XALute

A Phase 3, Open-label, Multicenter, Randomized Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Chemotherapy

Based on protocol amendment 3 dated 23 September 2025

Study Contacts

Inclusion Criteria

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

Key Inclusion Criteria:

101. Subject has provided informed consent(s) prior to initiation of any study specific activities/procedures.
102. Age ≥ 18 years (or ≥ legal age within the country if it is older than 18 years) at the time of signing the informed consent.
103. Subject must have histological, pathological and/or cytological confirmation of adenocarcinoma of the prostate. Mixed histologies (eg, adenocarcinoma with neuroendocrine component) are not permitted.

Key Inclusion Criteria (cont)

104. mCRPC with ≥ 1 metastatic lesion that is present on baseline computed tomography (CT), magnetic resonance imaging (MRI), or bone scan imaging obtained within 28 days prior to enrollment.

105. Evidence of progressive disease, defined as 1 or more PCWG3 criteria:

    - Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL. This must be assessed locally for eligibility (see Protocol Schedule of Activities Section 1.3).
    - Soft-tissue progression defined as an increase ≥ 20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-target lesions.
    - Progression of bone disease defined by the appearance of at least 2 new bone lesions(s) by bone scan (as per the 2+2 PCWG3 criteria).

106. Subjects must have prior orchiectomy and/or ongoing androgen-deprivation therapy and a castrate level of serum testosterone (< 50 ng/dL or < 1.7 nmol/L). This must be assessed locally for eligibility (see Protocol Schedule of Activities Section 1.3).

107. Prior progression on at least one ARDT (enzalutamide, abiraterone, apalutamide, darolutamide).

Key Inclusion Criteria (cont)

108. Prior treatment with only one taxane therapy in the mCRPC setting. Note: Prior treatment with docetaxel in the

mHSPC setting is permitted; however, subjects must have also received one, and only one, taxane therapy in the mCRPC setting.

110. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

111. Adequate organ function, defined as follows:

- Hematological function:
  - White blood cell count ≥ 2.5 x 10^9/L AND absolute neutrophil count ≥ 1.5 x 10^9/L.
  - Platelet count ≥ 100 x 10^9/L.
  - Hemoglobin ≥ 9 g/dl (90 g/L) without transfusion within 14 days of screening assessment used for eligibility.
- Renal function:
  - Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 30 ml/min/1.73 m^2.
- Hepatic function:
  - AST and ALT ≤ 3 X upper limit of normal (ULN) (or ≤ 5 X ULN for subjects with liver involvement).
  - Total bilirubin (TBL) ≤ 1.5 X ULN (or ≤ 2 X ULN for subjects with liver involvement). For patients with known Gilbert's Syndrome, TBL ≤ 3 X ULN is permitted.
- Pulmonary function:
  - Baseline oxygen saturation > 92% on room air at rest and no oxygen supplementation.

Key Inclusion Criteria (cont)

- Cardiac function:
  - Left ventricular ejection fraction > 50% (screening echocardiography only required in subjects with known history of cardiac disease, prior MI, angina pectoris, coronary artery bypass graft [CABG], angioplasty, stent placement).

112. Life expectancy of ≥ 12 weeks per treating physician's assessment.

Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Prior & Concomitant Therapy

201. Prior STEAP1-targeted therapy.
202. Any anticancer therapy, immunotherapy, or investigational agent within 4 weeks prior to first dose of study treatment, with the following exceptions:
    - Androgen receptor pathway inhibitors (ARPIs; abiraterone, enzalutamide, darolutamide, apalutamide): minimum washout of 2 weeks prior to the first dose of study treatment.
    - Androgen suppression therapy (eg, luteinizing hormone-releasing hormone/gonadotropin-releasing hormone [LHRH/GnRH] analogue, agonist, or antagonist) is permitted.
203. Prior PSMA RLT within 3 months of first dose of study treatment unless subjects received < 2 cycles of therapy.
205. Prior palliative radiotherapy within 2 weeks of first dose of study treatment. Subjects must have recovered from all radiation-related toxicities.
206. Concurrent cytotoxic chemotherapy, ARDT, immunotherapy, radioligand therapy, PARP inhibitor, biological therapy, investigational therapy. Note: Prior treatment with a PARP inhibitor is permitted as long as not within 4 weeks before first dose of study treatment.
225. Prior radionuclide therapy (Radium-223) within 2 months of first dose of study treatment.

