

Inclusion Criteria:

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male, at least 18 years old, with documented adenocarcinoma of the prostate defined by histological/pathological confirmation.
2. ECOG Performance Status 0, 1, or 2 and have an estimated life expectancy of ≥ 6 months from Day 1.
3. Have metastatic disease (defined as ≥ 1 metastatic lesion(s) present on baseline CT, MRI or bone scintigraphy).
4. Have castration-resistant prostate cancer (CRPC) (defined as disease progressing despite castration by orchiectomy or ongoing use of luteinizing hormone-releasing hormone [LHRH] analogues) and must have a castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L) at Screening.
5. Must have received a minimum of 12 weeks of prior therapy on their first ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide), received in either the mCSPC, nmCRPC, or mCRPC treatment settings, with documented evidence of disease progression while receiving this ARPI. No washout period is required prior to enrollment into this trial. Participants may have received docetaxel in the mCSPC setting as per the CHAARTED or STAMPEDE treatment regimens (up to 6 cycles of docetaxel) provided the last dose of docetaxel was ≥ 6 months prior to screening and ≥ 4 cycles of docetaxel were administered.
6. Have a disease that is progressing at study entry, despite a castrate testosterone level (< 50 ng/dL or < 1.7 nmol/L), by the demonstration of at least one of the following:
 - a) Two consecutive rising PSA values during the receipt of the ARPI assessed sequentially at least one week apart, with the final measurement required to be a minimum of 2.0 ng/mL for study entry. Only the last measurement must meet or exceed 2.0 ng/mL, OR
 - b) Progressive disease (PD) or new lesion(s) in the viscera or lymph nodes as per RECIST v1.1 or in bone as per PCWG3. Any ambiguous results are to be confirmed by other imaging modalities (e.g., CT or MRI scan).
7. Have a disease that is PSMA-positive, as demonstrated by a ⁶⁸Ga-PSMA-11 PET/CT or PET/MRI scan and confirmed as eligible by the Sponsor's appointed BICR. Imaging-based eligibility review will be performed in two stages:
 - a. Presence of metastases for exclusion: Screening CT and MRI will be assessed to exclude participants with brain metastasis with long-axis ≥ 1 cm.
 - b. PSMA PET eligibility: Screening ⁶⁸Ga-PSMA-11 PET/CT or PET/MRI will be assessed along with CT, MRI, and bone scans utilizing tumor-to-liver ratio (TLR) for PSMA positivity-based inclusion and exclusion. TLR is defined as the ratio of tumor lesion SUV_{max} to liver SUV_{mean} derived from a 3 cm 3D spherical region of interest (ROI).

PSMA positivity is defined as:

At least 1 lesion with PSMA TLR ≥ 2 .

PSMA exclusion criteria:

The presence of any of the following will result in the patient being **ineligible** for this trial:

- i. Visceral metastatic lesions that are ≥ 1 cm that have a PSMA TLR < 1
 - ii. Lytic bone metastatic lesions with a soft tissue component of at least 1 cm with a TLR < 1
 - iii. At least one metastatic lymph node lesion with short axis ≥ 2.5 cm with a TLR < 1
8. Must have recovered to $\leq$ Grade 1 from all clinically significant toxicities related to prior therapies (i.e., surgery, local radiotherapy, ARPI, chemotherapy, etc.) except for alopecia. Specific conditions may be discussed with the medical monitor (MM) as needed.
9. Have adequate organ function at Screening:
 - a) Bone marrow:
 - i. Platelets $\geq 150 \times 10^9/L$.
 - ii. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$.
 - iii. Hemoglobin ≥ 10 g/dL (with no red blood cell [RBC] transfusion in the previous 4 weeks).
 - b) Liver function:
 - i. Total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN). For participants with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted.
 - ii. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
 - c) Renal function:
 - i. Creatinine clearance ≥ 45 mL/min determined using the Cockcroft-Gault formula.
10. Have the capacity to understand the study and be able and willing to comply with all protocol requirements.
11. Participants must comply with the radiation protection rules (including hospital admissions and isolation) that are used by the treating institution to protect their contacts and the public, especially if a female partner of the participant is or could be pregnant.
12. For enrollment in France, verification and confirmation of the participant's social security affiliation is required.
13. Must agree to practice adequate precautions to prevent pregnancy in a partner and to avoid potential problems associated with radiation exposure to the unborn child (Recommendations related to contraception and pregnancy testing in clinical trials Version 1.1 [Clinical Trial Facilitation Group {[CTFG, 2020](#)}])).

Exclusion Criteria:

Participants will be excluded from the study if any of the following criteria apply:

1. Is unable to understand or is unwilling to sign a written informed consent document or to follow investigational procedures in the opinion of the Investigator.
2. Has prostate cancer (PC) associated with pathological findings consistent with small cells or any histology other than adenocarcinoma of the prostate. If there are minor ($<20\%$) elements of neuroendocrine histology, this is acceptable.
3. Participants with a history of other malignancies that could significantly impact life expectancy or interfere with disease assessment will be excluded. **Exceptions** apply to participants with:

- a) Prior malignancy that has been adequately treated and has remained disease-free for at least 3 years (maybe confirmed by a scan etc.).
- b) Adequately treated non-melanoma skin cancer.
- c) Superficial (non-muscle invasive) bladder cancer that is controlled and stable.
- 4. Has received prior treatment with mAb J591 or HuJ591 or any other PSMA targeted therapy.
- 5. Have received chemotherapy in the mCRPC setting (note: prior docetaxel uses in the mCSPC setting with CHAARTED or STAMPEDE regimens is permitted if the last dose of therapy was ≥ 6 months prior to screening and ≥ 4 cycles of docetaxel were administered).
- 6. Has known allergies, hypersensitivity, or intolerance to the IMP or its excipients.
- 7. Has received prior systemic anti-cancer therapy (e.g., chemotherapy, immunotherapy, or biological therapy) and/or radiation therapy within 4 weeks of enrollment (excluding ARPI and/or LHRH analogues).

OR

if any significant AEs have not resolved to National Cancer Institute (NCI) AE Criteria ≤ 2 .

OR

are receiving other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.

- 8. Has received prior treatment with radioisotopes, including but not limited to: ⁸⁹Strontium, ¹⁵³Samarium, ¹⁸⁶Rhenium, ¹⁸⁸Rhenium, ²²³Radium, or hemi-body irradiation within 6 months prior to enrollment.
- 9. Has received another investigational therapy within 4 weeks of enrollment.
- 10. Has known brain metastases with long-axis ≥ 1 cm.
- 11. Has a history of seizure and/or stroke within the past 6 months.
- 12. Has clinical or radiologic findings indicative of impending spinal cord compression or experience symptomatic spinal cord compression.
- 13. Has evidence of a serious active or sub-clinical infection or angina pectoris (New York Heart Association [NYHA] Class III or IV), significantly prolonged QT interval or other serious illness(es) involving the cardiac, respiratory, central nervous system, renal, hepatic or hematological organ systems, that might impair the ability to complete this study or could interfere with determination of causality of any adverse effects experienced in this study, or which require treatment that could interact with study treatment, particularly with enzalutamide.
- 14. Has received treatment with any PARP inhibitors (i.e., olaparib) or with any platinum based anti-neoplastic drugs.