Final Publication Number: 2516TiP

✉ Louise Emmett | Louise.Emmett@svha.org.au

PSMAcTION trial-in-progress: a phase 2/3 randomized trial of [^{225}Ac]Ac-PSMA-617 (^{225}Ac-PSMA-617) versus standard of care in patients with PSMA-positive metastatic castration-resistant prostate cancer who progressed on or after [^{177}Lu]Lu-PSMA therapy

Louise Emmett,[1] Matthias Eiber,[2] Oliver Sartor,[3] Neal Shore,[4] Xiao X Wei,[5] Xiaohong Li,[6] Praseeda Thaikalloor,[7] Liane Pinto,[8] Mike Sathekge[9]

[1]Theranostics and Nuclear Medicine, St Vincent's Hospital, Sydney, NSW, Australia; [2]Technical University of Munich, Munich, Germany; [3]LCMC Health Center, New Orleans, LA, USA; [4]START Carolinas Research Center, AUC Urology Specialists, Myrtle Beach, SC, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Novartis Institutes for BioMedical Research, Cambridge, MA, USA; [7]Novartis Pharmaceuticals UK Limited, London, UK; [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [9]Nuclear Medicine Department, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa

Scan to obtain:
- Poster

https://tinyurl.com/LouiseEmmett2516TiP

Poster presented at the European Society for Medical Oncology (ESMO) Congress 2025, held on 17–21 October 2025 in Berlin, Germany.

INTRODUCTION

- The prostate-specific membrane antigen (PSMA)-targeted radioligand therapy [^{177}Lu]Lu-PSMA-617 prolongs radiographic progression-free survival (rPFS) in patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) in the taxane-naive setting (PSMAfore) and rPFS and overall survival (OS) in the post-taxane setting (VISION).[1,2]
- ^{225}Ac is a high-energy alpha emitter that has higher linear energy transfer and a shorter tissue path length than the beta emitter ^{177}Lu, resulting in an increased likelihood of double-stranded DNA breaks over single-stranded ones and potentially fewer off-target effects.[3–6]
- [^{225}Ac]Ac-PSMA-radioligand therapy has shown preliminary evidence of clinical efficacy in patients with mCRPC and may represent a viable treatment option in patients who have received previous lines of therapy.[5–7]
- PSMAcTION (NCT06780670) aims to evaluate the efficacy and safety of [^{225}Ac]Ac-PSMA-617 (^{225}Ac-PSMA-617) versus investigator's choice of standard of care (SoC) in adults with PSMA-positive mCRPC who have previously received androgen receptor pathway inhibitors (ARPIs), taxane chemotherapy and [^{177}Lu]Lu-PSMA (^{177}Lu-PSMA) radioligand therapy.

METHODS

Study design

- PSMAcTION is an open-label, multicentre, randomized, phase 2/3 study of ^{225}Ac-PSMA-617 versus SoC in patients with PSMA-positive mCRPC who have had disease progression on or after ^{177}Lu-PSMA treatment.
  - Phase 2 is designed to gather information to support the proposed ^{225}Ac-PSMA-617 dosage for phase 3.
  - Phase 3 will evaluate the efficacy and safety of ^{225}Ac-PSMA-617 versus investigator's choice of SoC.

Patient population

Key inclusion criteria	Key exclusion criteria
• PSMA-positive mCRPC confirmed by PSMA PET/CT • ≥ 1 metastatic lesion identified on screening or baseline CT, MRI or bone scan performed ≤ 28 days before randomization • Histologically or cytologically confirmed adenocarcinoma of the prostate • Previous treatment with ARPI and taxane-based chemotherapy, and disease progression on or after ≥ 1 cycle of ^{177}Lu-PSMA • Castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L) • Documented progressive mCRPC (based on PSA, soft tissue or bone progression) • ECOG PS 0–2 • eGFR above the threshold specified by the sponsor	• Baseline xerostomia ≥ Grade 2 as per CTCAE v5 • Previous treatment with Sr-89, Sm-153, Re-186/188, Ra-223, hemi-body irradiation, ^{177}Lu-PSMA or [^{177}Lu]Lu-DOTA therapies within 6 weeks before randomization • Previous use of any investigational agents within 28 days prior to randomization • Previous use of any ^{225}Ac-based investigational compound • History of untreated and or/symptomatic CNS metastases • Uncontrolled hypertension, myocardial infarction, angina pectoris or coronary artery bypass graft within 6 months before informed consent • Concurrent acute kidney injury, chronic kidney disease, serious uncontrolled infection or uncontrolled diabetes

ARPI, androgen receptor pathway inhibitor; CNS, central nervous system; CT, computed tomography; CTCAE v5, Common Terminology Criteria for Adverse Events version 5; DOTA, dodecane tetra-acetic acid; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; eGFR, estimated glomerular filtration rate; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Study treatments and procedures

- In phase 2, patients will be randomized to two different ^{225}Ac-PSMA-617 dosages to support the optimal dosage for phase 3.
- Patients will receive ^{225}Ac-PSMA-617 for up to 6 cycles (**Figure 1**).
- In phase 3, approximately 420 patients will be randomized to receive ^{225}Ac-PSMA-617 for up to 6 cycles or investigator's choice of SoC (ARPIs, cabazitaxel, docetaxel, carboplatin, radium-223 dichloride and sipuleucel-T) (**Figure 1**).
- Crossover to the ^{225}Ac-PSMA-617 arm will not be permitted for any patient randomized to the SoC arm.
- An end-of-treatment (EOT) visit will be performed within 7 days of the last day of study treatment, or from the date of treatment discontinuation for any reason in either treatment arm.
- Safety follow-up will occur at 56 and 30 days (+7) after the last administration of ^{225}Ac-PSMA-617 and SoC, respectively.
- Long-term follow-up will include safety and efficacy assessments for up to 5 years after EOT.

