Clinical Study Protocol

Clinical Study of the Efficacy of Icotinib in Patients with Clinically Diagnosed Lung Cancer Carrying EGFR sensitive mutations Detected by ctDNA Testing

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Abbreviation List

AE	Adverse Event (AE)
ALT	Alanine aminotransferase (serum alanine transaminase)
AST	Aspartate aminotransferase (serum aspartate transaminase)
CRF	Case Report Form
CR	Complete Response
CT	Computed tomography
CTC-AE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor (EGFR)
FACT-L	Functional Assessment of Cancer Therapy – Lung
FISH	Fluorescence *In Situ* Hybridization
HIV	Human immunodeficiency virus/Human immunodeficiency syndrome
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IRC	Independent Review Committee
ITT	Intent-to-Treat
MRI	Magnetic Resonance Imaging
NSCLC	Non–Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
pCR	Pathological complete response
PD	Progressive Disease
PR	Partial Response
PS	Physical Status
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SRS	Stereotactic radiosurgery
TKI	Tyrosine kinase inhibitor
ULN	Upper Limit of Normal

1 Study Background and Rationale

1.1 Overview of Non-Small Cell Lung Cancer

Lung cancer is the most common cause of death among various malignancies, worldwide [1]. It is estimated that there are more than 1.4 million new cases and more than 1.2 million deaths worldwide each year. The World Health Organization estimates that there are about 130,700 new lung cancer cases and 106,300 deaths each year in China [2], with non-small cell lung cancer (NSCLC) accounting for about 80% of these cases. With the development of molecular biology technology, individualized treatment based on molecular typing has significantly improved the survival and prognosis of patients with advanced lung cancer, with the most representative therapies as small molecule tyrosine kinase inhibitors targeting EGFR (EGFR-TKIs). According to "*the Guidelines of Chinese Society of Clinical Oncology (CSCO): Lung Cancer*" and "*the Chinese Guidelines for Diagnosis and Treatment of Primary Lung Cancer - National Health Commission of the People's Republic of China*", EGFR-TKIs are recommended for first-line use in patients with advanced NSCLC who carry EGFR sensitive mutations; and EGFR-TKIs can also be used for second- or third-line treatment in patients with advanced NSCLC. Studies have confirmed that patients with NSCLC harbouring EGFR sensitive mutations can benefit from EGFR-TKI therapy [3-4].

1.2 First-line Treatment of EGFR-mutated Non-small Cell Lung Cancer

1.2.1 Introduction to EGFR

The EGFR (epidermal growth factor receptor) is a tyrosine kinase receptor, whose gene is located in the p13-q22 region of Chromosome 7, with a full length of 200 kb, consisting of 28 exons encoding 1,186 amino acids. With a glycoprotein molecular weight of approximately 170 kDa, it is widely distributed in all tissue cells except mature skeletal muscle cells, body wall endoderm and hematopoietic tissue. The EGFR family has four structurally similar receptor molecules: ErbBl (EGFR), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4), all belonging to the receptor tyrosine kinases (RTKs). They all contain one extracellular ligand-binding domain, one transmembrane domain and one cytoplasmic domain with tyrosine kinase activity. Its intracellular region is highly homologous to the erbB oncogene product [5]. The mechanisms of aberrant EGFR activation include those such as amplification of the receptor itself, overexpression of the receptor ligand, activating mutations, and lack of negative regulatory pathways, among which the mutational activation of EGFR is the most significant factor contributing to the aberrant biological behavior of tumor cells.

1.2.2 Implications of EGFR Sensitive Mutations in the Treatment of Lung Cancer

EGFR mutations mainly occur in the first four exons (18-21) of the intracellular tyrosine kinase (TK) region, which can lead to ligand-independent activation of the EGFR pathway, called activating mutations, including deletion, substitution, duplication or insertion. Deletion mutations occur mainly in exon 19 (19DEL), and substitution mutations most commonly occur in L858R of exon 21, both of which account for approximately 85-90% of the mutations. In the treatment of lung cancer, specific molecularly targeted drugs have unique advantages because conventional chemotherapy lacks specificity and achieves limited efficacy while causing greater side effects. For advanced NSCLC patients with EGFR-sensitive mutations, first-line EGFR-TKI has a significantly better efficacy than platinum-containing two-drug chemotherapy, with an ORR of 60-80% and a median PFS of 9-13 months, among which representative agents are gefitinib, erlotinib and icotinib.

1.2.3 Clinical Profile of EGFR-TKI and Icotinib

Antitumor drugs that target EGFR include small molecule EGFR kinase inhibitors (EGFR-KIs) and anti-EGFR antibodies. Small molecule EGFR-KIs specifically and competitively bind to the ATP-binding site of the EGFR-kinase functional region, inhibiting its activity and thereby

blocking signaling associated with cancer cell proliferation and metastasis.

EGFR-TKIs, represented by gefitinib and erlotinib, have made great progress in the treatment of NSCLC and have become the standard of care for advanced EGFR-mutated NSCLC. It is based on several randomized controlled studies comparing EGFR-TKIs and chemotherapy in the first-line treatment of patients with advanced NSCLC carrying EGFR-sensitive mutations, including the IPASS and OPTIMAL. As published in 2009, IPASS assessed first-line therapy with gefitinib (Iressa®) versus carboplatin/paclitaxel in Asian patients with lung adenocarcinoma cancer. A total of 1217 patients were enrolled, in the 261 patients with EGFR mutations who received gefitinib had increased response rate (71.2% vs 47.3%) and significantly longer PFS (9.5 vs 6.3 months, HR 0.48, $p<0.001$) compares with chemotherapy[6]. OPTIMAL is a randomized, phase III clinical study sponsored by the Chinese Thoracic Oncology Group (CTONG) comparing the efficacy of erlotinib versus gemcitabine/carboplatin as first-line therapy in 165 patients with advanced NSCLC carrying EGFR sensitive mutations. The results showed that the median PFS (13.1 vs 4.6 months; HR 0.16, $p<0.0001$) and Quality of life were significantly better in erlotinib-treated patients than in those on chemotherapy, while there was no difference in OS between the two groups [7]. However, subgroup analysis showed that patients receiving chemotherapy alone had a very short survival, with a median OS of 11.7 months (21 cases), while 20.6 months (33 cases) in the patients receiving EGFR-TKI only, and up to 30.4 months (94 cases) in the patients receiving chemotherapy after EGFR-TKI treatment, suggesting that EGFR-TKI makes an important contribution to the improvement of survival in the patients with EGFR sensitive mutations [8].

Similar to gefitinib and erlotinib, icotinib is also an oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which belongs to the Category 1.1 new drugs. The distinctive feature of these drugs is that while inhibiting the growth of tumor cells, they can significantly improve the quality of life of patients, especially without the hematopoietic inhibitory effect on bone marrow commonly shown in traditional chemotherapy drugs, and belong to the non-cytotoxic agents targeting antitumor. A large phase III clinical study showed that icotinib demonstrated an efficacy of 64.8% and a median PFS of 9.9 months in patients with progressive lung cancer with histologically confirmed EGFR-sensitive mutations. Subgroup analysis suggested that the benefit was more pronounced in patients with deletion of exon 19 of the EGFR gene. The main adverse effects were rash, diarrhea and elevated transaminases, and were well tolerated[9].

ICOGEN was a randomised, double-blind, double-dummy, parallel-controlled, multicenter phase 3 trial designed to assess the safety and efficacy of icotinib and gefitinib in locally advanced or metastatic NSCLC patients with one or two prior chemotherapies. A total of 399 patients were enrolled. The primary objective, PFS, was 4.6 months in the icotinib group and 3.4 months in the gefitinib group without significant difference ($p=0.1300$), but the absolute value of the icotinib group was obvious better than that of the gefitinib group.In the FAS, the median OS was 14 months in the icotinib group versus 15.6 months in the gefitinib group, without statistical difference between the two groups ($p=0.7924$). Comparing the median time to progression (TTP) between the two groups, it was 5.2 months for icotinib and 3.7 months for gefitinib, $p=0.0653$. The objective response was 27.6% vs 27.2% and the disease control rate (DCR) was 75.4% vs 74.9%, respectively [10].

As for the safety, the overall incidence of adverse reactions was 60.5% in the icotinib group and 70.4% in the gefitinib group ($P<0.05$). Diarrhea, rash, and elevated transaminases were common, with diarrhea at 18.5% in the icotinib group and 27.6% in the gefitinib group, rash at 40% in the icotinib group and 49.2% in the gefitinib group, and elevated transaminases at 8% in the icotinib group and 12.6% in the gefitinib group. Cases with CTCAE grade 3 or higher were 5 in the icotinib group and 9 in the gefitinib group, and there were no cases in the icotinib group and 4 in the gefitinib group that withdrew from the study due to adverse reactions.

Thus, the results of the ICOGEN study suggest that icotinib is comparable to gefitinib in terms

of efficacy, but has a better safety profile than gefitinib. Icotinib is the best option as the first-line treatment for patients with advanced NSCLC with EGFR-sensitive mutations.

