Informed Consent Form

A Single-Arm, Multicenter, Exploratory Study of ctDNA Dynamic Monitoring-Guided Befotertinib Combined with Radiotherapy in the Treatment of EGFR- Mutated Oligometastatic NSCLC

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You are being considered for participation in "A Single- Arm, Multicenter, Exploratory Study of ctDNA Dynamic Monitoring- Guided Befotertinib Combined with Radiotherapy in the Treatment of EGFR- Mutated Oligometastatic NSCLC." It is important for you to understand what the study involves before deciding whether to participate. Please read this information carefully and ask any questions you may have. The Ethics Committee of The Fourth Hospital of Hebei Medical University has reviewed the purpose and proposed procedures of this study and has provided a favorable opinion. You may discuss this with your family, friends, or your treating physician before making a decision.

1. What is this study and why is it being conducted?

The treatment strategy for non-small cell lung cancer (NSCLC) has undergone a revolutionary shift from traditional chemotherapy to precision targeted therapy over the past two decades. The epidermal growth factor receptor (EGFR) mutation, as one of the most important driver genes in NSCLC, occurs in up to 40-50% of the Asian population. EGFR tyrosine kinase inhibitors (TKIs), by selectively blocking the EGFR signaling pathway, have significantly improved clinical outcomes for mutation-positive patients and have become the standard first-line treatment option for these patients.

In advanced NSCLC, approximately 20%-50% of patients present with oligometastases at diagnosis. Oligometastasis is considered an intermediate state in the natural history of tumor progression from localized primary tumor to widely disseminated metastatic disease, specifically characterized by limited metastatic lesions distributed in specific, limited organs besides the primary site, including the brain, adrenal glands, and liver. The development of advanced radiotherapy techniques such as minimally invasive surgery and stereotactic body radiotherapy (SBRT) has made local control possible for some patients with oligometastatic NSCLC.

Studies have shown that aggressive local therapy on top of systemic treatment for oligometastatic patients can provide better survival benefits. A multicenter randomized trial reported that local consolidative therapy (LCT), including radiotherapy or surgery, improved median PFS in oligometastatic NSCLC patients after first-line systemic therapy. It is particularly

noteworthy that EGFR mutation-positive NSCLC patients are more likely to present with an oligometastatic phenotype and respond well to targeted therapy, providing an ideal window for combination with local therapy. Although the combination of EGFR-TKIs and radiotherapy for EGFR mutation-positive oligometastatic NSCLC has shown certain survival benefits, several key issues remain to be resolved. These include the timing of radiotherapy intervention, the selection and optimization of radiotherapy regimens, whether different mutation subtypes have differential responses to TKI+radiotherapy, and the safety management of the combined treatment.

Circulating tumor DNA (ctDNA), as a core component of liquid biopsy, has shown great potential in the field of tumor precision medicine in recent years. Compared to traditional tissue biopsy, ctDNA testing offers advantages such as being non-invasive, repeatable, and overcoming tumor heterogeneity, making it particularly suitable for dynamically monitoring tumor evolution and treatment response. In the management of advanced NSCLC, the application of ctDNA has expanded from simple mutation detection to multiple dimensions including minimal residual disease (MRD) assessment, prognostic stratification, efficacy prediction, and guiding subsequent treatment.

