Informed Consent Form

Study Title: A real-world study to explore therapeutic changing mode of locally therapy during 1L lorlatinib treatment in unresectable ALK+ NSCLC patients

Informed Consent Form Version: 3.0, September 25, 2024

Research Institute: Peking University Cancer Hospital

Main researcher: Zhao Jun

Patient Name:

Patient's initials:

Dear (Sir/Madam),

We invite you to participate as a subject in a clinical trial. This informed consent form provides you with some information to help you decide whether to participate in this clinical trial. Please take some time to carefully read the following content, and if you have any questions or terms that are unclear, you can discuss them with the relevant physician.

Your participation in this study is completely voluntary. This research has been reviewed by the Ethics Committee.

1. Research Background

According to the Chinese National Cancer Center, lung cancer is the deadliest malignant tumor in China, with non-small cell lung cancer (NSCLC) accounting for 80%-85% of lung cancer cases. Usually diagnosed in advanced stages, surgery and local radiotherapy are no longer effective methods of cure at this stage. The investigational drug in this study, lorlatinib, is a new third-generation TKI targeting ALK-positive NSCLC developed by Pfizer.

Research data show that compared to the second-generation ALK TKIs, lorlatinib has better efficacy and wider coverage of ALK resistance mutations. Furthermore, lorlatinib can penetrate the blood-brain barrier, resulting in higher exposure in the central nervous system (CNS). Phase I and II clinical trial data indicate that lorlatinib,

when used after failure with first-generation, second-generation, or both ALK TKIs, exhibits superior antitumor activity. Particularly in patients with baseline CNS metastases (including leptomeningeal disease), there is still significant intracranial efficacy when lorlatinib is used after prior treatment failure. A phase II clinical trial currently ongoing in China demonstrates that the overall antitumor activity, brain metastases efficacy, and safety profile of lorlatinib are highly consistent with data from global phase II studies, solidifying lorlatinib's advantage in overcoming ALK TKI resistance.

CROWN study is a global, randomized, Phase III clinical trial comparing the efficacy of lorlatinib (n=149) and crizotinib (n=147) in untreated ALK-positive advanced NSCLC patients (both were standard first-line therapies at study initiation). The first stage data analysis showed that, by blinded independent central review (BICR), the lorlatinib group did not reach mPFS (NR; 95% CI, NR-NR), while the control crizotinib group had mPFS of 9.3 months (95% CI, 7.6-11.1 months). The percentage of patients without disease progression at 12 months was 78% in the lorlatinib group and 39% in the crizotinib group (risk ratio 0.28; 95% CI, 0.19-0.41; P<0.001; one-sided test). Across all patient subgroups based on baseline characteristics and stratification factors, lorlatinib had better PFS benefits compared to crizotinib. The second stage data analysis showed that the lorlatinib group continued to have a NR mPFS (95% CI, NR-NR), while the crizotinib group had a mPFS of 9.3 months (95% CI, 7.6-11.1 months). The 24-month PFS rates for the lorlatinib group and the 36-month PFS rates were 68.2% and 63.5%, respectively, significantly higher than the crizotinib group's 21.5% and 18.9% (risk ratio 0.25; 95% CI, 0.184-0.388). For patients with measurable brain metastases at baseline, the lorlatinib group achieved a 72% intracranial complete response rate (CR) and an 83% intracranial objective response rate (ORR). BICR assessment found that compared to crizotinib treatment in both the intention-to-treat (ITT) population and patients with or without baseline brain metastases, lorlatinib treatment extended intracranial progression time. After a median follow-up of over 36 months, 8 out of 37 patients with baseline brain metastases had intracranial progression, while only 1 out of 112 patients without baseline brain metastases had intracranial progression, suggesting that lorlatinib not

only has the ability to eliminate existing intracranial metastases but also prevents the emergence of new brain metastases.