1.3 Report about EGFR Mutations in Non-lung Cancer Lesions

Several studies have shown that the EGFR gene is mutated or amplified in a variety of tumor cells, in addition to non-small cell lung cancer. Dong Xi *et al.* [11] experimentally observed the expression of EGFR in gastric cancer tissues and explored its clinical significance, and the results showed that the positive rate of EGFR was 56.5% for the 124 gastric cancer patients, significantly higher than that of normal gastric tissues adjacent to cancer, and the expression of EGFR was positively correlated with the depth of tumor infiltration and pathological stage, and they finally concluded that the high expression of EGFR was associated with the invasion and development of gastric cancer. Heng Zhou found a 64.9% EGFR-positive mutation rate through pathological observation of 74 breast cancer patients, and concluded that combined detection of EGFR and VEGF is important for assessing lymph node metastasis in breast cancer. Yue-Long Cui [12] investigated the relationship between EGFR intranuclear translocation and cisplatin resistance in esophageal cancer by detecting EGFR expression in chemotherapy-sensitive and chemotherapy-resistant esophageal cancer tissues, and found that the mRNA expression of EGFR was significantly higher in the resistant group than in the sensitive group, and found a significant increase in EGFR expression in the nucleus of EC9706/DDP cells, suggesting that EGFR intranuclear translocation is associated with cisplatin resistance in esophageal cancer. Another study has shown that 70-90% of colorectal cancer patients have high EGFR expression in their tumor tissues [13]. In addition, Shi-Yun Feng [14] applied immunohistochemistry to detect the expression of PTEN, Ki-67, and EGFR in thymoma tissues and quantified the results to reveal the pathogenesis of thymoma through the expression of the three in thymoma. The results showed that the positive expression rate of EGFR in 52 thymoma tissue specimens was 48.08%, concluding that the positive expression level of EGFR was closely related to Masaoka staging, i.e., a gradually increased positive expression rate with the progress of staging. Thus, EGFR is mutated or amplified in a variety of tumor cells, except in lung cancer, and is strongly associated with tumor progression, metastasis, and drug resistance.

Although, EGFR is highly expressed in non-lung cancer malignancies, EGFR mutations are rare. In addition, EGFR mutations have not been reported in benign pulmonary lesions such as tuberculosis globules, inflammatory granulomas, hamartoma, teratomas, adenomatous hyperplasia, and pulmonary consolidation. Based on these results, an EGFR-positive detection result suggests a high probability of lung carcinogenicity.

1.4 Current Status of EGFR Gene Testing

1.4.1 Difficulties in Tissue Sampling for Clinical EGFR Testing

Currently, tissue specimens remains to be the “gold standard” for EGFR gene testing. However, in clinical practice, tumor tissue specimens are not available from all patients to complete the genetic testing. Even in prospective clinical trials, less than 50% of patients had sufficient tumor tissue specimens for EGFR gene testing. Patients who are old, in poorer physical condition or with severe underlying disease often refuse to undergo this invasive test due to concerns about the risks associated with the sampling procedure. In addition, for some patients even with biopsies performed, the genetic testing is not practical because the tissue specimens may be small or do not contain enough tumor cells. Moreover, some patients with advanced disease are simply unsuitable for tissue specimens by invasive biopsy due to factors of tumor growth site. Still, due to the heterogeneity of the tumor, it is difficult to indicate the overall tumor condition of the patient with just some local tissue from biopsy. Finally, the genetic status of tumor tissue is constantly changing throughout the disease process, and it is imperative to screen the EGFR-mutated population through other simpler but more effective sampling routes to enable better efficacy of EGFR-TKI targeted therapy.

1.4.2 Value of Blood EGFR Testing

Recent studies have shown that free tumor DNA from peripheral blood of tumor patients has very similar genetic characteristics to the genome of tumor tissue [15], and the cfDNA content of tumor patients is 10-fold higher than that of normal subjects. Several studies have explored the feasibility of peripheral blood cfDNA for EGFR mutation detection, with a consistency of approximately 59-88% compared with tissue specimens, sensitivity of approximately 43-82%, and specificity of approximately 90-100% [16]. In addition, EGFR mutation status in peripheral blood cfDNA may correlate well with the efficacy of EGFR-TKIs, with significantly longer PFS in mutants compared to wild ones [17]. These findings suggest that peripheral blood cfDNA can be used for the detection of EGFR mutations.

The presence of tumor heterogeneity results in that small biopsy specimens may not fully reflect the overall information of the tumor, while ctDNA can compensate to some extent for the bias of genetic testing due to tumor heterogeneity. In addition, dynamic tissue specimen sampling is very difficult in clinical practice, and ctDNA testing can better enable the timely, quantitative, dynamic detection of genetic variation.

1.4.3 Development of Molecular Diagnostic Techniques for EGFR Mutations

In 2014 the European Medicines Agency (EMA) approved ctDNA testing to detect EGFR mutation status, and in 2015 the China Food and Drug Administration (CFDA, already renamed to NMPA) approved the use of ctDNA specimens obtained from blood (plasma) for EGFR testing when tissue specimens are not available. The traditional classical Sanger sequencing method is the gold standard for DNA sequencing [18], with sequencing lengths up to 1000 bp and almost 100% accuracy, but suffers from low throughput, high cost and time consuming, which seriously affect its large-scale application. As assays continue to advance, novel but more efficient and comprehensive high-throughput assays, known as Next-Generation Sequencing (NGS), have emerged. The core principle of NGS technology is sequencing while synthesizing, and its basic steps include library preparation, generation of monoclonal DNA clusters, and sequencing reactions [19]. Compared with the first generation sequencing technology (Sanger), the next generation sequencing technology has the following characteristics: (1) high throughput. Next-generation sequencing technology does not rely on traditional capillary electrophoresis, and its sequencing reactions are performed on the chip, allowing millions of sites on the chip to be sequenced simultaneously; (2) lower cost. The cost per Mb base of next-generation sequencing technology is 96.0%-99.9% lower than that of Sanger sequencing; (3) high sensitivity; (4) short read length, which does not facilitate splicing during subsequent data analysis; and (5) the polymerase chain reaction (PCR) process may introduce bias and mismatch [20].

In contrast, the established and commonly used method for blood EGFR detection is the amplification refractory mutation system (ARMS) method, which has a sensitivity of 65%-88% and a specificity of 98%-100% for detecting plasma EGFR-sensitive mutation compared to EGFR detection in tumor tissues [21-23]. ADx-Super-ARMS technology (Amoy Diagnostics Co., Ltd.) makes liquid biopsy for EGFR mutation more sensitive and easier to implement, providing results within 120 minutes, and can be widely used in a variety of diagnostic laboratories, which is currently the only one in China and has higher sensitivity than similar foreign technologies. Droplet Digital Polymerase Chain Reaction (ddPCR) is a new generation of molecular detection technique, which involves dividing the reaction system containing nucleic acid molecules into thousands of nano-scale water-in-oil droplets before conventional PCR amplification, then performing PCR amplification for each droplet simultaneously, and collecting the fluorescence signal in each droplet in turn after the amplification is completed [24]. Because of its unique principle, it has the advantages of high sensitivity, high specificity and absolute quantification, and can truly realize "liquid biopsy" of tumor by combining with peripheral blood circulating tumor DNA testing. The ddPCR technology can accurately detect plasma EGFR mutation, which is more helpful for accurate

screening of the population benefiting from EGFR-TKI-targeted therapy, timely monitoring of efficacy and early detection of drug resistance [25].

In clinical practice, some people with imaging implied lung adenocarcinoma may usually refuse or are unable to undergo puncture biopsy to obtain specimens for pathological diagnosis and genetic testing, while the use of ctDNA to detect EGFR mutations is clinically feasible. Therefore, the aim of this study is to investigate whether the administration of EGFR-TKI can benefit the population when their potential EGFR mutations are detected using ctDNA in the absence of known pathological status.

2 Study Objective

The aim of this study is to observe the efficacy of icotinib in treatment-naive patients clinically diagnosed with peripheral lung cancer, with unknown pathology status, and positive for blood EGFR sensitive mutations (EGFR 19del and/or 21L858R) test (positive for any of the tests by SARMS, ddPCR, and NGS).

2.1 Primary Objective

To observe the ORR of icotinib in treatment-naive patients clinically diagnosed with peripheral lung cancer, with unknown pathology status, and positive for blood EGFR sensitive mutation (EGFR 19del and/or 21L858R) test (positive for any of the tests by SARMS, ddPCR, and NGS).

2.2 Secondary Objective

To explore the consistency of positive blood epidermal growth factor receptor-sensitive mutations (EGFR 19del and/or 21L858R) (positive for any of the tests by SARMS, ddPCR, and NGS) with pathological confirmation of lung cancer.

To observe the PFS, OS and DCR of icotinib in treatment-naive patients diagnosed with lung cancer based on imaging data, with unknown pathology status, and positive for blood EGFR sensitive mutation (EGFR 19del and/or 21L858R) test (positive for any of the tests by SARMS, ddPCR, and NGS).

To analyze the consistency among SARMS, ddPCR, and NGS tests.

