## Title

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# Efficacy and Toxicity of [$^{177}$Lu]Lu-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer: Results from the U.S. Expanded-Access Program and Comparisons with Phase 3 VISION Data

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The phase 3 VISION trial demonstrated that [$^{177}$Lu]Lu-PSMA-617 prolonged progression-free survival and overall survival (OS) in prostate-specific membrane antigen [PSMA]–positive metastatic castration-resistant prostate cancer (mCRPC) patients who progressed on taxane-based chemotherapy and androgen receptor–signaling inhibitors (ARSIs). The U.S. expanded-access program (EAP; NCT04825652) was opened to provide access to [$^{177}$Lu]Lu-PSMA-617 for eligible patients until regulatory approval was obtained. This study aimed to evaluate the efficacy and safety profile of [$^{177}$Lu]Lu-PSMA-617 within the EAP and compare the results with those from the VISION trial. **Methods:** Patients enrolled in the EAP at 4 institutions in the United States with available toxicity and outcome data were included. Outcome measures included OS, a prostate-specific antigen (PSA) response rate (RR) of at least 50%, and incidences of toxicity according to Common Terminology Criteria for Adverse Events version 5.0. Differences in baseline characteristics, outcome data, and toxicity between the EAP and VISION were evaluated using *t* testing of proportions and survival analyses. **Results:** In total, 117 patients with mCRPC who received [$^{177}$Lu]Lu-PSMA-617 within the EAP between May 2021 and March 2022 were eligible and included in this analysis. Patients enrolled in the EAP were more heavily pretreated with ARSI (≥2 ARSI regimens: 70% vs. 46%; $P < 0.001$) and had worse performance status at baseline (Eastern Cooperative Oncology Group score ≥ 2: 19% vs. 7%; $P < 0.001$) than VISION patients. EAP and VISION patients had similar levels of grade 3 or higher anemia (18% vs. 13%; $P = 0.15$), thrombocytopenia (13% vs. 8%; $P = 0.13$), and neutropenia (3% vs. 3%; $P = 0.85$) and similar PSA RRs (42% vs. 46%; $P = 0.50$) and OS (median: 15.1 vs. 15.3 mo; $P > 0.05$). **Conclusion:** Patients with PSMA-positive mCRPC who received [$^{177}$Lu]Lu-PSMA-617 within the EAP were later in their disease trajectory than VISION patients. Patients enrolled in the EAP achieved similar PSA RRs and OS and had a safety profile similar to that of the VISION trial patients.

**Key Words:** mCRPC; PSMA PET; VISION; EAP

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Direct delivery of radiation to prostate cancer cells while minimizing damage to normal tissue is enabled by $^{177}$Lu-labeled radiopharmaceutical therapy targeting the prostate-specific membrane antigen ([$^{177}$Lu]Lu-PSMA) (*1*). The phase 3 VISION trial demonstrated that [$^{177}$Lu]Lu-PSMA-617 prolonged overall survival (OS) and radiographic progression-free survival in patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who progressed on taxane-based chemotherapy and androgen receptor–signaling inhibitors (ARSIs) (*1*). These results paved the way for approval of this therapy by the U.S. Food and Drug Administration in March 2022.

Randomized phase 3 clinical trials are the gold standard for evaluating the safety and efficacy of new drugs. Nevertheless, clinical trials require strict inclusion and exclusion criteria, which are often not representative of the patient populations encountered in clinical practice. Data from real-world studies are increasingly important to provide evidence of treatment effectiveness in clinical practice (*2*).

The U.S. expanded-access program (EAP; NCT04825652) was opened in April 2021 to provide access to [$^{177}$Lu]Lu-PSMA-617 for eligible patients until regulatory approval was obtained. Although the EAP eligibility criteria closely mirrored those from the VISION trial, the EAP lacks the rigor and standardization of clinical trial data, thus allowing for consideration of a broader and more diverse pool of patients resembling a real-world scenario.

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This study aimed to evaluate the efficacy and safety profile of [$^{177}$Lu]Lu-PSMA-617 within the EAP and compare the results with those from the VISION trial.