Exploratory analysis from the FLAURA study showed that in the osimertinib treatment group, patients with plasma ctDNA EGFR mutation clearance and those with persistent positivity at week 3 had median PFS of 19.8 months and 11.3 months, respectively, and at week 6, 19.8 months and 11.1 months, respectively, suggesting a potential correlation between early clearance of plasma ctDNA EGFR mutations and better prognosis. Other third-generation EGFR-TKIs such as aumolertinib have also explored the correlation between plasma ctDNA EGFR clearance status and prognosis. ctDNA analysis from the phase II ACHIEVE study showed a baseline ctDNA non-clearance rate of 81.7%, and patients with ctDNA clearance detected on day 1 of the second treatment cycle (C2D1) had significantly better PFS than patients with persistently positive ctDNA ($p<0.001$, HR=4.63). Both the FLAURA2 and MARIPOSA studies showed that intensified first-line strategies improved PFS compared to osimertinib monotherapy. Biomarker analysis from FLAURA2 suggested that patients with detectable ctDNA at baseline might benefit more from the combination of osimertinib and chemotherapy, indicating that ctDNA positivity could be a predictive biomarker for treatment intensification. Similarly, other studies have found that persistent ctDNA after the initial phase of systemic treatment suggests a suboptimal treatment response. Overall, monitoring dynamic changes in ctDNA is expected to become a powerful tool for monitoring efficacy, predicting prognosis, and guiding subsequent treatment.

Befotertinib, as a third-generation EGFR-TKI independently developed in China, has demonstrated excellent clinical activity in the IBIO-102 and IBIO-103 studies: first-line treatment of EGFR-mutated advanced NSCLC achieved a median PFS of 22.1 months, the longest PFS data among current third-generation EGFR-TKIs. On September 28, 2023, the NMPA approved bepotertinib mesylate capsules for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitution mutations.

Based on the aforementioned current status and unmet treatment needs for EGFR mutation-positive oligometastatic NSCLC, we have designed this study to explore the feasibility of ctDNA dynamic monitoring-guided befotertinib combined with radiotherapy in the treatment of EGFR mutation-positive oligometastatic NSCLC.

2. Who will be invited to participate in this study?

This study plans to enroll a total of 84 voluntary patients.

Patients meeting the following criteria will be eligible for this study:
(1) Age 18-75 years at the time of signing the informed consent form, both males and females are eligible;
(2) Histologically confirmed newly diagnosed or treatment-naïve oligometastatic stage IV NSCLC (AJCC 9th edition staging) with ≤3 involved organs and ≤5 metastatic lesions. Regional lymph node involvement (regardless of number) is not counted as metastatic sites; non-regional lymph node involvement is classified as a metastatic lesion;
(3) Presence of EGFR sensitizing mutation (19Del, 21L858R);
(4) Has at least one measurable lesion based on RECIST v1.1 criteria;
(5) ECOG PS score: 0-1 points;
(6) Life expectancy ≥12 weeks;
(7) No prior systemic anti-tumor therapy for advanced NSCLC before starting the study drug, including standard chemotherapy, biologic therapy, targeted therapy, immunotherapy, or investigational drug treatment; patients who have received adjuvant or neoadjuvant therapy (chemotherapy and/or radiotherapy) are allowed if there has been no progression within 6 months after completion of such therapy;
(8) Adequate organ function:
1) Hematology tests: (no blood transfusion, G-CSF use, or medical correction within 14 days before screening)
a. Hemoglobin (HB) ≥90 g/L;
b. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
c. Platelet count (PLT) ≥100 × 10^9/L;
d. White blood cell count (WBC) ≥4.0 × 10^9/L and ≤15 × 10^9/L;
2) Blood biochemistry tests: (no blood transfusion or albumin infusion within 14 days before screening)
a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) both ≤1.5 × ULN (≤5 × ULN if liver metastases are present);
b. Alkaline phosphatase (ALP) ≤2.5 × ULN;
c. Total bilirubin (TBiL) ≤1.5 × ULN;
d. Albumin (ALB) ≥30 g/L;
e. Serum creatinine (Cr) ≤ 1.5 × ULN, and creatinine clearance (CrCL) ≥ 60 mL/min (Cockcroft-Gault formula);
f. Activated partial thromboplastin time (APTT) ≤1.5 × ULN, and International Normalized Ratio (INR) or prothrombin time (PT) ≤1.5 × ULN;
(9) Women of childbearing potential should agree to use contraceptive measures (such as

intrauterine device, contraceptive pills, or condoms) during the study and for 6 months after study completion; a negative serum or urine pregnancy test within 7 days before enrollment is required, and the patient must not be breastfeeding; male patients should agree to use contraceptive measures during the study and for 6 months after study completion;
(10) Voluntary participation in the study, signing the written informed consent for the study, good compliance, and provision of blood samples.

