 or 4 adverse events. [^{177}Lu]Lu-PSMA-617 is a new effective therapy class and a potential alternative to cabazitaxel.

Critique:

As the study was conducted in Australia, the treatment of prostate cancer may differ compared to the United States. Patients were deliberately chosen to observe the maximum benefit of treatment based on their PSMA and PET-CT scan. About 28% of patients screened were not included in the study due to not meeting the stringent eligibility criteria. Patients with lower PSMA expression or discordant 2-[^{18}F]FDG-avid may not benefit from treatment

n = 831 • Sartor O, de Bono J, Chi KN, et al. • International, open-label, phase 3 trial

Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer

STUDY DESIGN

To investigate the efficacy and safety of ^{177}Lu-PSMA-617 (Lu) plus protocol-permitted standard care in a specific population of previously treated patients with metastatic castration-resistant prostate cancer who were selected for prostate-specific membrane antigen (PSMA) positivity on the basis of PSMA positron-emission tomographic (PET) imaging

N= 831
Lu (n= 551)
Standard care (n= 280)

The standard of care could be modified physician discretion but could not include cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223 [223Ra]), immunotherapy, or other investigational drugs

METHODS

Inclusion criteria: Age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) score 0 to 2, life expectancy > 6 months, confirmed prostate cancer, positive 68Ga-PSMA-11 PET/CT scan, prior orchiectomy and/or ongoing androgen-deprivation therapy and castrate level of serum testosterone (< 1.7 nmol/L), received at least one novel androgen axis drug (NAAD), previously treated with at least 1 but no more than 2 taxane regimens, progressive mCRPC and ≥ 1 metastatic legion confirmed by scan 28 days or less prior to study initiation

Intervention: At clinical sites throughout North America and Europe, patients were randomized (2:1) to receive either Lu 7.4 GBq (200 mCi) once every 6 weeks for four cycles plus protocol-permitted standard care or standard care alone. Two additional cycles (up to six cycles total) were allowed if there was evidence of response. Follow-up occurred every 8 weeks for 24 weeks, then every 12 weeks thereafter.

Primary outcome: Imaging-based progression-free survival and overall survival

Secondary/safety outcomes: Time to first symptomatic skeletal event, adverse events

RESULTS

Primary outcome: ^{177}Lu-PSMA-617 plus standard care prolonged

- Imaging-based progression-free survival (median, 8.7 vs. 3.4 months; HR for progression or death, 0.40; 99.2% CI, 0.29 to 0.57; p <0.001)
- Overall survival (median, 15.3 vs. 11.3 months; HR for death, 0.62; 95% CI, 0.52 to 0.74; p< 0.001).

Secondary outcomes: Time to first symptomatic skeletal event: 11.5 months versus 6.8 months (control) HR 0.50 (0.40 to 0.62).

Safety outcomes: The incidence of adverse events of grade 3 or above was higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not adversely affected.

CONCLUSIONS

Radioligand therapy with ^{177}Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer.

Critique: The unblinded design limits the strength of the results. While the treatment was found to be safe, follow-ups for adverse events were limited to 30 days after the last dose of study drug. There were more patients in the Lu group that discontinued due to adverse events compared to standard care which denotes possible intolerability to treatment.

n = 40 • Satapathy S, Mittal BR, Sood A, et al. • Randomized, parallel-group, open-label, phase 2, noninferiority trial

^{177}Lu-PSMA-617 versus docetaxel in chemotherapy-naïve metastatic castration-resistant prostate cancer: a randomized, controlled, phase 2 non-inferiority trial

STUDY DESIGN

To prospectively compare the efficacy and safety of ^{177}Lu-PSMA-617 and docetaxel in chemotherapy-naive mCRPC patients

N= 40
Lu (n= 20)
Docetaxel (n= 20)

Primary outcome: Best PSA response rate (PSA-RR) defined as the proportion of patients achieving a ≥ 50% decline in PSA from baseline

Secondary/safety outcomes: Best objective response rate (ORR), molecular response rate (MRR), toxicity

