

CAAA617A12004 Study Results Synopsis for Public Disclosure

Title

Comparing the lutetium (¹⁷⁷Lu) vipivotide tetraxetan arm of the PSMAfore clinical trial to a switch in androgen receptor pathway inhibitor (ARPI) as external control arm (ECA) using a real-world data source for patients with metastatic castration-resistant prostate cancer (mCRPC) after progression on prior ARPI- (PSMAfore External control arm)

Keywords

Overall survival, ¹⁷⁷Lu-PSMA-617, metastatic castrate resistant prostate cancer aka androgen pathway modulator-resistant prostate cancer, androgen receptor pathway inhibitor

Rationale and background

Prostate cancer is the most common non-skin cancer among men in the United States (US), with an estimated 313,780 new diagnoses in 2025 (SEER Cancer Stat Facts). Most patients are initially diagnosed with localized prostate cancer, but about 10% of patients are diagnosed with de novo metastatic prostate cancer (mPC), and 25% of localized prostate cancer diagnoses will progress to mPC (SEER Cancer Stat Facts). Castration resistant prostate cancer (CRPC) is defined as disease progression while on androgen deprivation therapy (ADT) despite serum testosterone at castrate levels. For patients who develop mCRPC, treatment choice is dependent on which therapies the patient received prior to their mCRPC status (Henríquez et al, 2021).

The exposure of interest in this study, lutetium (¹⁷⁷Lu) vipivotide tetraxetan (also known as ¹⁷⁷Lu-PSMA-617 or ¹⁷⁷Lu-PSMA-617), is a targeted radioligand therapy that contains a prostate-specific membrane antigen (PSMA) targeting component bound to radioactive lutetium. ¹⁷⁷Lu-PSMA-617 was initially approved by the Food and Drug Administration (FDA) on 23 Mar 2022 for the treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy (Food and Drug Administration, 2022). On 28 Mar 2025, the FDA expanded the indication to include adult patients with PSMA-positive mCRPC who have been treated with ARPI therapy and are considered appropriate to delay taxane-based chemotherapy, based on the PSMAfore trial (Food and Drug Administration, 2022).

While the PSMAfore trial demonstrated a clear benefit in radiographic progression-free survival (rPFS) for patients receiving ¹⁷⁷Lu-PSMA-617 (trial control arm [TCA]) compared to those who have a change in ARPI (trial treatment arm [TTA]), interpretation of overall survival (OS) outcomes is challenging due to the substantial proportion of patients who crossed over from the control arm to the treatment arm following progression (Morris et al, 2024). This crossover may have influenced the ability to fully capture differences in OS between groups. The use of real-world data (RWD) offers an opportunity to evaluate the effectiveness of ¹⁷⁷Lu-PSMA-617 compared to taxane-naïve patients treated with change in ARPI who meet key eligibility criteria aligned with the PSMAfore trial in a real-world setting (external control arm [ECA]). Less exposure to ¹⁷⁷Lu-PSMA-617 in the ECA may also mitigate the mixture of effects introduced by patients in the TCA of PSMAfore crossing over to receive ¹⁷⁷Lu-PSMA-617.

Research question and objectives

The primary objective of this study was to compare the OS of the PSMAfore TTA with the real-world overall survival (rwOS) of an ECA for adult patients with mCRPC who have initiated an ARPI after progression on a prior ARPI (i.e., received an initial ARPI, progressed, and then switched to a subsequent ARPI) and who have not received treatment with a taxane or PSMA radioligand therapy.

The secondary objective of this study was to compare OS of patients in the PSMAfore TCA to the rwOS of an ECA. The ECA included taxane-naïve mCRPC US-based patients treated with a change in ARPI after progression on prior ARPI.

The study also included two exploratory objectives that performed the primary and secondary analyses using an expanded RWD ECA cohort which included patients from the US, United Kingdom (UK), and Germany who had a change in ARPI for any reason (e.g., toxicity, progression). The expanded RWD ECA is reflective of the real-world eligible cohort of patients.

Study design

This is a study of OS and rWOS among adult patients diagnosed with mCRPC using PSMAfore trial data and retrospectively collected RWD for an ECA and an expanded ECA. The TTA of PSMAfore consists of adult PSMA+ mCRPC patients who received 177Lu-PSMA-617 after progression on a second-generation ARPI (abiraterone, enzalutamide, apalutamide, darolutamide). The TCA of PSMAfore includes patients receiving a change in ARPI.

Patient-level data from the ECA and the expanded ECA were used in combination with patient-level data from the TTA and TCA, in time-to-event analyses to understand the impact of 177Lu-PSMA-617 on OS.

