Application of personalized minimal residual disease in predicting therapeutic efficacy in metastatic hormone-sensitive prostate cancer

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Project name ： Application of personalized minimal residual disease in predicting therapeutic efficacy in metastatic hormone-sensitive

Sponsor: The First Affiliated Hospital of Anhui Medical University

Responsible departments: Urology

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Participating units: Anhui University

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Program summary

Project name	Application of personalized minimal residual disease in predicting therapeutic efficacy in metastatic hormone-sensitive prostate cancer
Research purpose	A prospective, single-center, observational study is conducted on patients initially diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC). minimal residual disease (MRD) testing is used to explore the real-world efficacy responses of mHSPC patients with different gene mutation characteristics to treatment regimens, and further analyze the relevant factors affecting the efficacy, providing a basis for the clinical precision diagnosis and treatment of mHSPC patients.
research design	Prospective, single-center, observational study
study population	Patients with Metastatic hormone-sensitive prostate cancer
Total number of cases	50 cases

Case selection	*1. Inclusion criteria:* ● Aged over 18 and under 85; ● Histopathological diagnosis is prostate acinar adenocarcinoma, ductal adenocarcinoma, and intraductal carcinoma; ● Clear distant metastases found by imaging (meeting RECIST criteria); ● Patients diagnosed with locally advanced (N1) and metastatic (M1) prostate cancer. ● Have not received endocrine therapy or other systemic anti-tumor treatment before; ● ECOG score 0-2 points, expected survival time> 6 months; ● The patient has normal organ function; ● Blood test (no blood transfusion or blood products within 14 days): ● Hemoglobin (HGB) ≥90 g/L; ● Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L（1500 /mm^3）； ● Platelets (PLT) ≥75×10^9/L； ● White blood cell count (WBC) ≥3 × 10^9/L； ● Biochemical examination: ● Total bilirubin (TBIL) ≤ upper limit of normal (ULN); ● Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 ULN; ● Creatinine clearance (CCr) ≥ 30 ml/min (Cockcroft-Gault formula); ● Coagulation function: prothrombin international normalized ratio (INR) ≤1.5 or prothrombin time (PT) < 4 seconds; ● Patients agree to sign informed consent and are able to attend planned study visits, provide clinical information, and cooperate with other study procedures.

	Exclusion criteria ● Histopathological diagnosis is neuroendocrine/small cell prostate cancer; ● No clear distant metastases are found by imaging (in accordance with RECIST criteria); ● Previous treatment history: including neoadjuvant and adjuvant therapy; ● The samples submitted for inspection fail to meet quality control requirements. ● Patients with endocrine, metabolic system diseases or other serious digestive system diseases; ● Patients with chronic hepatitis, cirrhosis, chronic nephritis, renal insufficiency and other diseases; ● Patients with a history of immunodeficiency, including HIV positive or suffering from other acquired or congenital immunodeficiency diseases, or a history of organ transplantation; ● History of other malignant tumors; ● Enrollment in other clinical trials; ● Unable to obtain clinical information required for the study (e.g., patients lost to follow-up); ● Other cases that the researchers consider unsuitable for inclusion.
intervention plan	This is a prospective, single-center, observational study designed to observe the therapeutic response of metastatic hormone-sensitive prostate cancer (mHSPC) patients with different gene mutation characteristics to treatment regimens. The study will recruit 50 mHSPC patients from the First Affiliated Hospital of Anhui Medical University and design a personalized minimal residual disease (MRD) kit based on the data of the biopsy before treatment. The blood routine, biochemical indicators, sex hormone levels, prostate multi-parameter magnetic resonance imaging (Mp-MRI),

	quantitative whole-body bone examination, and PSMA-PET-CT examination of the study cohort patients will be recorded. During the treatment, MRD will be tested every three months, and the MRD level, blood routine, biochemical markers, sex hormone levels, and PSA levels; patients in the study cohort will undergo prostate multiparametric magnetic resonance imaging (Mp-MRI) and quantitative whole-body skeletal examination every three months. If PSA progression occurs during follow-up, the PSA recheck frequency will be customized. This prospective, observational study will explore the response efficiency of mHSPC patients with different gene mutation types to treatment regimens through MRD detection, analyze the relevant factors affecting the efficacy, and provide a basis for the precise clinical diagnosis and treatment of mHSPC patients.
Evaluation index	Effectiveness evaluation index ● Diagnostic accuracy: MRD positive rate, the fluctuation of MRD value, etc. ● Clinical efficacy: progression-free survival (PFS), overall survival (OS), biochemical recurrence rate, and clinical remission rate.
	Safety evaluation index ● Incidence of related drug allergy adverse events (AE) and serious adverse events (SAE)
Statistical methods	Descriptive statistical analysis, survival analysis, missing data processing
Study period	January 2026 - August 2027

