Clinical Trial Protocol

Randomized, prospective, open-label phase II clinical study of adjuvant icotinib (12 months) versus observation in patients with stage IB epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) after complete resection **(CORIN Study)**

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Sponsor: Betta Pharmaceuticals Co., Ltd., Hangzhou, China

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Synopsis

Title	Randomized, prospective, open-label phase II clinical study of adjuvant icotinib (12 months) versus observation in patients with stage IB epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) after complete resection
Sponsor	Betta Pharmaceuticals Co., Ltd., Hangzhou, China
Objectives	To investigate the efficacy of icotinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) as a postoperative adjuvant therapy for stage IB mutant type non-small cell lung cancer (NSCLC) without chemotherapy. **Primary endpoint:** 3-year disease-free survival (DFS). **Secondary endpoints:** disease-free survival (DFS), overall survival (OS), central nervous system (CNS)-related DFS, safety and tolerability.
Study Design	Randomized, prospective, open-label phase II clinical study
Number of Subjects	128
Target Population	EGFR-mutant stage IB (based on 7th TNM staging) NSCLC without postoperative chemotherapy

Inclusion criteria	**Inclusion criteria related to disease:** • Postoperative histopathology has confirmed stage IB NSCLC with R0 resection by TNM staging, accompanied with positive EGFR mutation; • Have not received other chemotherapy, radiation therapy or biological therapy; • Adjuvant chemotherapy was not planned; • The treatment starts within 4 weeks after surgery; • No signs of tumor recurrence based on examinations prior to treatment. **Hematology, Biochemistry and Organ Functions:** • Lung function: FEV1>50; • Hemoglobin ≥90 g/L (this level can be maintained or exceeded by blood transfusion); • Absolute neutrophil count ≥2.0×10^9/L; • Platelet count ≥100×10^9/L; • Total bilirubin ≤ 1.5 times the upper limit of normal (ULN); • ALT and AST ≤ 2.5 times the ULN; • Creatinine ≤ 1.25 times the ULN; and creatinine clearance ≥ 60 mL/min; • No pregnancy for women of childbearing age (15 to 49 years). **General inclusion criteria:** • Subjects have obtained informed consent form signed by the patient or his/her legal representative; • Subjects have good compliance; • Subjects can take medicines orally; • Subjects are males or females aged ≥18 years; • Subjects have ECOG Performance Status Scale of 0-1 and life expectancy of greater than 1 year; • Male and female subjects of childbearing age agree to take reliable measures for contraception before entering the study, during the study and up to 8 weeks after drug discontinuance.

Exclusion criteria	• Subjects have received any other systemic anticancer therapy for NSCLC, including cytotoxic drug therapy, targeted drug therapy (including tyrosine kinase inhibitors or monoclonal antibodies), experimental treatment; • Subjects have received local radiotherapy for NSCLC; • Subjects have incomplete physiological functions of the upper gastrointestinal tract, or malabsorption syndrome, or intolerance to oral medications, or active gastrointestinal ulcers; • There are clinically objective evidences (pathology or imaging evidences) to confirm tumor recurrence before the start of treatment; • Subjects have suffered from cancers other than NSCLC, excluding cervical carcinoma in situ, cured basal cell carcinoma, urothelial tumors [including Ta and Tis] within the five years prior to the start of treatment in this study; • Subjects are known to be allergic to icotinib or any components of this drug product; • Subjects have a history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis requiring hormonal therapy, or any active interstitial lung disease with clinical evidences; • Subjects are found to have idiopathic pulmonary fibrosis by CT scan at the baseline; • Subjects have eye inflammation or eye infection that is not completely controlled, or any condition that may cause the above eye diseases; • Subjects have suffered from any unstable systemic disease, including active infection, uncontrolled hypertension, unstable angina, angina occurring within the recent 3 months, congestive heart failure (≥New York Heart Association [NYHA] Class II), myocardial infarction (6 months before enrollment), severe arrhythmia requiring drug therapy, liver, kidney or metabolic diseases; • Subjects have known HIV infections; • Subjects combined with additional components of small cell lung cancer; • Pregnant or breastfeeding women; • Subjects have a history of definite neurological or psychiatric disorders, including epilepsy or dementia; • Other circumstances deemed inappropriate by the Investigator.

Duration of study	It is planned to enroll 128 patients based on about 6 patients enrolled each month; and the time for enrollment is about 24 months; the minimum survival follow-up period is 3 years, and the total study period will last about 60 months.
Study Drug Dosage/ Route of Administration/Regimen	**Group A (icotinib group):** Patients start to receive oral icotinib 125 mg, tid, for 12 months after R0 resection of NSCLC, or discontinue treatment due to tumor recurrence or intolerance. **Group B (control group)** Patients are followed up after R0 resection of NSCLC.
Study Procedure	After patients have signed the informed consent forms (ICFs) and meet the inclusion and exclusion criteria, they will be randomly assigned to the icotinib group and the control group. Patients need to be evaluated. The patients receive the visits once every 3 months during the dosing period, and once every 6 months for the survival follow-up until the disease recurrence or death. The Investigator shall contact the patient, the patient's family, or the patient's current physician by phone at least once every 3 months after recurrence, to collect the long-term follow-up information on survival. Any patient who withdraws from study treatment for reasons other than recurrence (except patient's withdrawal of informed consent, loss to follow-up, death) should continue to receive the objective tumor evaluation every 6 months to collect the information on recurrence.
Safety	All patients who have received at least one treatment with study drug will be included as the effective population for safety analysis. The patient's physical examination results, vital signs, adverse events, and abnormal laboratory test results will be summarized. Adverse events should be reported and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
Statistical Analysis	The sample size is 128 for the following considerations: based on previous studies, the 3-year DFS for stage IB NSCLC is about 60%, the hazard ratio (HR) is 0.5, the test power (1- β) is 80%, and the test level (α) is two-sided 10%; enrollment period of 24 months, and total study period of 60 months.

Summary

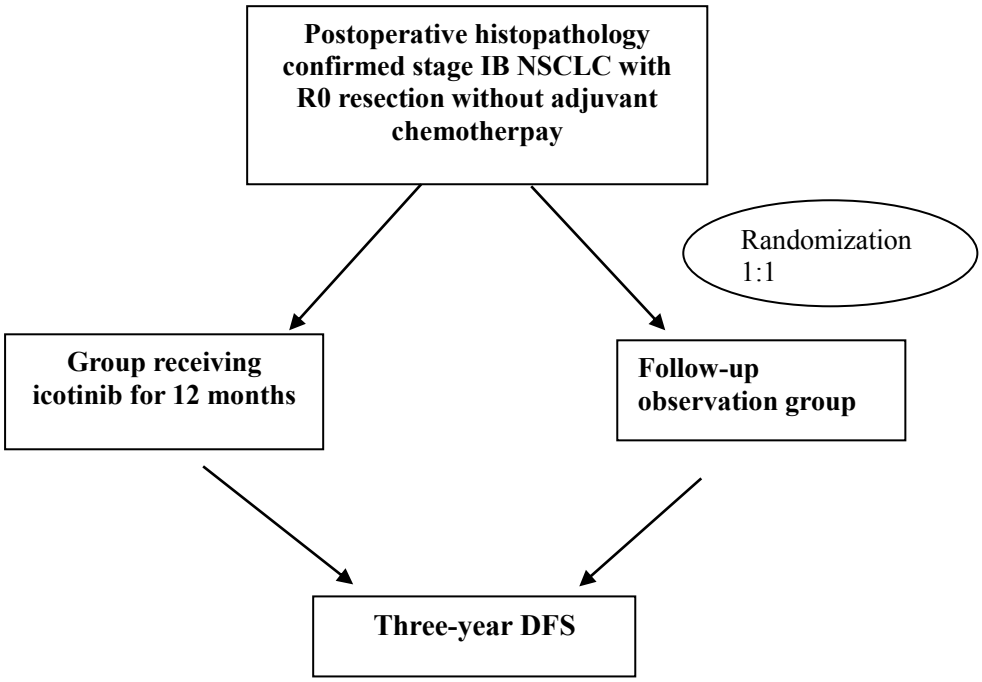

Postoperative histopathology confirmed stage IB NSCLC with R0 resection without adjuvant chemotherpay
Randomization 1:1
Group receiving icotinib for 12 months
Follow-up observation group
Three-year DFS