2.3 Exploratory Objective

Dynamic monitoring of multiple mutant genes;

Detection of biomarkers in patients' urine;

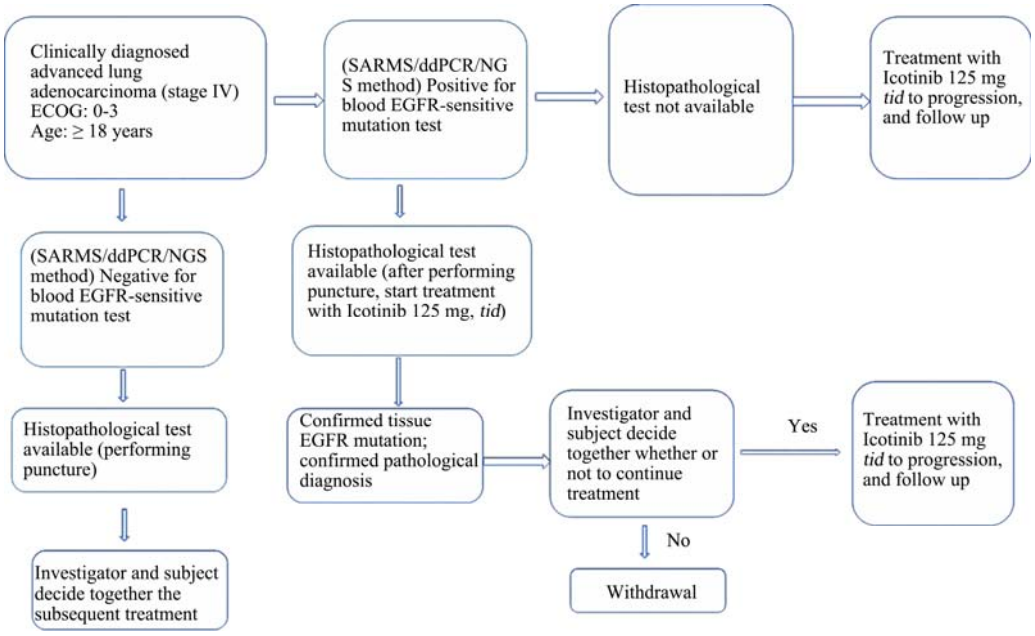
3 Study Design

3.1 Study Design and Plan

This is a prospective, open-label, single-arm, multicenter clinical study, aiming to observe the efficacy of icotinib in treatment-naive patients clinically diagnosed with peripheral lung cancer, with unknown pathology status, and positive for blood EGFR sensitive mutations (EGFR 19del and/or 21L858R) test (positive for any of the tests by SARMS, ddPCR, and NGS).

This trial includes two groups. The first group includes patients who are diagnosed with peripheral lung cancer based on radiographic data, and whose tissue specimens are not obtained for pathological diagnosis due to □ technical reasons (e.g., a tiny nodule, etc.); □ the patient's own reasons (e.g., no desire for tissue biopsy); or □ failure to collect pathological tissue from the patients after a puncture or multiple punctures and a positive epidermal growth factor receptor (EGFR) sensitive mutation (EGFR 19del and/or 21L858R) by a blood test (positive in any of the tests by SARMS, ddPCR, and NGS). Patients in this group will be treated with icotinib until PD.

The second group includes subjects who agree to undergo a pathological biopsy and whose specimens are likely to be obtained, but in cases where the pathological diagnosis and tissue EGFR mutation results are not known, a blood EGFR mutation test will first be performed (positive in any of the tests by SARMS, ddPCR, and NGS) and those who are positive will be given icotinib after a puncture. If a subject's pathological diagnosis and tissue EGFR mutation are confirmed during the treatment, the investigator and the subject will jointly decide whether to continue treatment with icotinib until PD. Patients with a negative blood test (not enrolled) will undergo a puncture to collect pathological tissue if available.



3.2 Selection of Subjects

Eligible patients were diagnosed with stage IV peripheral lung cancer by the investigator based on radiographic data, who are unable to receive radical resection or radical radiotherapy (including conventional radiotherapy and SBRT) and positive for EGFR sensitive mutation (EGFR 19del and/or 21L858R) by a blood test (positive in any of the tests by SARMS, ddPCR, and NGS).

3.2.1 Inclusion Criteria

– **Disease-related inclusion criteria:**

- Patients who are diagnosed with peripheral lung cancer and whose pathological diagnosis is not yet confirmed;
- Positive EGFR sensitive mutation (EGFR 19del and/or 21L858R) by a blood test (positive in any of the tests by SARMS, ddPCR, and NGS);
- Inability to undergo radical surgery or radical radiotherapy;
- Patients who have not received anti-tumor treatments such as surgery, chemotherapy, radiotherapy, and biological therapy;
- Palliative radiotherapy to bone metastases is allowed, provided that there is no ongoing radiotherapy-related toxicity;
- Age ≥ 18 years and expected survival time > 12 weeks;
- ECOG 0-3;
- Radiographically evaluable lesions and at least one unidimensionally measurable lesion with the maximum diameter ≥ 10 mm by spiral CT according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1). None of the lesions that have received radiotherapy can be used as a target lesion.
- **Hematology, biochemistry and organ function:**
- Bone marrow: Absolute neutrophil count (ANC) ≥ $1.5*10^9$/L; platelets ≥ $100*10^9$/L;
- Hemoglobin ≥ 8 g/dL;
- Liver: Serum bilirubin ≤ 1.5 × ULN; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (or AST & ALT ≤ 5 × ULN if there is liver metastasis);
- Kidney: Serum creatinine ≤ 1.5 × ULN;
- All laboratory values should be stable in the absence of ongoing supportive treatment;
- Asymptomatic brain metastases, or symptomatic brain metastases that are well controlled with local therapy (surgery and/or radiotherapy) and requiring no hormone maintenance therapy;
- No malabsorption or other gastrointestinal disorders that may affect drug absorption.
- **General inclusion criteria:**
- Subjects understand and voluntarily sign a written informed consent form (ICF) prior to any trial procedures;
- Subjects can take oral drugs;
- Women of childbearing potential must have a negative pregnancy test within 7 days before starting treatment; all patients (male or female) should use adequate barrier contraception throughout the treatment and for 4 weeks after the end of treatment.

3.2.2 Exclusion Criteria

- Any systemic anti-tumor treatment for lung cancer, including cytotoxic drug therapy, targeted drug therapy (including tyrosine kinase inhibitors or monoclonal antibodies), immunotherapy, or anti-tumor treatment received in other clinical trials;
- Local radiotherapy for lung cancer;
- Known allergy to icotinib or any of the ingredients in this product;

- Presence of large symptomatic pleural effusions, pericardial effusions, ascites, etc.
- Evidence of a severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease) as judged by the investigator;
- Any unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, angina within the last 3 months, congestive heart failure (≥ New York Heart Association [NYHA] Class II), myocardial infarction (within 6 months prior to enrollment), serious arrhythmia requiring medication, hepatic, renal or metabolic diseases);
- Patients who have had other cancers other than NSCLC within 5 years prior to the start of treatment in this study. Cervical carcinoma in situ, cured basal cell carcinoma, and epithelial tumors of the bladder [including Ta and Tis] are excluded;
- Previous interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis requiring hormone therapy, or any active interstitial lung disease with clinical evidence;
- Presence of idiopathic pulmonary fibrosis on CT scan at baseline;
- Ocular inflammation or infection that is not completely controlled, or any condition that may lead to one of these eye conditions;
- Diagnosed with Human immunodeficiency virus (HIV) infection;
- Participation in other clinical trials of anti-tumor drugs within 4 weeks prior to enrollment;
- Previous history of definite neurological or psychiatric disorders, including epilepsy or dementia;
- Pregnant or lactating women
- Evidence of any other significant clinical or laboratory findings that make the patient unsuitable for the study;
- Patients who have previously been registered to receive this study treatment or withdrew from this study;
- Patients with chronic toxicity ≥ NCI-CTC 4.0 Grade 2 (excluding alopecia) who have not been cured;
- Other conditions that are considered inappropriate by the investigator.

3.3 Sample Size and Study Duration

A total of 120 patients are planned for this study. The study will take about 15 months based on an enrollment of 8 subjects per month.

3.4 Withdrawal of Subjects from the Study

Withdrawal refers to a situation where patients discontinue their treatment for various reasons during the clinical study.

A patient will withdraw from the study if:

- The patient or his/her legal representative requests withdrawal;
- Continued participation will be detrimental to the patient's health, in the opinion of the investigator;

A patient must withdraw from the study if:

- Experiences other serious adverse reactions that, in the opinion of the principal investigator or his or her designee, require treatment interruption;

- Has poor compliance;
- Suffers from other complications that, in the opinion of the investigator, will significantly affect the evaluation of the patient's clinical condition and require discontinuation of treatment in this study;
- Suffers from other malignancies that require treatment;
- Lost to follow-up;
- Uses prohibited drugs or other substances that, in the opinion of the investigator, may cause toxicity or deviation of the study results;
- Died.

All patients who withdraw from the study should have the reason for withdrawal recorded on the case report form (CRF) and in the medical records.

All patients withdrawn due to adverse events or abnormal laboratory values should be followed up until the adverse events are recovered or stable, and the subsequent results of these events should be recorded. If any patient dies during the trial or within 30 days after completion of the trial, the investigator should be informed. The cause of death must be recorded in detail on the *Serious Adverse Event (SAE) Report Form* within 24 hours.

3.5 Treatment Plan

3.5.1 Treatment Procedures

Blood samples will be collected from patients having signed the informed consent form for a plasma ctDNA test and other tests.