Chapter1 Research Background

Prostate cancer is a global health problem. It is the second most common malignant tumor in the world, with the sixth highest incidence among all male tumors and the fifth leading cause of cancer death in men [1]. In the United States, prostate cancer ranks first in the male incidence spectrum, accounting for 29.06% of all male cases, and second in the male malignant tumor death spectrum, accounting for 10.92% of all male cancer deaths [2]. The incidence and mortality of prostate cancer in Asia are much lower than those in Europe and the United States, but have shown a clear upward trend in recent years, and its growth rate is faster than that of developed countries in Europe and the United States [3,4]. The number of prostate cancer patients in China has also increased significantly in recent years: according to the latest data released by the National Cancer Center Cancer Registry Office in 2022, the 2016 cancer incidence results in China based on statistics from 487 tumor registries across the country show that the age-standardized total incidence of prostate cancer has surpassed kidney tumors and bladder tumors, ranking first among male genitourinary tumors [5].

The age of onset of prostate cancer gradually increases after the age of 50, with the peak age being around 75 years old, and the highest incidence rate is between 81 and 90 years old. In addition to the influence of age, environmental factors, obesity and genetic factors are also related to the occurrence of prostate cancer [6]. Related studies have shown that only 1/3 of patients with newly diagnosed prostate cancer have clinically localized prostate cancer. Most patients are diagnosed with prostate cancer in the middle and late stages, and most patients have already progressed to distant metastasis or local metastasis [7].

The metastasis of prostate cancer is an important stage of the disease that seriously affects the prognosis of prostate cancer patients. According to data from China, patients with metastatic prostate cancer account for 51.4% to 54% of new prostate cancer patients [8]. According to the sensitivity of prostate cancer cells to androgens, metastatic prostate cancer can be divided into metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC). The results of the UFO (A Sub-group Analysis of United in Fighting for Prostate Cancer Registry) analysis of 705 cases of metastatic prostate cancer patients from 7 centers in China showed that 76.9% of patients in the middle and late stages of the disease in my

country belong to metastatic hormone-sensitive prostate cancer (mHSPC). Newly diagnosed mHSPC will eventually develop into mCRPC, and patients with mCRPC generally have a poor prognosis. Both domestic and foreign prostate cancer diagnosis and treatment guidelines point out that delaying the entry of patients in the mHSPC stage into the mCRPC stage and prolonging the survival of patients are the main treatment goals of the mHSPC stage.

In recent years, breakthroughs have been made in the diagnosis and treatment of mHSPC patients. Compared with traditional combined treatment models, the overall survival rate of patients with metastatic prostate cancer has been significantly improved through new combined treatment regimens based on castration therapy (new endocrine therapy drugs or chemotherapy drugs) [9]. However, there is currently no effective program for early efficacy testing and follow-up of patients undergoing drug treatment. Commonly used clinical methods include serum PSA monitoring and serum testosterone monitoring; PSA may rise briefly after inflammation, hyperplasia, bleeding, or some medical procedures, resulting in false positive results, and some patients may experience clinical progression without PSA elevation, resulting in false negative results [10]; approximately 13% to 38% of patients undergoing medical castration have serum testosterone levels that cannot be reduced to castration levels, and 24% of patients will experience a temporary increase in testosterone levels to more than 50 ng/dl during long-term treatment, also known as the "breakthrough effect" [11]. Therefore, there is currently no standardized and effective testing program during treatment.

Metastatic hormone-sensitive prostate cancer is a disease with high genetic and clinical heterogeneity. Although clinical studies have confirmed that new endocrine combined castration therapy can effectively improve the prognosis of such patients, patients vary in their economic situation, physical condition, tumor stage, tumor metastasis site, molecular differences, etc., and their individualized prognosis is also different. How to accurately monitor the efficacy of medication regimens is of great significance for determining the most suitable population, assessing prognosis, adjusting treatment plans, disease stratification, and reducing the burden on patients and society.