## MATERIALS AND METHODS

### Patients

This retrospective analysis included 117 patients enrolled in the EAP at 4 institutions across the United States (UCLA [61/117, 52%], University of California San Francisco [9/117, 8%], Tulane [27/117, 23%], and Johns Hopkins [20/117, 17%]) with available toxicity and outcome data. Inclusion and exclusion criteria for the EAP are provided in the supplemental materials (available at http://jnm.snmjournals.org). Eligible patients must have had PSMA-positive mCRPC by VISION criteria and have previously received at least 1 ARSI and 1 taxane-based chemotherapy regimen (*1*). Eligible patients must have had adequate organ function by VISION criteria and not have received concurrent cytotoxic chemotherapy, immunotherapy, radiopharmaceutical therapy, or investigational therapy. This retrospective analysis was approved by the Institutional Review Boards, which waived the study-specific consent requirement. The central study-specific protocol is provided in the supplemental materials. Predefined and readily available data from patient medical records were collected retrospectively at each participating institution.

### Procedures

All patients underwent a baseline [$^{68}$Ga]Ga-PSMA-11 (85/117, 73%) or [$^{18}$F]DCFPyL (32/117, 27%) PET/CT scan (PSMA PET/CT). The scans were interpreted locally by nuclear medicine physicians according to the VISION PET criteria to define eligibility for treatment (*1*). Patients enrolled in the EAP received 7.4 GBq (200 mCi) ± 10% of [$^{177}$Lu]Lu-PSMA-617 once every 6 wk for up to 6 cycles. Treatment cycles continued until disease progression, severe toxicity, or patient withdrawal. Laboratory tests (comprehensive metabolic panel, estimated glomerular filtration rate, complete blood count, and prostate-specific antigen [PSA] level) were performed within 4 wk of each cycle and 4–6 wk after the last cycle.

### Outcomes

Hematologic toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 5.0. The percentage of patients with any grade of toxicity and with toxicity of grade 3 or higher was calculated. Only VISION patients who were randomized to the [$^{177}$Lu]Lu-PSMA-617 arm and received at least 1 treatment dose were included in the toxicity analysis. Efficacy outcome measures included PSA response rate (RR), PSA progression-free survival, and OS. PSA progression-free survival was calculated from the time of treatment initiation to PSA progression or death, whichever occurred first. PSA progression was defined according to the Prostate Cancer Working Group Criteria 3 (*3*). PSA RR and OS were tested for comparison with VISION data. OS was calculated from 4 wk before treatment initiation to death from any cause or the last follow-up alive. The rationale for starting the time of OS at 4 wk before treatment initiation was to match the OS calculation in the VISION trial, that is, from the time of randomization. PSA RR was calculated as the percentage of patients who achieved at least a 50% PSA decline relative to baseline at any time during treatment. The cutoff for data analysis was November 15, 2023.

### Statistical Analysis

Results are presented as median and range for continuous variables and as number and percentage for categoric variables. The median and 95% CI were calculated for survival outcomes using Kaplan–Meier analyses. Survival rate and the corresponding 95% CI at 12, 18, and 24 mo were extracted. OS was considered statistically different between the VISION and EAP cohorts if the survival rates in the VISION patients at all 3 time points were not covered by the estimated 95% CI of the survival rates in the EAP cohort. Baseline characteristics, efficacy, and toxicity data from the VISION trial were extracted from the publication (*1*), and differences between EAP and VISION were evaluated using *t* tests of proportions. A *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22 (IBM Corp.).

## RESULTS

All 117 mCRPC patients who received [$^{177}$Lu]Lu-PSMA-617 within the EAP at participating institutions between May 2021 and March 2022 were eligible and included in this analysis. The median time between baseline PSMA PET/CT and the first cycle of [$^{177}$Lu]Lu-PSMA-617 was 6.9 wk (IQR, 4.1–10). The EAP patients received a median of 4 treatment cycles and a median cumulative injected activity of 28.1 GBq of [$^{177}$Lu]Lu-PSMA-617 per patient.

### Baseline Characteristics

Patients enrolled in the EAP were similarly pretreated with taxane-based chemotherapy (≥2 taxane regimens: 47% vs. 40%; $P = 0.16$) and more heavily pretreated with ARSI (≥2 ARSI regimens: 70% vs. 46%; $P < 0.001$). Four of 117 (3%) patients in the EAP were chemotherapy-naïve. A higher proportion of EAP patients than of VISION patients had an Eastern Cooperative Oncology Group (ECOG) score of 2 or more at baseline (19% vs. 7%; $P < 0.001$). The EAP patients were also more likely to have nodal disease on baseline PSMA PET/CT (61% vs. 50%; $P = 0.031$), and the proportion of patients with lung ($P = 0.90$), liver ($P = 0.35$), and bone ($P = 0.76$) disease on baseline PSMA PET/CT was similar between the EAP patients and the VISION patients. Detailed patient characteristics at baseline for both cohorts are provided in Table 1.

