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

Date: July 13, 2023

Informed Consent Form

We invite you to participate in a multicenter, randomized, open-label clinical study titled "Rezvilutamide 6-months Course Compared with Long-Term Androgen Deprivation Therapy (ADT) + Docetaxel Chemotherapy in High Tumor Burden Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)". The study is led by Jiangsu Provincial People's Hospital and involves several renowned hospitals nationwide, including Jiangsu Cancer Hospital. Approximately 100 eligible subjects over the age of 18 who voluntarily participate will be enrolled in the study across these hospitals. The research has been reviewed and approved by the Ethics Committee of Jiangsu Provincial People's Hospital, and Dr. Huali Xin, the Director of Urology Department at our hospital, is responsible for this project. Our center plans to enroll 50 subjects. It is crucial for you to read and understand this informed consent form before agreeing to participate in this study. This document explains the research objectives, procedures, potential benefits, and risks you may face. It also outlines other treatment options available to you and your rights. You have the right to withdraw from the study at any stage. If you decide to participate, you will receive a copy of the informed consent form signed by both you and the researchers.
Why conduct this research?

Prostate cancer is the second most common malignant tumor in men globally in terms of incidence and the sixth most common cause of cancer-related deaths. The incidence of prostate cancer in China is lower than in Western countries, but it has been rapidly increasing in recent years. According to the latest statistics from the National Cancer Center, in 2015, there were approximately 60,300 new cases of prostate cancer and 26,600 deaths in China, ranking it as the 7th most common and 10th most lethal cancer in males. The incidence of prostate cancer is even higher in major cities, such as Beijing, Shanghai, and Guangzhou, where the incidence rates in 2009 were 19.30/100,000, 32.23/100,000, and 17.57/100,000, respectively, ranking them as the 5th, 5th, and 7th most common cancers among urban males. With the aging population and Westernized lifestyle, it is expected that the incidence of prostate cancer in China will continue to rise rapidly. Additionally, unlike Western countries, where only 10-15% of initial cases of prostate cancer are metastatic, in China, 20-30% of initial cases are already metastatic. Androgen deprivation therapy (ADT) with or without first-generation androgen receptor (AR) antagonists (such as bicalutamide, nilutamide) is the standard first-line treatment for metastatic prostate cancer. Although most patients initially respond to treatment, the disease progresses from metastatic hormone-sensitive prostate cancer (mHSPC) to metastatic castration-resistant prostate cancer (mCRPC) after an average of 18-24 months. The main mechanisms leading to castration resistance are continued adrenal androgen secretion, intratumoral androgen synthesis, AR overexpression, and acquired AR signaling pathway reactivation due to functional mutations.

The CHAARTED study showed that compared to ADT alone, ADT plus docetaxel significantly prolonged overall survival in mHSPC patients with high tumor burden (HR=0.63, P<0.001). Therefore, both domestic and international guidelines recommend ADT plus docetaxel as a treatment choice for high tumor burden mHSPC. In 2022, the latest data from a Phase III clinical study comparing second-generation anti-androgen therapy plus ADT plus docetaxel versus docetaxel plus ADT in the PEACE-1 study showed that the triple combination therapy of abiraterone plus ADT plus docetaxel significantly prolonged radiographic progression-free survival (rPFS) (HR=0.50, P<0.001) and overall survival (OS) (HR=0.75, P=0.017) in high tumor burden patients compared to the ADT plus docetaxel group.
According to the ARASENS study [12], compared to the placebo+ADT+docetaxel group, the darolutamide+ADT+docetaxel group significantly reduces the risk of death (HR=0.68, P<0.001). The 2022 Pan-Asia ESMO guidelines and 2022 CSCO guidelines have updated to include the abiraterone+ADT+docetaxel triple combination regimen in the treatment recommendations for high tumor burden mHSPC, and the darolutamide+ADT+docetaxel in the mHSPC recommendations.