Minimal residual disease (MRD) refers to a small amount of tumor cells or tiny

lesions that remain in the patient's body during or after treatment and cannot be detected by imaging. It is the primary cause of tumor recurrence [12]. Studies have shown that continuous MRD liquid biopsy monitoring based on circulating tumor DNA (ctDNA) can predict the time of postoperative recurrence of tumor patients earlier, which is an average of 8.7 months earlier than the median time of recurrence that can be detected by imaging [13]. A hidden gram tumor may contain up to 1×108cells, all of which are associated with blood circulation due to their need for oxygen and nutrients [14]. Therefore, it is possible to detect these radiologically occult tumors through ctDNA analysis. A new generation of highly sensitive and specific ctDNA tests has been developed for solid tumors, called molecular residual disease (MRD) tests, which can detect micro metastases. MRD tests have a deep detection limit of more than 98% analytical sensitivity and a high specificity of more than 95% under certain conditions to ensure the detection of occult diseases [15]. Related studies have shown that quantifying ctDNA changes is not only associated with tumor activity, but also can predict patient prognosis. In particular, the assessment of ctDNA growth rate or doubling time can further stratify ctDNA-MRD-positive patients (dividing them into better and worse prognosis groups), providing an effective solution to guide clinical decision-making. Studies have shown that personalized tumor ctDNA analysis is more valuable than ctDNA-MRD positive or negative results, and has certain advantages in determining the risk of recurrence, predicting tumor outcomes, identifying patients who may need additional treatment after radical resection, detecting recurrence during monitoring, and predicting the growth rate of tumor burden [16]. MRD testing is of great significance for determining the efficacy of drugs, judging the patient's current stage of prostate cancer, adjusting treatment plans, and evaluating prognosis [17]. It is conducive to formulating effective individualized and precise treatment plans for metastatic hormone-sensitive prostate cancer.

Based on the above background, this study aims to construct a cohort of patients with mHSPC and conduct a prospective, observational study. We will obtain prostate tissue and peripheral blood specimens from newly diagnosed mHSPC patients for whole-exome sequencing (WES) and develop a personalized MRD detection kit for single mHSPC patients. We will test the efficacy of castration combined with novel endocrine therapy in these patients. We will also investigate the genetic mutation

profiles of mHSPC patients and observe, record, and follow up patients according to specific treatments. The results will be described, compared, and analyzed. We will explore how MRD testing can be used to assess efficacy and prognosis under different genetic mutation profiles, thereby enabling precise medication and efficacy testing for mHSPC patients.

Chapter2 Research purpose

A prospective, single-center, observational study is conducted on patients newly diagnosed with mHSPC. MRD testing is used to explore the real-world efficacy responses of mHSPC patients with different gene mutation characteristics to treatment regimens, and further analyze the relevant factors affecting the efficacy, providing a basis for the clinical precision diagnosis and treatment of mHSPC patients.

Chapter3 Research method

3.1 Research design

This is a prospective, single-center, observational study designed to observe the therapeutic response of metastatic hormone-sensitive prostate cancer(mHSPC) patients with different gene mutation characteristics to treatment regimens. The study will recruit 50 mHSPC patients from the First Affiliated Hospital of Anhui Medical University and design a personalized minimal residual disease (MRD) kit based on the data of the biopsy before treatment. The blood routine, biochemical indicators, sex hormone levels, prostate multi-parameter magnetic resonance imaging (Mp-MRI), quantitative whole-body bone examination, and PSMA-PET-CT examination of the study cohort patients will be recorded. During the treatment, MRD will be tested every three months, and the MRD level, blood routine, biochemical markers, sex hormone levels, and PSA levels; patients in the study cohort will undergo prostate multiparametric magnetic resonance imaging (Mp-MRI) and quantitative whole-body skeletal examination every three months. If PSA progression occurs during follow-up, the PSA recheck frequency will be customized. This prospective, observational study will explore the response efficiency of mHSPC patients with different gene mutation types to treatment regimens through MRD detection, analyze the relevant factors

affecting the efficacy, and provide a basis for the precise clinical diagnosis and treatment of mHSPC patients.

3.2 Study population

This study plans to recruit 50 mHSPC patients from the First Affiliated Hospital of Anhui Medical University between September 2025 and April 2027. Patients with metastatic hormone-sensitive prostate cancer from the First Affiliated Hospital of Anhui Medical University and cooperative units who met the enrollment conditions and signed informed consent forms will be included.

