Official title: Randomized Controlled Study on the Efficacy and Safety of Intermittent Darolutamide Treatment in the Triple Therapy of metastatic hormone sensitive prostate cancer.

Date: December 11, 2023

Summary of the Plan

Research Title:	Randomized Controlled Study on the Efficacy and Safety of Intermittent Darolutamide Treatment in the Triple Therapy of metastatic hormone sensitive prostate cancer.
Plan Number:	
Version Number	2.0
Version Date	November 21, 2023
Study Drug:	Darolutamide
Principal Investigator:	Hua Lixin
Participating Center:	Jiangsu People's Hospital
Research Objective:	To evaluate the efficacy and safety of intermittent use of darolutamide compared to long-term use in combination with ADT and docetaxel in the treatment of mHSPC patients.
Study Endpoints:	• Primary Endpoint: • Radiographic Progression Free Survival (rPFS) Secondary Endpoints: • Overall Survival (OS) • Time to castration-resistant prostate cancer (Time to mCRPC) • Time to pain progression (TTPP) • Safety • Quality of Life (QOL)
Study Population:	Patients enrolled are those with metastatic hormone-sensitive prostate cancer (mHSPC)
Study Design and Treatment Regimen	Patients will firstly receive 6 months of darolutamide in combination with docetaxel and ADT treatment. 1. When the patient reaches: 1. PSA ≤ 0.2ng/ml 2. Or PSA > 0.2ng/ml but with more that 90% decrease comparing baseline 3. Without newly discovered metastatic lesions. They will be randomly assigned in a 1:1 ratio to either continuous treatment group or intermittent treatment group (1) Continuous treatment group: Darolutamide: 600mg,

	bid+ADT: Leuprorelin (3.6mg qm or 10.8mg q3m) or goserelin 80mg qm until mCRPC; (2) Intermittent treatment group: Only ADT as background treatment without Darolutamide. PSA check every three months, when the patient's PSA > 1ng/ml (or PSA > 1ng/ml and PSA has risen by more than 20% comparing baseline), restart the darolutamide, until mCRPC. 2. When the patient: 1. PSA > 0.2ng/ml and has not decreased by 90% compared to baseline 2. Or has new metastatic lesions, they will exit the study. Imaging assessment will be conducted every 3 months
Key Inclusion Criteria	Patients must meet all of the following criteria to be eligible for this study: 1. Male aged ≥18 years; 2. Histologically or cytologically confirmed prostate adenocarcinoma; 3. Metastatic disease (confirmed by conventional imaging); 4. ECOG performance status of 0-1; 5. Suitable for ADT and docetaxel treatment; 6. Good bone marrow, kidney, and liver function: 1. (1) Hematological examination (no blood transfusion or use of hematopoietic growth factors within 7 days before screening): 1. Hemoglobin (HB) ≥ 90g/L; 2. Absolute neutrophil count (ANC) ≥ 1.5×109/L; 3. Platelets (PLT) ≥ 80×109/L; 2. (2) Blood biochemistry examination (no blood transfusion or albumin within 7 days before screening): 1. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN 2. Total bilirubin (TBIL) ≤ 2.0 × ULN; 3. Serum creatinine (Cr) ≤ 2.0×ULN; 7. Willing to participate in this study, sign an informed consent form, and

