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PSMACare trial-in-progress: a phase 2 trial of [^{177}Lu]Lu-PSMA-617 with or without ARPI in patients with PSMA-positive non-metastatic castration-resistant prostate cancer

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INTRODUCTION

- The prostate-specific membrane antigen (PSMA)-targeted radioligand therapy [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolongs radiographic progression-free survival (rPFS) with a manageable safety profile in patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) in post-taxane (VISION) and taxane-naive (PSMAfore) settings.[1,2]
- Approximately 97% of patients with non-metastatic CRPC (nmCRPC) by conventional imaging have PSMA-positive disease.[3]
- Androgen deprivation therapy (ADT) and second-generation androgen receptor pathway inhibitors (ARPIs) are the standard of care for patients with nmCRPC.[4]
- However, nearly 60% of patients with nmCRPC progress and develop metastatic disease within 5 years.[5]
- ^{177}Lu-PSMA-617 may act synergistically with ARPIs and ADT to delay metastatic progression.[6]
- The PSMACare trial (NCT05849298) evaluates the efficacy and safety of ^{177}Lu-PSMA-617 with and without ARPIs in patients with PSMA-positive CRPC and no evidence of metastases by conventional imaging (computed tomography [CT]/magnetic resonance imaging [MRI] and bone scan).

METHODS

Study design

- PSMACare is an ongoing international, prospective, open-label, multicentre, randomized, non-comparative phase 2 trial.

Patient population

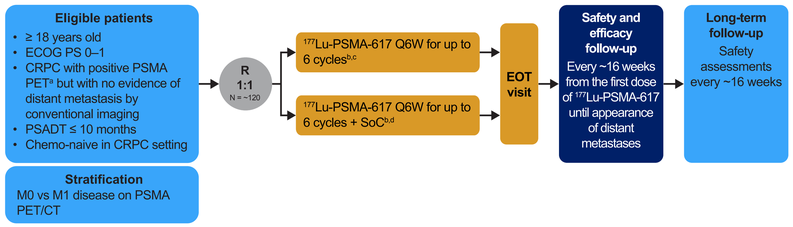
Key inclusion criteria	Key exclusion criteria
• PSMA-positive disease confirmed by PET/CT at baseline, using [^{68}Ga]Ga-PSMA-11 (or [^{18}F]DCFPyL; USA only) – PET/CT scans are assessed by BICR based on PROMISE criteria[7] – Participants with M1 disease on PSMA PET scans are allowed to participate • Negative by conventional imaging (CT/MRI and/or bone scan) for M1 disease • Histologically or cytologically confirmed adenocarcinoma • CRPC demonstrated during continuous ADT/post orchiectomy • Ongoing ADT with a GnRH agonist/antagonist or prior bilateral orchiectomy • Castrate level of serum testosterone (< 50 ng/dL) on GnRH agonist or antagonist therapy or after bilateral orchiectomy • ECOG PS 0–1 • PSA doubling time of ≤ 10 months	• Prior or present evidence of M1 disease by conventional imaging (CT/MRI and/or bone scan) • Unmanageable concurrent bladder outflow obstruction or urinary incontinence • Prior therapy with second-generation ARPIs • Prior therapy with CYP17 inhibitors • Prior therapy with radiopharmaceutical agents • Prior PSMA-targeted radioligand therapy • Prior immunotherapy • Prior chemotherapy, unless given as adjuvant/neoadjuvant and completed more than 2 years before randomization • Use of oestrogens, 5α reductase inhibitors, steroidogenesis inhibitors or first-generation anti-androgens within 28 days before randomization • Radiation therapy (EBRT and brachytherapy) within 28 days before randomization • Concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, PARP inhibitors, biological therapy or investigational therapy

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BICR, blinded independent central review; CRPC, castration-resistant prostate cancer; CT, computed tomography; CYP17, cytochrome P450 17A1; EBRT, external beam radiation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; [^{18}F]DCFPyL, piflufolastat (^{18}F); GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging; PARP, poly(ADP-ribose) polymerase; PET, positron emission tomography; PROMISE, Prostate Cancer Molecular Imaging Standardized Evaluation; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Study treatments and procedures

- Approximately 120 patients will be randomized 1:1 to receive ^{177}Lu-PSMA-617 (7.4 GBq ± 10% every 6 weeks, up to 6 cycles) or ^{177}Lu-PSMA-617 + ARPI (apalutamide, darolutamide or enzalutamide) (**Figure 1**).
  - Randomization will be stratified by PSMA-positive distant metastasis on PSMA PET/CT as assessed by BICR.
  - Ongoing treatment with ADT is mandatory in both arms.
- Best supportive care is permitted in both arms.
- Patients randomized to ^{177}Lu-PSMA-617 plus ARPI may continue to receive ARPI beyond 36 weeks (i.e. after ^{177}Lu-PSMA-617 is completed) at the investigator's discretion.
- Patients may also continue to receive ARPI following discontinuation from ^{177}Lu-PSMA-617 for any reason.
- Efficacy follow-up assessments will occur every 16 weeks from date of the first administration of ^{177}Lu-PSMA-617, continuing until appearance of distant metastases.
- Safety follow-up visits will be aligned with the efficacy follow-up visits and will continue until the global end of study.