3.2.1 Inclusion criteria:

- Aged over 18 and under 85;
- Histopathological diagnosis is prostate acinar adenocarcinoma, ductal adenocarcinoma, and intraductal carcinoma;
- Clear distant metastases found by imaging (meeting RECIST criteria);
- Patients diagnosed with locally advanced (N1) and metastatic (M1) prostate cancer.
- Have not received endocrine therapy or other systemic anti-tumor treatment before;
- ECOG score 0-2 points, expected survival time> 6 months;
- The patient has normal organ function;
- Blood test (no blood transfusion or blood products within 14 days):
- Hemoglobin (HGB) ≥90 g/L;
- Absolute neutrophil count (ANC) ≥ 1.5 × 109/L（1500 /mm3）；
- Platelets (PLT) ≥75×109/L；
- White blood cell count (WBC) ≥3 × 109/L；
- Biochemical examination:
- Total bilirubin (TBIL) ≤ upper limit of normal (ULN);
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 ULN;
- Creatinine clearance (CCr) ≥ 30 ml/min (Cockcroft-Gault formula);
- Coagulation function: prothrombin international normalized ratio (INR) ≤1.5 or prothrombin time (PT) < 4 seconds;
- Patients agree to sign informed consent and are able to attend planned study visits, provide clinical information, and cooperate with other study procedures.

3.2.2 Exclusion criteria:

- Histopathological diagnosis is neuroendocrine/small cell prostate cancer;
- No clear distant metastases are found by imaging (in accordance with RECIST criteria);
- Previous treatment history: including neoadjuvant and adjuvant therapy;
- The samples submitted for inspection failed to meet quality control requirements.
- Patients with endocrine, metabolic system diseases or other serious digestive system diseases;
- Patients with chronic hepatitis, cirrhosis, chronic nephritis, renal insufficiency and other diseases;
- Patients with a history of immunodeficiency, including HIV positive or suffering from other acquired or congenital immunodeficiency diseases, or a history of organ transplantation;
- History of other malignant tumors;
- Enrollment in other clinical trials;
- Unable to obtain clinical information required for the study (e.g., patients lost to follow-up);
- Other cases that the researchers consider unsuitable for inclusion.