Table 1 Study Flow Chart

	Study period	Screening		Randomization				Follow-up after recurrence [M]
				Group A (icotinib group)		Group B (control group)		
				C1-C2 C=3 months	5-year survival follow-up C=6 months Survival follow-up after 5 years C= 12 months	C1-C2 C=3 months	5-year survival follow-up C=6 months Survival follow-up after 5 years C= 12 months	C=3 months
		Day -42 to Day -0	Day -7 to Day 0	Day 1		Day 1		
Screening management	Informed Consent/Demographics/ Medical History [A]	×						
	Inclusion/exclusion criteria review		×					
	Urine pregnancy test [B]		×					
Safety data	ECG [C]	×						
	ECOG Performance Status/Height/ Weight/Vital Signs [D]		×	×	×	×	×	
	Adverse event [E]	×		×	×	×	×	
	Subsequent treatment and survival							×
	Medication record [F]			×		×		
Preoperative and follow-up examinations	Physical examination	×	×	×	×	×	×	
	Enhanced chest CT + enhanced upper abdominal CT [G]	×		×[G]	×[G]	×[G]	×[G]	
	Assessment of other sites[H]	×						
	Clinical Biochemistry/Hematology/Urine Routine [I]	×		×	×	×	×	
	FACT-L and LCS Questionnaire [J]		×	×	×	×	×	
	Tissue specimens or sections for biomarker studies [K]	×						
	Blood specimens for biomarkers (optional) [L]	×		×	×	×	×	
	Pulmonary function/HIV antibody/tumor markers	×						

Study Process Footnotes

A. Complete medical history (including a complete medical and surgical history of all relevant diseases), demographics, history of prior surgery, combined medication, concomitant diseases, allergies, and history of smoking. In particular, the history of previous and current pulmonary disease and/or systemic disease involving the lungs (e.g., connective tissue disease) should be inquired.

B. It must be negative for premenopausal women of childbearing potential. For a suspected pregnancy event during the trial, the pregnancy test must be repeated, and a positive result must be reported immediately.

C. LVEF should be examined for an abnormal ECG with clinical symptoms.

D. Vital signs including heart rate, blood pressure, respiratory rate, and body temperature.

E. In case of any spontaneous ocular symptoms, new or worsening respiratory symptoms (e.g., cough, shortness of breath), immediate and appropriate medical assistance should be given to the patient. Any symptoms should be treated as clinical routine and, if they meet the definition, are also reported as adverse events or serious adverse events (SAEs). Adverse events are collected from signing of the informed consent of the patient. After the study is terminated, all unresolved adverse events or serious adverse events are to be followed until solved, unless the Investigator deems them unlikely to be relieved due to the patient's own disease. All new adverse events and serious adverse events within 30 days of the last dose of the study should reported (serious adverse events should be reported to the Ethics Committee of the GASTO Research Center and the National Medical Products Administration within 24 hours), and followed up until solved as described above. The most severe level of toxic reaction within each course of treatment is recorded in the CRF.

F. Data on combined medication are collected, including drug dose, route of administration, schedule of administration, start date, indications, end date, and reason for end, and must be recorded from randomized use of the study drug until 1 month after drug discontinuation. The treating physician receives this information from the patient's hospital efficacy follow-up visits every 30 days. By knowing the routinely prescribed medications, the treating physician evaluates whether clinically significant improvement in pulmonary symptoms is likely to result from changes in the patient's combined medication over the past 30 days.

G. Pre-operative and evaluation of tumor recurrence imaging must include chest-enhanced CT, upper abdomen-enhanced CT. Tumor evaluation during the follow-up period is performed every 6 months with a window phase of +/- 7 days, covering the chest and upper abdomen. All imaging studies could be replaced by PET/CT.

H. Brain MRI was scheduled every 12 months. Bone scans and other examinations are "recommended" during the screening period to rule out distant metastases. Usually hospitals will routinely examine them. Subsequently, bone scans and other examinations will be done with clinical indications.

I. Hematology (hemoglobin, erythrocyte pressure, platelets, leukocytes, absolute neutrophil values, absolute lymphocyte values) / blood biochemistry (glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, blood urea nitrogen, total protein, albumin, ALT, AST, alkaline phosphatase, total bilirubin, etc.) / urinalysis (urine specific gravity, pH value, urine glucose, urine protein and occult blood) should be completed within 7 days before the first dose, at each follow-up visit and 7 days before and after withdrawal from the study, and when clinically indicated, with specific additional frequency as appropriate.

J. The patient self-assessment outcome questionnaire FACT-L and LCS Version 4 should be completed at each efficacy evaluation.

K Tissue specimens will be taken during surgery.

L. For each efficacy visit cycle, 10 ml of whole blood is taken for biomarker analysis prior to treatment, and the blood sample is processed and transported for storage.

M. The time window for follow-up after recurrence is every 90 days ±7 days.

1. Background

Lung cancer is the leading cause of cancer deaths worldwide[1], among which non-small cell lung cancer (NSCLC) accounts for more than 80% of newly diagnosed lung cancer cases[2]. Even among early-stage (stage IB) patients, the 5-year survival rate is only 58%, suggesting that this group of patients is still at certain risk of recurrence [3], making combination of local control of the tumor and systemic therapy an important treatment modal for patients with surgically resectable NSCLC[4].

In studies of postoperative adjuvant therapy for NSCLC, a large meta-analysis made by the Non-small Cell Lung Cancer Collaborative Group in 1995 included 4767 patients. Results showed that the platinum-containing adjuvant chemotherapy regimen increased the 5-year overall survival (OS) by 5%[5], and although the results showed no statistically significant difference (P=0.08), they initially established the place of the platinum-containing regimen in adjuvant chemotherapy for NSCLC. In the following decade, several randomized controlled clinical trials have compared various postoperative cisplatin-containing adjuvant chemotherapy regimens with surgery treatment alone. Several large randomized controlled clinical trials have been reported in the 21st century, some of which[6-8] confirmed the overall survival benefit of adjuvant chemotherapy, but some[9,10] still yielded negative results. In 2008, LACE made a meta-analysis of five large sample clinical trials after 1995[11], with 4584 patients and a median follow-up of 5.2 years. Results showed that the overall survival rate was benefited in the chemotherapy group (HR=0.89, p=0.005), with a 5-year survival rate increased by 5.4%, and the DFS in the chemotherapy group was also benefited (HR=0.84, p<0.001), with a 5-year DFS increased by 5.8%. Such meta-analysis also clarified the role of the 4-cycle platinum-containing regimen in increasing the 5-year survival rate in patients with stage II-IIIA NSCLC after complete resection. It is worth mentioning the CALGB9633 study, a randomized controlled study applying paclitaxel + carboplatin for adjuvant chemotherapy in all patients at stage IB, whose subgroup analysis confirmed that patients with tumor greater than 4 cm in diameter benefit from postoperative adjuvant chemotherapy[12].

