Official title：Evaluating the Efficacy and Safety of Cytoreductive Prostatectomy combined with Triple or Dual Systemic therapy in patients with Metastatic Hormone-Sensitive Prostate Cancer

Date: March 20, 2024

Research Purpose: The primary research purpose is to evaluate:
The radiographic progression-free survival (rPFS) of metastatic hormone-sensitive prostate cancer (mHSPC) patients treated with androgen deprivation therapy (ADT) + second-generation antiandrogens ± chemotherapy combined with cytoreductive prostatectomy (CRP).

Secondary research purposes include:

1) Evaluating the safety of CRP in mHSPC patients during the perioperative period.
2) Assessing other efficacy indicators of ADT + second-generation antiandrogens ± chemotherapy combined with CRP in treating mHSPC, including time to PSA recurrence, time to castration-resistant prostate cancer (CRPC), overall survival (OS), overall survival rate, postoperative complication rate, and quality of life score assessed by the EORTC QLQ-C30 questionnaire.

Study Endpoints

1) The primary endpoint is rPFS.

Secondary endpoints include:
Safety endpoints: AE incidence, severity, abnormal laboratory indicators.
Efficacy endpoints: Time to PSA recurrence, time to CRPC, OS, overall survival rate, postoperative complication rate, and quality of life score assessed by the EORTC QLQ-C30 questionnaire.

Study Population: Patients with metastatic hormone-sensitive prostate cancer (mHSPC). Sample Size Determination: Subjects will be randomly assigned in a 1:1 ratio to receive either cytoreductive prostatectomy (CRP) combined with ADT+ second-generation antiandrogens ± chemotherapy (Group A) or ADT+ second-generation antiandrogens ± chemotherapy (Group B). Each group plans to enroll 100 cases, for a total of 200 cases.

Study Design: This trial is a multicenter, prospective, randomized controlled clinical study aimed at evaluating the effectiveness and safety of cytoreductive prostatectomy combined with ADT + second-generation antiandrogen ± chemotherapy in the treatment of metastatic hormone-sensitive prostate cancer. The plan is to include 200 eligible subjects.

Group A: Subjects will orally take one of the second-generation antiandrogen drugs (240 mg of apalutamide once daily; 240 mg of Rezvilutamide once daily; 600 mg of darolutamide twice daily; 240 mg of enzalutamide once daily; 1000 mg of abiraterone once daily + 5 mg of prednisone twice daily), while also receiving LHRH analogs or LHRH antagonists for ADT treatment for at least 6 months. PSA and serum testosterone concentrations will be measured at 4 weeks, 3 months, and 6 months. Imaging examinations will be performed again at 6 months to assess the treatment response to ADT. Patients with PSA levels below 1.0 ng/ml, relief or stabilization of bone metastases, and no new lymph node or visceral metastases will be considered for CRP treatment.

Group B: Subjects will orally take one of the second-generation antiandrogen drugs (240 mg of apalutamide once daily; 600 mg of darolutamide twice daily; 240 mg of enzalutamide once daily; 1000 mg of abiraterone once daily + 5 mg of prednisone twice daily), while also receiving LHRH analogs for ADT treatment. During the subjects' treatment, dose adjustments can be made in the event of intolerable toxic reactions (see dose adjustment plan for details). If the symptoms are not relieved after dose adjustment, the experimental drug treatment should be discontinued. Stratification factors include: 1) Visceral metastases; 2) Tumor burden. High tumor burden is defined as meeting at least one of the following conditions: 1) Bone scan indicating ⩾6 bone metastases (with at least one outside the pelvis or spine); 2) CT/MRI revealing visceral metastases (excluding lymph nodes).

Inclusion Criteria:

Patients must meet all of the following criteria to be included in this trial: (1) Male aged ≥18 and ≤75; (2) Histologically confirmed prostate adenocarcinoma; (3) Evidence of metastasis confirmed by magnetic resonance imaging (MRI)/computed tomography (CT) scan, bone scan, or histology; (4) Clinical stage M1a (distant lymph node positive), M1b (bone metastasis), or M1c (visceral organ metastasis); (5) Prostate cancer has not received local treatment (e.g., prostate radiotherapy, cryotherapy, etc.); (6) The surgeon believes the prostate can be removed; (7) Initiation of Androgen Deprivation Therapy (LHRH agonist/LHRH antagonist) treatment, with or without combined anti-androgen therapy, for no more than 12 weeks prior to randomization; (8) ECOG performance status of 0 or 1; (9) Laboratory tests meet the following requirements:Hematology: neutrophil absolute count ≥1.5×10^9/L, platelet count ≥100×10^9/L, hemoglobin ≥9.0g/dL;

Renal function: serum creatinine≤1.5×ULN;Hepaticfunction:alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5×ULN, total bilirubin (TBIL) ≤1.5×ULN; Left ventricular ejection fraction at least 50%; (10) Voluntary participation with the subject's own informed consent.