3.3 Research Technology Route (Figure 1)

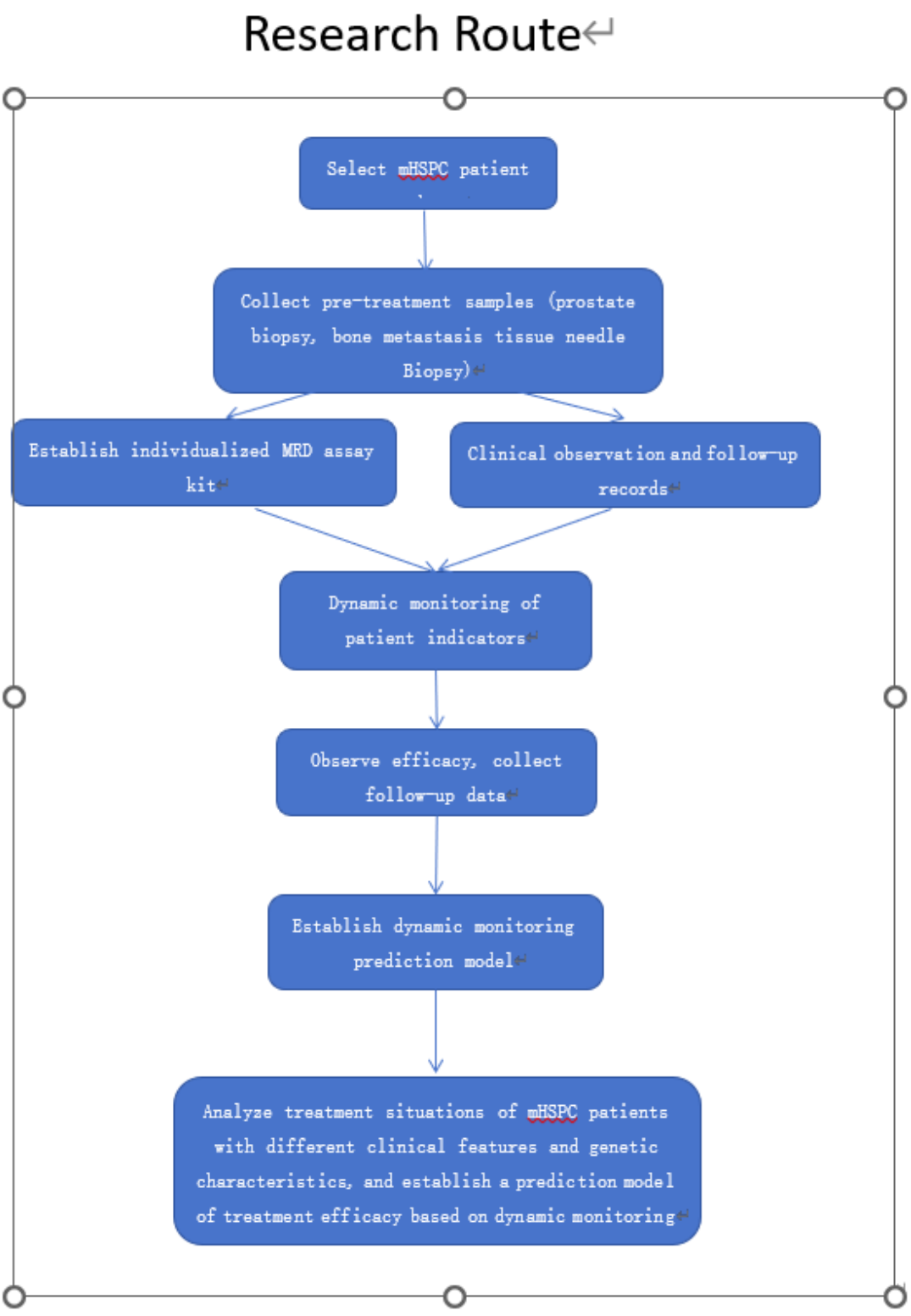

Figure 1 Technology Roadmap

3.3.1 Calculate the number of cases required to achieve the intended purpose of the study based on statistical principles

This study is an observational study. According to previous studies, the actual number of patients required is approximately 50 [17-19]. The clinical and auxiliary examination items to be conducted, the number of measurements, the amount of blood or tissue samples collected each time, the number of collections, and the total number of samples collected.

3.3.2 Initial diagnosis process

A personalized MRD kit is constructed based on the prostate needle biopsy tissue, bone metastasis needle biopsy tissue, whole genome sequencing (WGS), single-cell sequencing, spatial transcriptomics sequencing (STS) of the first puncture tissue for subsequent testing, and the blood routine, biochemistry, sex hormones, prostate multi-parameter magnetic resonance imaging (Mp-MRI), quantitative whole-body bone imaging, PSMA-PET-CT examination, etc. of the patients in the study cohort are recorded.