With the clinical research and progressive application of the targeted drug EGFR-TKI, it plays a more and more important role in the treatment of patients with non-small cell lung cancer. In particular, clinical studies such as IPASS, OPTIMAL and EURTAC show that EGFR-TKI has a significantly better objective

efficacy than first-line chemotherapy regimens in the treatment of patients with EGFR mutations at stage IIIB-IV, and therefore has become the first-line treatment standard for this population. Postoperative adjuvant targeted therapy for NSCLC is currently a hot topic of research, for example, a phase III randomized clinical trial (BR.19 study) investigated the efficacy of postoperative adjuvant gefitinib therapy for NSCLC at stage IB-IIIA[13]. The patients were randomized to receive postoperative gefitinib or placebo for 2 years, and 503 patients were enrolled between 2002 and 2005 with median treatment duration of 4.8 months. The results showed a DFS of 4.2 years and an OS of 5.1 years in the gefitinib-treated group, indicating that the lifetime of the patients was not significantly prolonged when compared with that of the placebo group, but patients with EGFR mutations were not selected for this trial. Another RADIANT phase-III clinical study included patients with positive EGFR at stage I-IIIA (IHC or FISH) with postoperative erlotinib for 2 years to evaluate the role of erlotinib in adjuvant therapy, with a placebo control group, and the population enrolled in this study was also not selected on the basis of EGFR mutations[14]. In 2011, MSKCC retrospectively analyzed 167 lung adenocarcinoma patients with stage I-III EGFR mutations from 2002-2008, 56 of whom were treated with targeted therapy in the perioperative period, and a survival analysis comparison with patients without targeted therapy showed that the former had a higher 2-year DFS than that of the latter (89% vs 70%), and despite that the p-value (0.06) was not statistically significantly different, the adjuvant targeted therapy group showed a trend of benefit[15]. A phase-II clinical study was reported in the SELECT study at the ASCO meeting in 2012, that is, patients with stage IA-IIIA mutant lung cancer were treated with postoperative erlotinib for 2 years following standard adjuvant chemotherapy or adjuvant radiotherapy. This study enrolled a total of 36 patients, of which 11 patients were on the drug for less than 2 years. After a median follow-up period of 2.5 years, the 2-year DFS rate was as high as 94%.

Icotinib (trade name: Conmana®) is a small molecule targeted anti-cancer drug developed independently in China for treating advanced NSCLC, and belongs to the same class of EGFR-TKIs as gefitinib and erlotinib. with clinical approval from the SFDA in 2006, a series of clinical studies have been completed, including the safety and tolerability and pharmacokinetic phase-I clinical studies in patients with NSCLC administered three times a day, the results showed good tolerability and determined a follow-up dosing regimen of 125 mg repeated over 8 hours[16]. An ICOGEN study[17], namely a

"randomized, double-blind, double-modeled, parallel-controlled, multicenter phase-III clinical trial evaluating the efficacy and safety of erlotinib and gefitinib in patients with locally advanced or metastatic non-small-cell lung cancer who had received one or two prior chemotherapies", enrolled 399 patients. The primary efficacy evaluation indexes PFS for both were 4.6 months vs. 3.4 months, OS were 13.3 months vs. 13.9 months, and ORR and DCR were similar between the two groups, as 27.6% vs. 27.2% and 75.4% vs. 74.9%, respectively. In terms of safety, the incidence rate of adverse reactions was 60.5% in the ectetinib group, which was significantly lower than that of 70.4% in the gefitinib group, and the difference between the two groups was statistically significant. The incidence rates of rash were 40% and 49.2%, respectively, the incidence rates of diarrhea were 18.5% and 27.6%, respectively, and no interstitial pneumonia occurred in either group. Therefore, the results of the ICOGEN study showed that erlotinib was comparable to gefitinib in terms of efficacy, but had a better safety superior to gefitinib.

The ICOGEN study found in the exploratory index EGFR gene mutation study 69 cases of positive EGFR mutation, with an overall mutation rate of 51%, of which exon 19 accounted for 60.3% of the mutant population and exon 21 L858R for 29.1%. Conmana® has an efficacy significantly better in patients with EGFR mutations than that in wild-type patients, with an efficacy rate of 59% in mutation patients and 5.1% in wild-type patients. Median PFS was 6.6 months in mutation patients and 2.4 months in wild-type patients, and median OS was nearly two years in mutation patients, nearly one year longer than that in wild-type patients. For this reason, , mutations in EGFR exon 19 and exon 21 are equally predictive of the efficacy of erlotinib similar to gefitinib or erlotinib in treating non-small cell lung cancer[18].

However, it is unclear whether EGFR-mutant NSCLC at stage IB can benefit from postoperative adjuvant treatment with erlotinib. Based on the above study background, we randomized patients after stage-IB NSCLC R0 resection with positive EGFR mutation to the study group (with control of adjuvant erlotinib for 12 months) to observe the efficacy and safety of erlotinib in this group of patients, and to answer whether adjuvant TKI therapy can be used to prolong the survival time of patients after surgery for stage-IB EGFR-mutant NSCLC.

Objectives

2.1. Primary objective

To investigate the efficacy of icotinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) as a postoperative adjuvant therapy for stage IB mutant type non-small cell lung cancer (NSCLC). Primary endpoint: 3-year DFS.

3. Study Design

3.1. Study design and plan

This is a randomized, prospective, open-label phase II clinical study to evaluate the efficacy and safety of icotinib as adjuvant therapy in patients with stage IB EGFR-mutant non-small cell lung cancer (NSCLC) after R0 resection. A total of 128 patients will be enrolled in the study and will be randomly divided into icotinib treatment group and control observation group. Patients in the icotinib group are given icotinib 125 mg, tid, orally, for 12 consecutive months, or discontinue due to disease recurrence or intolerable toxicity reaction.

3.2 Selection of subjects

EGFR-mutant stage IB (based on 7th TNM staging) NSCLC without postoperative chemotherapy.

3.2.1 Inclusion criteria

Inclusion criteria related to disease:

- Postoperative histopathology has confirmed stage IB NSCLC with R0 resection by TNM staging, accompanied with positive EGFR mutation;
- Have not received other chemotherapy, radiation therapy or biological therapy;
- Adjuvant chemotherapy was not planned;
- The treatment starts within 4 weeks after surgery;
- No signs of tumor recurrence based on examinations prior to treatment.

Hematology, Biochemistry and Organ Functions:

- Lung function: FEV1>50;
- Hemoglobin ≥90 g/L (this level can be maintained or exceeded by blood transfusion);
- Absolute neutrophil count ≥2.0×10^9/L;
- Platelet count ≥100×10^9/L;
- Total bilirubin ≤ 1.5 times the upper limit of normal (ULN);
- ALT and AST ≤ 2.5 times the ULN;
- Creatinine ≤ 1.25 times the ULN; and creatinine clearance ≥ 60 mL/min;
- No pregnancy for women of childbearing age (15 to 49 years).

General inclusion criteria:

- Subjects have obtained informed consent form signed by the patient or his/her legal representative;
- Subjects have good compliance;
- Subjects can take medicines orally;
- Subjects are males or females aged ≥18 years;
- Subjects have ECOG Performance Status Scale of 0-1 and life expectancy of greater than 12 weeks;
- Male and female subjects of childbearing age agree to take reliable measures for contraception before entering the study, during the study and up to 8 weeks after drug discontinuance.

3.2.2 Exclusion criteria

- Subjects have received any other systemic anticancer therapy for NSCLC, including cytotoxic drug therapy, targeted drug therapy (including tyrosine kinase inhibitors or monoclonal antibodies), experimental treatment;
- Subjects have received local radiotherapy for NSCLC;
- Subjects have incomplete physiological functions of the upper gastrointestinal tract, or

malabsorption syndrome, or intolerance to oral medications, or active gastrointestinal ulcers;

- There are clinically objective evidences (pathology or imaging evidences) to confirm tumor recurrence before the start of treatment;
- Subjects have suffered from cancers other than NSCLC, excluding cervical carcinoma in situ, cured basal cell carcinoma, urothelial tumors [including Ta and Tis] within the five years prior to the start of treatment in this study;
- Subjects are known to be allergic to icotinib or any components of this drug product;
- Subjects have a history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis requiring hormonal therapy, or any active interstitial lung disease with clinical evidences;
- Subjects are found to have idiopathic pulmonary fibrosis by CT scan at the baseline;
- Subjects have eye inflammation or eye infection that is not completely controlled, or any condition that may cause the above eye diseases;
- Subjects have suffered from any unstable systemic disease, including active infection, uncontrolled hypertension, unstable angina, angina occurring within the recent 3 months, congestive heart failure (≥New York Heart Association [NYHA] Class II), myocardial infarction (6 months before enrollment), severe arrhythmia requiring drug therapy, liver, kidney or metabolic diseases;
- Subjects have known HIV infections;
- Subjects combined with additional components of small cell lung cancer;
- Pregnant or breastfeeding women;
- Subjects have a history of definite neurological or psychiatric disorders, including epilepsy or dementia;
- Other circumstances deemed inappropriate by the Investigator.