METHODS

Inclusion criteria: Biopsy-proven adenocarcinoma prostate and castration-resistant disease; metastatic disease on Ga-PSMA-11 PET/CT with significant PSMA expression; chemotherapy-naive patients (but prior novel anti-androgen allowed); ECOG performance score ≤ 2; adequate hematological, renal, and liver function reserve

Intervention: Patients were randomized (1:1) to receive ^{177}Lu-PSMA-617 or docetaxel. Patients in the ^{177}Lu-PSMA-617 group received up to 4 cycles of approximately 6.0 to 7.4 GBq per cycle of ^{177}Lu-PSMA-617 intravenously at 8-week intervals. Patients in the docetaxel arm received docetaxel 75 mg/m^2 intravenously once every 3 weeks up to a maximum of 10 cycles with prednisone 5 mg twice daily orally during the chemotherapy course, and prophylactic pegfilgrastim 6 mg subcutaneously on day 2. A prespecified noninferiority margin of -15% was used for the primary outcome.

RESULTS

Primary outcome: In the intention-to-treat analysis, the best PSA-RR in the ^{177}Lu-PSMA-617 group was achieved in 10/20 patients (50%) versus 8/20 patients (40%) in the docetaxel arm; p= 0.53).

Secondary outcomes: Best ORR occurred in 5/13 patients (39%) in the ^{177}Lu-PSMA-617 arm compared to 6/19 patients (32%) in the docetaxel arm (95% CI -24 to 38; p= 0.69).

Best MRR in the ^{177}Lu-PSMA-617 and docetaxel arms were observed in 6/14 (43%) and 6/19 (32%) patients, respectively (95% CI -19 to 41; p= 0.51).

Safety outcomes: Treatment-emergent grade 3 to 5 adverse events occurred in 30% of patients in the ^{177}Lu-PSMA-617 arm and 50% of patients in the docetaxel arm (p= 0.2).

The most common adverse events of any grade in the ^{177}Lu-PSMA-617 and docetaxel arms respectively were nausea/vomiting (20% vs. 35%), fatigue (45% vs. 35%), diarrhea (0 vs. 30%), constipation (25% vs. 5%), dryness of mouth (60% vs. 0), loss of appetite (40% vs. 30%), generalized pain (30% vs. 10%), anemia (70% vs. 75%), leukopenia (25% vs. 20%), and thrombocytopenia (25% vs. 30%).

CONCLUSIONS

^{177}Lu-PSMA-617 was demonstrated to be safe and non-inferior to docetaxel in the treatment of mCRPC and could, thus, be potentially employed earlier in the disease course rather than being solely reserved for advanced end-stage disease.

Critique:

The open-label design and small sample size may have introduced certain biases and confounding to the analysis, which may limit ramification of the results. Additionally, non-inferiority was only demonstrated in the per protocol analysis and not seen in the intention to treat analysis.

n = 69 • Sadaghiani MS, Sheikhbahaei S, Werner RA, et al. • Meta-analysis

^{177}Lu-PSMA radioligand therapy effectiveness in metastatic castration-resistant prostate cancer: An updated systematic review and meta-analysis

STUDY DESIGN

To evaluate the effectiveness of PSMA-PRLT in CRPC

N= 69 studies; 4,157 participants

METHODS

Inclusion criteria: Retrospective or prospective studies of ^{177}Lu-labeled, small molecule PRLT ligand in humans with CRPC including randomized and nonrandomized trials; published in English; evaluated survival or PSA response; published from 2019 to July 2020

Comparisons: ^{177}Lu-PSMA 617 and/or 177Lu-PSMA I&T I&T (imaging and treatment) vs. various controls

Outcomes: Efficacy: overall survival, ≥ 50% PSA decrease after PRLT

RESULTS

^{177}Lu-PSMA-617 treatment was associated with a statistically significant higher response of ≥ 50% PSA decrease compared to controls (odds ratio 5.33, 95% CI 1.24 to 22.90, p< 0.05). This figure was generated from a meta analysis of the only two RCT's.