Study endpoints

Phase 2 primary endpoints	
• Safety, defined as the type, incidence and severity of AEs and SAEs and deaths • Tolerability, defined as dose interruptions, reductions, discontinuation, dose intensity and duration of exposure • Biochemical response rate	
Phase 2 secondary endpoints	
• rPFS • PFS • ORR	• DCR • OS
Phase 3 primary endpoints	
• rPFS, defined as the time from the date of randomization to the date of the first documented radiographic disease progression, or death • OS, defined as the time from the date of randomization to the date of death	
Phase 3 secondary endpoints	
• PFS • ORR • DCR • DoR • Time to soft tissue progression	• Time to symptomatic skeletal event • PSA50 • Patient-reported disease related symptoms and HRQoL • Patient-reported pain severity • Safety

AE, adverse event; DCR, disease control rate; DoR, duration of response; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PSA50, prostate-specific antigen 50; rPFS, radiographic progression-free survival; SAE, serious adverse event.

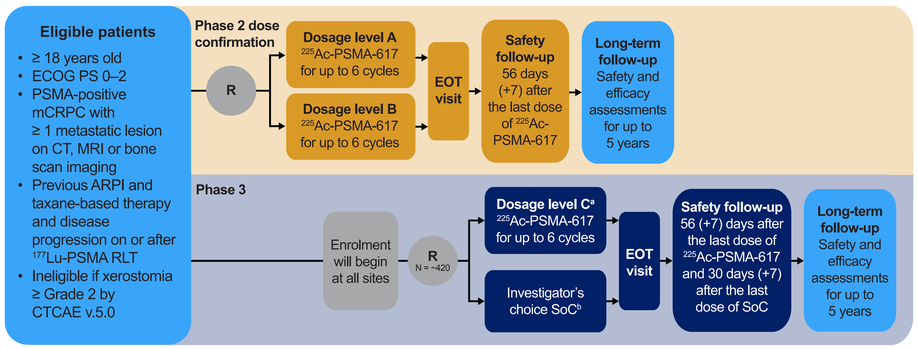
Statistical analysis

- Median OS and rPFS and 95% confidence intervals (CIs) will be estimated using the Kaplan–Meier method; hazard ratios with 95% CIs will be calculated using stratified Cox models.
- The first interim efficacy analysis for OS is planned to coincide with the final rPFS analysis.

Study status

- An upcoming protocol amendment will aim to optimize eligibility criteria, study procedures and operational aspects.
- As of August 2025, patient enrolment has commenced in 13 sites across seven countries (**Figure 2**).

Figure 1. Study design



[a]The dosage selected for phase 3 will be determined based on the safety, tolerability and efficacy data collected in phase 2.
[b]The number of SoC treatment cycles will be determined at the investigator discretion, in accordance with mCRPC treatment guidelines. Crossover to the ^{225}Ac-PSMA-617 arm will not be permitted.
ARPI, androgen receptor pathway inhibitor; CT, computed tomography; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; EOT, end-of-treatment; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; PSMA, prostate-specific membrane antigen; R, randomization; RLT, radioligand therapy; SoC, standard of care.

Figure 2. PSMAcTION: participating countries

References

1. Morris MJ *et al. Lancet* 2024;404:1227–39
2. Sartor O *et al. N Engl J Med* 2021;385:1091–103
3. Kratochwil C *et al. J Nucl Med* 2016;57:1941–4
4. Kratochwil C *et al. J Nucl Med* 2017;58:1624–31
5. Yadav MP *et al. Theranostics* 2020;10:9364–77
6. Feuerecker B *et al. Eur Urol* 2021;79:343–50
7. Sathekge MM *et al. Lancet Oncol* 2024;25:175–83

Acknowledgements

The authors thank the patients and their families, and all site investigators and personnel participating in the study. We thank Benedikt Feuerecker, Jongbong Lee and Ying Fei Li of Novartis for their contributions to the study. Under the direction of the authors, Sophie Adams, PhD, of Oxford PharmaGenesis, Oxford, UK provided medical writing support, funded by Novartis, in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022).

First author disclosures

Dr Louise Emmett reports grants or contracts from Clarity Pharma, Prostate Cancer Foundation Challenge Award and Novartis; honoraria from Astellas and Novartis; advisory board or speaker fees from Advancell, Astellas, Clarity Pharma and Novartis; trial support from Novartis; and leadership or fiduciary role with Executive Committee ARTnet.

Funding

This study was funded by Novartis.