### Toxicity

EAP patients had similar rates of grade 3 anemia or higher (18% vs. 13%; $P = 0.15$), thrombocytopenia (13% vs. 8%; $P = 0.13$), neutropenia (3% vs. 3%; $P = 0.85$), and leukopenia (5% vs. 2%; $P = 0.19$) and higher rates of grade 3 or higher lymphopenia (34% vs. 8%; $P < 0.001$). A similar proportion of patients in EAP and VISION discontinued treatment because of any grade of toxicity (13% vs. 12%; $P = 0.78$).

Incidences of toxicity for both cohorts are detailed in Table 2 and Figure 1. In EAP patients with a baseline ECOG of 2 or higher,

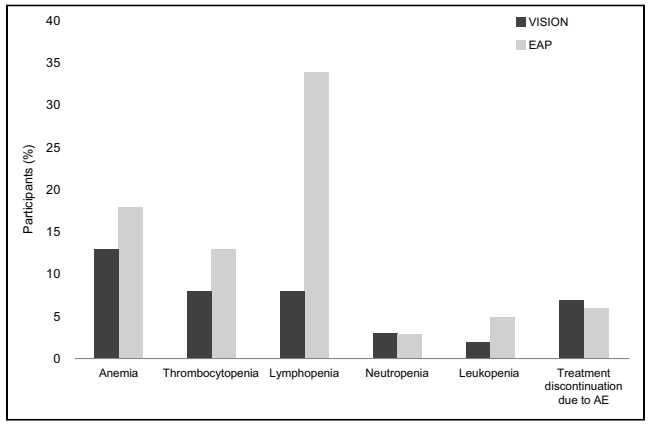


**FIGURE 1.** Comparison of toxicity data between EAP and VISION. AE = adverse events.

**TABLE 1**
Comparison of Baseline Characteristics and Outcome Data Between EAP and VISION

| Characteristic | VISION ($n$ = 551) | EAP ($n$ = 117) | $P$ |
|---|---|---|---|
| Baseline characteristics | | | |
| Age (y)* | 70 (48–94) | 71 (52–86) | |
| Race | | | |
| White | 486 (88%) | 89 (76%) | <0.001 |
| Black or African-American | 34 (6%) | 9 (8%) | 0.54 |
| Asian | 9 (2%) | 3 (3%) | 0.49 |
| Other | 2 (0%) | 0 (0%) | 0.51 |
| Missing | 20 (4%) | 16 (14%) | <0.001 |
| Time since diagnosis (y) | 7.4 (0.9–28.9) | 8.8 (0.9–30.2) | |
| Gleason score at diagnosis | | | |
| 8–10 | 324 (59%) | 66 (56%) | 0.63 |
| Unknown | 42 (8%) | 14 (12%) | 0.12 |
| Previous ARSI | | | |
| One regimen | 298 (54%) | 35 (30%) | <0.001 |
| More than one regimen | 253 (46%) | 82 (70%) | <0.001 |
| Previous taxane therapy | | | |
| One regimen | 325 (59%) | 58 (50%) | 0.06 |
| Two regimens | 220 (40%) | 55 (47%) | 0.16 |
| Hemoglobin (g/dL)† | 11.8 (7.6–15.9) | 11.2 (7.4–15.2) | |
| PSA (ng/mL)‡ | 77.5 (0–6,988) | 97.3 (0.1–4235) | |
| ECOG 0–1 | 510 (93%) | 88/108 (81%) | <0.001 |
| Site of disease | | | |
| Lung | 49 (9%) | 10 (9%) | 0.90 |
| Liver | 63 (11%) | 17 (15%) | 0.35 |
| Lymph node | 274 (50%) | 71 (61%) | 0.031 |
| Bone | 504 (91%) | 106 (91%) | 0.76 |
| Outcome data | | | |
| OS | 15.3 (14.2–16.9) | 15.1 (11.7–18.5) | |
| PSA response (≥50% decline) | 177/385 (46%)§ | 47/111 (42%) | 0.50 |

*Data are missing for 1 patient.
†Data are missing for 5 patients.
‡Data are missing for 7 patients.
§Data are for 385 patients randomized to [$^{177}$Lu]Lu-PSMA-617 after March 5, 2019.
Qualitative data are number and percentage; continuous data are median and range or, for OS data, median and 95% CI. VISION data include intention-to-treat population from [$^{177}$Lu]Lu-PSMA-617 arm.

the rates of grade 3 anemia or higher (16% vs. 29%; $P$ = 0.20), thrombocytopenia (13% vs. 13%; $P$ = 1.00), and lymphopenia (36% vs. 23%; $P$ = 0.37) were similar to those in EAP patients with an ECOG of 0–1. The rates of grade 3 neutropenia or higher (0% vs. 8%; $P$ = 0.014) and leukopenia (1% vs. 13%; $P$ = 0.018) were lower in EAP patients with a baseline ECOG of 2 or higher than in those with an ECOG of 0–1.