Pooled analysis of data for overall survival based on HR of any PSA decline revealed a significant difference with ^{177}Lu-PSMA therapy (HR 0.26; 95% CI 0.18 to 0.37; p< 0.00001).

Pooled analysis of data for overall survival based on HR of ≥ 50% PSA decrease was significantly different with ^{177}Lu-PSMA therapy (HR 0.52; 95% CI 0.40 to 0.67; p < 0.00001).

No statistically significant difference was observed in PSA response between ^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617.

CONCLUSIONS

PRLT results in a higher proportion of patients responding to therapy based on ≥ 50% PSA decline compared to controls. Any PSA decline and ≥50% PSA decline showed survival prolongation after PRLT.

Critique:

Only two of the 62 included studies were randomized controlled trials, and data were mainly extracted from retrospective studies with a small number of patients. Moreover, there was substantial heterogeneity in the included RCTs regarding the comparison of ^{177}Lu-PSMA with controlled studies.

ADVERSE EFFECTS

Most common reaction (≥ 20%): Fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation

Most common laboratory abnormalities (≥ 30%): Decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium

Clinically significant adverse reactions described in warnings and precautions: Myelosuppression and renal toxicity

CONTRA-INDICATIONS

None

STORAGE

Shelf life: 120 hours (5 days) from the date and time of calibration

Storage: Store below 30°C (86°F). Do not freeze. Store in the original package to protect from ionizing radiation (lead shielding).

DRUG INTERACTIONS

No significant drug interactions

In Vitro studies:

CYP450 enzymes: Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. Vipivotide tetraxetan did not induce CYP1A2, 2B6 or 3A4; and did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A in vitro.

Transporters: Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2. Vipivotide tetraxetan did not inhibit BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 in vitro.

SAFETY CONSIDERATIONS

BOXED WARNINGS

None

WARNINGS & PRECAUTIONS

Risk From Radiation Exposure: Minimize radiation exposure during and after treatment with Pluvicto™ consistent with institutional good radiation safety practices and patient treatment procedures. Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation. After administration of Pluvicto™, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days. Advise patients to refrain from sexual activity for 7 days and to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

Myelosuppression: Perform complete blood counts. Withhold, reduce dose, or permanently discontinue Pluvicto™ and clinically treat based on severity.

Renal Toxicity: Advise patients to remain well hydrated and to urinate frequently before and after administration of Pluvicto™. Perform kidney function laboratory tests. Withhold, reduce dose, or permanently discontinue Pluvicto™ based on severity.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 14 weeks after the last dose.

Infertility: Pluvicto™ may cause temporary or permanent infertility.

USE IN SPECIFIC POPULATIONS

Pregnancy: The safety and efficacy of Pluvicto™ have not been established in females. Based on its mechanism of action, Pluvicto™ can cause fetal harm

Lactation: The safety and efficacy of Pluvicto™ have not been established in females. There are no data on the presence of lutetium Lu 177 vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

Females and Males of Reproductive Potential: Based on its mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment with Pluvicto and for 14 weeks after the last dose; the recommended cumulative dose of 44.4 GBq of Pluvicto™ results in a radiation absorbed dose to the testes within the range where Pluvicto™ may cause temporary or permanent infertility

Pediatric Use: The safety and effectiveness of Pluvicto™ in pediatric patients have not been established.

Geriatric Use: No overall differences in effectiveness were observed between patients ≥ 75 years of age and younger patients.

DOSAGE & ADMINISTRATION

Recommended Dosage: 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 doses, or until disease progression, or unacceptable toxicity

Dosage Modifications: 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 Pluvicto™. If a treatment delay due to an adverse reaction persists for > 4 weeks, treatment with Pluvicto™ must be discontinued. The dose of Pluvicto™ may be reduced by 20% to 5.9 GBq (160 mCi) once; do not re-escalate the dose. If a patient has further adverse reactions that would require an additional dose reduction, treatment with Pluvicto™ must be discontinued.

Renal Impairment: No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. The pharmacokinetics and safety of Pluvicto™ have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

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