EGFR tyrosine kinase inhibitor combined with synchronous or sequential chemotherapy for advanced NSCLC patients of gradual progression after first-line EGFR-TKI therapy: a randomized controlled study

Subject's initials: _____ Patient number：_____

You are invited to participate in a clinical study. Before deciding whether or not to participate, please be sure to understand why the study was conducted, how your data will be used, what the study involves, and the benefits, risks, and discomfort that may be brought to you. Please take a moment to read the following carefully. If you like, you can also discuss it with your family doctor.

What is the background and purpose of this study?

It is unavoidable that almost all patients develop acquired resistance to EGFR-TKI and how to delay drug resistance is a difficult problem. At present, the mode of EGFR-TKI failures include dramatic progression, gradual progression and local progression. It is recommended that the patients with gradual progression continue oral EGFR-TKI. However, there is no evidence-based medicine that chemotherapy combined with TKI could provide more benefit than first continuing EGFR-TKI and then chemotherapy alone for patients who arrived gradual progression after EGFR-TKI therapy. Advanced EGFR-activating non-small cell lung cancer (NSCLC) patients who occurred gradual progression after first-line EGFR-TKI treatment were randomized into two groups:

synchronous therapy group and sequential therapy group. The synchronous therapy group continued using EGFR-TKI and add pemetrexed plus cisplatin at the same time; the sequential therapy group continued using EGFR-TKI alone until the investigator judged that continuation was adiaphorous, and switched to chemotherapy (pemetrexed plus cisplatin) alone. The primary endpoint was PFS, for the sequential group, PFS was PFS1(gradual progression to discontinue EGFR-TKI) plus PFS2(chemotherapy alone). The secondary end point were objective response rate(ORR), disease control rate(DCR), overall survival(OS)，and safety. By comparing two different treatment models aims to find the most appropriate clinical strategy to prolong the duration from gradual progression to eventual failure, which has great practical significance for clinical and scientific research work.

You were invited to participate in this study because you have been diagnosed with non-small cell lung cancer and have been identified with EGFR positive mutation. For patients with EGFR positive mutation, first generation EGFR-TKI is the standard first-line treatment. However, EGFR-TKI resistance is unavoidable. We hope to seek new treatment model to delay your drug resistance. The study will also use mass spectrometry technology to detect genetic alteration and peripheral blood immune cell phenotype change during the EGFR-TKI therapy in order to further understand the mechanism of drug resistance.

Do I have to attend?

It is up to you to decide whether to participate in this research. Even if you decide not to participate in this study, the treatment and medical attention that you should be

received would not be affected. If you decide to participate, you will be required to sign the written informed consent. Even if you decide to participate, you can withdraw from the study evaluation and/or study treatment at any time. This will not affect the standard treatment you receive. With your consent, your attending physician/general practitioner will inform you the detailed information about the study that you will participate. In addition, the study doctor may determine that continuation to participate in the study is adiaphorous, thus you will withdraw from the study. If you do not want to participate in this study, you can also receive other medications to treat the disease. If you choose not to participate in this study, your research doctor will explain to you the other treatment you can get.

What happens if I participate in the study?

The study included the screening period, treatment period, and follow-up period. The total time of the study depends on your effect and the time of occurring disease progression.

Screening period: Used to confirm that you can participate in this study. After you have signed the agreement, the study doctor will assess your situation to confirm that you are eligible for the study. If applicable, disease status assessments and other clinical tests you performed before signing the informed consent to participate in the study (as part of your normal clinical care) may also be used by this study. Your research doctor will discuss this with you.

Treatment period and follow-up period: If you meet all the criteria for participating in the study, you will be randomized into two groups: the synchronous therapy group

were added pemetrexed plus cisplatin treatment along with continuation of EGFR-TKI; the sequential therapy group continued receiving EGFR-TKI until investigator judged that continuation was adiaphorous, and then switched to pemetrexed plus cisplatin chemotherapy. You will be required to visit in outpatient once a month. Once you stop the study treatment, you will have a "ending visit". If you discontinue study treatment for reasons other than disease progression, the “progressive follow-up visit” will continue until confirming that disease progress has occurred. After confirming that disease progress has occurred, you will enter the "follow-up period" of the study treatment.

After you complete the study, your research doctor will decide how to continue treating your cancer.

You can withdraw from the study evaluation and/or study treatment at any time during the study, and this will not affect the standard treatment you will receive. If you or your doctor choose to stop the study treatment, we will ask you to continue to participate in the study visit or keep in touch unless you decide to withdraw from the study completely.

The study doctor can choose to discontinue your participation in the study for any of the following reasons without your consent: you cannot continue the study; you have not followed the study doctor's instructions; you have suffered research-related injuries, or any other the reason.

If you decide to withdraw completely from this study, we recommend that you accept the research exit procedure that the study doctor considers necessary. After that,

you will no longer be contacted or data collected for research. However, we may collect your survival information from publicly available sources at the end of the study.

If you experience an adverse event during your final study visit or withdrawing your visit, your research doctor may wish to contact you and ask for details until the adverse event is completely resolved.

Biomarker studies - In this study, exploratory biomarker studies were conducted to better understand the disease and drug effects. Biomarkers are substances found in the body that help measure or predict disease progression or therapeutic effects. The purpose of the biomarker study is to learn more about the disease and how this treatment affects your cancer cells and/or the rest of your body's cells. Some of the samples that you may provide during the study may be used to explore new ways of analyzing samples in the future. These new methods allow us to observe many different substances generated in the body. In the future we may want to study whether these substances are related to the disease.

