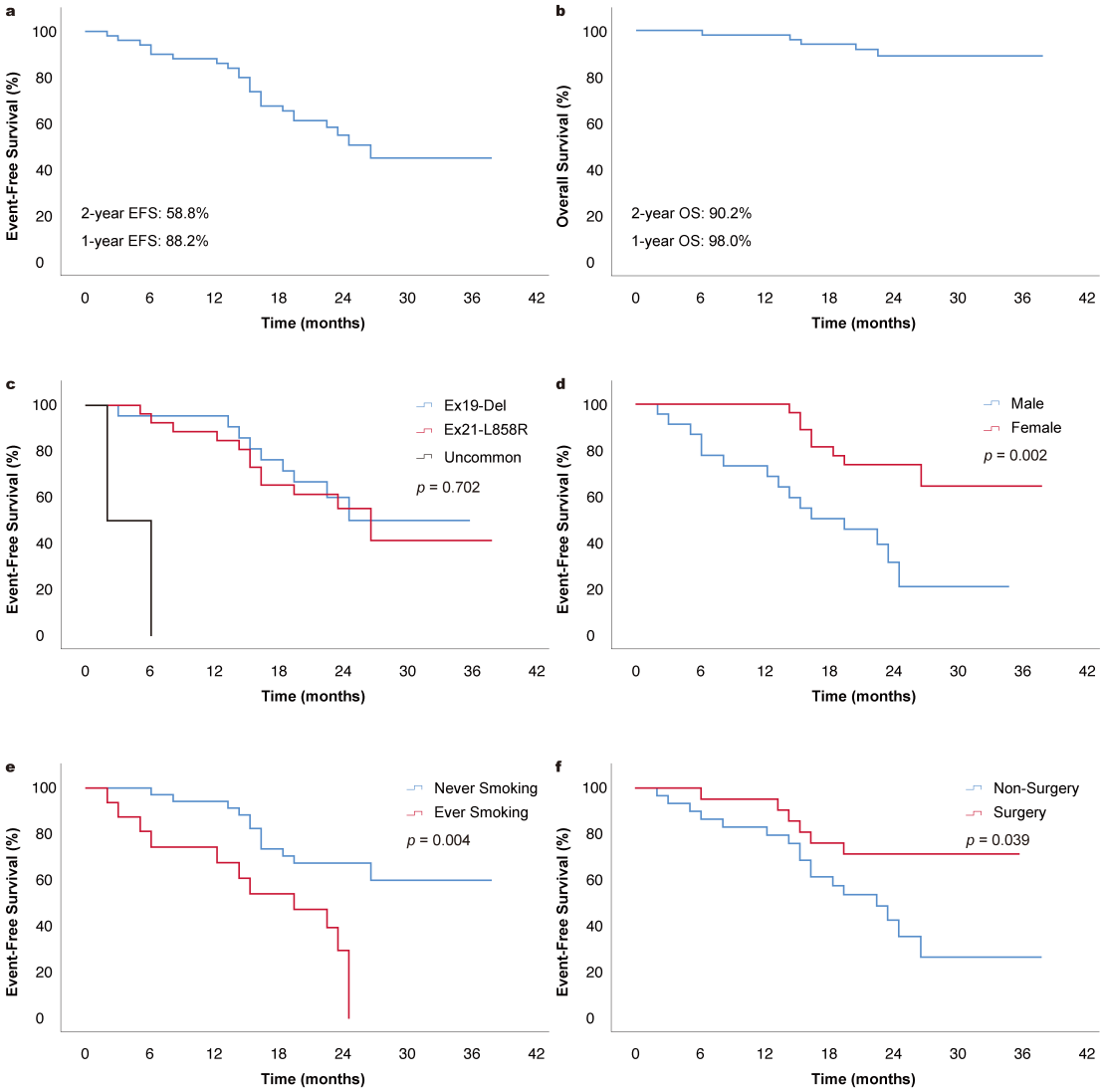
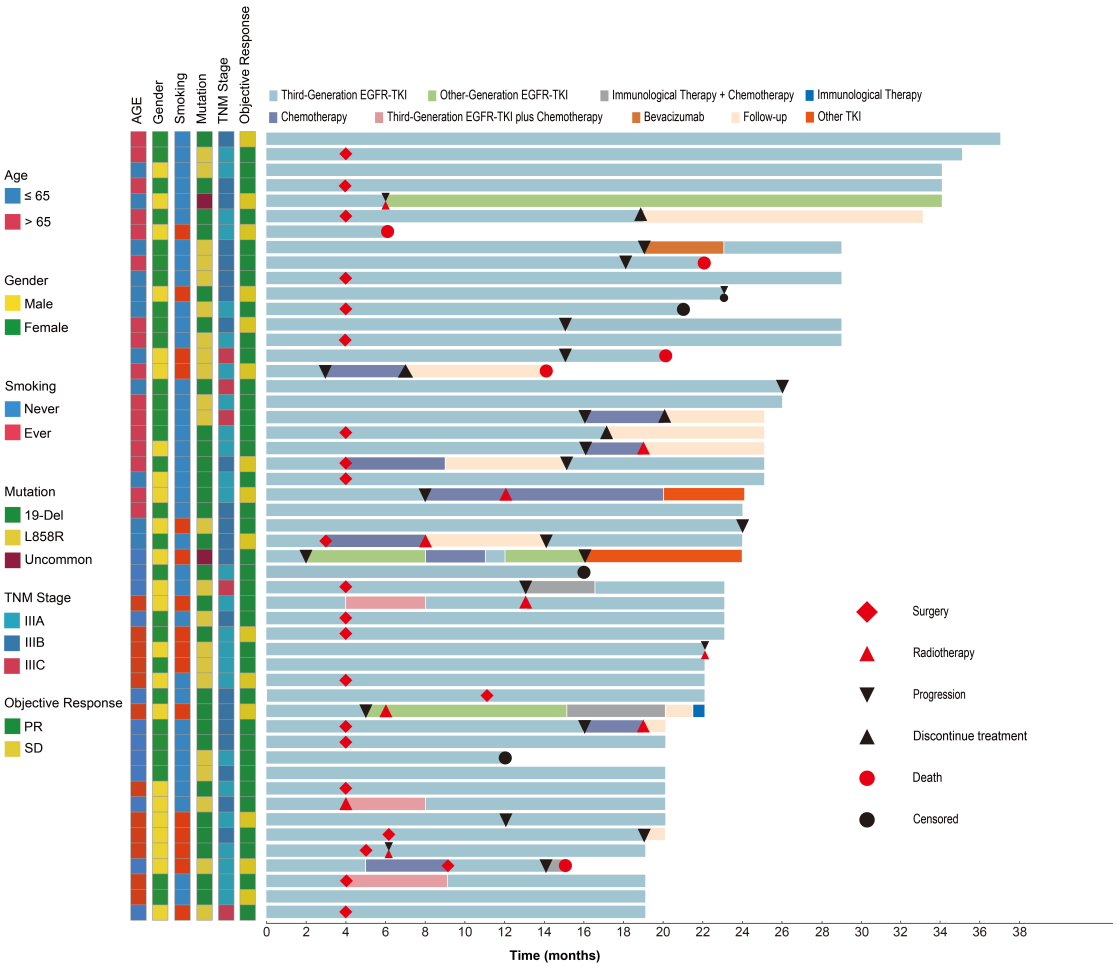
Supplementary Table 1. The characteristics of patients with uncommon *EGFR*-mutant subtypes (N =2)