The steps of the ctDNA test are as follows:

1. Prepare three 10 ml STRECK DNA BCT disposable vacuum cell-free blood collection tubes or three 8 ml EDTA anticoagulant vacuum blood collection tubes and twelve to eighteen 2 ml enzyme-free EP tubes before drawing blood. Stick a label on each tube, indicating the trial name, subject screening ID, subject initials, site name, visit period, and date of blood draw.

2. At screening, collect whole blood samples using a 10 ml STRECK DNA BCT disposable vacuum cell-free blood collection tube, 8 ml per tube and 3 tubes in total, and complete the corresponding specimen collection record. Transfer these tubes to each central laboratory for plasma separation within 14 days and for further processing and testing according to the standard operating procedures of SARMS, ddPCR, and NGS tests;

3. At each visit during treatment and at the end of treatment, the following two options are acceptable depending on the availability of 4°C centrifuges and -80°C refrigerators at each site:

(1) If 4°C centrifuge and -80°C refrigerator are not available, collect whole blood samples using a 10 ml STRECK DNA BCT disposable vacuum cell-free blood collection tube, 8 ml per tube and 3 tubes in total, and complete the corresponding specimen collection record. Transfer these tubes to each central laboratory for plasma separation within 14 days;

(2) If 4°C centrifuge and -80°C refrigerator are available, collect whole blood samples using an 8 ml EDTA anticoagulant blood collection tube, 8 ml per tube and 3 tubes in total, and separate the whole blood within 2 hours: ① centrifuge the tubes containing whole blood at 3500 rpm for 10-15 min using a 4°C centrifuge; ② aspirate the upper plasma with a pipette and dispense it into 2 ml EP tubes, about 2 ml of plasma/tube; ③ transfer the lower tangible cell precipitate (i.e. the white blood cell layer between yellow plasma and red blood) after centrifugation into 2 ml EP tubes and complete the label on each EP tube; ④ store the above EP tubes containing plasma and tangible cell

precipitate and the lower red blood cells after centrifugation in a -80°C refrigerator and complete the label and the specimen storage record; and transport the stored blood samples to each central laboratory via a designated transportation company at a low temperature within the specified time and store them in a -80°C refrigerator.

(3) Further process and test the samples according to the standard NGS testing procedures.

Patients meeting the inclusion and exclusion criteria will start medication.

Patients are required to visit the clinic for evaluation, and make a return visit 4 weeks after the start of treatment and then every 8 weeks for routine examinations until tumor progression or occurrence of intolerable toxicity.

After the investigators complete the study and record disease progression at each stage, it is required to contact each patient or his/her family or current treating physician by telephone at least every 12 weeks to collect long-term follow-up information on survival. Patients who discontinue study treatment for any reason other than progression (except for withdrawal of consent, loss to follow-up, and death) should continue to receive objective tumor evaluation every 12 weeks to collect information on disease progression.

3.5.2 Dose Reduction and Discontinuation of Icotinib

The dose of icotinib hydrochloride can be reduced or discontinued at any time during the study due to adverse events.

- Icotinib is well tolerated in clinical application and discontinuation is generally not required. According to the literature, the incidence of interstitial lung disease (ILD) in Eastern populations treated with gefitinib and erlotinib is 2-3% and 1-2%, respectively. No development of ILD was observed in the ICOGEN clinical study.
- Patients with ILD often present with acute dyspnea, accompanied by cough, slight fever, respiratory discomfort, and arterial oxygen desaturation. The symptoms can develop very severely in the short term and lead to death. Radiography often reveals pulmonary infiltrates or interstitial ground-glass opacities.
- Patients should be closely monitored for signs of ILD during the treatment by their treating physician. If any patient develops a new acute or progressively worsening dyspnea or cough, treatment with icotinib should be interrupted and relevant examinations should be performed immediately. Once ILD is confirmed, the medication should be discontinued and the patient should be treated accordingly.
- Rash and diarrhea are the main adverse reactions associated with icotinib hydrochloride. Other known adverse reactions include dry skin, fatigue, pruritus, nausea, vomiting, and abdominal pain. The dose can be reduced according to the most severe systemic toxicity, as shown in Table 1. All toxicities should be graded according to NCICTC-AE 4.0.
- In case of any AE considered by the investigator to be related to the study drug (see Table 2), the treatment should be discontinued until the AE resolved and restarted at a reduced dose of icotinib hydrochloride. The daily dose of icotinib hydrochloride should be reduced as shown in Table 1.

Table 1 Dose Reduction Regimen

Initial Dose	First Dose Reduction	Second Dose Reduction
375 mg/day (125 mg Tid)	250 mg/day (125 mg Bid)	None

The following guidelines in Table 2 provide an overview of dose modification methods according to the most common toxic side effects.

Table 2 Guidelines for Dose Modification and Management of Toxic Side Effects Associated with Icotinib

Toxicity	Grade	Treatment	Dose Modification
Keratitis	Grade 2	Interrupt treatment Ophthalmologic evaluation	Interrupt until resolved and restart at a reduced dose. Patients should continue to receive routine ophthalmologic evaluation during the treatment.
	≥ Grade 3	Discontinue treatment and seek advice from an ophthalmologist.	
Diarrhea	Grade 1	No intervention required	None
	Grade 2	Loperamide (initial dose 4 mg, followed by 2 mg every 2-4 hours until no diarrhea for 12 hours)	None**
	Grade 3		Interrupt until resolved to ≤ Grade 1, and restart at a reduced dose.
	Grade 4	Discontinue treatment	
Rash	Grade 1	No intervention required	None
	Grade 2	Any of the following medications: Minocycline [a], topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)	None**
	Grade 3		Interrupt until resolved to ≤ Grade 2, and restart at a reduced dose.
	Grade 4	Discontinue treatment	
Other toxicities	≥ Grade 2 prolonged and clinically significant toxicities	Treat as appropriate	Interrupt until resolved to ≤ Grade 1, and restart at a reduced dose.

*** Patients should discontinue the study if they have not recovered from the toxicity after 14 days of discontinuation;**

*** Patients should discontinue the study if the toxicity is still intolerable or remains at Grade 3 or above after dose reduction. Dose modifications are allowed up to 2 times for each group. See Table 2 for details**

3.5.3 Concomitant Therapies and Smoking

All concomitant medications and treatments (including start/end dates and indications) must be recorded in the patient's raw data and in the appropriate sections of the case report form (CRF).

All patients concomitantly taking drugs metabolized by CYP3A4 should be closely monitored for possible adverse reactions due to these drugs.

Smoking will affect the pharmacokinetics of icotinib. The smoking status of patients should be recorded, including the number of cigarettes smoked and duration per day, throughout the treatment. All patients are advised to quit smoking during the course of treatment.

3.5.4 Discontinuation Criteria

- When an adverse event occurs and it is considered difficult to continue the trial;
- When the underlying disease (or symptom) becomes worsened and it is considered difficult to continue the trial;
- When a subject is found not to meet the inclusion or exclusion criteria after administration;
- When a serious deviation from the trial protocol is found;
- When it is considered difficult to comply with the trial protocol;

- When a subject requests withdrawal from the trial;
- When the investigator considers it difficult to continue the trial.

3.5.5 Concomitant Medications

3.5.5.1 Prohibited Medications

- Bevacizumab and all drugs targeting VEGF, VEGFR, or EGFR (including registered and investigational drugs).
- All other anti-tumor drugs except for icotinib, including investigational drugs (e.g., investigational antibiotics, antiemetics, etc.) and Chinese herbal medicines indicated for treatment of tumors.

3.5.5.2 Permitted Medications

- Non-anti-tumor Chinese herbal medicines or acupuncture, vitamins/trace elements are permitted without affecting the study endpoints, at the discretion of the investigator.
- Patients may also receive symptom reduction and supportive treatments for pre-existing diseases.

3.5.6 Treatment Compliance

The dose of icotinib taken and the date of administration should be recorded in the CRF for each patient in each course of treatment. Reasons for dose delay, dose reduction or missed dose should also be recorded in the CRF.

Patient compliance with treatment and trial protocol includes voluntary compliance with all aspects of the protocol, including compliance with therapeutic drugs, compliance with all blood collections required for safety evaluation, and compliance with regular postoperative follow-ups. Patients who do not take the drug on time, or do not cooperate with examinations, or do not return on time may be excluded from the study according to the opinion of the principal investigator. Patients may withdraw from the study after discussion with and obtaining consent from the principal investigator if they have discontinued the treatment for >2 weeks due to adverse reactions that cannot be improved or cannot be relieved even with optimal symptomatic and supportive treatments.

3.6 Study Endpoints

The primary efficacy endpoint of this study is objective response rate (ORR = CR + PR).

The secondary endpoints include: consistency among SARMS, ddPCR, and NGS tests;

Consistency between positive blood EGFR sensitive mutation and pathologically confirmed lung cancer;

Progression-Free Survival (PFS)

Overall Survival (OS)

Disease Control Rate (DCR)

3.6.1 Efficacy Endpoints

Objective response rate (ORR): ORR will be determined separately for all patients according to RECIST 1.1. Incomplete or partial tumor evaluation results will not be used to calculate response rates unless the lesions included in the above examinations have demonstrated disease progression. It includes cases of complete response (CR) and partial response (PR).