3.3.3 Genetic testing sample collection plan (Figure 2)

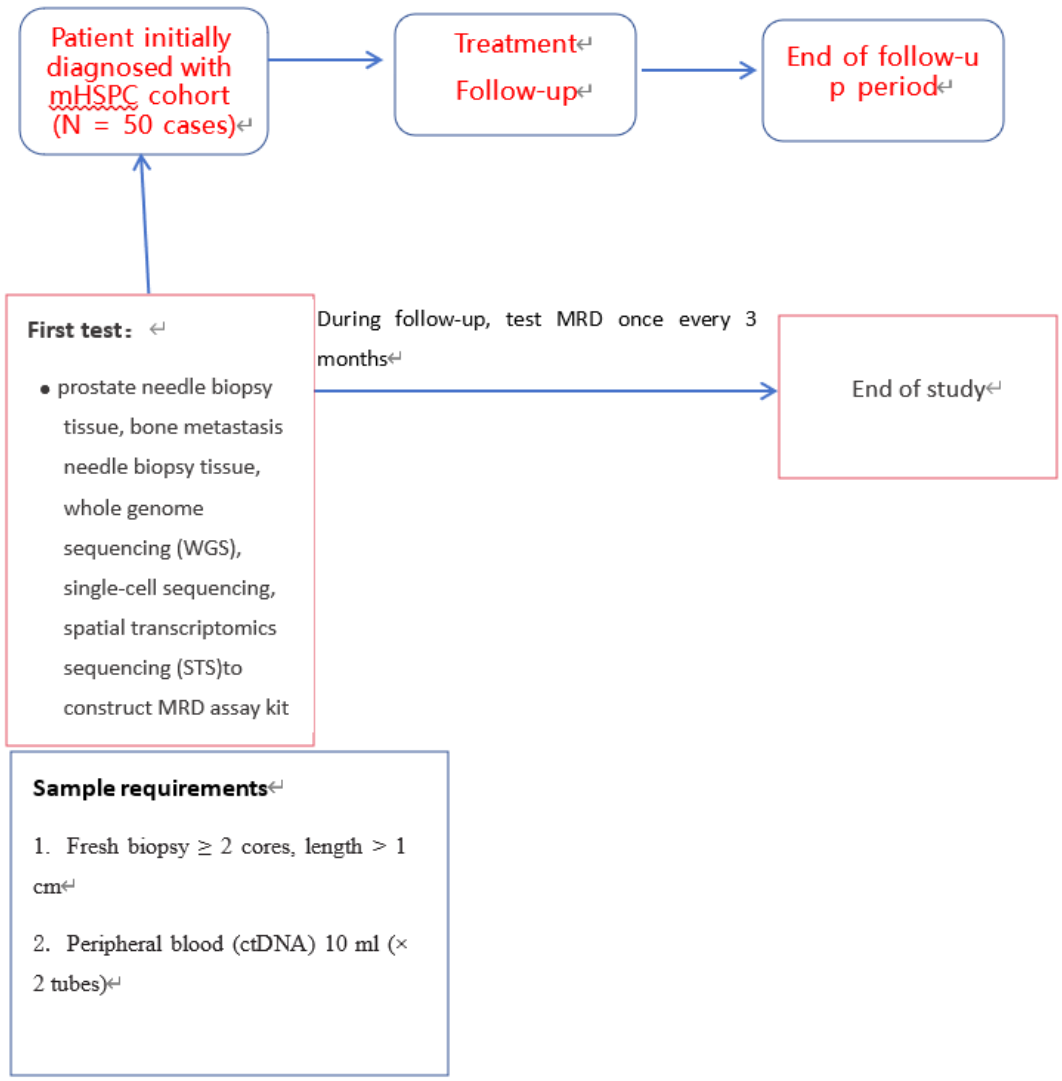

Figure 2. Sample collection plan

3.3.4 Follow-up process

Follow-up visits are conducted every three months during treatment. These visits included MRD levels, complete blood counts, biochemical profiles, sex hormones, and serum PSA levels. Multiparametric magnetic resonance imaging (MRI) of the prostate and quantitative whole-body bone scintigraphy are also performed every three months. If PSA progression occurred during follow-up, the frequency and frequency of PSA rechecks could be adjusted as appropriate.

3.3.5 Criteria for evaluating therapeutic efficacy, including methods for evaluating parameters, observation time, recording, and analysis;

- Main indicators: MRD positivity rate and changes in MRD levels
- Secondary indicators: clinical remission rate, progression-free survival (PFS)and overall survival (OS)

3.3.6 Prognostic Assessment

- Association analysis: The association between MRD level and recurrence risk and overall survival is evaluated.
- Risk stratification: Patients are divided into high-risk, intermediate-risk, and low-risk groups according to their MRD levels, and the prognostic differences among the groups are analyzed.
- Time to progression to CRPC: the time from patient enrollment to progression to CRPC (CRPC criteria: The patient's testosterone level reaches a castrate level of <50 ng/dL or <1.7 nmol/L, and one of the following conditions occurs: Biochemical progression, Radiographic progression)
- Time to biochemical progression: from the time of enrollment to the time when the patient has two consecutive PSA elevations;
- 6ne-year biochemical progression-free rate: the percentage of patients without biochemical recurrence within 1 year among all enrolled patients

3.3.7 The storage procedures for subject codes, random number tables, and case report forms;

- The enrolled patients are coded sequentially before and after enrollment and recorded in the case report form.

Chapter4 Recording requirements for adverse events and the reporting methods, handling measures, follow-up methods, timing, and outcomes of serious adverse events;

This study is an observational study. All treatment regimens are clinical standard treatment regimens. Adverse events are handled according to standard treatment. Any clinical adverse events and abnormal laboratory test results that occur during clinical

treatment must be recorded in detail, their relevance to treatment must be evaluated, and the severity of all adverse events must be judged.