	have good compliance
Exclusion Criteria:	1. No metastatic disease; 2. Prior treatment with: a) Second-generation ARis or other experimental ARis b) CYP17 enzyme inhibitors such as abiraterone acetate or oral ketoconazole for anti-tumor treatment of prostate cancer c) Chemotherapy or immunotherapy prior to randomization for prostate cancer 3. Received radiotherapy within 2 weeks before starting 6 months of darolutamide + docetaxel + ADT treatment; 4. Stroke, myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass surgery, congestive heart failure (New York Heart Association class III or IV); 5. History of malignant tumors; 6. Planned receipt of other anti-tumor treatment during the study treatment period; 7. Known allergy to the above drug components; 8. Difficulty swallowing, chronic diarrhea, intestinal obstruction, and various factors affecting drug intake and absorption; 9. Refusal to sign the informed consent form; 10. Investigator's opinion that the participant is not suitable for inclusion.
Assessment Criteria:	Safety assessment: Adverse events will be evaluated using NCI-CTC AE 5.0 criteria. Efficacy assessment: Response will be evaluated using RECIST 1.1 criteria.
Safety Indicators	Blood and biochemical tests (ALT, AST, TB, DB, BUN, Cr, electrolytes), 12-lead electrocardiogram, coagulation function, etc.
Termination of Treatment Standard:	1. When one of the following occurs after 6 months of treatment with Darolutamide + Docetaxel + ADT: a. PSA > 0.2ng/ml and has not decreased by 90% compared to baseline b. Presence of newly discovered metastatic lesions 2. The patient has completed the prescribed treatment and follow-up plan. 3. Disease progression (PD) is determined based on the efficacy evaluation criteria, i.e., progression to mCRPC. Definition of progression to mCRPC:

	Either of the following conditions is met: a. Biochemical progression: Testosterone < 50ng/dl or 1.7nmol/l, PSA > 2ng/ml, continuous increase of more than 50% compared to baseline b. Radiographic progression: Bone scan reveals ≥2 new bone lesions or RECIST assessment shows enlargement of soft tissue lesions 4. The investigator considers it necessary to terminate the treatment in the best interest of the patient. 5. Occurrence of intolerable or unexpected adverse reactions or serious adverse events. 6. Inability to complete the treatment according to the trial protocol even after dose adjustment for grade 3/4 adverse events. 7. Patients with treatment delay > 4 weeks. 8. Medical or ethical reasons affecting the continuation of the study. 9. Poor patient compliance. 10. Use of other anti-tumor drugs that affect efficacy assessment (e.g., chemotherapy, targeted therapy, or biologic therapy). 11. Death. 12. Other situations deemed necessary for the patient to withdraw from the study.
Withdrawal from the Study	Reasons for subject withdrawal from the study may include: 1. Subject withdrawal of informed consent, refusal to continue follow-up. 2. Discovery of subject's ineligibility after enrollment. 3. Medical imaging or clinical features indicating disease progression. 4. Occurrence of clinical adverse events, abnormal laboratory tests, or comorbidities, and the investigator deems continued participation not in the subject's best interest. 5. Subject experiences a pregnancy event during the study. 6. Loss to follow-up or death. 7. Other reasons deemed by the investigator as unable to continue the treatment.
Termination of the Study	Termination of the trial refers to the premature cessation of the entire trial as per

	the protocol. The purpose of terminating the trial early is mainly to protect the rights of the subjects, ensure the quality of the trial, and avoid unnecessary economic losses. Early termination of the clinical trial should be promptly communicated to all involved parties. 1. Discovery of unexpected, significant, or unacceptable risks to the subjects. 2. Major errors in the trial protocol identified during the trial execution. 3. Ineffectiveness of the investigational drug treatment or continuation of the trial is deemed meaningless. 4. Severe delays in subject enrollment or frequent protocol deviations, making trial completion extremely difficult.
Sample size:	80 cases