Progression-free survival (PFS): PFS is defined as the time from the date of randomization

until the occurrence of disease progression, which could be a progression confirmed by radiography or death prior to disease progression. Patients who are alive and have not progressed as of the date of analysis will be censored at the date of their last radiographic evaluation.

3-year OS rate and 5-year OS rate: OS is defined as the time from the administration of study drug until death due to any cause. The 3-year OS rate refers to the probability that the patient is still alive at 3 years from the administration of the study drug. The 5-year OS rate refers to the probability that the patient is still alive at 5 years from the administration of the study drug.

Tumor response and disease progression will be assessed by the investigator according to RECIST criteria.

Duration of response was calculated in all patients with confirmed PR or CR according to RECIST criteria. Duration of response is measured from the time of first documentation of PR or CR until death or progression of disease (whichever is earlier). Patients who are alive and have no PD as of the date of analysis will be censored at the date of their last imaging evaluation.

3.6.2 Safety Measures

All patients who have received at least one dose of study drug will be considered as the valid population for safety analysis. Physical examination results, vital signs, adverse events and laboratory abnormalities of patients will be summarized. Adverse events should be reported and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

3.6.3 Study Period

The start date of study is defined as the date of signing ICFs.

3.6.3.1 Study Visit

The screening visit should be performed within 28 days prior to the start of study drug.

The treatment period refers to the period from the first dose of study drug to the withdrawal of study drug of the patient.

The end-of-treatment visit should be performed within 7 days (+/- 5 days) after the patient discontinues study drug for reasons other than death and loss to follow-up.

Patients who discontinue study drug will enter the post-treatment follow-up period. This period should include contact with the patient every 3 months until death to collect data on overall survival.

3.6.3.2 Imaging Evaluation

Screening period: CT scans of the chest and abdomen must be performed at least within 28 days before enrollment, and tumor measurements should be recorded in the CRF according to RECIST criteria.

Treatment period: The first response evaluation will be performed 4 weeks after the start of treatment, followed by evaluation of target lesions by CT scan every 8 weeks, and tumor measurements will be recorded in the CRF according to RECIST criteria. Other examinations will be performed as indicated by symptoms.

After the end of treatment: CT scans of target lesions should be performed at least every 8 weeks +/- 5 days, and tumor measurements should be recorded in the CRF according to RECIST criteria. Other examinations will be performed as indicated by symptoms.

3.6.3.3 Observation and Measurement

Subjects participating in this study will be evaluated according to the study flow chart and

subsequent outline in the appendix.

3.7 Study Procedures

3.7.1 Screening Period

Within 28 days prior to the start of administration of study drug

- ICFs should be signed prior to any study-related procedure;
- The 12-lead ECG at baseline should be performed and signed by the investigator;
- Brain MRI should be performed to rule out brain metastases only if there are neurological symptoms (suggestive of brain metastases).
- Tumor assessment at baseline: CT scan containing at least target lesions should be performed, and it can be performed within 28 days prior to the start of administration of study drug.

Screening Period – within 7 days prior to the start of administration of study drug

- Stage and grading of the primary tumor at initial diagnosis and the current stage to be recorded/confirmed;
- Demographics, complete medical history, surgical history, and smoking history, including prior anticancer therapy;
- Complete physical examination (PE), including ECOG performance status score, height, body weight and detailed systemic examination;
- Vital signs (including heart rate, blood pressure, respiratory rate, and temperature);
- All concomitant diseases, concomitant medications and their indications to be recorded;
- Hematology: hemoglobin, hematocrit, platelet count, white blood cell count and classification, including absolute neutrophil and lymphocyte counts;
- Biochemistry panel: including blood glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, etc.;
- Urinalysis: including specific gravity, pH value, urine glucose, urine protein and occult blood;
- A total of 24 ml whole blood to be collected for molecular marker test;

3.7.2 Treatment Period

Response evaluation will be performed 4 weeks after the start of treatment and every 8 weeks thereafter. The laboratory test, imaging evaluation and quality of life assessment during treatment are shown in the flow chart.

	Pre-treatment	Treatment period		End of treatment [12]	Post-progression follow-up [13]
		4 Weeks	Every 8 weeks until progression		
Activities	Screening period	28 ± 7 days	Every 8 weeks ± 7 days	within 7 days	Every 12 weeks ± 7 days
ICFs of patients	X (within 28 days)				The following information will be collected via telephone visit or clinic visit: 1. Survival information of patients; 2. Changes in anticancer treatment regimens, including all new therapies
Medical history [1]	X (within 7 days)				
Complete physical examination [2]	X (within 7 days)				
Inclusion/exclusion criteria	X				
12-lead ECG	X (within 28 days)	X	X	X	
Vital signs and ECOG score	X	X	X	X	
CT or MRI scan of the brain [3]	X (within 28 days)	X	X		
Chest and abdomen CT or B-scan ultrasonography [4]	X (within 28 days)	X	X		
Imaging Evaluation [5]	X (within 28 days)	X	X (every 8 weeks)----------→		
Hematology [6]	X (within 7 days)	X	X	X	
Biochemistry panel [7]	X (within 7 days)	X	X	X	
Urinalysis [8]	X (within 7 days)	X	X	X	
Blood biomarkers [9]	X (within 7 days)	X	X	X	
Tissue samples (paraffin-embedded) [10]	X				
PRO-Fact L and LCS questionnaire [11]	X	X	X	X	
Toxicity/AE evaluation	----------→				
Concomitant diseases and medications	----------→				

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1. Complete medical history, demographics, past surgical history, concomitant medications, concomitant diseases, allergic history, and smoking history.
2. Complete physical examination, ECOG performance status score, NYHA heart disease classification, height, body weight, vital signs and detailed examination of various systems of the body.
3. Only patients with neurological symptoms at baseline are required to undergo CT scan/MRI of the head to rule out brain metastases.
4. Patients with abdominal color Doppler ultrasonographic findings or symptoms suggestive of abdominal visceral metastasis at baseline are required to undergo abdominal CT scan/MRI evaluation.
5. Tumor evaluation and CT scan during treatment should be performed at 4 weeks after treatment for the first time, and then every 8 weeks thereafter. In case of withdrawal of a patient due to progression of disease, it will not be required to repeat the CT scan at the end of study visit.
6. Hematology includes: hemoglobin, hematocrit, platelet count, white blood cell count, absolute neutrophil count, and absolute lymphocyte count.
7. Biochemistry panel includes: blood glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, blood urea nitrogen, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, etc.
8. Urinalysis includes: specific gravity, pH, urine glucose, urine protein, and occult blood. Urinalysis will be required at screening, and urine dipstick test will be performed during subsequent course of treatment.
9. A total of 20 ml whole blood will be retained before treatment, during treatment and at the end of treatment respectively. If the patient continues the administration of Icotinib after progression of disease, 20 ml whole blood will be retained when the investigator determines that there is any progression of disease.
10. A total of 10 slices of 5 um tissue samples (paraffin-embedded) will be retained at screening.
11. The patient self-rating outcome questionnaires FACT-L and LCS (Version 4) should be completed prior to all other study procedures.
12. Provided that a subject discontinues the study drug for any reason (except death or loss to follow-up), an end-of-treatment evaluation should be performed at the time of discontinuation. If treatment is discontinued for any reason other than progression of disease (except for withdrawal of informed consent of the patient), imaging evaluation should be performed within 7 days and every 8 weeks thereafter until progression of disease. If the investigator considers that the patient can continue to benefit from Icotinib treatment, administration at the original dose can be continued until progression of disease is determined by the investigator, and tumor evaluation should be performed every 8 weeks during treatment.

13. Follow-up after progression of disease should be performed every 3 months until death of patient.

3.7.3 After the End of Treatment

After the end of treatment, examination should be performed every 8 weeks until progression of disease (see the flow chart).

* If the investigator believes that the patient will continue to benefit from icotinib treatment after determining disease progression based on RECIST criteria, the same dose of icotinib can be continued until the investigator determines disease progression. In the period, the patient cannot receive any other concomitant anti-tumor treatment. CT scan should be performed every 8 weeks during treatment to evaluate target lesions, and other examinations should be performed as indicated by symptoms.

3.7.4 Interim Visits

Interim visits should be performed as clinically indicated. Associated clinically significant laboratory abnormalities and adverse events should be recorded in the CRF and original data. If multiple laboratory tests are performed on the same day, only one set of test values needs to be recorded in the CRF. However, all abnormal values in repeated laboratory tests should be recorded in the CRF.

3.7.5 Follow-up after Progression of Disease

Patients will be contacted (by visit or telephone visit) every 12 weeks to acquire the information on overall survival and post-study chemotherapy. Follow-up should be performed every 12 weeks until death of patient. The following information should be made available during each follow-up:

- Survival status of patient;
- If death has occurred, the date and cause of death should be recorded;
- All new anticancer treatments (including third-line and other anticancer treatments after progression) should be recorded.

3.8 Data Quality

To follow the guidelines of Good Clinical Practice (GCP), the monitor will visit each site on a regular basis to ensure compliance with the study protocol, GCP and relevant laws. The visit will involve on-site check of case report form (CRF) for completeness and legibility, cross-check against original documents, and clarification of management-related matters.