We may also want to study whether these substances change with different treatments, such as the treatment you received in the study. In addition, we may use the above results for diagnostic tests (diagnostic tests are any type of medical procedure that help diagnose or detect a disease or help guide treatment decisions). All the above results will not affect the treatment given by your doctor.

For exploratory analysis, we will collect the following samples:

1. ctDNA- to detect immune cell phenotype and gene state: collect 8ml peripheral blood (collecting by tube with EDTA-K2 anticoagulant) at prior treatment,

one month and every 2 months later.

2. Immune cell phenotype- to detect immune cell phenotype: collect 5ml peripheral blood (collecting by tube with heparin sodium) at prior treatment, one month and every 2 months later.

What must I do?

You must be willing to participate in the planned visit. In addition, it is important that you need to follow the treatment instructions. It is also important that you inform the doctor of any other medication you have taken before and during the study.

What adverse events, risks, and discomforts may occur during the study?

EGFR-TKI and chemotherapeutic drugs are mature drugs that are already on the market, and the toxic and adverse event are already well known, therefore, there are no new risk to participate in this study in our projection. The only possible risk is that if you are randomized to the synchronize group, the adverse event of the two therapy may overlap. However, our previous study indicates that the EGFR-TKI plus chemotherapy in first-line non-small cell lung cancer patients did not appear grade 3/4 adverse event, so it is expected that the adverse event of participating in this study should be accepted. And because the types of adverse event are already known, we will take all measures to prevent the occurrence of risk. We encourage you to report every discomfort that you encounter.

Most Risks associated with EGFR-TKI are mild and will relieve or resolve after appropriate treatment.

The common side effect is diarrhea - very common (>10%). Rash and acne – common (>1% and <10%) to very common (>10%), dry skin – common (>1% and <10%) to very common (>10%). Such skin side effects can be treated with creams and lotions or antibiotics.

Risks associated with chemotherapy - The chemotherapeutic drugs used in this study are pemetrexed and cisplatin. Common side effects are nausea, vomiting, myelotoxicity and so on. These can be prevented by antiemetic, protecting gastric mucosa, preventative measure to prevent the disease of white blood cell and blood platelet.

Risks related to research operations: during the study period, the study doctor will collect your peripheral blood samples. However, because the peripheral blood volume is small and this is usual medical procedure, the risk is not significant.

What are the benefits of participating in research?

We hope that the new treatment mode could delay your resistance to the first generation EGFR-TKI, so it will help you. However, there is no guaranteed. It may slow down the speed that your disease worsens or shrink your tumor size. You may also not receive any direct health benefits during or after the study. However, your participation in the study will provide us with information on treatment of non-small cell lung cancer, which will benefit others in the future. The information obtained in the study will help us to provide better treatment for patients with NSCLC in the future.

What happens if new information appears?

Any new information about research drugs that appears during the study may affect your decision that weather continue participating in the study and study doctor will inform the new information to you.

What is the cost of participating in this study?

All trial drugs are listed, so you will pay for medicine according to local health insurance policies.

How will my personal information be used?

Signing this written informed consent indicates that you have agreed to study physicians and their research center personnel to collect and use your personal information ("research data") in this study. These data include your: date of birth, sex, race, and personal data about physical or mental health or illness. There is no expiration date for the license to use your research data, but you can notify the study doctor to withdraw the informed consent at any time.

Research doctors will use research data to conduct research. The results of this study may be published in the medical literature, but your identity will not be opened. You have the right to obtain research data kept by the research doctor. You are also entitled to correct inaccuracies in your personal data. If you have the above requirements, please contact your research doctor. If you withdraw the informed consent, the research doctor will no longer use your research data or share it with others.

By signing this informed consent agreement, I agree that my research data can be

used under the conditions described in this informed consent form.

Who can I contact if I need more information or help?

If there is a study-related injury, or as a research subject you have questions about the study drug and the rights that you have, please contact:

Research doctor: Tianqing Chu Contact number: 18017321311

Address: Shanghai Chest Hospital, building 3, 8th floor

I have spoken orally received information about the above study and have read the attached written information.

I have had the opportunity to discuss the research and ask questions.

I agree to participate in this study. I am very clear that my participation is entirely voluntary.

I understand that I can withdraw from the study at any time, and I can withdraw my consent for the use of my sample alone, and my future treatment will not be affected.

By signing this information and informed consent, I agree that my personal data, including data on my physical and mental health status, demographic data, and ethnic or national data, may be used on the conditions described in this informed consent, including transfer to countries outside China.

By signing this information and informed consent, I agree that my peripheral blood samples are used for biomarker analysis.

I know I will get a copy of subject information and informed consent.

Informed consent

Subject's signature_____

Date of signature_____

(Must be signed and dated by the subject himself)

_____ Subject's name (regular script)

Informed consent investigator's signature_____

Date of signature_____

_____Informed consent investigator's name (regular script)

If the subject is a minor or unable to sign for himself, a legal representative is required to sign it. The relationship between the subject and the legal representative should be indicated. If the subject is unable to read or write, the witness with no interest is required to sign it.

Legal agent's signature_____

Date of signature_____

_____ Legal agent's name (regular script)

_____The relationship between legal agent and subject (regular script)

_____ Uninterested witness's signature

_____ Date of signature

_____ Uninterested witness's's name (regular script)