### Efficacy

Three of 117 (3%) patients with missing PSA levels and 3 of 117 (3%) patients with undetectable PSA levels at baseline were not included in the PSA RR analysis. Fifty-nine of 111 (53%) patients had any PSA decline during treatment, and 47 of 111 (42%) had at least a 50% PSA decline. Eighty of 114 (70%) patients experienced PSA progression at the last follow-up. The median PSA progression-free survival was 5.6 mo (95% CI, 3.2–8.0 mo). Seventy-two of 117 (62%) patients were deceased at the last follow-up. Median follow-up was 19.1 mo (95% CI, 16.1–22.9 mo). The median OS was 15.1 mo (95% CI, 11.7–18.5 mo).

The PSA RR was similar in the EAP and VISION patients (42% vs. 46%; $P$ = 0.50) (Table 1). The OS rate at 12, 18, and 24 mo in the EAP versus the VISION patients was 57% (95% CI, 48%–67%) versus 62%, 42% (95% CI, 33%–53%) versus 43%, and 27% (95% CI, 18%–39%) versus 29%, respectively. The OS rate in VISION was covered by the estimated 95% CI from the EAP at 12, 18, and 24 mo; hence, it was concluded that OS was

**TABLE 2**
Comparison of Toxicity Data in Patients Who Received [$^{177}$Lu]Lu-PSMA-617 Within EAP and VISION Trial

| | Any grade AE | | | Grade ≥ 3 AE | | |
|---|---|---|---|---|---|---|
| Event | VISION ($n$ = 529) | EAP ($n$ = 117) | $P$ | VISION ($n$ = 529) | EAP ($n$ = 117) | $P$ |
| Anemia* | 168 (32%) | 44 (42%) | 0.04 | 68 (13%) | 19 (18%) | 0.15 |
| Thrombocytopenia† | 91 (17%) | 51 (49%) | <0.001 | 42 (8%) | 13 (13%) | 0.13 |
| Neutropenia‡ | 45 (9%) | 32 (32%) | <0.001 | 18 (3%) | 3 (3%) | 0.85 |
| Lymphopenia‡ | 75 (14%) | 65 (66%) | <0.001 | 41 (8%) | 34 (34%) | <0.001 |
| Leukopenia† | 66 (12%) | 49 (47%) | <0.001 | 13 (2%) | 5 (5%) | 0.19 |
| $^{177}$Lu-PSMA-617 discontinuation due to AE | 63 (12%) | 15 (13%) | 0.78 | 37 (7%) | 7 (6%) | 0.69 |

*Data are missing for 12 patients.
†Data are missing for 13 patients.
‡Data are missing for 18 patients.
AE = adverse event.

similar in the EAP and VISION patients ($P > 0.05$). OS in EAP patients with a baseline ECOG of 0–1 and at least 2 was 15.9 mo (95% CI, 13.2–19.9 mo) and 6.6 mo (95% CI, 5.0 mo to not reached), respectively.

## DISCUSSION

This multicenter retrospective analysis assessed the efficacy and toxicity profile of [$^{177}$Lu]Lu-PSMA-617 in 117 mCRPC patients treated under the EAP in the United States. Prior studies reported on the efficacy and toxicity of [$^{177}$Lu]Lu-PSMA-617 in a real-world setting before drug approval; hence, inclusion criteria were heterogeneous and different from those used in the VISION trial and recommended in the current drug label (*4*,*5*). Patients enrolled in the EAP were required to meet eligibility criteria used in the VISION trial, which enabled an unbiased comparison of efficacy and toxicity.

The high-grade toxicity rates observed in the EAP were similar to those reported in the VISION trial. Grade 3 or higher anemia, thrombocytopenia, and neutropenia were observed in 18% versus 13%, 13% versus 8%, and 3% versus 3% of patients in the EAP versus VISION cohorts, respectively. The efficacy outcomes were similar in the EAP and VISION patients, that is, PSA RR was 42% and 46%, respectively, and median OS was 15.1 and 15.3 mo, respectively.