In addition, recent clinical studies have shown that continuing TKI therapy after disease progression in oligometastatic NSCLC patients is an effective strategy, targeting tumor cells that still rely on the EGFR pathway, to prevent disease recurrence after discontinuation of targeted therapy. Furthermore, for oligometastatic patients (defined as having residual lesions in up to 3 organs, with a total of no more than 5 lesions), a combination of local treatments such as surgery, local ablation, or radiotherapy may be considered to improve disease control and consequently enhance long-term survival prognosis.

2. Research Purpose.

This study is a prospective, observational, multicenter, parallel-group real-world study, the main purpose of which is to evaluate whether first-line lorlatinib combined with local treatment (surgery, ablation, radiotherapy, etc.) can prolong the treatment termination time (TTD) in unresectable ALK-positive NSCLC patients in the real world.

3. Research Process

This study enrolled inoperable ALK-positive NSCLC patients. Patients were orally administered 100mg of lorlatinib at approximately the same time each day, continuously without interruption in the absence of drug-related toxicity. After 4 weeks of lorlatinib treatment, patients underwent imaging evaluation. Patients achieving PR or SD with limited metastases (up to 3 organs and a total of no more than 5 lesions) continued lorlatinib treatment and underwent imaging evaluation every 8-12 weeks. If two consecutive imaging evaluations indicated no reduction in target lesions, the researchers would hold a multidisciplinary team consultation (MDT) and, based on the patient's personal preference, decide whether to proceed with local therapy. Local therapy included but was not limited to surgery, ablation, and radiation therapy. Following local therapy, patients continued to take lorlatinib. Patients achieving CR or with multiple metastases continued lorlatinib treatment without any local therapy.

In addition, patients will have peripheral venous blood samples collected at baseline, after 4 weeks of treatment with lorlatinib, after local treatment, and at the time of disease progression for NGS testing of ctDNA.

4. matters that require your cooperation for participating in the research:

If you decide to participate, your attending physician/research doctor will explain the details of the informed consent to you and ask you to sign the informed consent form.

After you join the study, the research doctor will collect your data information, including: age at diagnosis, gender, height, weight, physical examination, smoking status, pathological diagnosis, laboratory test results (such as blood routine, urine routine, etc.), ALK gene detection methods and results, imaging examinations (such as CT, MRI, etc.). Regular checks are required to ensure your safety.

You will take lorlatinib orally at approximately the same time each day and continue oral administration daily. After 4 weeks of lorlatinib treatment, you will undergo imaging evaluation. Peripheral venous blood NGS gene testing will be performed at baseline, after 4 weeks of lorlatinib treatment, and at disease progression.

During the research period, if you experience any discomfort or any unexpected situations, including seeking treatment at other medical institutions, regardless of whether it is related to the study, please promptly inform your doctor so that they can make a judgment and provide appropriate medical treatment or advice to ensure your safety.

5. you can voluntarily participate, refuse, or withdraw from this study.

If eligible, you may voluntarily participate in the research and sign the informed consent form.

Regardless of whether you are willing to participate in the study, it will not affect the doctor's routine treatment of you.

Even if you decide to participate in the study, you can still withdraw at any time. Withdrawing from the study will not affect your future treatment. After you withdraw from the study, the researchers will no longer contact you for research purposes or

collect data. The data that has already been collected will be used and stored as research data.

The sponsor may also terminate the study for other reasons, in which case you will be notified immediately.

6. Participating in research may bring potential benefits.

If you agree to participate in this study, you may or may not benefit directly from medical care.

Through peripheral blood NGS gene testing, dynamic analysis can be conducted to determine whether there are molecular changes during your targeted therapy, and the results of the test may guide your subsequent treatment plan. We hope that the information obtained from your participation in this study can be of guiding significance to patients with similar conditions in the future.

7. participate in the study of possible adverse reactions, risks, and handling methods.