Patients with any of the following will not be eligible for this study:
(1) Small cell lung cancer or non-small cell lung cancer mixed with histological types such as small cell lung cancer or neuroendocrine carcinoma;
(2) Confirmed EGFR exon 20 insertion mutation or non-classical mutations such as L861Q, G719X, S768I, etc.;
(3) Patients who have previously received systemic anti-tumor therapy for advanced/metastatic NSCLC (e.g., chemotherapy, targeted therapy, biologic therapy, immunotherapy, etc.);
(4) Patients with symptomatic brain metastases, carcinomatous meningitis, spinal cord compression, or imaging (CT or MRI) findings of brain or leptomeningeal disease at screening (patients with previously treated brain metastases who have completed treatment ≥4 weeks before enrollment and have stable symptoms without progression can be enrolled, but must be confirmed by cranial MRI, CT, or venography to have no symptoms of cerebral hemorrhage);
(5) Known history of hypersensitivity to the active or inactive excipients of Befotertinib or to drugs with similar chemical structures or classes;
(6) Factors that significantly affect oral drug absorption, such as inability to swallow, chronic diarrhea, intestinal obstruction, etc.;
(7) History of interstitial lung disease, drug-induced interstitial lung disease, or radiation pneumonitis requiring steroid treatment;
(8) Any evidence of severe or uncontrolled systemic disease, including uncontrolled hypertension, diabetes, active bleeding, etc., that in the investigator's judgment would compromise patient participation or protocol compliance, or any active infection including uncontrolled hepatitis B, hepatitis C, or human immunodeficiency virus (HIV);
(9) QTc prolongation >470 ms or any clinically significant arrhythmia;
(10) Any condition that, in the investigator's judgment, would preclude participation in this study, such as patients deemed unlikely to comply with study protocol, constraints, and requirements, or other situations at the investigator's discretion.

3. How is this study conducted?

If you agree to participate in this study, after signing the written informed consent form, the study doctor will conduct medical history inquiry and physical examination to determine if you meet the study inclusion criteria; you will need to undergo laboratory tests such as blood biochemistry, complete blood count, urinalysis, coagulation function, electrocardiogram, and imaging evaluation. If within the specified window period, previous relevant test results can be used.

After confirming that you meet the criteria, you can enter this study and receive Befotertinib

treatment. Peripheral blood will be collected 8 weeks (±7 days) later for ctDNA and TCR testing. Those who test positive for ctDNA will undergo treatment intensification with Befotertinib combined with radiotherapy; those who test negative will continue with Befotertinib monotherapy. Peripheral blood will be collected from subjects for ctDNA and TCR testing at 1 month (±7 days) after completion of radiotherapy.

To participate in this study, you need to come to the hospital for follow-up visits at the time points specified in the study protocol, i.e., at week 4 and week 8 of medication, and then every 8 weeks thereafter. Follow-up visits include safety assessments (including but not limited to physical examination, vital signs, ECOG performance status, complete blood count, blood biochemistry, coagulation function, D-dimer, 12-lead ECG) and tumor evaluation (including but not limited to chest plain/contrast-enhanced CT, abdominal ultrasound, brain MRI, superficial lymph node ultrasound, PET-CT, etc.).

All adverse events occurring during your treatment period also need to be monitored: from signing the informed consent until 30 days after the last dose of the study drug. Protocol-specified study tests, including complete blood count, urinalysis, blood biochemistry, ECG, etc., must be completed before each cycle of medication. Medication can only continue after safety assessment is completed.