3.3 Duration of study

It is planned to enroll 128 patients based on about 6 patients enrolled each month; and the time for

enrollment is about 24 months; the minimum survival follow-up period is 3 years, and the total study period will last about 60 months.

3.4 Withdrawal of patient from study treatment

3.4.1 Withdrawal criteria

3.4.1.1 Withdrawal time and method

Patients may withdraw from study treatment and evaluation at any stage of the study, for the following reasons:

Patients are free to withdraw voluntarily from the trial at any time, and future treatment is not affected;

The Investigator and the Sponsor deem that there are any safety reasons (adverse events);

The Investigator and the Sponsor believe that the patient is poor in compliance to study protocol;

Death;

Loss to follow-up;

Other situations where Investigator believes that the patient should withdraw from the study.

The Investigator deems that the patient should withdraw from the study in the following cases:

Patients receive antitumor therapy other than this study protocol during the treatment period;

Patients have severe allergic reactions to investigational drug, such as exfoliative rash or hypersensitivity reactions of grade 3 to 4;

There is any other serious adverse reaction that, in the opinion of the principal investigator or his or her designated study personnel, requires a discontinuation of treatment;

Patients have severe poor compliance;

The urine β-HCG test results of patients suggest pregnancy. Investigator should report this pregnancy as a clinical trial pregnancy report form;

Other diseases are complicating the study, which in the Investigator’s opinion will significantly affect the assessment of the patient's clinical condition and require discontinuation of this treatment regimen;

Other malignancies requiring treatment occur;

Patients are lost to follow up;

Prohibited drugs or other substances that in the Investigator's opinion may cause toxic reactions or bias study results are used.

Icotinib is discontinued for more than 2 consecutive weeks due to adverse reactions.

Patient dies.

3.4.1.2 Withdrawal procedure

For patients who withdraw from the study, the Investigator shall ask about the reasons for withdrawal and whether any adverse events occurred. If possible, the Investigator should visit and evaluate patients who withdraw from the study. The reason and date of withdrawal (date of last dose) must be documented on the case report form (CRF). Patients should return all remaining study drugs.

Upon withdrawal from the trial, if there is a new or worsening laboratory test result of CTC grade 3 or 4, the patient must undergo further testing and the results should be documented in the appropriate section of the CRF until the laboratory test result returns to CTC grade 1 or 2, unless the test result is unlikely to improve due to the disease itself. The Investigator shall document their comments on these cases in the CRF and in the medical record.

All study-related toxicities and SAEs at study discontinuation must be followed until they are resolved, unless, in the Investigator's opinion, the condition is unlikely to be relieved because of the disease itself.

After the patient discontinues study treatment, the Investigator shall track all existing or new AEs that occur within 30 days of the last dose of study drugs, and report all new AEs and SAEs that occur within this period of time (SAE must be reported to the Sponsor within 24 hours) and follow up until the adverse event is resolved as described above. If a patient dies during the trial or within 28 days after the trial, the Investigator shall document the cause of death in detail on the serious adverse event (SAE) report within 24 hours.

3.4.1.3 Substitute of withdrawn cases

There is no substitute of patients who withdraw early from the study.

3.5 Treatment plan

3.5.1 Treatment schedule

The enrolled patients are randomized to a group treated with icotinib for 12 months or a control group. Patients of the icotinib group are administrated with 125 mg of icotinib orally, tid, for 12 consecutive months after surgery, or discontinued due to disease recurrence or intolerable toxic reactions, and the control group is merely followed up.

3.5.2 Discontinuation of icotinib

- Due to good tolerance when used alone clinically, icotinib generally does not need to be discontinued. As reported in the literature, the incidences of interstitial lung disease (ILD) in Eastern populations treated with gefitinib and erlotinib are 2-3% and 1-2%, respectively. The interstitial lung disease is not observed in the ICOGEN clinical study.
- Patients with interstitial lung disease usually present with acute dyspnea with cough, hypothermia, respiratory distress, and arterial oxygen desaturation. The symptoms can be severe and fatal in a short period of time. Radiological examination often shows pulmonary infiltrates or interstitial ground-glass opacities.
- The treating physician should closely monitor for signs of interstitial lung disease during treatment and interrupt icotinib therapy if the patient develops a new acute attack or progressive worsening of dyspnea or cough, and perform relevant tests immediately. When interstitial lung disease is confirmed, the drug should be discontinued and the patient should be treated accordingly.

3.5.3 Combined treatment and smoking

All combined medications and treatments (including start/stop dates and indications) must be documented in the patient's original data as well as in the appropriate section of the CRF.

All patients taking combined drugs metabolized via CYP3A4 should be closely monitored for possible adverse effects of these drugs.

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

3.5.4 Concomitant medication

3.5.4.1 Drugs not allowed to be used

- Bevacizumab and any drug that targets VEGF, VEGFR or EGFR (including registered or investigational drugs).
- Any other anti-cancer drug is not allowed except for study-specified icotinib, including investigational drugs (e.g., investigational antibiotics, antiemetics, etc.) and herbal medicines with anti-tumor indications.

3.5.4.2 Permissible drugs

- Non-anti-cancer herbal medicines or acupuncture, vitamins/trace elements are also allowed without affecting the study endpoints observed and are under the control of the Investigator.
- Patients may receive palliative treatment and supportive treatment for their pre-existing disease.

3.5.5 Treatment compliance

The dose and date of administration of icotinib taken for each course of therapy for each patient should be documented in the CRF. Reasons for delayed administration, medication reduction, or missed doses should also be documented in the CRF.

Patient compliance with treatment and regimen includes voluntary compliance with all aspects of the regimen, including compliance with therapeutic agents, compliance with all blood collections required for safety assessment, and compliance with regular follow-up visits. Patients who do not take their medications on time, or who do not cooperate with tests, or who do not return to the study on time may be excluded

from the study based on the assessment of the principal investigator. Patients who discontinue icotinib due to unimprovable adverse reactions that do not resolve even with optimal symptomatic and supportive therapy may be withdrawn from the study if the duration of discontinuation is longer than 2 weeks, after discussion with and consent from the principal investigator.

3.6 Study endpoints

The primary efficacy endpoint in this study is 3-year disease-free survival (DFS).

Secondary endpoints include disease-free survival (DFS), central nervous system (CNS)-related DFS, overall survival (OS), safety, and tolerability.

Exploratory analysis: to evaluate the efficacy of adjuvant icotinib for patients with completely resected stage IB NSCLC based on the AJCC 7th and 8th edition of staging.

To evaluate the efficacy of adjuvant icotinib for patients with completely resected stage IB NSCLC based on sensitive EGFR mutation and all EGFR mutations (including atypical EGFR mutations).

3.6.1 Efficacy endpoints

Three-year Disease-Free Survival (DFS) is defined as the proportion of patients who were disease free at 3 years.

Disease-free survival (DFS) is defined as the time between the date of randomization and the first confirmation of disease recurrence or death from any cause (whichever occurred first).

Central nervous system (CNS)-related DFS is defined as the time from randomization to CNS recurrence or death, whichever occurred first.