Setting

The PSMAfore trial is an open-label, multicenter, global Phase III study of adult male patients with PSMA-positive mCRPC aged 18 years or older who progressed once after treatment with an ARPI and who have not been exposed to a taxane-containing regimen (except in the adjuvant or neoadjuvant setting and treatment was completed ≥ 12 months before index date). Patients in the TTA were treated with 177Lu-PSMA-617 in an earlier line of therapy (LOT) than the drug approval indicates. Patients in the TCA were treated with a change in ARPI (index therapy; abiraterone or enzalutamide) after progression on one prior ARPI. Enrollment in PSMAfore began on 15 Jun 2021, and data collection for the final OS analysis concluded on 01 Jan 2025.

Patients in the ECA were selected from a health research database that included electronic health records from patients in US, UK and Germany. Patients were required to be 18 years or older at index date and have a chart-confirmed diagnosis of mCRPC. Patients also must have been taxane-naïve and had evidence of treatment with a change in ARPI treatment (index therapy) from 01 Jul 2018 through 31 Aug 2023 immediately following progression on prior ARPI and were followed-up until loss to follow-up or death, through 30 Jun 2025. Patients in the ECA were refreshed from the original PSMAfore ECA study with a more recent data cutoff date of 30 June 2025, extended from the original cutoff of 30 Nov 2023, allowing for updated mortality and censor dates.

For the exploratory analyses, the expanded RWD ECA cohort included patients who had a change in ARPI for any reason (e.g., progression, toxicity) after treatment with an initial ARPI and expanded inclusion/exclusion criteria imposed in the ECA to better reflect the real-world 177Lu-PSMA-617 -eligible population. In addition, the expanded ECA cohort included patients outside the US (specifically, the UK and Germany), aiming to make it more representative to the global PSMAfore cohorts and supporting the generalizability of conclusions from the primary and secondary analyses to a global population.

The expanded ECA cohort had an increased index therapy window of 01 Jul 2018 through 27 Mar 2025 (aligned with the approval of 177Lu-PSMA-617 for the PSMAfore indication) and patients were followed-up until loss to follow-up or death, through 30 Jun 2025. Additional exclusion criteria requiring custom abstraction, such as untreated brain metastases and active additional malignancies, were not implemented as a part of the expanded ECA.

Subjects and study size, including dropouts

A total of 227 and 232 patients from PSMAfore were included in the TTA and TCA respectively. Patients in the TTA and TCA made up the safety set. In the ECA, 500 US based patients from the health research database were included in the analysis after they were determined to have met PSMAfore trial-like inclusion/exclusion criteria. The expanded ECA included 1,525 patients from the US, and UK, and Germany health research databases.

Variables and data sources

The outcome variable of interest for all objectives was OS for patients in the PSMAfore trial and rwOS for patients in the ECA, and the exposure of interest was treatment with 177Lu-PSMA-617 (TTA) as compared with index ARPI (ECA and TCA). Important baseline characteristics included, but were not limited to: age, factors related to disease severity and prognosis (e.g., stage at initial prostate cancer diagnosis), and factors related to prior ARPI exposure (e.g., duration of treatment on first ARPI in which there was progression).

The source population for the trial data (TTA and TCA) was the final OS data from the Novartis Phase III PSMAfore study. The source population and data for the ECA are de-identified, secondary RWD derived from the health research databases. The data are collected from electronic health records (EHRs) used by cancer care providers across the US, UK and Germany.

Statistical methods

The primary analysis compared treatment with 177Lu-PSMA-617 in the TTA with treatment with a change in ARPI in the ECA. The Kaplan-Meier (KM) product limit estimator was used to estimate median OS and median rwOS (with corresponding 95% confidence intervals [CIs]) using propensity score weights to balance the study arms on potential confounding factors. Multiple imputation was used to mitigate the impact of missing data. Additionally, Cox proportional hazards regression was used in the weighted sample with robust variance estimators, yielding hazard ratios (HRs) and corresponding 95% CIs for treatment with 177Lu-PSMA-617 in the TTA compared with a change in ARPI in the ECA. The secondary analysis compared treatment with a change in ARPI in PSMAfore (TCA) with treatment with a change in ARPI in RWD (ECA). Similar methods to those described for the primary analysis were used for secondary analysis to compare the OS between the TCA and the ECA.

Similarly, the exploratory analyses used identical statistical methods as the primary and secondary analyses. The list of covariates included in the propensity score methods was further limited to strong prognostic factors to preserve statistical efficiency and limited to clinical variables with data capture on the full eligible cohort (i.e., excluding variables requiring additional curation such as comorbidities).