Second-generation antiandrogen therapy has improved treatment benefits for advanced prostate cancer patients, and the safety of these treatment regimens should not be overlooked considering the effectiveness of tumor control. For example, long-term use of abiraterone in combination with prednisone can lead to peripheral edema, hypokalemia, liver toxicity, and increased risk of cardiovascular events. Long-term use of enzalutamide increases the risk of falls in the elderly and may increase the risk of tremors, cognitive impairment, and psychiatric disorders. At the same time, due to the need for elderly patients to take other medications for underlying diseases, enzalutamide and apalutamide are CYP inhibitors, which may cause the accumulation of drugs that require degradation through the CYP pathway in the body. Researchers have already paid attention to the safety issues of such drugs and compared the daily life and physical function side effects of enzalutamide and darolutamide, and the impact on the quality of life of elderly patients. At the same time, influenced by economic factors, in some underdeveloped areas, there are still many patients who cannot afford long-term high-cost second-generation antiandrogen drug treatment, so they have to give up such treatment [D].

Therefore, based on the above analysis, we should think deeply and consider the duration of second-generation antiandrogen therapy in combination with tumor control, drug safety, and economic factors. This study was designed to compare the efficacy and quality of life differences between a 6-month course of relugolix and a long-term course in combination with ADT+docetaxel in high tumor burden mHSPC subjects.

The primary objective of this study is to evaluate whether a 6-month course of relugolix in the triple therapy regimen is non-inferior to a long-term course of relugolix in improving radiographic progression-free survival (rPFS) in high tumor burden mHSPC patients.

What do you need to do if you participate in the study?

This study is a multicenter, randomized, positive drug-controlled, open-label clinical trial. It evaluates whether a 6-month course of degarelix in combination with androgen deprivation therapy (ADT) and docetaxel is non-inferior to a long-term course of degarelix in improving radiographic progression-free survival (rPFS) in patients with high tumor burden metastatic hormone-sensitive prostate cancer (mHSPC). The experimental group will receive degarelix (6 months) + ADT (long-term) + docetaxel (6 cycles), while the control group will receive degarelix (long-term) + ADT (long-term) + docetaxel (6 cycles). The entire study plans to enroll 100 patients with high tumor burden mHSPC, who will be randomly assigned in a 1:1 ratio to the experimental and control groups, with stratification factors including: 1. ECOG performance status > 0; 2. Presence of visceral metastasis. Participants are allowed to receive a maximum of 3 months of ADT treatment (with or without antiandrogen therapy) before cycle 1 day 1 (C1D1) of the study. Up to 4 weeks prior to C1D1, participants can undergo transurethral resection of the prostate or receive palliative radiotherapy or surgery for symptomatic metastatic disease (e.g., spinal cord compression or bone pain). Participants who have undergone prior ADT treatment must not have evidence of soft tissue disease progression (according to RECIST 1.1 criteria) or clinically significant prostate-specific antigen (PSA) increase (defined as ≥50% increase from the lowest level after reaching castration levels of testosterone) before C1D1. Participants who have received antiandrogen therapy prior to enrollment must discontinue it before C1D1 and beyond.

This study includes a screening period of up to 28 days to determine if subjects meet the eligibility criteria and complete the baseline assessments. During the treatment period of the study, subjects will receive investigational drug treatment according to the assigned group, until disease progression, intolerable toxicity, withdrawal of informed consent, or the investigator determines it necessary to withdraw the subject from the study.

Throughout the entire treatment period, subjects will continue to receive androgen deprivation therapy (ADT) (either through medication or surgical castration). Subjects receiving medication-based castration will follow the instructions in the drug package insert. Efficacy assessments for soft tissue and bone imaging will be conducted based on RECIST 1.1 criteria (see appendix) and the adjusted PCWG3 criteria (see section 8.1.1). An Independent Review Committee (IRC) will review the imaging evaluations from each study center.

Survival follow-up will begin after the last dose of medication on day 30 and will occur every 2 months through clinical or telephone follow-up. During these follow-ups, information regarding survival status, bone-related events (if they did not occur prior to the survival follow-up), and subsequent anti-tumor treatments will be

collected until subjects experience death, loss to follow-up, withdrawal of informed consent, or termination of the study by the sponsor.