Overall survival (OS) is defined as the time between randomization and death from any cause. The 1-year overall survival is defined as the probability that the patient is alive for 1 year from the date of randomization. The 2-year overall survival is defined as the probability that the patient is alive for 2 years from the date of randomization. The 5-year overall survival is defined as the probability that the patient is alive for 5 years from the date of randomization.

The time that patients who are alive as of the date of analysis and are free of disease recurrence have

their last imaging evaluation is taken as the cutoff time.

3.6.2 Safety indicators

All patients who have received at least one study drug treatment will serve as a valid population for safety analysis. Physical examination findings, vital signs, adverse events and abnormal laboratory test results of the 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.

3.7 Research process (see Table 1 for flow chart)

3.7.1 Screening period

- Sign an informed consent prior to any study-related operations.
- Acquire demographic information, and complete medical, surgical and smoking histories.
- Record/confirm the TNM stage of the primary tumor at the time of diagnosis.
- Evaluate tumor at chest-enhanced CT scan, upper abdomen-enhanced CT.
- Perform cranial enhanced MRI. Bone scan is performed only in patients with clinical symptoms. All examinations may be replaced by PET/CT.
- Take tumor tissue specimen and perform EGFR detection.
- Confirm that the subject meets the inclusion/exclusion criteria as specified in the study protocol.
- Perform physical examination: heart rate, blood pressure, respiratory rate, body temperature, height, weight and ECOG physical status scoring.
- Document all concomitant diseases and combined medications and their indications.
- Carry out routine blood tests: hemoglobin, HCT (hematokrit), platelet count, white blood cell count, and neutrophils.
- Perform blood biochemical tests: including blood glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), total protein, albumin, ALT, AST, alkaline phosphatase, total bilirubin, etc.

- Carry out a 12-lead electrocardiogram (ECG) examination at baseline stage, and check and sign by The Investigator.
- Perform urine pregnancy test on all female patients of childbearing age. Postmenopausal women who have been menopausal for at least 2 years and women who have undergone sterilization are not required to have the urine pregnancy test.
- Carry out routine urine tests: pH value, urine sugar, urine protein, ketone bodies, occult blood, urine bilirubin, red blood cells, and white blood cells.
- Perform HIV antibody tests.
- Perform pulmonary function tests.
- Perform tumor marker screening; collect biomarker blood sample specimen.
- Adverse events: signs and symptoms that exist prior to enrollment (prior to signing informed consent) and persist at enrollment should be documented per medical history. Any signs and symptoms that develop or worsen after enrollment (even before drug therapy) should be recorded as adverse events according to NCI-CTCAE Version 4.0.
- Distribute study drugs.

3.7.2 Visits

Efficacy evaluation visits and subsequent visits (every 90 days ±7 days for the first 6 months and every 180 days ±7 days until 5 years)

- Perform physical examinations (heart rate, blood pressure, respiratory rate, temperature, body weight and ECOG physical status scoring).
- Perform laboratory tests (hematology/blood biochemistry/urinary routine); perform ECG/pregnancy test.
- Collect biomarker samples (optional): take 10 ml of whole blood for molecular marker screening before treatment.
- Carry out tumor evaluation: it must include chest enhanced CT and upper abdomen enhanced CT. The follow-up period during treatment is every 3 months with an interval of +/- 7 days, covering the

chest and upper abdomen. All imaging tests can be replaced by PET/CT. Cranial MRI was scheduled every 12 months. Bone scan will be performed only when clinically indicated.

- Document adverse events and combined medications since the last visit.
- Make an appointment for a next visit.

End of visit/visit at study withdrawal

If a subject discontinues study drug therapy for any reason (other than death or visit missing), an end-of-treatment evaluation should be performed at the time of discontinuation, which includes:

1. Simple physical and vital signs examination, and ECOG behavioral status assessment
2. Lab tests: complete blood count (CBC), biochemistry, electrolytes, and urinalysis
3. 12-lead electrocardiogram
4. Documentation of adverse events: If an adverse event persists at the end of treatment, or if a new adverse event is judged by the Investigator to be related to investigational drug, information about the adverse event should be collected until 30 days after the end of treatment (this can be done by telephone visit). Follow-up should continue until the adverse event has resolved or stabilized, unless the Investigator determines that the adverse event is caused by the patient's own disease. If a patient dies within 30 days after the end-of-treatment visit, the Investigator should notify the GASTO within 24 hours and record the detailed cause of death on the Serious Adverse Event (SAE) form.
5. Record of combined medications
6. Preserve biomarker samples (optional): 10 ml of whole blood for molecular marker screening.

3.7.3 Survival follow-up

In case of postoperative recurrence, telephone survival follow-up is made every 3 months after recurrence until 5 years after surgery or death. The following information should be obtained during each follow-up visit:

- Patient survival.
- If dead, record the date of death and cause of death in detail.

- The disease status, and the date of recurrence after the operation should be recorded in detail (for patients without recurrence at the last follow-up).
- Detailed documentation of follow-up anti-cancer treatment.

Note: Patients who have developed tumor recurrence will be followed up according to local medical practice at the discretion of the clinician.

3.7.4 Temporary visits

Temporary visits should be performed as clinically indicated. Corresponding clinically significant abnormal laboratory tests and adverse events should be documented in the CRF and in the original data. If multiple laboratory tests are performed on the same day, only the last set of values from these tests should be recorded in the CRF. However, all abnormal values from repeated laboratory tests should be recorded in the CRF.

3.8 Quality of data

In order to follow the guidelines of the Good Clinical Practice (GCP), the monitor visits each center at regular time to ensure compliance with the study protocol, GCP and relevant laws. The visits include on-site checks for completeness and clarity of CRFs, cross-checking of CRFs and original documentation, and resolving questions regarding data queries.

3.9 Archiving

The information entered in the CRF must match the original documentation. Study documents and all original information should be retained until 15 years after the end of the trial, until a written notification of destruction from the Sponsor is received.

4 Study Drug

4.1 Icotinib

4.1.1 Name, physicochemical properties, description, strength, ingredients, usage, storage of investigational drug

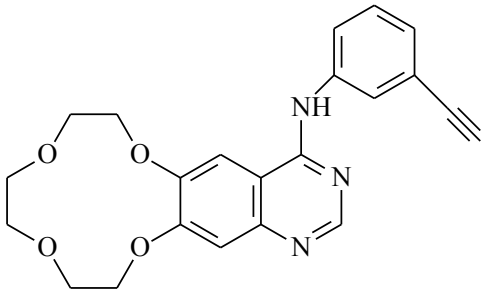
Drug name

Trade name: Conmana®

Generic name: icotinib hydrochloride tablets

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

Structural forma:



, HCl

Molecular formula: $C_{22}H_{21}N_3O_4HCl$

Molecular weight: 427.88

Physicochemical properties

Physicochemical properties: icotinib hydrochloride is an 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℃. The absorption coefficient ($E^{1\%}_{1cm}$) at the wavelength of 340 nm is 500-520.

Description: Brown-red film-coated tablets, off-white after removing the coating

Strength: 125 mg.

Ingredient: The main ingredient is icotinib hydrochloride.

Administration: Oral, one tablet once, tid.

StoragePreserve in tightly closed containers and protected from light.

5 Ethical and legal issues

5.1 Independent Ethics Committee (IEC)

In accordance with the requirements of GCP, Chinese laws and regulations and relevant organizations, all study sites participating in this study shall obtain the approval documents of the Ethics Committee before the start of the study. Where necessary, the amendments or review of the Ethics Committee shall be obtained and forwarded to the Investigator.

5.2 Ethical guidance for this study

The procedures for operation, assessment, and documentation covered in this study protocol are intended to ensure that the study personnel comply with the clinical practice guidelines and the guiding principle detailed in the Declaration of Helsinki. The implementation of this study will also follow Chinese Good Clinical Practice.