Prior & Concomitant Therapy (cont)

227. Treatment with live and live-attenuated vaccines within 4 weeks before the first dose of study treatment.
230. Prior CD3-directed therapy

Disease Related

207. Patients with a history of central nervous system (CNS) metastasis. Note: Subjects with treated, asymptomatic, and clinically stable dural metastases are eligible.
208. Unresolved toxicities from prior anti-tumor therapy not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 events grade above 1 or baseline, with the exception of alopecia or toxicities that are stable and well-controlled AND there is an agreement to allow inclusion by both the investigator and the sponsor.

Other Medical Conditions

209. History of malignancy that is expected to alter life expectancy or may interfere with disease assessments. Subjects with prior history of malignancy that have been adequately treated and who have been disease-free for > 3 years are eligible, as are subjects with adequately treated non-melanoma skin cancer or superficial bladder cancer.
210. History of allergic reactions or acute hypersensitivity reactions to the components of the study therapies and their analogs. Subjects with known contraindications to high-dose corticosteroids are also excluded. Subjects with a known hypersensitivity to docetaxel and pursuing intention to treat with second ARDT are eligible.
211. Active autoimmune disease that has required systemic treatment (except replacement therapy) within the past 2 years or any other diseases requiring immunosuppressive therapy while on study.

Other Medical Conditions (cont)

212. History or evidence of inflammatory bowel disease (ulcerative colitis or Crohn's disease) or any other gastrointestinal disorder causing chronic nausea, vomiting, or diarrhea (defined as CTCAE ≥ grade 2).
213. Evidence of interstitial lung disease or active, non-infectious pneumonitis, or uncontrolled asthma.
214. Recent history of arterial or venous thrombosis (eg, stroke, transient ischemic attack, pulmonary embolism, or deep vein thrombosis) within 6 and 3 months prior to first dose of study treatment, respectively. Note: Subjects with a history of venous thrombosis must be on stable anticoagulation.
215. Recent history of myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association ≥ class II) within 12 months of first dose of study treatment, with the exception of ischemia or non-ST segment elevation myocardial infarction controlled with stent placement and confirmed by a cardiologist more than 6 months prior to first dose of study treatment.
216. Known:
    - Human immunodeficiency virus (HIV) infection (subjects with HIV infection on antiviral therapy and undetectable viral load are permitted with a requirement for regular monitoring for reactivation for the duration of treatment on study).
    - Hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response after antiviral therapy are allowed).
    - Hepatitis B infection (subjects with hepatitis B surface antigen [HBsAg] or core antibody that achieve sustained virologic response with antiviral therapy are permitted with a requirement for regular monitoring for reactivation for the duration of treatment on the study).

Other Medical Conditions (cont)

217. Concurrent serious medical conditions, including, but not limited to, uncontrolled hypertension, uncontrolled infection, contraindications to or unacceptable risk associated with receiving the intended SOC control arm therapy (cabazitaxel, enzalutamide or abiraterone, depending on the planned intention to treat) or other significant co-morbid conditions including somatic or psychiatric disease/condition that in the opinion of the investigator would impair study participation or cooperation.
218. History of solid organ transplant.
219. Major surgical procedures within 4 weeks prior to first dose of study treatment. Port placement is not considered a major surgical procedure.
226. Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as determined by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, corrected QT interval by Fredericia prolongation > 480 ms, electrolyte disturbances, etc), or patients with congenital long QT syndrome.
228. Patients receiving antiviral therapy who meet the aforementioned criteria are eligible only if their antiviral regimens do not pose significant drug-drug interactions with the study treatments.

Prior/Concurrent Clinical Study Experience

221. Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(ies). This does not apply to other investigational

procedures or participation in observational research studies.

229. Subjects who have previously participated in a clinical trial involving xaluritamig, regardless of whether they received xaluritamig or any other therapy as part of that trial.

Other Exclusions

222. Male subjects who are unwilling to abstain from donating sperm during treatment and male subjects with a pregnant partner or partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 6 months after the last dose of xaluritamig, an additional 4 months after last dose of cabazitaxel, an additional 3 months after last dose of enzalutamide, or an additional 3 weeks after last dose of abiraterone acetate. Refer to Protocol Section 11.5 for additional contraceptive information.
223. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.
224. History or evidence of any other clinically significant disorder, condition, or disease (except for those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety, sor interfere with the study evaluation, procedures, or completion.