

Supplementary Methods

Full Eligibility Criteria

Inclusion Criteria

Patients were eligible to be included in the study only if all of the following criteria apply:

1. Patient has provided informed consent/assent before initiation of any study-specific activities/procedures.
2. Age ≥ 18 years.
3. Histologically or cytologically confirmed mCRPC who are refractory to a novel antiandrogen therapy (abiraterone acetate and/or enzalutamide, apalutamide, or darolutamide) and had treatment failure with 1–2 taxane regimens including for metastatic hormone-sensitive prostate cancer (or who are deemed medically unsuitable to be treated with a taxane regimen or have actively refused treatment with a taxane regimen). A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane.
 - a. Dose exploration phase: Novel antiandrogen therapy must have been given for treatment of metastatic disease.
4. Patients must have undergone bilateral orchiectomy or be on continuous androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist or antagonist.
5. Total serum testosterone ≤ 50 ng/dL or 1.7 nmol/L.
6. Evidence of progressive disease, defined as 1 or more PCWG3 criteria:
 - a. PSA level ≥ 1 ng/mL that had increased on at least 2 successive occasions at least 1 week apart.
 - b. Nodal or visceral progression as defined by RECIST 1.1 with PCWG3 modifications.
 - c. Appearance of ≥ 2 new lesions in bone scan.

7. ECOG performance status of 0–1.
8. Life expectancy ≥ 3 months.
9. Adequate organ function, defined as follows:
 - a. Hematologic function: absolute neutrophil count $\geq 1 \times 10^9/L$ (without growth factor support within 7 days from screening assessment)
 - i. Absolute neutrophil count $> 1.5 \times 10^9/L$
 - ii. Platelet count $\geq 75 \times 10^9/L$ (without platelet transfusion within 7 days from screening assessment)
 - iii. Hemoglobin ≥ 9 g/dL (90 g/L; without blood transfusion within 7 days from screening assessment)
 - b. Renal function
 - i. Estimated glomerular filtration rate based on Modification of Diet in Renal Disease) calculation ≥ 30 mL/min/1.73 m²
 - c. Hepatic function
 - i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 3 \times$ upper limit of normal (ULN; or $< 5 \times$ ULN for patients with liver involvement)
 - ii. Total bilirubin $< 1.5 \times$ ULN (or $< 2 \times$ ULN for patients with liver metastases)
 - d. Cardiac function
 - i. Left ventricular ejection fraction $> 50\%$ (2D transthoracic echocardiogram [ECHO] is the preferred method of evaluation; multi-gated acquisition scan is acceptable if ECHO is not available)
 - ii. Baseline electrocardiogram QTcF ≤ 470 msec

Exclusion Criteria

Patients were excluded from the study if any of the following criteria apply:

Disease Related

1. Pathologic finding consistent with pure small cell, neuroendocrine carcinoma of the prostate or any other histology different from adenocarcinoma.
2. Radiation therapy within 4 weeks of first dose (or local or focal radiotherapy within 2 weeks of first dose).
3. Untreated central nervous system (CNS) metastases or leptomeningeal disease.

Patients with a history of treated CNS metastases were eligible if there was radiographic evidence of improvement upon completion of CNS-directed therapy and no evidence of interim progression between completion of CNS-directed therapy and the screening radiographic study.

Other Medical Conditions

4. Prior major surgery within 4 weeks of first dose.
5. Confirmed history or current autoimmune disease or other diseases resulting in permanent immunosuppression or requiring permanent immunosuppressive therapy.
6. Symptoms and/or clinical signs and/or radiographic signs that indicated an acute and/or uncontrolled active systemic infection within 7 days before the first dose of treatment. Simple urinary tract infections and uncomplicated bacterial pharyngitis were permitted if responding to active treatment and after consultation with sponsor. Screening for chronic infectious conditions was not required.
7. Positive test for human immunodeficiency virus (HIV).
8. Exclusion of hepatitis infection based on the following results and/or criteria:
 - a. Positive for hepatitis B surface antigen (HBsAg; indicative of chronic hepatitis B or recent acute hepatitis B).
 - b. Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) was necessary. Detectable hepatitis B virus DNA suggested occult hepatitis B.