If you withdraw from the study for any reason, it is still recommended that you continue disease progression or survival follow-up. For disease progression follow-up, it is still recommended to perform efficacy evaluation every 8 weeks until disease progression, death, or initiation of new anti-tumor therapy is observed. After disease progression, survival follow-up will begin, conducted via phone or other effective follow-up methods you agree to, recording whether you receive new anti-tumor therapy subsequently, and if so, recording the start and end times of your new treatment regimen.

4. What are the risks and adverse reactions of participating in this study?

Befotertinib mesylate was approved by the National Medical Products Administration (NMPA) in November 2023 for the "first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletion (19del) or exon 21 (L858R) substitution mutations."

All drugs have adverse reactions, and any study carries certain risks. The study drug may contain substances that could cause you to become ill, uncomfortable, or harmed. During your participation in the study, you may experience adverse reactions related to the study drug, as well as risks and discomfort associated with procedures. The researchers will closely monitor your symptoms and adverse reactions; and may provide you with treatments or management to help alleviate adverse reactions. If the study doctor believes you cannot tolerate these adverse reactions, study drug treatment may be paused or permanently discontinued.

The known adverse reactions of Befotertinib mesylate are primarily thrombocytopenia, headache, rash, anemia, leukopenia, and elevated alanine aminotransferase. Researchers do not yet fully

understand all the effects of the study drug on you, so it is crucial that you report any symptoms or discomfort immediately to the researchers, whether you believe they are caused by the study drug or not.

Radiotherapy is an important treatment modality, and the following toxic reactions may occur during treatment:
Skin reactions: The skin in the irradiated area may become red, swollen, itchy, peel, or develop pigmentation. In severe cases, blisters, ulcers, or necrosis may occur. Common in areas with thin or folded skin such as the neck, armpits, and groin.
Gastrointestinal reactions: Abdominal or pelvic radiotherapy may cause nausea, vomiting, diarrhea, and loss of appetite; head and neck radiotherapy may cause mouth ulcers, dry mouth, and throat pain, affecting eating and swallowing.
Bone marrow suppression: Radiotherapy may suppress bone marrow hematopoietic function, leading to decreased white blood cells, red blood cells, and platelets. Leukopenia increases the risk of infection, anemia results from decreased red blood cells, and thrombocytopenia may lead to bleeding tendency.
Fatigue and weakness: Increased energy consumption during radiotherapy often leads to extreme fatigue and weakness, affecting daily life and activity capacity.

During this trial, the study doctor will closely observe the occurrence of adverse events. Unexpected adverse events related to the study drug may also occur during this study. If this happens, your study doctor will inform you of these unexpected situations and ask if you wish to continue participating in the study. If you decide to withdraw from the study, your study doctor will also arrange for your safety follow-up.

The study medication may not necessarily completely improve your condition. Therefore, during your participation in this clinical trial, your condition may achieve complete or partial remission, but it is also possible that your condition may not change or may progress.

Reproductive Risks
Currently, there are no data on the use of Befotertinib mesylate in pregnant women, and the potential safety risks to the fetus are unknown. Based on its mechanism of action, the use of this product in pregnant women may cause harm to the fetus.

For safety reasons, all women of childbearing potential and male subjects must practice abstinence or use study-approved contraception during the study drug treatment period and for at least 3 months after stopping treatment.

For women of childbearing potential, if you are currently breastfeeding, pregnant, or planning to become pregnant, you cannot participate in this study. During screening, you will undergo a pregnancy test to ensure that pregnant women do not participate in this study. You must use contraception throughout the study period to avoid adverse effects on fetal development and health. It is crucial that you contact the doctor immediately if you think you have become pregnant during the study. If you become pregnant during the study, you will be discontinued

from the study, and the study doctor will discuss with you what to do.

For male subjects, participation in this study may damage your sperm, thereby potentially harming a child you conceive. This harm is currently unpredictable. Please inform your partner of this risk to an unborn child. It should be understood that if your partner becomes pregnant, you need to inform your study doctor immediately, and she should also inform her doctor immediately.