Figure 1. Study design



[a]Positive PSMA PET may include M0/N1 (local metastases, e.g. local lymph nodes) and M1 (distant metastases); M0 by conventional imaging is mandatory.
[b]Per protocol, patients in both arms may receive BSC, including ADT. [c]ARPI use is prohibited. [d]SoC includes ADT plus enzalutamide, darolutamide or apalutamide; for PSMA PET M1, SBRT is allowed.
ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BSC, best supportive care; CRPC, castration-resistant prostate cancer; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status score; EOT, end of treatment; M0, non-metastatic or locoregional metastases; M1, distant metastases; PET, positron emission tomography; PSADT, prostate-specific antigen doubling time; PSMA, prostate-specific membrane antigen; Q6W, every 6 weeks; SBRT, stereotactic body radiotherapy; SoC, standard of care.

- The study duration will be approximately 60 months.
- At the end of the study, participants will be eligible to join a long-term safety follow-up study.

Study endpoints

Primary endpoints	
• PSA response rate, defined as the proportion of participants who have a post-baseline PSA nadir value of ≤ 0.2 ng/mL confirmed by a second PSA measurement ≥ 4 weeks later	
Secondary endpoints	
• MFS, defined as time from randomization to the first evidence of radiographically detectable bone/soft tissue distant metastasis by conventional imaging using RECIST 1.1, or death • rPFS, defined as time from randomization to the date of first documented radiographic disease progression by conventional imaging using RECIST v1.1, or death • OS • Second progression-free survival • Time to symptomatic progression • Time to initiation of cytotoxic chemotherapy	• Time to first symptomatic skeletal event • Time to distant metastasis development • Time to local radiological progression • Time to initiation or change of therapy • Time to PSA progression • Time to PSA response • PSA50 response rate • PSA90 response rate • HRQoL • Safety and tolerability

Endpoints requiring radiographic assessment were evaluated by conventional imaging using RECIST 1.1 criteria.
HRQoL, health-related quality of life; MFS, metastasis-free survival; OS, overall survival; PSA, prostate-specific antigen; PSA50, prostate-specific antigen 50% response; PSA90, prostate-specific antigen 90% response; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiographic progression-free survival.

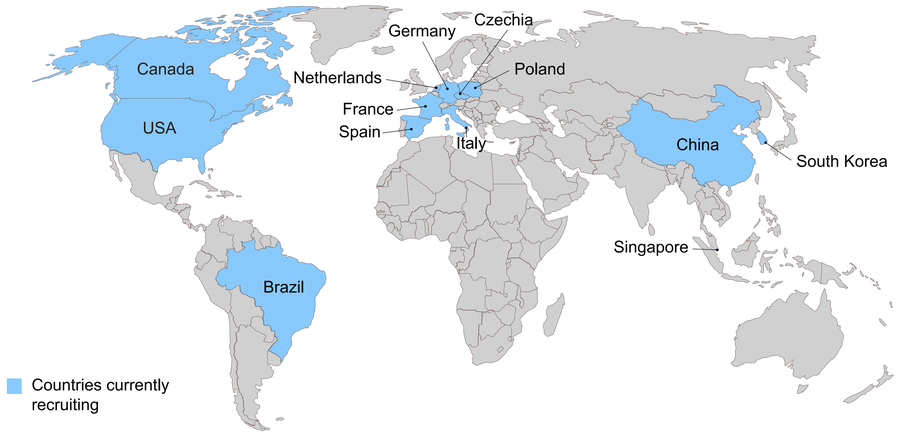
Statistical analysis

- No formal hypothesis will be tested.
- No statistical comparison between treatment arms will be performed.
- The PSA response rate will be estimated per treatment group, along with two-sided exact binomial 95% confidence intervals.[8]
- Patients with no post-baseline assessment (e.g. due to study discontinuation) will be defined as non-responders for the primary analysis.
- Time to event analyses using Kaplan–Meier method will be used for secondary endpoint analyses.
- The full analysis set will be used for efficacy-related endpoint analyses.
- The safety set will be used for safety-related analyses which will summarize on-treatment events.

Study status

- A protocol amendment is currently undergoing health authority evaluation. This amendment is designed to introduce more flexible inclusion/exclusion criteria in order to expand eligible patient population, leveraging new clinical evidence and enhancing study feasibility.
- As of August 2025, patient enrolment has commenced in 13/13 countries (**Figure 2**).

Figure 2. PSMACare: participating countries



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