| ID | ECOG | Smoking | Mutation | TNM | Cycle | c-Regression | | | Surgery |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | RECIST | Primary Tumor | Node | |
| 005 | 0 | Never | S768I | IIIB (N2) | 3 | SD | Shrink 4% | SD | Without |
| 030 | 0 | Ever | G719X | IIIB (N2) | 2 | PR | Shrink 32% | SD | Without |

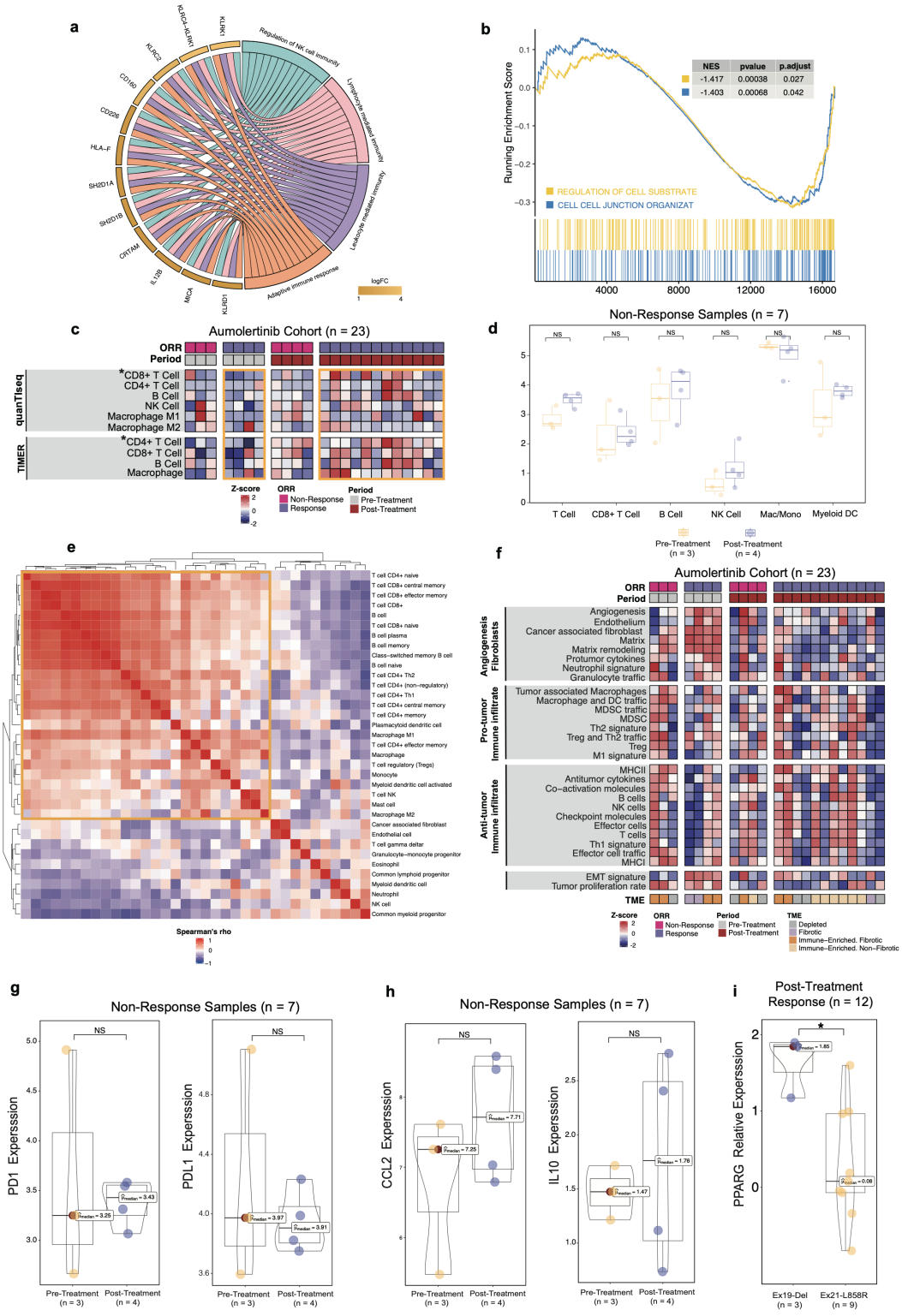



**Supplementary Figure 1: Kaplan-Meier estimates of patients' EFS and OS for the ITT population.**

The EFS (a) and OS (b) of total ITT (n=51). The EFS of ITT between (c) different mutation subtypes, (d) males and females, (e) different smoking status, and (f) different surgical treatment status. *P*-value was calculated using stratified log-rank test, with $p < 0.05$ considered statistically significant. Source data are provided as a Source Data file. EFS: event-free survival; ITT: intention-to-treat; NR: not reached. Source data are provided as a Source Data file.