The EAP patients were more heavily pretreated with ARSI, had worse ECOG performance status, and had higher proportions of lymph node involvement at baseline than the VISION patients. Taken together, these findings suggest that postchemotherapy mCRPC patients who received [$^{177}$Lu]Lu-PSMA-617 in the EAP were later in their disease trajectory than was the VISION population. However, the efficacy of [$^{177}$Lu]Lu-PSMA-617 was similar between the EAP and VISION. Previous reports found that baseline characteristics of CRPC patients enrolled in clinical trials are different from real-world evidence (*6*). However, there was only weak evidence to suggest that the clinical trial setting alone significantly impacts the positive outcomes of participants in phase 3 registration trials (*7*). Seventy percent of EAP patients received at least 2 regimens of ARSI, and only 46% of patients received 2 regimens of taxane-based chemotherapy, suggesting that second-line ARSIs are still preferred over cabazitaxel despite results from the CARD trial (*8*). Overall, the present findings highlight the favorable toxicity profile and antitumor activity of [$^{177}$Lu]Lu-PSMA-617 even in heavily pretreated late-stage mCRPC patients.

Strengths of this study include its multicentric design, the use of a prospective patient cohort, and the fact that inclusion criteria closely mirrored those from the VISION trial. Main limitations include retrospective data collection and the lack of direct comparison for statistical significance of all relevant data.

## CONCLUSION

Patients with PSMA-positive mCRPC who received [$^{177}$Lu]Lu-PSMA-617 within the U.S. EAP were later in their disease trajectory than was the VISION patient population. The efficacy and safety profile of [$^{177}$Lu]Lu-PSMA-617 in the EAP were similar to those reported in the VISION trial.

**KEY POINTS**

**QUESTION:** How does the efficacy and safety profile of [$^{177}$Lu]Lu-PSMA-617 in the EAP compare with the results from the phase 3 VISION trial?

**PERTINENT FINDINGS:** Patients with PSMA-positive mCRPC treated with [$^{177}$Lu]Lu-PSMA-617 in the EAP were later in their disease trajectory than the VISION trial patients but had similar PSA RRs and OS and a similar safety profile.

**IMPLICATIONS FOR PATIENT CARE:** [$^{177}$Lu]Lu-PSMA-617 demonstrated antitumor activity and a favorable toxicity profile in patients with late-stage mCRPC.

## DISCLOSURE

Andrei Gafita was supported by the Prostate Cancer Foundation (21YOUN18). Jeremie Calais reports grants from support to his institution from Lantheus, Novartis, and Point Biopharma. He also reports consulting activities (advisory boards, speaker, masked reader) for Advanced Accelerator Applications, Amgen, Astellas, Bayer, Blue Earth Diagnostics Inc., Curium Pharma, DS Pharma, Fibrogen, GE HealthCare, Isoray, IBA RadioPharma, Janssen

Pharmaceuticals, Monrol, Lightpoint Medical, Lantheus, Novartis, Nucleus Radiopharma, Pfizer, Point Biopharma, Progenics, Radiomedix, Radiopharm Theranostics, Sanofi, Siemens-Varian, SOFIE, and Telix Pharmaceuticals outside the submitted work. Johannes Czernin is a founder of SOFIE Biosciences and holds equity in the company and in intellectual property invented by him, patented by the University of California, and licensed to SOFIE Biosciences. He is a founder and board member of Trethera Therapeutics and holds equity in the company and in intellectual property invented by him, patented by the University of California, and licensed to Triangle. He serves on the medical advisory board of Actinium Pharmaceuticals and on the scientific advisory boards of POINT Biopharma, RayzeBio, and Aktis Oncology. Oliver Sartor received grants or contracts from Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, In Vitae, Janssen, Lantheus, Merck, Novartis, Sanofi, and Point Biopharma; received support for attending meetings or travel from Bayer, Lantheus, and Sanofi; participated on a data safety monitoring board or advisory board for Pfizer, Merck, Janssen, Advanced Accelerator Applications, Novartis, and AstraZeneca; has stock or stock options in AbbVie, Cardinal Health, Clarity Pharmaceuticals, Convergent, Eli Lilly, Abbot, Ratio, United Health Group, and Telix; received consulting fees from Advanced Accelerator Applications, Amgen, ART BioScience, Astellas Pharma, AstraZeneca, Bayer, Clarity Pharmaceuticals, EMD Serono, Fusion Pharmaceuticals, Isotopen Technologien, Janssen, MacroGenics, Novartis, Pfizer, Point Biopharma, Ratio, Sanofi, Telix Pharmaceuticals, and TeneoBio; and received payment for expert testimony from Sanofi. Channing Paller reports consulting activities for Bayer, Pfizer, and Janssen and research or clinical trial grants from Merck and AstraZeneca. No other potential conflict of interest relevant to this article was reported.

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