Exclusion Criteria: Patients with any of the following cannot be included in this study: (1) The surgeon believes the disease is unresectable; (2) Initiation of Androgen Deprivation Therapy (ADT) treatment, with or without combined anti-androgen therapy, for more than 12 weeks; (3) Life expectancy less than 2 years; (4) Active spinal cord compression; (5) History of prior local treatment for prostate cancer; (8) Planned receipt of other anti-tumor therapy during the study treatment period; (9) Known allergy to the above drug components; (10) Difficulty swallowing, chronic diarrhea, intestinal obstruction, and other factors affecting drug intake and absorption; (11) Diseases with a possibility of experiencing seizures within 12 months prior to C1D1 (including transient ischemic attack, stroke, and consciousness disorders requiring hospitalization); (12) Active cardiac disease within 6 months prior to C1D1, including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure; (13) Other malignant tumors within 5 years before C1D1 (excluding completely cured in situ cancer and tumors judged by the investigator to progress slowly); (14) Unwillingness to adopt effective contraception during the entire study treatment period and within 30 days after the last dose; (15) Presence of comorbidities (such as poorly controlled hypertension, severe diabetes, neurological or psychological disorders, etc.) or other situations that may have serious consequences; (16) Refusal to sign the informed consent; (17) Investigator believes the individual is not suitable for inclusion.

Termination of Research Treatment Criteria:

Researchers may decide to terminate the investigational drug treatment for subjects in the following circumstances:

1. The subject withdraws informed consent to continue the research treatment;
2. The subject meets the criteria for radiographic disease progression (as determined by RECIST 1.1 and modified PCWG3 criteria);
3. Bone-related events (such as radiation or surgery for bones, pathological fractures, spinal cord compression, or changes in anti-tumor treatment to relieve bone pain);
4. Any clinical adverse reactions, abnormal laboratory tests, or concurrent diseases, etc., which the researcher believes continuing the research is not in the best interest of the patient;
5. Other necessary situations where the researcher believes it is necessary to withdraw from the study.

Safety assessment:

Safety assessment is conducted using the NCI-CTC AE 5.0 standard. From the time of the subject's signing of the informed consent form until 30 days after the last dose, all adverse events (AEs) of the subjects are observed and recorded, including clinical symptoms, vital sign abnormalities, abnormalities in laboratory tests, and their correlation with the investigational drug. Subjects undergo safety assessments during the screening period, baseline, and post-dosing, including physical examinations, ECOG performance status assessment, laboratory tests, and electrocardiogram examinations. Unscheduled visits may be conducted based on the occurrence of subject AEs, in addition to the scheduled visits as per the protocol.

Efficacy assessment:

1. rPFS;
2. Time to biochemical progression-free survival;
3. Time to castration-resistant prostate cancer (CRPC);
4. Overall survival (OS), overall survival rate;
5. Incidence of postoperative complications;
6. Quality of life assessment using the EORTC QLQ-C30 questionnaire.

Statistical methods:

Data Set Analysis

Full Analysis Set (FAS): The most complete and representative set of subjects, including all randomized subjects as much as possible.

Per Protocol Set (PPS): Within the FAS, it includes subjects with primary endpoint data, good compliance, and no major protocol violations.

Safety Set (SS): The set of subjects who have received the investigational drug at least once and have safety assessment data.

- Efficacy Analysis

FAS and PPS will be used, with priority given to FAS results. The secondary efficacy endpoints for each group will be calculated separately.

Study timeline: The study aims to complete enrollment within 3 years and the overall trial within 5 years.