The study personnel cannot modify the study protocol without the written consent of the Ethics Committee and the Sponsor. However, for the purpose of eliminating the risk factor for patients in an emergency, the study personnel can deviate from or modify the study protocol without prior consent/support from the Ethics Committee/Institutional Review Board/Sponsor. Deviations or modifications and the reasons should be submitted to the Ethics Committee/Institutional Review Board/Sponsor as quickly as possible; where appropriate, a proposal for protocol amendments should be submitted. The study personnel shall give adequate explanations and describe all deviations or modifications to the study protocol.

5.3 Notice to patients and informed consent

The study information and ICFs should be provided to patients. Prior to the start of the study, the study personnel shall provide ICFs and all other written documentations approved in writing by the Ethics Committee to the patients. The approval letter of Ethics Committee, the approved Notice to Patients/ICFs must be archived in the study documentation.

A signed informed consent must be obtained from patients before any procedure related to this study is performed for them.

5.4 Confidentiality

All records regarding patient's identity are kept confidential and will not be made public to the extent permitted by applicable laws and/or regulations. Only personnel related to this trial, for example, the Investigator and study nurse, can know the patient's identity information.

The patient's name will not appear in the CRF. Only the patient's ID and initials are recorded in the CRF. A patient's name appearing in any other document (e.g., a pathology report), must be erased in the copy of the document. The study reports stored in the computer must comply with the local laws on data protection. The patient's identity will also be kept private when the study results are published.

The Investigator will maintain a name list to identify the patients' records.

5.5 Conditions for amendment to the study protocol

Protocol amendments to the ongoing trial can be made only after mutual consultation between the Sponsor and the principal investigator. Materials prepared by the Sponsor for protocol amendment should be reviewed in advance by principal investigator, biostatisticians and other relevant personnel. Except for the emergency adjustment to eliminate imminent harm to the patients in the study or the adjustment related to the logistics and management of the study, such as changes to the monitor, phone number, all protocol amendments must be submitted to and approved by the Ethics Committee, and submitted to the regulatory authority when necessary. The Investigator can implement adjustments only after the approval of these agencies.

5.6 Conditions for termination of the study

The Sponsor and principal investigator reserve the right to terminate the study at any time. When the study is terminated, both the Sponsor and the principal investigator will ensure that the patient's interests and benefits are fully considered.

5.7 Preservation of Study Documentation, Medical Report Forms, and Records

5.7.1 Preservation of Investigator's documentation

In order to ensure that the conduct of the study is fully documented and that the study data can be validated subsequently, the Investigator shall retain comprehensive and accurate records of the conduct of the study. These documents should be divided into two categories: (1) Investigator's study documents, (2) original clinical records of patients.

Investigator's study documents include the clinical trial protocol and amendments, approval documents of the Independent Ethics Committee and the government, ICF sample, drug-related records, personnel's curriculum vitae, and other relevant documents/correspondences, etc.

Patient's original clinical records (often pre-defined prior to the start of the study, key efficacy/safety parameters recorded other than the medical reports) usually include inpatient/outpatient records, physician and nurse's records, appointment letters, original laboratory reports, ECG, imaging reports, pathology reports and specialized assessment reports, signed ICF, consulting letters and correspondences, patient screening and recruitment forms. The Investigator shall preserve the two types of documents for at least 15 years after the study is completed or discontinued. Then these documents can be destroyed in accordance with local regulations. The Investigator shall give a prior notice to the Sponsor if he/she intends to hand over these study records to other organizations or transport them to other areas.

If the Investigator cannot guarantee the archiving requirements of any or all documents at the study site, the Investigator and the Sponsor should make special arrangement to pack these documents in the well-sealed boxes other than the study site, so that these sealed documents can be returned to the Investigator in the event of a regulatory audit. If the original records are required for subsequent treatment of patients, the corresponding photocopies should be preserved other than the study site.

5.7.2 Original records and background data

The Investigator should provide the Sponsor with any background data information from the study

documentation and clinical record data as required, which is more important when errors are suspected to have occurred in the data transcription. It should also be necessary to be able to access to the complete study records in case of special issues and/or government questions or requests for audit and inspection, but at the same time the patient's right to privacy should be protected.

5.7.3 Audit and inspection

The Investigator should be aware that, upon formal notification, original records pertaining to the study should be prepared and made available to the appropriate qualified person or his/her designee, or the inspector of the health department. The data reconciliation in the case report form must be performed directly against the original records.

5.7.4 Case report form

For each eligible patient, his/her case report form (CRF) must be completed and signed by the principal investigator or an authorized representative of the study personnel. This also applies to the CRF of patients who fail to complete the clinical trial (even if the CRF has been filled out during the screening period). If a patient withdraws from the study treatment, the reason for withdrawal must be recorded in the CRF. If a patient withdraws from the study because of a treatment-limiting adverse event, a comprehensive effort should be made to clearly document the results. The Investigator shall ensure the data accuracy, integrity, legibility and timeliness in the CRF and all required reports reported to the Sponsor.

6 Monitoring of study

If the patient confidentiality complies with local requirements, the responsible monitor (or designee) will regularly contact and visit the Investigator and will be allowed to review various trial records (CRF and other relevant data) as required.

The monitor is responsible for regularly checking the CRF, verifying compliance with the study protocol, and checking input data for integrity, consistency, and accuracy throughout the study. The monitor shall be granted access to laboratory test reports and other patient's records, to check the entries on the CRF. The Investigator (or his/her designee) agrees to work with the monitor to ensure that any issues

identified during the monitoring visits are resolved.

7 Statistics and Analysis Plan

7.1 Statistical analysis

7.1.1 Baseline and demographic characteristics

The baseline data include demographic characteristics, tumor stage, medical history, surgical approach, concomitant medications, and vital signs, etc. The measurement data are described with the mean, standard deviation, median, minimum, and maximum; and the count data are described with frequency and percentage.

7.1.2 Primary efficacy

The primary efficacy variable in this study is the 3-year disease-free survival (DFS).

7.1.3 Secondary efficacy

Analysis of secondary efficacy variables includes:

- Disease Free Survival (DFS).
- Central nervous system (CNS)-related DFS.
- Overall survival (OS).
- Safety analysis: Safety and tolerability, quality of life. Adverse events and their most severe response grades will be summarized according to the criteria of NCI CTCAE version 4.0, and will also be summarized according to the severity and its relationship with the study drug. Descriptive summaries of laboratory test results focus on the outliers. Laboratory abnormalities will also be summarized by the most severe level in NCI CTCAE version 4.0.

7.2 Analysis types

Intention-to-treat population

Statistical analysis will be performed in the intention-to-treat (ITT) population. ITT population is defined as all enrolled patients.

Safety analysis population

All patients who have received the study drug for at least once will be included in the safety analysis. Safety parameters will be analyzed and presented based on the treatment the patient has received.

7.3 Safety analysis

For all patients in the safety population, the following safety parameters will be analyzed and presented based on the treatment the patient has received:

- Adverse event
- Serious adverse event
- Laboratory parameters
- Vital signs, including ECOG performance status

Adverse events and their most severe reaction grades will be summarized according to the criteria of the NCI CTC-AE version 4, and will also be summarized by the severity of the event and its relationship with the study drug. Descriptive summaries of laboratory test results focus on outliers. Laboratory abnormalities will also be summarized by the most severe level in the NCI CTC-AE version 4.

8. Safety Principles

8.1 Precautions/warnings

Icotinib

The common adverse drug reactions (ADRs) of icotinib are rash (39.5%), diarrhea (18.5%), elevated aminotransferase (8.0%), most of which are of grades I and II and usually occur within 1-3 weeks after medication. Usually the ADRs are reversible and can disappear automatically, and there is no need of special treatment.

Warnings and precautions for icotinib are as follows:

1. According to the literature, the incidence of interstitial lung disease (ILD) is 2-3% and 1-2% in the

Eastern population treated with gefitinib and erlotinib, respectively. Interstitial lung disease is not observed in the ICOGEN clinical study. Patients with interstitial lung disease usually experience acute dyspnea with cough, low-grade fever, respiratory discomfort, and unsaturated arterial oxygen. In a short period of time, the symptoms can become severe and cause death. Radiographic examination often shows pulmonary infiltration or interstitial ground-glass opacities.

