Official title: A Multi-center, Randomized, Open-label Clinical Trial Comparing a 6-month vs Long-term Course of Rezvilutamide With ADT Plus Chemotherapy in High Tumor Burden mHSPC

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Project name	A Multi-center, Randomized, Open-label Clinical Trial Comparing a 6-month vs Long-term Course of Rezvilutamide With ADT Plus Chemotherapy in High Tumor Burden mHSPC .
Primary Objective:	To explore whether a 6-month course of Rezvilutamide in the triple therapy regimen is non-inferior to long-term Rezvilutamide treatment in improving radiographic progression-free survival (rPFS) in patients with high tumor burden metastatic hormone-sensitive prostate cancer (mHSPC). Secondary Objectives: To evaluate and compare the time to prostate-specific antigen (PSA) progression, time to next bone-related event, time to initiation of subsequent anti-prostate cancer treatment, and objective response rate (ORR) between the 6-month course of Rezvilutamide and long-term androgen deprivation therapy (ADT) plus docetaxel treatment in patients with high tumor burden mHSPC. To assess and compare the incidence of adverse events between the 6-month course of Rezvilutamide and long-term ADT plus docetaxel treatment in patients with high tumor burden mHSPC. Exploratory Objectives: To observe the circulating tumor cell status at 6 months, 12 months, 18 months, and 24 months in patients with high tumor burden mHSPC receiving the triple therapy regimen.
Primary Study Endpoints:	Radiographic progression-free survival (rPFS) Secondary Study Endpoints: Time to prostate-specific antigen (PSA) progression Time to next bone-related event (including fractures, spinal cord compression, radiation therapy, or surgery targeting the bones) Time to initiation of subsequent anti-prostate cancer treatment Objective response rate (ORR) Quality of life assessment scores Exploratory Study Endpoint: Circulating tumor cell detection rate

Study Subjects	Patients with mHSPC have a confirmed pathology of prostate adenocarcinoma with high tumor burden, which is defined by having at least one of the following conditions: 1) Bone scan showing ≥4 bone metastatic lesions (with at least one site outside the pelvis or spine). 2) CT/MRI revealing visceral metastatic lesions (excluding lymph nodes).
Numbers	In this study, a total of 100 cases were included.
Study design	The study design is a single-center, randomized, positive drug-controlled, open-label clinical trial. The subjects were randomized and stratified based on the following factors: 1. ECOG performance status (whether greater than 0). 2. Presence of visceral metastatic lesions (excluding lymph nodes).
Drugs	Rezvilutamide Luteinizing hormone-releasing hormone analogs (LHRHa) Docetaxel
Drugs regimen	Rezvilutamide: 240 mg, once daily, oral administration. Luteinizing hormone-releasing hormone analogs (LHRHa): Subcutaneous injection, every 1 or 3 months. Docetaxel: 75 mg/m2 body surface area, intravenous infusion, Day 1, every 21 days for 6 cycles. Prednisone: 5 mg, twice daily, oral administration, from Day 1 to Day 21.
Patients selection	Inclusion criteria: 1. Age ≥ 18 years, male. 2. Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1. 3. Histologically or cytologically confirmed prostate adenocarcinoma without evidence of neuroendocrine or small cell features. 4. High tumor burden, defined as having at least one of the following conditions: 1) Bone scan showing ≥4 bone metastatic lesions (with at least one site outside the pelvis or spine). 2) CT/MRI revealing visceral

	metastatic lesions (excluding lymph nodes). 5. Planned to receive or maintain androgen deprivation therapy (ADT) during the study period, either by continuous LHRHa treatment or previous bilateral orchiectomy (surgical castration), concurrently with 6 cycles of docetaxel chemotherapy. 6. Organ function levels must meet the following requirements: • Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L. • Platelets (PLT) ≥ 100 × 10^9/L. • Hemoglobin (Hb) ≥ 90 g/L. • Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN). • Alanine aminotransferase (ALT) ≤ 2.5 × ULN. • Aspartate aminotransferase (AST) ≤ 2.5 × ULN. • Blood urea nitrogen (BUN) (or urea) and creatinine (Cr) ≤ 1.5 × ULN. • Left ventricular ejection fraction (LVEF) ≥ 50%. 7. Judged by the investigator to be able to comply with the trial protocol. 8. Voluntarily participate in the clinical trial, understand the study procedures, and have signed the informed consent form.
	Exclusion criteria: 1. Prior treatment with ADT, chemotherapy, surgery, external beam radiation therapy, brachytherapy, radiopharmaceuticals, or investigational local therapies for prostate pain. However, the following cases are allowed for inclusion: • Up to 3 months of ADT (medical or surgical castration) with or without antiandrogen therapy