**Supplementary Figure 2: Swimming plot of clinical characteristics and follow-up.** PR: partial response; SD: stable disease. Source data are provided as a Source Data file.




**Supplementary Figure 3: Additional analysis of immune infiltration and gene expression in baseline and post-treatment samples.**

(a) GO chord diagram for the post-treatment group in response samples. (b) GSEA results for

downregulated pathways in the post-treatment response group. (c) Heatmap of quanTIseq scores, Timer scores for all samples (* indicates statistical significance between the pre-treatment group and the post-treatment group within response samples). (d) Variations in immune infiltration profiles between the pre-treatment group and the post-treatment group in the non-response samples. (e) Heatmap of the Spearman correlation of Xcell scores for different immune cell types within the treatment response samples. (f) Heatmap of GSVA scores for key TME pathways across all samples. (g) Variations in PD-1 and PD-L1 expression levels between the pre-treatment group and post-treatment group within non-response samples. (h) Variations in CCL2 and IL10 expression levels between the pre-treatment group and post-treatment group within non-response samples. (i) Variations in PPARG expression between the Ex19-Del group and the Ex21-L858R group within the post-treatment response samples (values represent relative changes calculated by subtracting each group's pre-treatment mean from their post-treatment response values). Centers, boxes, whiskers, and dots indicate medians, quantiles, minima/maxima, and outliers, respectively. Source data are provided as a Source Data file.

# Induction Aumolertinib Therapy for Stage III EGFR Mutation-Positive Non-small Cell Lung Cancer: A Single-Arm, Open-Label, Phase II Clinical Trial

Investigator: Professor Gening Jiang, Professor Zhang Peng

Institution: Shanghai Pulmonary Hospital of Tongji University

Study Period: Oct. 2020 to Dec. 2027

Version: 1.1

Version Date: 2024-8-30

**Protocol Summary**

| | |
|---|---|
| Title: | Induction Aumolertinib Therapy for Stage III EGFR Mutation-Positive Non-small Cell Lung Cancer: A Single-Arm, Open-Label, Phase II Clinical Trial |
| Version No.: | 1.1 |
| Research Institution: | Shanghai Pulmonary Hospital of Tongji University |
| Organization in Charge: | Shanghai Pulmonary Hospital of Tongji University |
| Principal Investigator: | Professor Gening Jiang, Professor Zhang Peng |
| Participants: | Patients with stage III EGFR mutation-positive non-small cell lung cancer. |
| Objectives: | To evaluate the efficacy and safety of induction Aumolertinib in the treatment of stage III EGFR mutation-positive non-small cell lung cancer. |
| Study Design: | Single-arm, open-Label, phase II clinical trial |
| Sample Size: | 56 in total |
| Test Drug: | Aumolertinib (trade name: Ameile) |
| Dosage and Mode of Administration | 110mg ,Tablet, PO,QD |
| Trial Content: | ① Induction/neoadjuvant treatment stage: the enrolled patients take Aumolertinib at a dosage of 110mg per day, 16 weeks in total; and receive CT scan re-examination within 1th post-therapy week. (To get an accurate ORR, the patients should receive CT scan several days later instead of doing it immediately after stopping taking Aumolertinib) (RECIST1.1).<br>② Surgical treatment stage: the patients who respond to Aumolertinib treatment (CR+PR) and could undergo surgery will receive radical resection combined with systematic lymph node dissection within two weeks (14 days) after Aumolertinib disscontinued.<br>③ Adjuvant treatment stage: The CR, PR and SD patients who have been treated surgically will take Aumolertinib at a dosage of 110mg per day for 48 weeks (combined with neoadjuvant). The SD and PD patients who could not receive operation and the PD patients who have received operation will be transferred into medical oncology or radiation oncology and receive comprehensive therapy (the comprehensive therapy is designed by the experts from thoracic surgery, oncology, radiation therapy, and respiratory medicine, which may include, but is not limited to: continued targeted neoadjuvant therapy (for some SD patients, chemotherapy, and/or radiotherapy). |
| Research Time: | 2020.10-2027.12 |