- c. Positive hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR was necessary. Detectable hepatitis C virus RNA suggested chronic hepatitis C.
- 9. History of arterial or venous thrombosis (eg, stroke, transient ischemic attack, pulmonary embolism, or deep vein thrombosis); for arterial thrombosis within 12 months of xaluritamig initiation; for venous thrombosis, 6 months and stable on anticoagulation.
- 10. Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association >class II) within 12 months of first dose of xaluritamig with the exception of ischemia or non-ST segment elevation myocardial infarction controlled with stent placement and confirmed by a cardiologist >6 months before first dose of xaluritamig.
- 11. Unresolved toxicities from prior antitumor therapy not having resolved to CTCAE version 5.0 grade 1, with the exception of alopecia or toxicities that are stable and well controlled AND there is agreement to allow by both the investigator and sponsor.
- 12. History of other malignancy within the past 2 years, with the following exception(s):
 - a. Malignancy treated with curative intent and with no known active disease present for ≥ 1 year before enrollment and felt to be at low risk for recurrence by the treating physician
 - b. Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
 - c. Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- 13. History or evidence of inflammatory bowel disease (ulcerative colitis or Crohn disease) or any other gastrointestinal disorder causing chronic nausea, vomiting, or diarrhea (defined as ≥ 2 CTCAE grade 2).
- 14. Evidence of interstitial lung disease or active, noninfectious pneumonitis, or uncontrolled asthma.

Prior/Concomitant Therapy

15. Prior STEAP1-targeted therapy.
16. Any anticancer therapy or immunotherapy within 4 weeks of start of first dose, not including luteinizing hormone-releasing hormone/GnRH analog (agonist/antagonist). Prior PSMA radionuclide therapy within 6 months before xaluritamig unless patients received ≤ 2 cycles of therapy (patient cannot have received PSMA radionuclide therapy <35 days before enrollment if 1 cycle was given, and <65 days if 2 cycles were given). Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days before enrollment were eligible.
17. Requirement for chronic systemic corticosteroid therapy (prednisone dose >10 mg/day or equivalent) or any other immunosuppressive therapies (including anti-TNF- α therapies) unless stopped (with adequate tapering) within 7 days before dosing.

Prior/Concurrent Clinical Study Experience

18. Patient was receiving treatment in another investigational device or drug study or >4 weeks since ending treatment on another investigational device or drug study. Other investigational procedures while participating in this study were excluded with the exception of investigational scans.

Other Exclusions

19. Male patients with a female partner of childbearing potential who were 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.
20. Patient has known sensitivity to any components of xaluritamig.
21. Patient 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 patient and investigator's knowledge.
22. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or

physician, if consulted, would pose a risk to patient safety or interfere with the study evaluation, procedures or completion.

Dose-limiting toxicities

DLTs were defined as any xaluritamig-related AEs occurring within 28 days following the first dose with any of the following criteria:

- Grade 5 toxicity (eg, death not due to disease progression)
- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia with significant hemorrhage of any duration
- Grade 4 neutropenia ≥ 5 days
- Grade 3 or 4 febrile neutropenia
- Grade ≥ 3 nonhematologic toxicity of any duration, except:
 - Grade 3 or 4 nausea, vomiting, or diarrhea that resolves in 3 days in the absence of maximal medical therapy
 - Grade 3 fatigue lasting < 5 days
 - Grade 3 hypertension that can be controlled with medical therapy
 - Increase of indirect (unconjugated) bilirubin indicative of M. Meulengracht/Gilbert's syndrome
 - Serum lipase and/or serum amylase CTCAE grade 3 present for ≤ 7 consecutive days without clinical signs or symptoms of pancreatitis
 - Grade 3 fever resolving to grade ≤ 1 within 3 days
 - Grade 3 transaminitis associated with CRS that resolves to grade ≤ 1 within 3 days
 - Lymphopenia or lymphocyte count decreased of any grade

- Laboratory parameters of grade ≥ 3 , not considered clinically relevant, and improved to grade ≤ 2 within 72 hours
- Aspartate aminotransferase or alanine aminotransferase values $>3\times$ ULN AND with serum total bilirubin (TBIL) level $>2\times$ ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (ie, criteria for Hy's law indicative of severe drug-induced liver injury [DILI]).
- Grade ≥ 3 nonhematologic toxicity that delays administration of study drug >14 days or results in administration of 75% or 50% for QW or Q2W schedules, respectively, or less of the anticipated dose.