During the treatment, the treating physician shall closely monitor the signs of interstitial lung disease; and if the patient develops a new acute attack or progressively worsening dyspnea and cough, the treatment with this product should be interrupted and relevant examinations should be performed immediately. When interstitial lung disease is confirmed, the drug should be discontinued and the patient should be treated accordingly.

High risk factors for ILD reported in the literature include smoking, poor performance status (PS ≥ 2), normal lung tissue coverage ≤ 50% on CT scan, and short time since the diagnosis of non-small cell lung cancer (<6 months), preexisting interstitial pneumonia, older age (≥55 years old), with heart disease. Patients with these high-risk factors should use this product for treatment with caution.

2. This product should be used with caution in patients with mild transient elevations of hepatic aminotransferases that have been observed in a small number of patients. Patients with moderately elevated aminotransferase levels or above need to suspend the drug, and monitor the aminotransferase until the increase is relieved or disappears, and the drug can be resumed (see [Administration and Dosage]).

3. Seek medical attention immediately if the following conditions worsen: New acute or progressively worsening dyspnea, cough; severe or persistent diarrhea, nausea, vomiting, or anorexia.

4. Effects on the ability to drive and operate machines: During the treatment with this product, symptoms of fatigue may occur, and patients with these symptoms should be reminded when driving or operating machines.

Clinically significant drug-drug interactions may occur with icotinib (see the Instruction for Use of Icotinib).

8.2 Adverse Events

Definition of Adverse Events

An adverse event is any unfavorable medical event that occurs in a patient or a patient receiving treatment with the study drug. Adverse events are not necessarily causally related to the drug. Thus, an adverse event can be any untoward and unexpected sign (including abnormal laboratory test results), symptom, or disease time-related to the study drug used, regardless of whether the event is considered to be related to the drug or not. Conditions in which preexisting symptoms are worsened during the study period are also reported as AEs.

Adverse events in humans (regardless of whether they are related to drug or not) include the following:

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

Failure to appear or achieve the clinically expected pharmacological effects will not be regarded as adverse events.

8.2.2 Classification of adverse events

All adverse events will be graded for severity using a 5-point scale (grades 1 to 5) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTC-AE 4.0) and reported in detail in the CRF.

8.2.3 Monitoring of adverse events

Patients must be closely monitored for adverse events. Such monitoring includes clinical laboratory tests. Adverse events should be assessed in terms of seriousness, severity and relationship with the investigational drug, etc.

The Investigator is responsible for evaluating the relationship between all adverse events and the study drug. However, the principal investigator can entrust other investigators who participate in this study to make the judgment, but he/she remains responsible for it.

8.2.4 The relationship between adverse events and study drug

The evaluation of the relationship between an adverse event and the study drug is a comprehensive clinical judgment based on all the information obtained when completing the CRF.

Circumstances assessed as "unrelated" may include: presence of alternative explanations, for example, traumatic bleeding at the surgical site; unreasonable, for example, a patient is hit by a car, but there is no indication that drug-induced disorientation contributes to the event; or cancer that develops only a few day after starting dosing.

An assessment of "Yes" indicates that there are reasonable reasons to suggest that the adverse event may be related to the study medication.

Factors to be considered when assessing the relationship between the adverse events and the study drug include:

- Occurring shortly after administration: This adverse event should occur after administration. The length of time between drug administration and the occurrence of the event should be considered in the clinical evaluation of this event.
- Disappearance of the event after cessation of dosing (cessation of stimulation) and reoccurrence after re-dosing (re-stimulation): full consideration should be given to the patient's response after drug withdrawal (cessation of stimulation) or the patient's response after re-dosing (re-stimulation).
- Underlying, concomitant, and intermittent diseases: The natural history of the disease, the course of treatment, and all other medical conditions the patient may have described in each report should be assessed.

- Concomitant medications or treatments: Other medications the patient is taking or other treatments the patient is receiving should be examined to determine if one of these may have contributed to the adverse event.
- Known response pattern for 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 conjunction with each patient's individual pharmacodynamic response.

8.2.5 Serious adverse events

Serious adverse events are all unfavorable medical events that meet one of the following conditions that occur in any medication situation:

- causing death;
- life threatening;
- leading to patient’s hospitalization or prolonged hospitalization of inpatients;
- leading to persistent or apparent incapacity or disability;
- Major medical event.

Life-Threatening: The term "life-threatening" is defined as "serious" and refers to the risk of death of a patient in the event of an adverse event. It does not refer to adverse events that could have resulted in death if the situation is assumed to be more exacerbated.

Hospitalization: Any adverse event leading to hospitalization of a patient or prolonged hospitalization of an inpatient is considered serious except for any one of the following:

- Stay in hospital for no more than 12 hours;

  or

- Admission is pre-planned (i.e. surgery or elective surgery that is scheduled prior to the start of the study);

or

- Hospital admissions are not associated with adverse events (e.g., hospitalization for convalescent purposes).

It should be noted that invasive treatment performed during hospitalization may meet the criteria for a "major medical event" and therefore may need to be reported as a serious adverse event based on clinical judgment. Also, if a stricter definition is specifically required by the local authority, the local regulations prevail.

Disability: a person's ability to perform daily life is severely impaired.

According to the standard definition, the term “sudden death” can only be used when the cause of death is cardiac. The terms death and sudden death are distinct and should not be used interchangeably.

Any clinical adverse event or abnormal laboratory test results that occur during the course of the study and achieve the degree of severity (as defined above), regardless of the treatment the patient is receiving, must be reported to the Sponsor, pharmaceutical regulatory authority, and the Ethics Committee within one working day after the Investigator becomes aware of the event.

Serious adverse events related to study treatment must be collected and reported regardless of how long it has been since the last dose, even if the trial has ended.

Serious adverse events unrelated to study treatment must be collected and reported during the study period and within 28 days after the last dose.

8.2.6 Unexpected adverse events

An unanticipated adverse event is any adverse drug reaction whose characteristics or severity are inconsistent with the Investigator’s Brochure. The suspected unexpected serious adverse reaction (SUSAR) refers to an unexpected serious adverse event related to the investigational drug.

8.2.7 Reporting of adverse events

All adverse events that occur after signing of the ICF by patients until within 28 days after the last

dose should be recorded in detail.

Documented records must be supported by raw data. Laboratory abnormalities deemed clinically relevant (e.g., those leading to premature withdrawal of patients from the study, requiring treatment, or triggering overt clinical manifestations, or those deemed clinically relevant by the study personnel) should be recorded as adverse events. A detailed description of each event should be provided, including start and end dates, severity, relationship to study drug, actions taken, and outcome of the event.

SAEs that occur from the signing of the ICF until within 28 days after the last dose and meet the definition, including laboratory abnormalities that meet the definition of SAE, must be immediately (within 24 hours after the study personnel is informed) reported to the personnel specified in the study documentation. The SAE report form must also be completed and sent to the specified personnel in the study documentation within 24 hours of being informed by the study personnel. SAEs related to study treatment must be collected and reported regardless of how long it has been since the last dose, even if the trial has ended.

Each SAE should be followed up until resolution or stabilization and an update should be submitted to the designated person. The grade 4 laboratory abnormalities (as per CTC-AE version 4.0) are not reported as serious adverse reactions unless the Investigator believes that the abnormality meets the criteria for an SAE**.** Grade 5 laboratory abnormalities as defined in the CTC-AE version 4.0 that occur and are indicative of disease at baseline should not be reported as SAEs, especially if these abnormalities are present but are still allowed by the protocol or have not been excluded from the study. If it is in doubt as to whether the anomaly should be reported as an SAE, the Investigator may consult with the Study Monitor. Laboratory abnormalities of CTC-AE grade 4 should be recorded on the page of “Laboratory Information” and periodically checked by the medical monitor. If it is uncertain whether an adverse event is caused by the study disease, it should be reported as an AE or SAE.