3.9 Archiving

The data entered into the case report form (CRF) must be consistent with the original documents, or directly recorded in the case report form. In case of direct recording in the CRF, the recorded contents will be used as the original data. The parameters of original data must be validated, and the information of data source must be recorded. Study documents and all original data should be preserved until a notice of destruction is received from the investigator.

4 Investigational Drug

4.1 Icotinib

4.1.1 Name, Physicochemical Properties, Properties, Strength, Ingredients, Dosage and Administration, and Storage of Clinical Investigational Drug

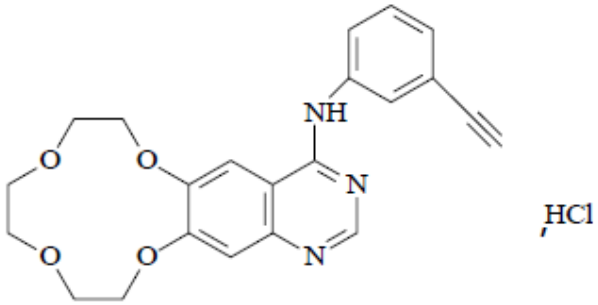
Drug Name

Trade Name: Conmana®

Generic Name: Icotinib Hydrochloride Tablets

Chemical Name: 4- [(3-ethynylphenyl) amino] - quinazoline [6,7-b] -12-crown-4- hydrochloride

Structural formula:



Molecular formula: $C_{22}H_{21}N_3O_4 \cdot HCl$

Molecular weight: 427.88

Physicochemical Properties

Physicochemical Properties: Icotinib hydrochloride is off-white to light yellow crystalline powder, odorless and non-hygroscopic. It is soluble in dimethyl sulfoxide, slightly soluble in acetonitrile-water (1: 1), methanol or chloroform, very slightly soluble in ethanol, and practically insoluble in water and acetonitrile. The melting point is 225~228°C. The absorption coefficient ($E^{1\%}_{1cm}$) at a wavelength of 340 nm ranges from 500 to 520.

Drug properties: This product is brownish-red film-coated tablet, which is off-white after removal of its coating.

Strength: 125 mg.

Ingredients: The main ingredient of this product is icotinib hydrochloride.

Dosage and Administration: p.o. 1 tablet/time, tid.

Storage: Store in sealed containers, and protect from light.

4.1.2 Package and Label

The investigational drug will be packaged in an aluminum-plastic plate and placed in a pre-labeled medicine box for administration of subjects. Each medicine will be labeled with the protocol number, patient number, drug batch number, dosing instructions, and manufacturer's name, and indicated with: "FOR CLINICAL STUDIES, NOT FOR SALE".

4.1.3 Drug Dispensing and Accountability

The investigational drug will be dispensed by the investigator.

At appropriate intervals, or until the end of the study, all unused drugs, as well as empty boxes and strips, must be returned to Betta Pharmaceuticals Co., Ltd. At the end of the study, the monitor will verify all unused items.

An inventory must be made available for inspection by the monitor.

5 Ethical and Legal Issues

5.1 Ethics Committee (EC) or Institutional Review Board (IRB)

In accordance with GCP, Chinese laws and regulations as well as the requirements of relevant organizations, all sites involved in the study should obtain the approval documents from the associated Ethics Committee/Institutional Review Board prior to the start of the study. If necessary, the extension, amendment or re-audit of the approval letter from Ethics Committee must be obtained and handed over to the investigator.

5.2 Ethical Guidance

The procedures involved in the operation, evaluation and preparation of documents in this study protocol are established to ensure that the investigators follow the guidelines of Good Clinical Practice (GCP) and the guidelines specified in the *Declaration of Helsinki*. This study will also be conducted in accordance with the relevant laws and regulations of China.

The investigator cannot modify the study protocol without obtaining the consent. However, in case of emergency, in order to remove risk factors to subjects, the investigator may deviate from or change the study protocol without prior consent/support from the Ethics Committee/Institutional Review Board/Sponsor. Deviations or changes and their reasons should be submitted to the Ethics Committee/Institutional Review Board/Sponsor as soon as possible. If appropriate, a recommendation for protocol modifications should be submitted. All deviations or changes to the study protocol must be fully interpreted and described by the investigator.

5.3 Subject Information and Informed Consent

Subjects should be provided with the main information and ICFs of the study. Before the study, the investigator must provide the subject with the written approval/favorable opinion of the ICFs and all other written information from the Ethics Committee/Institutional Review Board. The approval letter/approved subject information/ICFs from the Ethics Committee/Institutional Review Board must be archived in the study file.

ICFs must be obtained prior to any specific study procedure. The date when subjects participate in the study and sign the ICFs should be recorded in the associated documents of subjects.

5.4 Confidentiality

All records concerning the patient's identity should be kept confidential and, to the extent permitted by the relevant laws and/or regulations, will not be disclosed to the public.

Names of subjects will not be provided. Only the subject numbers and initials will be recorded in the case report form. In case the name of a subject appears on any other document (e.g. pathology report), the copy of the document must be obliterated. Study reports stored in computer must comply with relevant local laws on data protection. The subject's identity will also be kept confidential when the results of the study are published.

The investigator will maintain a record for ease of identification of subjects.

6 Statistical Methods and Determination of Sample Size

6.1 Statistical Analysis Plan

6.1.1 Analysis Population

Efficacy analysis will be performed in the intent-to-treat population (ITT), which is defined as all patients who receive at least one dose of study drug. The safety analysis population will include all patients who receive at least one dose of study drug. The response rate analysis population is defined as all patients in the ITT population with partial response or complete response as determined by RECIST criteria.

6.1.2 Baseline and Demographics

Baseline, demographics, baseline tumor characteristics, medical history, prior anticancer therapy, concomitant medications, vital signs, and trial discontinuation will be summarized by treatment group for all grouped patients. For continuous measurement, the mean, standard deviation, distribution range and median will be calculated; and the absolute value, frequency and percentage will also be calculated.

6.1.3 Efficacy Analysis

Efficacy analysis will be performed in the ITT population.

6.1.3.1 Primary Efficacy Analysis

The primary endpoint is objective response rate (ORR).

6.1.3.2 Secondary Efficacy Analysis

Progression-Free Survival (PFS)

Disease Control Rate (DCR)

Improvement of quality of life

Disease-related response

6.1.3.3 Safety Analysis

Adverse events and the grade of the most severe reaction will be summarized according to the criteria of NCI CTCAE (Version 4), and adverse events will also be summarized according to their seriousness and relationship to the study drug. The descriptive summary of laboratory test values mainly focuses on outliers. Laboratory abnormalities will also be summarized by the worst grade according to the NCI CTCAE (Version 4).

6.2 Determination of Sample Size

The purpose of this study was to observe the ORR of icotinib in treatment-naive advanced NSCLC patients with EGFR sensitive mutation as detected by blood test. Approximately 120 subjects are required to be enrolled.

According to previous literatures, it is estimated that the ORR of icotinib treatment in treatment-naive advanced NSCLC patients with EGFR sensitive mutation as detected by blood test is approximately 60%, with an allowable error of 10% and a significance level of 0.05%. It is estimated that at least 93 evaluable subjects are needed. Therefore, considering a dropout rate of not more than 20%, at least 117 subjects should be enrolled. Hence, it is finally proposed to enroll 120 treatment-naive NSCLC patients with EGFR sensitive mutation as detected by blood test.

7 Adverse Event

7.1 Precautions/Warnings

For the potential adverse reactions of Icotinib, please refer to the detailed prescription data in the package.

7.2 Monitoring of Adverse Event

Subjects must be closely monitored for adverse events, including clinical laboratory tests. Evaluation should be performed according to the seriousness and severity of adverse events and their relationship with the investigational drug.

The investigator is responsible for evaluation on the relationship between the study drug and all adverse events. However, the principal investigator may entrust other investigators participating in this study for judgment, but he/she is still responsible for this. The investigator must provide a list of qualified and delegated personnel.

7.3 Definition of Adverse Event

7.3.1 Adverse Event

An adverse event refers to any untoward medical occurrence in a patient or subject administered a study drug. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of study drug, whether or not considered drug-related.

Adverse events in humans (whether or not considered drug-related) include:

- Adverse events that occur during the use of drug by professionals;
- Adverse events caused by overdose (intentional or unintentional);
- Adverse events caused by drug abuse;
- Adverse events caused by drug withdrawal;
- Adverse events that occur just because of the patient's participation in the study (e.g. adverse events or serious adverse events due to discontinuation of antihypertensive drugs in the washout period) (such events must be reported as adverse events even if they are unrelated to the study drug).

Those which show no clinical pharmacological effects or fail to achieve the expected clinical pharmacological effects, and have been recorded in the associated part of the CRF are not considered as adverse events. However, if the criteria for "serious" adverse events are met, they should also be recorded and reported as serious adverse events. In this study, progression or worsening of an existing tumor must also be reported as a serious adverse event (SAE) if it meets the criteria for "serious" grade. The investigator should also report signs and symptoms due to progression or worsening of existing cancer.

7.3.2 Serious Adverse Event

A serious adverse event refers to any untoward medical occurrence at any dose that meets any of the following conditions:

- Fatal;

- Life-threatening;
- Leading to hospitalization or prolonged hospital stay;
- Leading to persistent or significant incapacity or disability;
- Congenital anomaly or birth defect;
- Significant medical event.