This study is an observational study, and common adverse drug reactions of the drug lorlatinib include:

- The severe hepatotoxic risk of co-administered potent CYP3A inducers.
- The central nervous system influences seizures, mental effects and cognitive function, emotions (including suicidal thoughts), speech, mental state, and changes in sleep.
- Hyperlipidemia
- Conduction block in the His-Purkinje system
- Interstitial lung disease / non-infectious pneumonia
- Hypertension
- Hyperglycemia

Pregnant women taking this study drug may cause harm to the embryo-fetus, fertile female patients should use effective non-hormonal contraception during and for at least 6 months after the end of treatment with this study drug.

For patients taking strong CYP3A inducers, discontinue the inducers for 3 plasma half-lives before starting the study drug.

Co-administration of this study drug with moderate CYP3A inducers can lead to a decrease in the plasma concentration of lorlatinib, potentially reducing the efficacy of this study drug. Avoid concomitant use of this study drug with moderate CYP3A inducers. If co-administration cannot be avoided, the dose of this drug should be increased. Moderate CYP3A inducers include: Aprepitant, Barbiturates, Bosentan, Carbamazepine, Efavirenz, Etravirine, Glucocorticoids, Modafinil, Nevirapine, Oxcarbazepine, Phenytoin, Phenobarbital, Primidone, Rifabutin, Rifampin, St. John's Wort, Pioglitazone, Topiramate.

Co-administration with potent CYP3A inhibitors can increase the plasma concentration of lorlatinib, potentially increasing the occurrence and severity of adverse reactions in this study. Avoid concomitant use of this study drug with potent CYP3A inhibitors. If co-administration cannot be avoided, reduce the dose of this study drug. Potent CYP3A inhibitors include: erythromycin, clarithromycin, ketoconazole, itraconazole, posaconazole, amiodarone, verapamil, diltiazem, nifedipine, doxycycline, levofloxacin, amiodarone.

The administration of this drug in combination with fluconazole may increase the plasma concentration of lorlatinib, which could potentially raise both the incidence and severity of adverse reactions associated with this agent. Avoid the concomitant use of this drug with fluconazole. If concomitant use cannot be avoided, then the dosage of this drug should be reduced.

Avoid concomitant use of this product with certain CYP3A substrates, as even minor changes in substrate concentrations may result in serious treatment failure. If concomitant use cannot be avoided, increase the dose of CYP3A substrates according to the approved product labeling.

Avoid concomitant use of this study drug with certain P-gp substrates, as minimal changes in substrate concentrations may lead to serious treatment failure. If concomitant use is unavoidable, increase the dose of P-gp substrates according to the approved product labeling.

The risks of drawing blood from the arm veins include: transient discomfort and bruising. Although rare, there is also a possibility of infection, bleeding, clotting, pallor, dizziness, shock symptoms, cerebral ischemic symptoms, needle phobia, local hematoma, hematoma, pain, slow or non-recovery of blood. The above events may occur in all similar examinations or procedures, and we hope you are aware of these situations before participating in this study.

Unknown risks: There may be some risks and adverse reactions that are currently unpredictable.

If any of the above situations occur during the research process, the researcher will handle it properly according to the actual situation, so please rest assured. If you experience any discomfort or reactions, please inform the researcher immediately for timely treatment.

8. Expenses related to participating in the research.

This research is a real-world study, and any data collected is what you need for your routine clinical treatment without adding any extra costs.

Collecting your plasma samples for next-generation sequencing testing at baseline, week 4 after receiving lorlatinib treatment, and at disease progression will be covered by the sponsor.

9. Compensation

Plasma samples collection for second-generation sequencing routine testing, no additional plasma samples collection, and no reimbursement fees for the time being.

10. Compensation.

If during the study you experience any adverse events and/or discomfort, please contact your doctor promptly. They will provide you with necessary medical care and

advice. If you are harmed by participating in the study, you will receive appropriate treatment and compensation in accordance with Chinese laws and regulations. Treatment and examinations required for other concurrent diseases are not covered within the scope of this study.

11. your information will be kept strictly confidential.