Data analysis:	• General analysis: Unless otherwise specified, this study will summarize the corresponding descriptive statistics based on the data type. Measures of central tendency such as mean, standard deviation (SD), median, minimum, and maximum will be used for quantitative data. Frequency and percentage will be used for categorical and ordinal data. Kaplan-Meier method will be used for time-event data to estimate the median time and the 95% confidence interval of the overall population. • Efficacy analysis: Data statistics will be conducted for PSA remission, complete remission rate (CR), partial remission rate (PR), objective remission rate (ORR), disease control rate (DCR). Kaplan-Meier method will be used to estimate the time and 95% confidence interval of the event endpoints (rPFS and OS), and to plot survival curves. • Safety analysis: Safety analysis will be based on all treated subjects. Adverse events will be graded according to NCI-CTCAE version 5.0, and descriptive statistics will be the primary summary method. AE, SAE, and other data will be statistically summarized according to groups. Abnormal changes in laboratory test results before the trial but after treatment, and their relationship with the investigational drug, will be described. The mean, standard deviation, median, minimum, and maximum values of vital signs and laboratory indicators before and after medication will be calculated, and paired t-tests will be used for comparison.
Projected progress of the trial	November 2023 - November 2028 Completion of enrollment within 12 months after the implementation of clinical research approval Follow-up period: 4 years

Informed Consent Form

We invite you to participate in a multicenter, randomized, open-label clinical study titled " Randomized Controlled Study on the Efficacy and Safety of Intermittent Darolutamide Treatment in the Triple Therapy of metastatic hormone sensitive prostate cancer". The study is led by Jiangsu Provincial People's Hospital and involves several renowned hospitals nationwide, including Jiangsu Cancer Hospital. Approximately 200 eligible subjects over the age of 40 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 150 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 primary objective of this study is to evaluate the efficacy and safety of intermittent use of darolutamide compared to long-term use in combination with ADT and docetaxel in the treatment of 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 the efficacy and safety of intermittent use of darolutamide compared to long-term use in combination with ADT and docetaxel in the treatment of mHSPC patients. The Continuous treatment group: Darolutamide: 600mg, bid+ADT: Leuprorelin (3.6mg qm or 10.8mg q3m) or goserelin 80mg qm until mCRPC; while the Intermittent treatment group: Only ADT as background treatment without Darolutamide., 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 Continuous treatment group: Darolutamide: 600mg, bid+ADT: Leuprorelin (3.6mg qm or 10.8mg q3m) or goserelin 80mg qm until mCRPC; while the Intermittent treatment group: Only ADT as background treatment without Darolutamide. 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:

8. Male aged ≥18 years;
9. Histologically or cytologically confirmed prostate adenocarcinoma;
10. Metastatic disease (confirmed by conventional imaging);
11. ECOG performance status of 0-1;
12. Suitable for ADT and docetaxel treatment;
13. Good bone marrow, kidney, and liver function:

    3. (1) Hematological examination (no blood transfusion or use of hematopoietic growth factors within 7 days before screening):

        1. Hemoglobin (HB) ≥ 90g/L;
        2. Absolute neutrophil count (ANC) ≥ 1.5×109/L;
        3. Platelets (PLT) ≥ 80×109/L;

    4. (2) Blood biochemistry examination (no blood transfusion or albumin within 7 days before screening):
        1. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
        2. Total bilirubin (TBIL) ≤ 2.0 × ULN;
        3. Serum creatinine (Cr) ≤ 2.0×ULN;

14. Willing to participate in this study, sign an informed consent form, and have good compliance

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. No metastatic disease;
6. Prior treatment with: a) Second-generation ARis or other experimental ARis b) CYP17 enzyme inhibitors such as abiraterone acetate or oral ketoconazole for anti-tumor treatment of prostate cancer c) Chemotherapy or immunotherapy prior to randomization for prostate cancer
7. Received radiotherapy within 2 weeks before starting 6 months of darolutamide + docetaxel + ADT treatment;
8. Stroke, myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass surgery, congestive heart failure (New York Heart Association class III or IV);
9. History of malignant tumors;
10. Planned receipt of other anti-tumor treatment during the study treatment period;
11. Known allergy to the above drug components;
12. Difficulty swallowing, chronic diarrhea, intestinal obstruction, and various factors affecting drug intake and absorption;
13. Refusal to sign the informed consent form;
14. Investigator's opinion that the participant is not suitable for inclusion.

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 darolutemide, 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: a) Compensation for participating in the study There will be no financial compensation for participating in this study or reimbursement of treatment-related costs.

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