4.1 Adverse events

Regardless of whether they are related to the study drug, any adverse medical event or clinically significant abnormality in laboratory test parameters that occurs during clinical treatment is considered an adverse event (AE). All adverse events must be described with respect to their onset, duration, treatment, and outcome, their severity, and their relevance to clinical treatment.

4.2 Severity of adverse events: The severity of adverse events is divided into mild, moderate and severe, and can be evaluated according to the following standards.

- Mild: Mild subjective symptoms that are tolerable and do not affect daily life activities. Symptoms are transient and resolve on their own during continued medication. No treatment is required.
- Moderate: Symptoms are severe, affecting the subject's daily activities, persisting for a long time, and resolving on their own or with symptomatic treatment. There is a possibility of interference with study medication use, requiring dose reduction or discontinuation.
- Severe: The subject's body functions are impaired and he loses the ability to work and live normally. The symptoms last for a long time and can only be relieved after stopping the drug and receiving appropriate treatment.
- Serious adverse events (SAEs): Serious adverse events are any unfavorable medical events that occur at any dose, such as those that lead to death or are life-threatening.

Note: In the definition of "serious," the term "life-threatening" refers to events/reactions in which the patient is already at risk of death at the time of the event/reaction; it does not refer to events/reactions in which death is hypothesized to occur if the severity of the event escalates. Important medical

events or reactions that may not be immediately life-threatening or result in death or hospitalization, but may endanger the patient or may require intervention to prevent one of the other outcomes listed in the above definition, should generally also be considered serious. Examples include: allergic bronchospasm requiring urgent treatment in the emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; the development of drug dependence or drug abuse, etc. In the event of an SAE, the investigator should immediately implement treatment measures to ensure the safety of the subject and report the SAE to the ethics committee and relevant competent authorities within 24 hours of the occurrence of the SAE.

- Important adverse events: Any event other than an SAE that results in the use of targeted medical measures (e.g., discontinuation of medication, dose reduction, and/or symptomatic treatment) or significant abnormalities in laboratory tests.

4.3 Evaluation of the association between adverse events and drugs

The association between the adverse event and the study drug is assessed as definitely related, probably related, possibly related, possibly unrelated, or definitely unrelated, based on whether the adverse event occurs in a reasonable time sequence with drug use, the type of drug reaction, and whether the reaction is alleviated, disappears, or reappears after drug discontinuation. The first three are considered possibly related to the study drug and are assessed as adverse drug reactions.

The relationship between adverse events and drugs is as follows:

- Definitely related: There is evidence of study drug use, the adverse event occurs in a reasonable temporal sequence with study drug use, and the adverse event is more plausible with study drug than with other explanations. There is a positive reaction to discontinuation of the drug and a positive reaction to repeated administration (if feasible).
- Probably related: There is evidence of drug use, and the adverse event occurs in a reasonable temporal sequence with the use of the study drug. The adverse event is more likely to be explained by the study drug than by other causes. There is a positive discontinuation reaction.

- Possibly Related: There is evidence of drug use, and the adverse event is reasonably temporally related to the use of the study drug. The adverse event can also be explained by other causes. Positive withdrawal reaction.
- Possibly unrelated: There is evidence of drug use, and the adverse event is more reasonably explained by other causes. The withdrawal reaction is negative or unclear.
- Definitely unrelated: The drug is not used, or there is no correlation between the time of drug use and the adverse event, or there is another clear cause for the adverse event.

4.4 The establishment and maintenance of research drug codes, unblinding methods, and regulations for breaking the blind in emergency situations;

- This study is an observational study and does not involve drug coding or unblinding.

4.5 Statistical analysis plan, definition and selection of statistical analysis data sets;

- Descriptive statistics: basic characteristics of patients, distribution of MRD levels.
- Full Analysis Set: According to the intention-to-treat (ITT) principle, efficacy analysis is performed on all cases of all enrolled patients who used the drug at least once.
- Safety Analysis Set: All enrolled cases, all patients who have used the trial drug at least once and have safety records after using the drug.
- Efficacy Analysis: The median time to CRPC progression and OS are estimated using the Kaplan-Meier method, and the median event and its one-sided 95% confidence interval are presented. SPSS software is used to perform statistical analysis on the efficacy indicator of 1-year biochemical progression-free rate.