Informed Consent Form

We invite you to participate in a multicenter, randomized, open-label clinical study titled " Clinical study assessing the efficacy and safety of cytoreductive prostatectomy in combination with dual/triple therapy for 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 research purpose is to evaluate:

The radiographic progression-free survival (rPFS) of metastatic hormone-sensitive prostate cancer (mHSPC) patients treated with androgen deprivation therapy (ADT) + second-generation antiandrogens ± chemotherapy combined with cytoreductive prostatectomy (CRP).

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

This study is a multicenter, randomized, open-label clinical trial. It evaluates whether the ADT + second-generation antiandrogens ± chemotherapy combined with CRP improves radiographic progression-free survival (rPFS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) compared to the patients without surgery. The experimental group will receive second-generation antiandrogen drugs (240 mg of apalutamide once daily; 600 mg of darolutamide twice daily; 240 mg of enzalutamide once daily; 1000 mg of abiraterone once daily + 5 mg of prednisone twice daily), while also receiving LHRH analogs or LHRH antagonists for ADT treatment for at least 6 months. PSA and serum testosterone concentrations will be measured at 4 weeks, 3 months, and 6 months. Imaging examinations will be performed again at 6 months to assess the treatment response to ADT. Patients with PSA levels below 1.0 ng/ml, relief or stabilization of bone metastases, and no new lymph node or visceral metastases will be considered for CRP treatment or brachytherapy. The entire study plans to enroll 200 patients with high tumor burden mHSPC, who will be randomly assigned in a 1:1 ratio to the experimental and control groups.

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.

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 drugs in experimental group include Rezvilutamide, Darolutamide, Apalutamide, Abiraterone, LHRH agonist, LHRH

antagonist and docetaxel (for 6 cycles), followed by local treatment for primary tumor, while the control group will receive the following drugs without local treatment. 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.

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:

Patients must meet all of the following criteria to be included in this trial: (1) Male aged ≥18 and ≤75; (2) Histologically confirmed prostate adenocarcinoma; (3) Evidence of metastasis confirmed by magnetic resonance imaging (MRI)/computed tomography (CT) scan, bone scan, or histology; (4) Clinical stage M1a (distant lymph node positive), M1b (bone metastasis), or M1c (visceral organ metastasis); (5) Prostate cancer has not received local treatment (e.g., prostate radiotherapy, cryotherapy, etc.); (6) The surgeon believes the prostate can be removed; (7) Initiation of Androgen Deprivation Therapy (LHRH agonist/LHRH antagonist) treatment, with or without combined anti-androgen therapy, for no more than 12 weeks prior to randomization; (8) ECOG performance status of 0 or 1; (9) Laboratory tests meet the following requirements:Hematology: neutrophil absolute count ≥1.5×10^9/L, platelet count ≥100×10^9/L, hemoglobin ≥9.0g/dL;
Renal function: serum creatinine≤1.5×ULN;Hepaticfunction:alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5×ULN, total bilirubin (TBIL) ≤1.5×ULN; Left ventricular ejection fraction at least 50%; (10) Voluntary participation with the subject's own 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.

Who should not participate in the study? (Exclusion criteria) You should not participate in this study if you have any of the following conditions:

(1) The surgeon believes the disease is unresectable; (2) Initiation of Androgen Deprivation Therapy (ADT) treatment, with or without combined anti-androgen therapy, for more than 12 weeks; (3) Life expectancy less than 2 years; (4) Active spinal cord compression; (5) History of prior local treatment for prostate cancer; (8) Planned receipt of other anti-tumor therapy during the study treatment period; (9) Known allergy to the above drug components; (10) Difficulty swallowing, chronic diarrhea, intestinal obstruction, and other factors affecting drug intake and absorption; (11) Diseases with a possibility of experiencing seizures within 12 months prior to C1D1 (including transient ischemic attack, stroke, and consciousness disorders requiring hospitalization); (12) Active cardiac disease within 6 months prior to C1D1, including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure; (13) Other malignant tumors within 5 years before C1D1 (excluding completely cured in situ cancer and tumors judged by the investigator to progress slowly); (14) Unwillingness to adopt effective contraception during the entire study treatment period and within 30 days after the last dose; (15) Presence of comorbidities (such as poorly controlled hypertension, severe diabetes, neurological or

psychological disorders, etc.) or other situations that may have serious consequences; (16) Refusal to sign the informed consent; (17) Investigator believes the individual is not suitable for inclusion.

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: 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 the regime in control group.

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