Results

All 18 covariates were balanced after propensity score weighting. The ECA has a shorter median follow-up time (19 months) compared to the TTA (23 months) and TCA (21 months). There were 333 (67%) deaths in the ECA compared with 138 (61%) and 155 (67%) in the TTA and TCA, respectively. The median OS for the TTA and TCA was 25.6 months (95% CI: 20.9, 29.7) and 22.6 months (19.6, 26.3), respectively. The median rwOS for the ECA was 22.7 months (21.5, 24.8), and it was 22.9 months (20.4, 29.8) after weighting against the TTA. In a covariate-adjusted Cox proportional hazards regression analyses comparing the TTA and TCA with the ECA (referent), an HR of 0.98 (0.76, 1.26) was observed for the TTA and 1.20 (0.92, 1.57) for the TCA. Results were robust to the two sensitivity analyses (using propensity score 1:1 matching and excluding patients with unknown Eastern Cooperative Oncology Group (ECOG) status).

In the exploratory analyses, the expanded ECA has a median follow-up time of 15 months compared to the ECA of 19 months, which may be primarily related to the expanded and more recent eligibility window for index ARPI. The rate of mortality events remains similar in the ECA (928; 61%). All 8 covariates were balanced after weighting. The median rwOS for the expanded ECA was 21.7 months (20.6, 22.7), and it was 20.9 months (19.7, 22.6) after weighting against the TTA. A significant difference was observed in OS for the TTA compared to the expanded ECA (referent), indicated by the weighted HR of 0.79 (0.66, 0.96). In sensitivity analyses, the conclusion remained significant after excluding patients with unknown ECOG, however, it was no longer significant when using 1:1 matching, likely due to a smaller sample size of the matched expanded ECA. OS was comparable between the TCA and the expanded ECA (referent), with a weighted HR of 0.86 (0.72, 1.03). Use of 2:1 matching resulted in increased precision (i.e., narrower CI) as expected with increased sample size, yielding an HR of 0.80 (0.64, 1.00). 3:1 matching further improved precision with an HR of 0.81 (0.66, 0.99).

Discussion

The primary analysis comparing OS among PSMAfore trial patients treated with 177Lu-PSMA-617 with rWOS among RWD ECA patients who changed to an ARPI following a prior ARPI did not provide evidence of a survival benefit for treatment with 177Lu-PSMA-617. After weighting, some ECA patients received heavy weights, which contributed to large variability in weights and resulted in a low effective sample size. This had a negative impact on statistical power and may have contributed to the inconclusive results.

The exploratory analysis 1, however, showed that 177Lu-PSMA-617-treated patients in the PSMAfore trial demonstrated a lower hazard of death when compared to patients in the expanded ECA. This result is likely due to the larger effective sample size for the expanded ECA after weighting to TTA, which enabled higher precision (i.e., a narrower confidence interval) compared with the primary analysis. Although the expanded approach adjusted for strong confounders and implemented a trial-like criteria, the differences in cohort selection and adjustment approach may be contributing to differences relative to the primary analysis.

Conclusion

Results of the present study provide evidence supporting an OS benefit of 177Lu-PSMA-617 for mCRPC compared to a broad cohort of real-world patients with mCRPC who received an ARPI immediately after one prior ARPI. While a statistically significant difference was observed, the results may be impacted by potential residual bias from several factors that limited the comparability of data from clinical trials and real-world patients. Future studies are needed to validate these results, which can involve constructing an RWD cohort that better emulates the trial cohort (e.g., include a higher number of global patients, include PSMA positive patients only, align operational definitions of confounder measurements). With 177Lu-PSMA-617 approved by the FDA, as more patients receive the drug in a real-world setting, a RWD study can also be conducted to compare the survival of real-world patients who received 177Lu-PSMA-617 to patients who switched to another ARPI.

References

Food and Drug Administration. FDA approves Pluvicto for metastatic castration-resistant prostate cancer. March 23, 2022. Accessed February 9, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer>

Henríquez, I., Roach, M. 3rd, Morgan, T.M., Bossi, A., Gómez, J.A., Abuchaibe, O. and Couñago, F. (2021) 'Current and emerging therapies for metastatic castration-resistant prostate cancer (mCRPC)', *Biomedicines*, 9(9), p. 1247, 17 September. doi:10.3390/biomedicines9091247. PMID: 34572433; PMCID: PMC8468423.

Morris, M.J., Castellano, D., Herrmann, K., de Bono, J.S., Shore, N.D., Chi, K.N., Crosby, M., Piulats, J.M., Fléchon, A., Wei, X.X. and Mahammedi, H. (2024) '177Lu-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', *The Lancet*, 404(10459), pp. 1227–1239, 28 September. doi:10.1016/S0140-6736(24)01809-4.

National Cancer Institute (n.d.) *SEER Cancer Stat Facts: Prostate Cancer*. Bethesda, MD: National Cancer Institute. Available at: <https://seer.cancer.gov/statfacts/html/prost.html> (Accessed: 10 March 2026)