If you agree to participate in this study, please sign this informed consent form. Prior to your inclusion in the study, your doctor will inquire about and record your medical history, and you will undergo screening tests such as MRI, CT, and hematology to confirm your eligibility based on inclusion criteria.

After enrollment, you will be randomly assigned to either the experimental group or the control group in a 1:1 ratio. The experimental group will receive enzalutamide (for 6 months), ADT, and docetaxel (for 6 cycles), while the control group will receive long-term enzalutamide, ADT, and docetaxel (for 6 cycles). Throughout the treatment period, you will need to undergo regular examinations and evaluations according to the study protocol. After completion of treatment, a survival follow-up will occur every 2 months.

3. What are the criteria for participating in this study? (Inclusion criteria) In order to participate in this study, you need to meet the following criteria:

4. Age ≥ 18 years, male.

5. Physical condition with ECOG score of 0-1.

6. Histological or cytological examination confirming prostate adenocarcinoma, without evidence of neuroendocrine differentiation or small cell features.

7. High tumor burden, defined as having at least one of the following conditions: 1) Bone scan showing ≥4 bone metastases (with at least one location outside of the pelvic or spinal bones); 2) CT/MRI revealing visceral metastases (excluding lymph nodes).

8. Planned study period of receiving or maintaining ADT (Androgen Deprivation Therapy), which entails continuous LHRHa treatment or previous bilateral orchiectomy (surgical castration), along with 6 cycles of docetaxel chemotherapy.

9. Organ function levels must meet the following requirements:

- Absolute neutrophil count (ANC) ≥ 1.5 × 109/L.
- Platelets (PLT) ≥ 100 × 109/L.
- Hemoglobin (Hb) ≥ 90 g/L.
- Total bilirubin (TBIL) ≤ 1.5 ×ULN (Upper Limit of Normal).
- Alanine transaminase (ALT) ≤ 2.5 × ULN.
- Aspartate transaminase (AST) ≤ 2.5 × ULN.
- Blood urea nitrogen (BUN) (or urea) and creatinine (Cr) ≤ 1.5 × ULN.

- Left ventricular ejection fraction (LVEF) ≥ 50%.

7. Ability to adhere to the study protocol, as determined by the investigator.
8. Voluntary participation in this clinical trial, understanding the study procedures, and having signed the informed consent.

If you require more detailed inclusion criteria for participating in this study or if you have any unclear phrases or information, please consult your research doctor.

4. Who should not participate in the study? (Exclusion criteria) You should not participate in this study if you have any of the following conditions:
5. Previous treatment with ADT (Androgen Deprivation Therapy), chemotherapy, surgery, external beam radiation therapy, brachytherapy, radioactive drugs, or experimental local treatments for prostate pain, such as radiofrequency ablation, cryotherapy, high-intensity focused ultrasound, etc. However, the following conditions allow enrollment: (1) up to 3 months of ADT treatment (medical or surgical castration) with or without anti-androgen therapy before the first day of the study cycle (C1D1), with no evidence of soft tissue disease progression (according to RECIST 1.1 criteria) or clinically significant PSA elevation before C1D1 (defined as an increase of ≥50% from the lowest level after reaching castrate levels of testosterone); (2) transurethral prostatectomy or up to one course of palliative radiotherapy or surgery at least 4 weeks prior to C1D1 for the treatment of symptoms caused by metastatic disease (e.g., spinal cord compression or bone pain). All adverse events related to these treatments must have at least a grade 1 resolution before starting the study treatment (according to NCI-CTCAE v4.03).
6. Previous use or planned use of second-generation anti-androgen receptor antagonists (such as enzalutamide, apalutamide, darolutamide), abiraterone acetate, or other investigational drugs that inhibit testosterone synthesis for the treatment of prostate cancer during the study treatment period.
7. Within 4 weeks before C1D1, you have received any of the following treatments:
    - 5α-reductase inhibitors (such as finasteride, dutasteride, etc.);
    - Estrogen, progesterone-like drugs, androgen, systemic corticosteroid treatment (except for temporary use for allergy purposes);
    - Known herbal medicines with anti-prostate cancer or PSA-lowering effects (e.g., saw palmetto);
    - Treatment in other clinical trials.
8. Confirmed brain tumor lesions by imaging diagnosis;
9. Planning to receive any other anti-tumor therapy during this trial;
10. Known allergy history to the components of relugolix, ADT, or chemotherapy drugs;