As required by local laws and regulations, SAEs must be reported to the Ethics Committee and the NMPA.

8.2.8 Treatment and follow-up of adverse events

Final results for each AE must be recorded on the CRF. All AEs will be followed up according to the

following guidelines:

About AE

Follow-up continues until one of the following circumstances has occurred:

- Resolved or improved to the extent at the baseline.
- Causality is reassessed as irrelevant.
- Death.
- Starting a new anti-cancer regimen.
- No further improvement is expected as confirmed by the Investigator.
- Clinical or safety data are no longer collected, or the database is eventually closed.

Unrelated severe or life-threatening AEs

Follow-up continues until one of the following circumstances has occurred:

- Resolved or improved to the extent at the baseline.
- Improvement of the severity to grade 2.
- Death.
- Starting a new anti-cancer regimen.
- No further improvement is expected as confirmed by the Investigator.
- Clinical or safety data are no longer collected, or the database is eventually closed.

Unrelated Grade 1 or 2 AEs :

Follow-up continues until one of the following circumstances has occurred:

- Resolved or improved to the extent at the baseline.
- Starting a new anti-cancer treatment
- No further improvement is expected as confirmed by the Investigator.
- Clinical or safety data are no longer collected, or the database is eventually closed.

8.2.9 Abnormal laboratory test results

Abnormal laboratory test results will be recorded in the CRF. Any abnormal laboratory test results that meet SAE criteria should be reported as SAE in addition to recorded as an AE in the CRF.

On the AE page of the CRF, any abnormal clinically significant laboratory test results caused by the treatment should be recorded as a single diagnostic result, i.e., these results meet one or more of the following:

- Occurrence of clinical complications.
- Leading to a change in the study medication (e.g., dose change, dosing suspension, or permanent discontinuation).
- Concomitant therapy changes (e.g., additions, interruptions, discontinuations, or any other changes of the concomitant medications, treatments, or medications) are required.

This applies to any laboratory safety and efficacy results that are obtained from the examinations performed after administration of the first dose of study drug and are/are not specified in any protocol. These results are outside of the laboratory reference range and meet the criteria for clinical significance.

This does not apply to any abnormal laboratory test results that are outside the laboratory reference range but do not meet the criteria for clinical significance (they will be analyzed and reported as laboratory abnormalities); AEs that are specifically excluded by the protocol; or results from AEs reported or being reported.

If there are medically significant unexplained laboratory abnormalities, the examinations should be repeated, and followed up until they return to the normal range and/or they are found to be adequately explained. If they have been clearly explained, they should be recorded on the CRF.

8.3 Pregnancy

If a female patient becomes pregnant during the study period, the study drug must be discontinued as directed and the Investigator shall be notified immediately. The Investigator shall report the pregnancy results to the Sponsor, the pharmaceutical regulatory authority, and the Ethics Committee through the Clinical Trial Pregnancy Report Form within 24 hours. The Investigator should give medical advices and discuss with the patient about the the risks of continuing the pregnancy and possible effects on the fetus. The patient should be monitored until the end of the pregnancy, and if the baby is born alive, the baby should be followed up. Pregnancy that occurs within 90 days of completion of study dosing should also be reported to the Investigator.

If the spouse of a male patient participating in the study becomes pregnant or becomes pregnant within 90 days of the end of the study medication, an informed consent form that is signed by the pregnant spouse must be obtained from the Pregnant Spouse Data Release Form, and the pregnant spouse should be followed up, and the pregnancy outcome should be reported to the Investigator and the Sponsor. The spouse should be consulted to discuss the risks of continuing the pregnancy and possible adverse effects on the fetus. The patient should be monitored continuously until the end of the pregnancy. If the baby is born alive, the baby should also be followed up.

9 Independent Review Committee (IRC)

An Independent Review Committee (IRC) consists of two radiologists with the certification for review and assessment of radiographic findings and one certified oncologist. They will review patient radiographic images (CT, MRI, PET/CT, bone scan) independently in accordance with RECIST 1.1 to confirm postoperative local recurrence or metastasis.

The review by an independent review committee does not determine eligibility for enrolment or the treatment of patients. The Investigator makes all treatment decisions based on local assessment results. The

analysis of OS and DFS is based on the Investigator's assessment results.

The imaging examinations (CT, MRI, PET/CT, bone scan) of the patients enrolled in this study during the baseline period and periodic postoperative follow-up visits need to be collected according to the imaging acquisition guidelines of this study, and transferred to the personnel of the Independent Review Committee.

10. References

[1] Jemal A, Bray F, Center MM et al. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] D'Addario G, Fruh M, Reck M et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v116-119.

[3] Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007;2:706 –714.

[4] Girard N, Mornex F. Radiotherapy for locally advanced non-small cell lung cancer. Eur J Cancer 2009;45S1:113-25.

[5] Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 1995;311:899-909.

[6] The International Adjuvant Lung Cancer Trial Collaborative Group: Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-60.

[7] Winton T, Livingston R, Johnson D, et al: Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.

[8] Douillard JY, Rosell R, De Lena M, et al: Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. Lancet Oncol 2006;7:719-27.

[9] Scagliotti GV, Roldano F, Torri V, et al: Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small cell lung cancer. J Natl Cancer Inst 2003;95:1453-1461.

[10] Waller D, Peake RJ, Stephens RJ, et al: Chemotherapy for patients with non-small cell lung cancer: The surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004;26:173-82.

[11] Pignon JP, Tribodet H, Scagliotti GV, et al. Lung Adjuvant Cisplatin Evaluation: a pooled analysis by the LACE collaborative group. J Clin Oncol, 2008, 26(21): 3552-59.

[12] Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups.J Clin Oncol. 2008;26:5043-51.

[13] Goss GD, Lorimer I, Tsao MS, et al. A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinb in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19. J Clin Oncol. 2010;28(20s Suppl):lba7005.

[14] Richardson F, Richardson K, Sennello G. et al.Biomarker analysis from completely resected NSCLC patients enrolled in an adjuvant erlotinib clinical trial (RADIANT). J Clin Oncol. 2009;27(20s Suppl):abstr 7520.

[15] Janjigian YY, Park BJ, Zakowski MF, et al. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations.J Thorac Oncol. 2011;6:569-75.

[16] Zhao Q, Shentu J, Xu N, et al. Phase I study of icotinib hydrochloride (BPI-2009H), an oral EGFR tyrosine kinase inhibitor, in patients with advanced NSCLC and other solid tumors. Lung Cancer. 2011. 73(2): 195-202.

[17] Shi Y, Zhang L, Liu X et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 2013; 14: 953-961.

[18] Ren GJ, Zhao YY, Zhu YJ, et al. Tumor gene mutations and messenger RNA expression: correlation with clinical response to icotinib hydrochloride in non-small cell lung cancer. Chin Med J (Engl). 2011. 124(1): 19-25.

11. Protocol Signature Page

Investigator's Statement

I have read this protocol and the study will be conducted in accordance with the moral, ethical and scientific principles stipulated in the Declaration of Helsinki and Chinese GCP. I agree to carry out this clinical study in accordance with the design and regulations of this clinical trial protocol.

I will be responsible for making medical decisions related to the clinical trial and ensuring that subjects are treated in a timely manner if they experience an AE during the trial. I am aware of the procedures and requirements for correct reporting of SAE, and I will document and report these events as required.

I guarantee that the data will be entered into the CRF in an accurate, complete, timely and legal manner. I will accept the monitoring or audit of the monitor or auditor dispatched by Sponsor and the audit and inspection of the pharmaceutical regulatory department to ensure the quality of the clinical trial.

I agree that the study results are used for application for drug registration.

I will provide a resume to the Ethics Committee and possibly the Drug Administration before the start of the study.

Investigator (signature):_____ Date:_____