During the study, your name, gender, and other personally identifiable information will be replaced by codes or numbers. The data collected in this trial will be saved in electronic spreadsheets on a computer, and will be treated confidentially in accordance with relevant regulations. Only the relevant doctors will have access to your personal information, and all research members and sponsors are required to keep your identity permanently confidential. Unless you give permission, your identity will not be revealed to members outside the research team, ensuring the protection of your privacy rights. The research results may be published in journals, but your personally identifiable information will not be disclosed. If the results of this study are publicly published, your personal identity will also remain undisclosed.

If you agree to participate in this study, members of government agencies or ethical review committees, sponsors and their authorized personnel may access your personal information at the clinical trial site, under the condition that confidentiality principles and relevant legal requirements are not violated, to verify the appropriateness of the research operations.

If you have signed the informed consent form, it means that you agree to allow the above-mentioned individuals to access it.

12. informed consent for obtaining biological samples.

This study will collect your peripheral blood samples, with a blood collection volume of 10ml each time. The samples will be stored in the sample repository of Beijing Jiinjia Medical Laboratory Co., Ltd. for 2 years, and the test results will be sent to you in electronic form via the linkdoc follow-up management platform.

Researchers will comply with current laws and regulations and relevant policies, follow recognized ethical guidelines, adhere to human genetic resource regulations, respect the conventions and habits of biomedical research, and standardize the collection and use of biological samples. The possibility of harm and impact on your

health caused by the collection of samples is very low.

13. informed consent for the use of biological samples and/or personal data for future research (secondary use)

Your peripheral blood sample will be stored in Free DNA preservation tubes provided by Beijing Genomics Institute Medical Laboratory Co.,Ltd at 10-30℃ for no more than 5 days. Subsequently, your peripheral blood sample will be separated into plasma and DNA will be extracted from it, followed by testing according to the experimental procedure. The remaining peripheral blood samples will be stored at the research institution and will be destroyed after 2 years.

The above sample is used for the purposes described in this informed consent form, and may also be used for future other clinical studies. If you agree to the use of biological samples and genetic data collected in this trial for future other clinical research, your consent may not be obtained again, but it will still be conducted after approval from the ethics committee.

Agree to the use of biological samples and/or personal data for future research (re-use):

☐ Yes ☐ No

14. Contact numbers for researchers and ethics office.

You can always learn about information and research progress related to this study. If you have any questions related to this study, please contact (phone number) or (researcher or relevant person's name).

If you need to know about the participants' rights in this research, you can contact the Ethics Committee of Beijing Cancer Hospital at 010-88196391, 88196861.

Informed Consent Signature - Consent Signature Page

If you fully understand the content of this research project and agree to participate in the study, you will sign this informed consent form, in duplicate, with one copy retained by the researcher and the other by the participant or a designated representative.

Clinical research project title: A real-world study exploring the combination of local therapy during first-line lorlatinib treatment in ALK-positive advanced NSCLC.

Subjects' Statement

I have read and understood this informed consent form, and have received relevant information about this study. I have had the opportunity to discuss this study with the doctor and ask questions. All the questions I raised have been satisfactorily answered.

I can consult the doctor for more information at any time.

2. I have the right to withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

3. I know that personal identity and privacy will be strictly kept confidential.

4. Finally, I have decided to agree to participate in this study and am willing to cooperate with the doctor to undergo examinations, treatment, and feedback.

Subject's name (in block letters):

Subject's Signature: _____

Date of Signature: Year Month Day

If applicable, signature of the legal representative or guardian of the subject:

Name of legal guardian or guardian (in regular script): Relationship with the subject:

Signature of legal representative or guardian: _____

Signature Date: Year Month Day

If applicable, signature of third-party witness:

Third-party witness name (in block letters): Contact information:

Signature of the third-party witness: _____

Date of Signature: Year Month Day

Researchers declare

I confirm that I have fully explained to the subjects the detailed information of this study, including their rights and potential benefits and risks, and have provided them with a

signed copy of the informed consent form.

Researcher Name (in regular script):

Researcher's signature: _____

Date of Signature: Year Month Day