11. Presence of factors that affect swallowing, chronic diarrhea, bowel obstruction, or the intake and absorption of medication;
12. History of epilepsy or a disease that can induce seizures within 12 months before C1D1 (including transient ischemic attack history, stroke, brain trauma with consciousness disorders requiring hospitalization);
13. Active heart disease within 6 months before C1D1, including severe/unstable angina pectoris, myocardial infarction, symptomatic congestive heart failure, and ventricular arrhythmia requiring medication treatment;
14. Any other malignant tumor within 5 years before C1D1, except completely resolved in situ cancer or malignant tumors with slow progression, as determined by the investigator;
15. Active HBV or HCV infection (HBV viral load ≥104 copies/mL, HCV viral load ≥103 copies/mL);
16. History of immune deficiency diseases (including HIV positive test, other acquired or congenital immune deficiency diseases) or organ transplantation;
17. Patients who are unwilling to use effective contraception during the entire study treatment period and 30 days after the last dose;
18. Based on the investigator's judgment, the presence of comorbidities (such as poorly controlled hypertension, severe diabetes, neurological or psychiatric diseases, etc.) or any other condition that may pose a significant risk to patient safety, potentially confound study results, or affect the patient's ability to complete the study.

5. When can the study be terminated if I participate?

1. If you agree to participate in this study, you can terminate the study after completing the research tasks under the guidance of the research team.
2. During the study, you may terminate it midway under the following circumstances: a) Withdrawing informed consent (participants decide to withdraw for any reason); b) Any clinical adverse events, abnormal laboratory test results, or comorbidities identified by the researchers that are not in the best interest of the participants to continue receiving treatment and participating in the study; c) Inability to follow the study protocol.

6. What are the available treatment options? If you do not agree to participate in this study, you can choose from ADT monotherapy, ADT combined with abiraterone, or ADT combined with docetaxel. To determine which treatment option is more suitable for you, you can further consult with the specialist in the outpatient department.

7. What are the risks of participating in the study? The use of enzalutamide, ADT, and docetaxel in this study may have potential side effects, including:

- Diarrhea: Participants should be closely monitored for signs and clinical symptoms of colitis, such as diarrhea, abdominal pain, bloody or mucous stools, and fever. In symptomatic participants, infection should be ruled out, and if the symptoms persist and/or are severe, an endoscopic evaluation should be considered. It is recommended that participants with diarrhea drink plenty of water. If adequate fluid intake cannot be achieved through oral intake, fluid and electrolyte replacement should be administered intravenously.
- Anemia: Blood transfusion and hematopoietic growth factors may be used under the guidance of the researchers.
- Neutropenia: Granulocyte colony-stimulating factor (G-CSF) can be used to treat grade 3-4 febrile neutropenia.
- Bone pain: Bisphosphonates can be used to reduce the occurrence of bone disease, bone pain, and fractures under the guidance of the researchers. In addition, non-opioid analgesics can be used for symptomatic treatment.
- Anti-infective drugs: Participants with documented complications of infection can be administered oral or intravenous antibiotics or other anti-infective drugs according to standard hospital treatment protocols.
- Seizures: In the event of status epilepticus, intravenous diazepam 10 mg, rapid intravenous infusion of 20% mannitol, or intravenous dexamethasone 10-20 mg should be administered to prevent and treat brain edema. Blood glucose, electrolytes, arterial blood gas, and body temperature should be checked, and symptomatic treatment should be provided if abnormalities are detected.