In any of the above situations, please inform your obstetrician that you are participating in this study. Your study doctor will request information about the pregnancy progress and outcome from you or your obstetrician. The study doctor will ensure that the study sponsor can access this information for safety monitoring follow-up.

Risks of Study Tests and Procedures
In addition to drug treatment, the tests and procedures in the study, including those involved in routine medical care, also carry certain risks:
Blood draw: Risks of drawing blood from the arm include brief discomfort and/or bruising. Although unlikely, infection, excessive bleeding, clotting, or fainting may also occur.
Blood pressure measurement: The blood pressure cuff may also cause you discomfort or bruising on the upper arm.
CT scan: A CT scan exposes you to a small amount of radiation. Although all radiation doses you receive in your lifetime accumulate, this small dose of radiation usually does not cause significant harm to your health.
Electrocardiogram (ECG): Risks include skin irritation and rash from wearing and removing the electrode patches.
Magnetic Resonance Imaging (MRI): MRI poses risks to you if you are pregnant or have artificial heart valves, pacemakers, metal plates, pins, or other metal objects (including bullets or shrapnel) in your body. You may also feel anxious due to lying in a confined space and being unable to move, and due to the noise of the machine. MRI does not cause any pain and does not expose you to radiation.
Bone scan: A bone scan exposes you to a small amount of radiation. Although all radiation doses you receive in your lifetime accumulate, the small dose of radiation received during a bone scan should not cause significant harm to your health.
Questionnaires: Some questions in the questionnaires may make you feel psychologically uncomfortable. You may refuse to answer them.
Other risks: All drugs carry the potential risk of allergic reactions, which could be life-threatening if not treated promptly. It is important that you report any symptoms and adverse reactions immediately, regardless of whether you think they are caused by the study drug.

5. What are the possible benefits for subjects participating in this study?

By participating in this study, we cannot guarantee that you will definitely benefit from the study treatment, nor can we accurately predict the chance of benefit. Although not guaranteed, you may still benefit from this study therapy.

Regardless of whether you personally benefit directly from the trial, your participation will help researchers obtain more reliable research data, which may be beneficial for selecting more scientific treatment methods and safe and effective therapies for you and patients with similar diseases in the future.

6. Are there alternative options if I do not participate in this study?

You may choose not to participate in this study, which will not have any adverse impact on your access to conventional treatment. You will not be discriminated against for this. Currently, for your condition, you can also choose other targeted drugs such as osimertinib, furmonertinib, aumolertinib, icotinib, and other similar drugs.

7. Is it mandatory to participate and complete this study?

Your participation in this trial is entirely voluntary. If you are unwilling, you may refuse to participate, which will not have any negative impact on your current or future healthcare. Even after you agree to participate, you can change your mind at any time and tell the researcher that you wish to withdraw from the trial. You will not be discriminated against or retaliated against for withdrawing from the trial, nor will it affect your right to receive normal medical services. When you decide to no longer participate in this trial, it is hoped that you will inform the researcher promptly, and the researcher can provide advice and guidance regarding your health condition.

You may terminate your participation in this study at any time for certain reasons, such as if you decide to withdraw; your study doctor decides you should withdraw; you no longer tolerate the study drug; you do not comply with the rules for participating in the study; the study doctor or sponsor stops the study, etc. If the study is stopped, we will inform you, and your study doctor will arrange your subsequent treatment. We will promptly inform you if any new information arises that might affect your decision to continue participating in this study.

8. How are study-related injuries handled?

The sponsor has purchased insurance for this study. If study-related injury occurs during the research process, please contact your study doctor, who will make a judgment and provide professional medical management. For study-related injuries, the sponsor will compensate according to Chinese laws, provided that you have followed the researchers' guidance. This compensation does not apply to any medical malpractice.