	prior to Cycle 1 Day 1 (C1D1) without evidence of radiographic disease progression (based on RECIST 1.1 criteria) or clinically significant PSA rise (defined as ≥50% increase from the lowest level after reaching castration levels of serum testosterone) before C1D1. • Transurethral prostatectomy or up to one course of palliative radiation therapy or surgery for symptomatic treatment of metastatic disease at least 4 weeks prior to C1D1. All adverse events related to these treatments must have improved to at least Grade 1 (according to NCI-CTCAE v4.03) before starting study treatment. 2. Prior use or planned use of second-generation androgen receptor antagonists (such as enzalutamide, apalutamide, darolutamide), abiraterone acetate, or other investigational drugs inhibiting testosterone synthesis for the treatment of prostate cancer during the study period. 3. Received the following treatments within 4 weeks before C1D1: • 5-alpha-reductase inhibitors (e.g., finasteride, dutasteride). • Estrogens, progestins, androgens, systemic corticosteroids (except for temporary use for allergic purposes). • Known herbal medicines with anti-prostate cancer or PSA-lowering effects (e.g., saw palmetto). • Participation in other clinical trials involving investigational treatments. 4. Confirmed brain tumor lesions on imaging. 5. Planned to receive any other anticancer treatment during the trial. 6. Known allergy or hypersensitivity to apalutamide, ADT, or chemotherapy components. 7. Presence of conditions that impede swallowing, chronic diarrhea, intestinal obstruction, or other factors affecting drug intake and absorption. 8. History of seizures or occurrence of conditions that can induce seizures within 12 months before C1D1 (including transient ischemic attack, stroke, traumatic brain injury with altered consciousness requiring hospitalization).

	9. Presence of active cardiac diseases within 6 months before C1D1, including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, and ventricular arrhythmias requiring medication. 10. Diagnosis of any other malignancy within 5 years before C1D1, except for completely resolved in situ cancer or malignancies with slow progression as determined by the investigator. 11. Active HBV or HCV infection (HBV viral load ≥ 10,000 copies/mL, HCV viral load ≥ 1,000 copies/mL). 12. History of immunodeficiency (including positive HIV test) or organ transplantation. 13. Unwillingness to use effective contraception during the entire study treatment period and for 30 days after the last dose. 14. Judged by the investigator to have conditions that pose a serious risk to patient safety, may confound study results, or may affect the patient's ability to complete the study (such as poorly controlled hypertension, severe diabetes, neurological or psychiatric diseases, etc.), or any other relevant circumstances.
Criteria of abandoning the study	The investigator may decide to discontinue the study drug treatment for a participant in the following circumstances: 1. The participant withdraws informed consent to continue receiving the study treatment. 2. The participant meets the criteria for radiographic disease progression in soft tissue and/or bone (as determined by each study center based on RECIST 1.1 and modified PCWG3 criteria, see section 4.3.1). 3. The participant experiences clinical disease progression accompanied by PSA progression (defined in section 8.1.2). Clinical progression is defined as worsening of prostate cancer-related symptoms that the investigator deems necessary to treat with any of the following: other anticancer treatments, radiation therapy, surgery, or intensified analgesic therapy (including the use of new opioid analgesics or increasing the dose or frequency of existing opioid analgesics). 4. The participant experiences any clinically significant adverse reactions, abnormal laboratory findings, or concurrent illnesses that, in the judgment of the investigator, make continued participation in the study

	not in the best interest of the participant. 5. The investigator deems it necessary to withdraw the participant from the study due to other reasons, such as poor compliance, inability to express a free will due to imprisonment or isolation, etc. 6. The participant dies or is lost to follow-up.
Criteria of candidates quitting	The discontinuation of study treatment for a participant does not automatically mean their withdrawal from the trial. The investigator may decide to withdraw a participant from the study in the following circumstances: 1. The participant withdraws informed consent for the collection of subsequent data. 2. The participant dies or is lost to follow-up. 3. The sponsor terminates the study.
Criteria of termination	If any of the following situations occur, the trial must be terminated: 1. Major errors are identified in the clinical trial protocol that make it difficult to effectively evaluate the drug. 2. The sponsor requests termination, ensuring the rights and safety of the participants. 3. Regulatory authorities or the ethics committee orders the termination of the trial for specific reasons.
Statistical approach	General Analysis: Unless otherwise specified, this study will employ the following methods for descriptive statistics. Continuous variables will be summarized using mean, standard deviation, median, maximum value, and minimum value. Categorical variables will be summarized using frequency and percentage. Time-to-event data will be analyzed using the Kaplan-Meier method to estimate survival rates and median survival time. When necessary, corresponding 95% confidence intervals will be provided for the aforementioned analyses. Efficacy Analysis: The efficacy analysis will involve the following methods: 1. Stratified Log-Rank test: It will be used to compare the rPFS (progression-free survival) between groups. The Kaplan-Meier method will be utilized to calculate the median time to rPFS, along with the two-sided 95% confidence interval. Additionally, a stratified Cox proportional hazards model will be employed to analyze the risk of the experimental group relative to the control group. The hazard ratio and its two-sided 95%

	confidence interval will be reported. 2. Kaplan-Meier method: This will be used to assess the time to PSA progression, time to next bone-related event, and time to initiation of next anti-prostate cancer treatment. Two-sided 95% confidence intervals will be provided for these analyses. 3. Clopper-Pearson method: It will be utilized to estimate the 95% confidence interval for the objective response rate (ORR). Furthermore, the overall analysis will include the summary of quality of life scores at various study visit points.
Study period	3 years