We will monitor your hematological and non-hematological toxicities through regular examinations, observe the efficacy of the drug, and take appropriate measures for symptomatic treatment of adverse events. If you experience any discomfort or adverse reactions, please contact the research doctor promptly. Since enzalutamide, ADT, and docetaxel are conventional treatments for prostate cancer in clinical practice, there is a possibility of experiencing these side effects/adverse reactions even if you do not participate in this clinical study. In addition, any treatment may be ineffective, and the disease may continue to progress due to treatment failure or the presence of other comorbidities.

8. What are the potential benefits of participating in the research? By participating in this study, there is a possibility that your condition may improve (or it may not). This research also helps determine which treatment methods can effectively and safely treat other patients with similar conditions to yours.

9. Are there any costs associated with participating in the research? The cost of medications and related examinations used in the study, as well as outpatient fees, transportation costs, medication costs, and examination fees, are the responsibility of the patient. There are no other subsidies. If any harm

occurs as a result of the trial, appropriate treatment and compensation will be provided according to relevant national regulations.

10. Compensation and compensation: a) Compensation for participating in the study There will be no financial compensation for participating in this study or reimbursement of treatment-related costs. b) Compensation/compensation after an injury occurs For participants who experience harm related to this study, the sponsor will bear the cost of treatment and provide corresponding financial compensation in accordance with Chinese laws and regulations.

11. Is personal information kept confidential? The results of this research project may be published in medical journals with the understanding and assistance of you and other participants. However, we will keep your research records confidential as required by law. The personal information of research participants will be strictly protected, and your personal information will not be disclosed unless required by relevant laws. When necessary, government authorities, hospital ethics committees, and other relevant researchers may have access to your data according to regulations.

12. Am I required to participate in the research? Participating in this study is completely voluntary. You have the right to refuse participation or withdraw from the study at any stage without discrimination or retaliation, and your medical treatment and rights will not be affected. If you decide to withdraw from this study, please contact your doctor for appropriate diagnosis and treatment of your condition.

13. What other treatment options are available if I don't participate in this research? If you do not agree to participate in this study, you can choose between ADT monotherapy, ADT combined with abiraterone, or ADT combined with docetaxel. To determine which treatment option is more suitable for you, you can further consult with the attending expert in the outpatient clinic.

14. Who can I consult if I have questions? If you have any questions regarding research information and participant rights or if any research-related harm occurs, you can contact the researchers and the ethics committee along with their contact details. Researchers: Lixin Hua; Shangqian Wang, phone: 13770561625; Medical Ethics Committee of Jiangsu People's Hospital, phone: 025-68306360.

Informed Consent Form
Signature page

Subject's Declaration: I have read the introduction to this study and my research personnel have fully explained and clarified the purpose, procedures, potential risks, and potential benefits of participating in this study, and have answered all my relevant questions. I voluntarily agree to participate in this study.

I agree □ or refuse □ to allow my research data and biological samples to be used for other studies besides this research.

Subject's Printed Name: Subject's Signature: Date: _____ Year _____ Month _____ Day Subject's Contact Phone Number: Mobile Number: _____

Legal Guardian's Printed Name: (if applicable) Relationship with the subject: Legal Guardian's Signature: Date: _____ Year _____ Month _____ Day Reason for the legal guardian's signature:

Witness's Printed Name: (if applicable) Witness's Signature: Date: _____ Year _____ Month _____ Day Reason for witness's signature:

Doctor's Statement: I have explained the relevant details of this study to the volunteer participating in this study and provided them with an original signed informed consent form. I confirm that I have provided a detailed explanation of the study, particularly regarding the ethical principles and requirements of risks and benefits, free participation, compensation, harm and compensation, voluntary participation, and confidentiality.

Doctor's Signature: Date: _____ Year _____ Month _____ Day Doctor's Contact Phone Number:
Medical Ethics Committee, Jiangsu Provincial People's Hospital, Contact Phone Number: 025-68306360