9. What are the costs and compensation for participating in this study?

To compensate for the inconvenience that participating in this study may cause you, Beta Pharma provides some Befotertinib as complimentary drug, specifically, the policy of "buy one month, get one month free for the first time"; meanwhile, the ctDNA testing costs during the study are fully covered by Beta Pharma. Radiotherapy during the study and examination costs related to

treatment are not within the free scope and need to be paid by you. Similarly, the costs of treatment and examinations required for other concurrent diseases, as well as the costs of switching to other treatments due to ineffective therapy, are also not within the free scope. This study does not provide transportation expense compensation.

10. How will the samples you provide for the study be handled?

This study requires the collection of subjects' blood samples. Blood samples collected according to the protocol requirements will be stored and transported to Hangzhou Xingyuan Future Medical Testing Laboratory (8th Floor, Block D, Beta Dreamworks, 188 Lianchuang Street, Wuchang Street, Yuhang District, Hangzhou City, Zhejiang Province) for ctDNA dynamic monitoring research. The samples you are tested on will be used only for the purposes described in this study and will not be used for other purposes. If there are leftover samples, they will be stored at the Hangzhou Xingyuan Future Medical Testing Center laboratory for up to 5 years before destruction. If you withdraw from the study, data (and any samples) collected before your decision to withdraw may still be used for the research. According to national regulations, if you withdraw informed consent for participation in this study, you have the right to request the destruction of all previously retained identifiable biological samples to prevent these samples from being used for further analysis.

11. Will the subject's personal information be kept confidential?

If you decide to participate in this study, your participation and personal data in the study will be kept confidential. Your identifying information will not be disclosed to anyone outside the research team unless your permission is obtained. Your records will be kept in locked file cabinets, accessible only to research personnel. Without violating confidentiality principles and relevant regulations, monitors, auditors, ethics committee members, and drug regulatory authority inspectors may review your original medical records to verify the research process and data. When the results of this study are published, none of your identifying information will be disclosed.

12. Who should I contact if I have questions or difficulties?

If you have any medical questions during the trial, you can contact your study doctor. This study protocol has been approved for implementation by the Medical Ethics Committee of The Fourth Hospital of Hebei Medical University. If your personal rights are infringed during the trial, you can directly contact the Ethics Committee at the telephone number: 0311-86095794.

Investigator Statement

I have informed the subject of the background, purpose, procedures, risks, and benefits of this study, provided sufficient time for them to read the informed consent form and discuss it with others, and have answered their questions regarding the study. I have informed the subject that they may contact me at any time regarding study-related issues, and may contact the Medical

Ethics Committee of Qingdao Central Medical Group at any time regarding issues related to their rights and interests, and have provided accurate contact information. I have informed the subject that they may withdraw from this study at any time without any reason. I have informed the subject that they will receive a copy of this informed consent form, which includes the signatures of both myself and the subject.

Investigator Signature: _____
Date: _____ Year _____ Month _____ Day
Contact Information: _____

Subject Statement

I have been informed of the background, purpose, procedures, risks, and benefits of this study. I have been given sufficient time and opportunity to ask questions, and I am satisfied with the answers provided. I have also been informed of whom to contact when I have questions or wish to obtain further information. I have read this informed consent form and agree to participate in this study. I understand that I may withdraw from this study at any time during the research period without any reason. I have been informed that I will receive a copy of this informed consent form, which includes the signatures of both myself and the investigator.

Subject Signature: _____
Date: _____ Year _____ Month _____ Day
Contact Telephone Number: _____

Legal Guardian Signature: _____
Date: _____ Year _____ Month _____ Day
Relationship of Guardian to Subject: _____
Guardian Contact Telephone Number: _____

Reason(s) Why Subject Cannot Sign the Informed Consent Form: _____

Witness Signature: _____
Date: _____ Year _____ Month _____ Day
Contact Telephone Number: _____