Life-threatening: The term "life-threatening" is defined as "serious" and refers to an adverse event (AE) in which the subject is at risk of death. It does not refer to those AEs that may cause death when the hypothetical situation has worsened.

Hospitalization: Any AE that results in hospitalization of a patient or prolongation of hospital stay of an inpatient is considered serious, unless it meets one of the following characteristics:

– Stay in the hospital under observation for no more than 12 hours;

Or

– Hospital admission is preplanned (i.e., surgery or selective surgery scheduled prior to the start of this study);

Or

– Admission is not associated with an AE (e.g., hospitalization for convalescence purposes).

It should be noted that any invasive treatment performed during hospitalization may meet the criteria of "significant medical event" and therefore may need to be reported as a serious AE based on clinical judgment. Furthermore, if local authorities have stipulated more stringent definitions, the local regulations shall prevail.

Disability: It refers to a person who is severely impaired in his/her ability to perform daily activities.

Significant medical event: Any AE that may jeopardize the subject and may require intervention to prevent a more serious condition is considered serious. Significant medical events are identified according to the "World Health Organization Adverse Reaction Terminology (WHOART) - Key Terms". These terms refer to, or describe, severe disease states.

Such events are reported as serious AEs because they may be associated with a serious disease state and because reporting as an SAE warrants special attention compared with other modes of reporting.

7.3.3 Unexpected Adverse Event

An unexpected AE is an adverse drug reaction, the characteristics or severity of which are not consistent with those described in this Investigator's Brochure (or in the package insert for the marketed product). Supplementation of important information on the characteristics or severity of known and documented AEs is also part of the reporting of unexpected AEs. For example, events that are more specific or more serious than those described in the Investigator's Brochure should be considered "unexpected". Specific examples include: (a) acute renal failure that has been designated an AE, followed by interstitial nephritis; and (b) hepatitis first reported as acute hepatic necrosis.

7.3.4 Relationship between Adverse Event and Investigational Drug

The evaluation of the relationship between an AE and the study drug is a comprehensive clinical judgment based on all the information obtained when completing the Case Report Form (CRF).

Evaluation of "unrelated" conditions may include:

1. Clear alternative explanation, such as traumatic bleeding at the operation site;

Or

2. Unreasonable, e.g., a subject was hit by a car, but there was no indication that the drug-induced disorientation led to the event; or cancer developed only a few days after starting the dosing.

An assessment of "Yes" indicates there is a reasonable possibility that the AE may be related to the study drug.

Factors to be considered when assessing the relationship of an AE to study drug include:

– Occurs shortly after drug intake: the AE should occur after drug administration. The clinical evaluation of an event should consider the time from drug administration to the occurrence of the event.

– The event disappears after drug withdrawal (stimulation cessation) and reoccurs after drug re-administration (repeated stimulation): The clinical course of the suspected event should be analyzed with full consideration of the subject's response after discontinuation (stimulation cessation) or the subject's response after re-administration (repeated stimulation).

– Underlying, concomitant and intermittent diseases: it is necessary to make an evaluation on the natural course of relevant diseases, treatment process and all other diseases the patients may suffer from in each report;

– Concomitant medication or treatment: Other medications administered to the subject or other treatments administered to the subject should be examined to determine if one of these may have caused the AE;

– Known pattern of response to a class of drugs: clinical/preclinical

– Pharmacology and pharmacokinetics of the investigational drug: The pharmacokinetic characteristics (absorption, distribution, metabolism and excretion) of the investigational drug should be considered in combination with the individual pharmacodynamic response of each subject.

7.3.5 Recording of Adverse Event

All AEs occurring after the subject signs the Informed Consent Form (ICF) must be completely recorded in the subject's CRF.

Records must be supported by original data. Laboratory abnormalities that are considered clinically relevant (e.g., those that result in early withdrawal of a subject from the study, require treatment to a subject, or trigger an apparent clinical manifestation, or are considered clinically relevant by the investigator) should be reported as AEs. Each event should be described in detail, including the start and stop date, severity, relationship with the investigational product, actions taken, and outcome of the event.

7.4 Reporting of Serious Adverse Event

Serious adverse events (SAEs) meeting the definition, including laboratory abnormalities meeting the definition of an SAE, that occur from the signing of the ICF through 30 days after the completion of the last dose must be reported immediately (within 24 hours of the investigator's awareness) to the designated person in the study document. The SAE Report Form must also be completed and submitted to the designated person in the study document within 24 hours of the investigator's awareness.

Each SAE should be followed up until it is resolved or stabilized, and an updated report should

be submitted to the designated person. Pure grade 4 laboratory abnormalities (according to CTCAE v3.0 criteria) are not to be reported as serious adverse reactions unless the investigator believes that the abnormality has met the International Conference on Harmonisation (ICH) criteria for SAEs (see Section 6.3.2 for definition). CTCAE v3.0 grade 4 laboratory abnormalities that occur at baseline and are manifestations of the disease should not be reported as SAEs, especially if they are still allowed by the Protocol or not excluded from the study. If there is a question as to whether an abnormality should be reported as an SAE, the investigator may consult with the study monitor. CTCAE grade 4 laboratory abnormalities should be recorded on the "laboratory data" page and checked periodically by the medical monitor.

According to the requirements of local laws and regulations, SAEs must be reported to the Ethics Committee and NMPA.

8 Data Management

8.1 Completion and Transfer of Case Report Form

The CRF of each included case will be completed by the investigator. After the completed CRFs are reviewed by the study monitor, they will be transferred to the data manager for data entry and management.

8.2 Data Entry and Modification

Data entry and administration are the responsibility of the Data Administrator designated by the Biostatistician. The data entry and management will be performed by the data manager using data entry program prepared by the EpiData software. Data are entered in duplicate to ensure the accuracy of data.

For the questions in the CRF, the Data Administrator generates a data response question (DRQ) and send it to the investigator through the clinical monitor. The investigator should reply and return as soon as possible. The Data Administrator modifies, confirms and enters the data according to the investigator's replies, and DRQ may be sent again if necessary.

8.3 Data Locking

After confirming that the established database is correct, the data are locked by the Principal Investigator (PI), the Sponsor, and the statistical analyst. The locked data documents will be not modified.

8.4 Data Processing

After all the trial data are entered and locked, the database will be submitted to the statistician for statistical analysis according to the requirements of the statistical plan. After completing the statistical analysis, the statistical analyst will write the statistical analysis report, which will be submitted to the PI of this trial to prepare the trial summary report. An independent third party will assume the biostatistics work, participate in the trial design and protocol implementation, be responsible for data administration and statistical analysis, and complete the statistical summary report.

9 Informed Consent

The PI ensures that the subjects are provided with complete and adequate verbal and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be informed that they are free to withdraw from the study at any time. Subjects should have the opportunity to ask questions and have time to consider the information given.

ICFs signed and dated by subjects must be obtained prior to performing any study-specific procedures.

The Principal Investigator must keep the original copies of the signed ICFs.

10 Appendix

10.1 Performance Status (ECOG Score)

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction. (Karnofsky 90-100 points)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. (Karnofsky 70-80 points)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60 points)
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40 points)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20 points)

10.2 TNM Staging System - UICC Criteria

Seventh edition for TNM staging

T staging of primary tumors

TX。 Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma *in situ.*

T1 Tumour < 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus. (Some rare superficial tumors confined to the bronchial wall are classified as T1 regardless of size, even if they involve above the main bronchus).

T1a Tumour ⩽ 2 cm in greatest dimension.

T1b Tumour > 2 cm but ⩽ 3 cm in greatest dimension.

T2 Tumour > 3 cm but ⩽7 cm or tumour with any of the following features:

Involves main bronchus, > 2 cm distal to the carina

Invades visceral pleura

Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumour > 3 cm but ⩽ 5 cm in greatest dimension.

T2b Tumour > 5 cm but ⩽7 cm in greatest dimension.

T3 Tumour > 7 cm or one that directly invades any of the following:

Chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium

Tumour in the main bronchus < 2 cm distal to the carina but without involvement of the carina

Associated atelectasis or obstructive pneumonitis of the entire lung

Separate tumour nodule(s) in the same lobe

T4 Tumour of any size that invades any of the following:

Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina

Separate tumour nodule(s) in a different ipsilateral lobe.

N staging of regional lymph nodes

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension.

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s).

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

M staging of distant metastasis

Mx Distant metastasis cannot be assessed.

M0 No distant metastasis.

M1 Distant metastasis.

M1a Separate tumour nodule(s) in a contralateral lobe

tumour with pleural nodules or malignant pleural/ pericardial effusion.

M1b Distant metastasis.

Clinical staging (AJCC 2009)

Concealed stage TXN0M0

Stage 0 TisN0M0

Stage IA T1N0M0

Stage IB T2aN0M0

Stage IIA T1N1M0, T2aN1M0, T2bN0M0

Stage IIB T2bN1M0, T3N0M0

Stage IIIA T4N0M0, T3-4N1M0, T1-3N2M0

Stage IIIB T4N2M0, T1-4N3M0

Stage IV T1-4N0-3M1

(The above stages are summarized in the following table)

T/M	N0	N1	N2	N3
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
	IIB	IIIA	IIIA	IIIB

T/M	N0	N1	N2	N3
	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
	IIIA	IIIA	IIIB	IIIB
M1a	IV	IV	IV	IV
	IV	IV	IV	IV
M1b	IV	IV	IV	IV

10.3 Response Evaluation Criteria in Solid Tumors RECIST 1.1

Tumor response and progression will be evaluated in this study using the new international standard (14) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. RECIST varies only in that the largest diameter (one-dimensional measurement) of the tumor lesion is applied.