- Safety analysis: Descriptive statistical analysis is primarily used, with a table describing all AEs that occurred during the trial. Laboratory test results are described as normal before the trial but abnormal after treatment, as well as the relationship between abnormal changes and the trial drug.

Chapter5 Data Management and Information Confidentiality

5.1 Construction of electronic case report forms (eCRFs) or study record forms

- The data manager constructs the eCRF based on the research plan, original case form and other information.

5.2 Data entry and modification

Data entry and modification are the responsibility of the researcher. Data should be sourced from and consistent with original documentation, such as original record sheets and laboratory test reports. All observations and test results from the trial should be entered into the form or database promptly, correctly, accurately, completely, clearly, in a standardized manner, and truthfully. The data manager is responsible for reviewing and managing the entered data. If any questions arise regarding the data, the data manager will send the corresponding queries to the researcher. The researcher will respond promptly to the queries sent by the data manager, and the data manager may raise further questions as necessary.

5.3 Confidentiality Plan for Research Participants (Subjects) Information

All information about research participants (subjects) must be kept strictly confidential. Participation in the study and personal data within the study are confidential. Information about research participants (subjects) and research data will be identified by study number, not by name. Identifiable information will not be disclosed to members outside the research team unless the participant (subject) has given their permission. All research team members are required to maintain the confidentiality of the identity of the research participants (subjects). Research

participant files will be kept in locked filing cabinets and accessible only to researchers. To ensure the research is conducted in accordance with regulations, members of government regulatory agencies or the ethics review committee may, if necessary, access the personal data of research participants (subjects) at the research site. No personal information about research participants (subjects) will be disclosed when the results of this study are published.

5.4 Research Data Confidentiality Plan

Research data are also confidential. All research members are required to keep the research data confidential. They are not allowed to disclose the research data to members outside the project team without the permission of the principal researcher, transfer the research data to external units without the permission of the hospital, or transfer research data involving human genetic resources to foreign units or domestic units with foreign capital without the approval of the National Human Genetics Office, except for the publication of research results that comply with regulatory requirements under normal circumstances.

Chapter6 Quality control and quality assurance of clinical research;

6.1 relevant training

The principal investigator will organize relevant training to ensure that the study is conducted in accordance with standard procedures. The completion of case report forms, study record forms, and other reports adhere to GCP principles and the study protocol. All data and information must be verifiable; to ensure the reliability of the study data, all observations and findings must be verifiable. Quality control will be applied at every stage of the study to ensure the reliability of all data and the accuracy of the study procedures. The principal investigator should ensure that researchers adhere to the trial protocol, confirm the accuracy of data and the completeness of records and reports, and ensure that informed consent is obtained from all subjects before the study begins. Any violations or deviations from the protocol should be reported to the ethics committee promptly.

6.2 research-related ethics;

This clinical trial must be conducted in accordance with the Declaration of Helsinki (2008 edition) and relevant Chinese clinical trial research standards and regulations. A trial protocol must be developed before the start of the clinical trial, jointly agreed upon and signed by the investigator and co-sponsor, and submitted to the hospital's ethics committee for approval before implementation. If this protocol needs to be revised during the actual implementation of the clinical trial, the revised protocol must be submitted to the ethics committee for approval before implementation. If significant new data regarding the investigational drug are discovered, the informed consent form must be revised in writing, submitted to the ethics committee for approval, and patient consent must be obtained again.

6.3 Methods of subject recruitment and process of obtaining informed consent;

This study is an observational study, and the enrolled patients are those receiving standard clinical treatment. Before the study begins, researchers must provide patients with detailed information about the clinical study, including the nature and purpose of the trial, possible benefits and risks, and the patient's rights and obligations. The clinical trial can only begin after the patient fully understands the information and agrees to it and signs the "Informed Consent Form."

6.4 The expected progress and completion date of the clinical study;

Expected start date: October 1, 2024

Estimated completion date for patient enrollment: March 20, 2025

Expected completion date: September 30, 2025

6.5 Follow-up and medical measures after the completion of the study;

This is an observational study that only collects patients' treatment and follow-up information. The end of the follow-up is the end point of the study, and there is no additional medical intervention.

6.6 the responsibilities of each party and other relevant provisions;

The First Affiliated Hospital of Anhui Medical University is the study sponsor, protocol developer, and principal investigator and is responsible for patient follow-up.

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