Measurable lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (recording the longest diameter) with a maximum diameter of ≥ 20 mm using conventional techniques (PE, CT, XR, MRI) or ≥ 10 mm using spiral CT scan. Spiral CT done to assess tumor response must be reconstructed with a layer thickness of 5 mm. All tumor measurements must be recorded in millimeters (or one-tenth of a centimeter).

Non-measurable lesions: All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm using conventional techniques or < 10 mm using spiral CT scans), are considered non-measurable. Bone lesions, meningeal lesions, ascites, pleural/pericardial effusion, lymphangitis of the skin/pneumonia, inflammatory breast disease, abdominal lesions (cannot be followed up by CT or MRI), and bladder lesions are all considered non-measurable.

Target lesions: A maximum of 2 of all measurable lesions per organ can be selected as target lesions and a maximum of 5 representative lesions of all involved organs can be selected as target lesions. All target lesions should be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (longest diameter of the lesion) and the repeatability of their accurate measurements (regardless of imaging techniques measurement or clinical measurement). The sum of the longest diameter (LD) of all target lesions is considered as the baseline sum LD. The baseline sum LD will be used as the reference value to objectively evaluate the tumor response by measuring the size of subsequent lesions. If more than 5 measurable lesions are present, those not selected as target lesions will be identified as non-target lesions along with the non-measurable lesions (see Section 9.3).

Non-target lesions: Include all non-measurable lesions (or sites of disease) and all measurable lesions except for the 5 target lesions selected. These lesions do not need to be measured but should be recorded as "present" or "absent" at baseline and at each follow-up visit.

Response assessments: All patients will have one of the following response assessments:

Complete response (CR): Disappearance of all clinical and radiographic evidence of tumor, including target and non-target lesions.

Partial response (PR): At least a 30% decrease in the sum of the LD of target lesions, reference the baseline sum LD.

Stable disease (SD): Stable state of the disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive disease (PD): At least a 20% increase in the sum LD of the measured lesions or the appearance of one or more new lesions, taking as reference the smallest total LD recorded since the treatment started. The appearance of any new lesion signifies disease progression. In exceptional

cases, unequivocal progression of the non-measurable lesion is also accepted as evidence of disease progression.

Response Assessment of Target and Non-Target Lesions

Target lesions	Non-target lesions	New lesions	Overall Response	Additional Requirements for Optimal Response
CR	CR	None	CR	Confirmed after > 4 weeks
CR	Non-CR/Non-PD	None	PR	Confirmed after > 4 weeks
PR	Non-PD	None	PR	
SD	Non-PD	None	SD	Maintained for at least > 4 weeks from baseline
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

*** Patients who experience an overall deterioration in their health status and require discontinuation of treatment should be reported as "symptomatic deterioration" if there is no objective evidence of disease progression at that time. Every effort should be made to observe and document objective disease progression even after discontinuation of treatment.**

10.4 NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

The NCI CTCAE version 4.0 will be used in this study to report toxicities and serious adverse events. The CTC4.03 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov/CTC3/ctc.htm).

10.5 Effective Management of EGFR TKI-associated Cutaneous Adverse Reactions

In clinical practice, reasonable preventive measures and patient education are the most critical steps (see Section VI).

When a skin lesion occurs, the lesion severity is first determined and then the lesion is treated step by step according to the severity:

- **Mild toxicity:** Patients may not require any form of intervention, and compound dexamethasone acetate, hydrocortisone (1% or 2.5% ointment), or clindamycin (10% gel) may also be applied topically. The dose of EGFR-TKI should not be altered due to mild toxicity. The severity of the rash is reassessed after 2 weeks and the condition is treated for moderate toxicity if it has worsened or does not improve significantly.
- **Moderate toxicity:** Topical use of 2.5% hydrocortisone ointment or erythromycin ointment, and oral clarityne; oral minocycline (doxycycline) should be given as early as possible to patients with subjective symptoms. The rash should be evaluated after 2 weeks; if the condition deteriorates or there is no significant improvement, the patient should enter the next level of treatment.
- **Severe rash:** The intervention measures are basically the same as moderate rash. If necessary, a pulse dose of methylprednisolone can be given, and the dose of EGFR-TKI can be reduced; if the adverse reaction is not adequately relieved after 2 ~ 4 weeks, drug interruption or treatment discontinuation should be considered.

10.6 Testing of Tumor Specimens

Blood samples for EGFR gene detection at screening: Specimens collected during screening are processed and shipped to a central laboratory for testing for mutations in the EGFR gene.

Blood samples for exploratory biomarker analysis and sampling time points. Blood samples will be periodically transported to the central laboratory for testing after sampling and centralization. See "SOP for Blood Sampling" below for details.

In order to ensure accurate and reliable testing of blood samples, EDTA should be used as the anticoagulant during the blood sampling. The specific operating procedures are as follows:

1. Prepare three 10 ml STRECK DNA BCT disposable vacuum cell-free blood collection tubes or three 8 ml EDTA anticoagulant vacuum blood collection tubes and twelve to eighteen 2 ml enzyme-free EP tubes before drawing blood. Stick a label on each tube, indicating the trial name, subject screening ID, subject initials, site name, visit period, and date of blood draw.

2. At screening, collect whole blood samples using a 10 ml STRECK DNA BCT disposable vacuum cell-free blood collection tube, 8 ml per tube and 3 tubes in total, and complete the corresponding specimen collection record. Transfer these tubes to each central laboratory for plasma separation within 14 days and for further processing and testing according to the standard operating procedures of SARMS, ddPCR, and NGS tests;

3. At each visit during treatment and at the end of treatment, the following two options are acceptable depending on the availability of 4°C centrifuges and -80°C refrigerators at each site:

(1) If 4°C centrifuge and -80°C refrigerator are not available, collect whole blood samples using a 10 ml STRECK DNA BCT disposable vacuum cell-free blood collection tube, 8 ml per tube and 3 tubes in total, and complete the corresponding specimen collection record. Transfer these tubes to each central laboratory for plasma separation within 14 days;

(2) If 4°C centrifuge and -80°C refrigerator are available, collect whole blood samples using an 8 ml EDTA anticoagulant blood collection tube, 8 ml per tube and 3 tubes in total, and separate the whole blood within 2 hours: centrifuge the tubes containing whole blood at 3500 rpm for 10-15 min using a 4°C centrifuge; aspirate the upper plasma with a pipette and dispense it into 2 ml EP tubes, about 2 ml of plasma/tube; transfer the lower tangible cell precipitate (*i.e.* the white blood cell layer between yellow plasma and red blood) after centrifugation into 2 ml EP tubes and complete the label on each EP tube; store the above EP tubes containing plasma and tangible cell precipitate and the lower red blood cells after centrifugation in a -80°C refrigerator and complete the label and the specimen storage record; and transport the stored blood samples to each central laboratory via a designated transportation company at a low temperature within the specified time and store them in a -80°C refrigerator.

(3) Further process and test the samples according to the standard NGS testing procedures.

10.7 New York Heart Association Functional Classification

	New York Heart Association (NYHA) Functional Classification
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
Class IV	Patient with cardiac disease resulting in inability to carry on any physical activity. Symptoms of heart failure or anginal syndrom may be present at rest. If any physical activity is undertaken, discomfort is increased.

10.8 Calculation of Creatinine Clearance

Cockroft-Gault calculation formula for female patients:

Creatinine clearance [ml/min] =

((140 - age) × actual body weight [kg] × 0.85)/(72 × serum creatinine [mg/dl])

Or

((140 - age) × actual body weight [kg] × 0.85)/(0.81 × serum creatinine [μmol/L])

Cockroft-Gault calculation formula for male patients:

Creatinine clearance [ml/min] =

((140 - age) × actual body weight [kg])/(72 × serum creatinine [mg/dl])

Or

((140 - age) ×actual body weight [kg])/(0.81×serum creatinine [μmol/L])

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12 Protocol Signature Page

Statement of Investigator

I have read this protocol and conduct this clinical study in accordance with the moral, ethical, and scientific principles stipulated in the Declaration of Helsinki and Chinese GCP. I agree to conduct this clinical study in accordance with the design and provisions of this protocol.

I will be responsible for making medical decisions related to the clinical trial to ensure that subjects are treated promptly in the event of AEs during the trial. I understand the procedures and requirements for correct reporting of SAEs, and I will record and report these events as required.

I guarantee that the data will be accurately, completely, timely and rightfully recorded in the CRF. I will cooperate with the monitoring and audit activities by the study monitor or auditor designated by the Sponsor, as well as the audit and inspection activities by the drug regulatory authority to ensure the quality of clinical study.

I will provide a *Curriculum Vitae* before the clinical study, which will be submitted to the Ethics Committee and possibly to the drug regulatory authority.

Investigator (Signature): _____ Date:_____