| | | | |
|---|---|---|---|
| Schedule: | Phase I<br>(up to primary endpoint) | FPI: | 2021.01 |
| | | LPI: | 2022.06 |
| | | LPLV | 2022.09 |
| | | SAR | 2022.12 |
| | | Publication | 2023.03 |
| | Phase II<br>(up to completion of follow-up) | LPLV | 2027.06 |
| | | CSR | 2027.12 |

| | |
|---|---|
| Endpoints: | Primary endpoint: objective response rate (ORR).<br>Secondary endpoints: pathological complete response (pCR) rate, major pathological response (MPR) rate, R0 resection rate, EFS, OS, adverse events.<br>Exploratory endpoints: Potential biomarkers, tumor microenvironment dynamics. |
| Statistical method: | All data will be presented on basis of the full analysis set. Continuous variables will be summarized according to the number of observed value, average value, standard deviation, median value, minimum value and maximum value; and categorical variables will be summarized by frequency counts and percentages for each category. The median time to events (death and progression) or censoring time, quartile Kaplan-Meier estimates and their 95% confidence intervals will be used to summarize EFS，OS. |
| Follow-up: | After surgery, the patients will be followed up in the outpatient 3 months later. If the patient has no recurs, the patients will be followed up in the outpatient every 6 months until the disease recurs or 5 years later. The outpatient follow-up examination includes symptom check, physical examination, chest CT scan, tumor biomarker examination, upper abdominal ultrasound examination, systemic ECT in case of bone pain, and cranial MRI in case of headache, vomiting, bilateral limb inequality, and walking instability, etc. In addition, the telephone follow-up will be made every 3 months from year 1 to 5 after treatment to obtain the data on disease recurrence and overall survival of patients. |

# CONTENTS

## 1. Background and Rationale

### 1.1 Epidemiology of Lung Cancer

Primary bronchial lung cancer is one of the most common malignant tumors. According to the latest data reported in 2018, lung cancer ranks first in terms of the incidence (11.6%) and the mortality (18.4%) among malignant tumors.[1] Similarly in our country, the data collected in 2015 show that lung cancer ranked first as well in terms of the incidence (19.6%) and the mortality (26.0%) among all malignant tumors, with an obvious increase compared with the incidence (13.0%) and the mortality (18.0%) in 2007. As analyzed by gender, lung cancer ranks first in terms of the incidence and the mortality among diseases suffered by male, while it ranks second in terms of the incidence (next only to breast cancer), and first in terms of the mortality among diseases suffered by female.[2-4] About 25% of the lung cancer patients all over the world live in the Asia-Pacific region, and lung cancer has become a powerful killer in the world, especially in Asia. According to the latest statistics of SEER (Surveillance, Epidemiology, and End Results) database, the 5-year overall survival rate of lung cancer is 19.4%.[5]

### 1.2 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) is the most common pathological type of all lung epithelial cancers except small cell lung cancer (SCLC), accounting for 80-85% of all lung malignant tumors.[6] The most common histological subtypes of NSCLC include adenocarcinoma and squamous cell carcinoma. However, any type of non-small cell lung cancer may occur under the effect from abnormal histological variation.[6] The TNM staging system proposed by the American Joint Committee on Cancer (AJCC) has been widely adopted by all countries in the world. The 8th edition of TNM staging system was promulgated on January 1, 2017, which was recognized as the best staging standard for prognosis of tumors.[7] Additionally, it was also recommended for the clinical research in the Guidelines (2017 edition) newly issued by the National Comprehensive Cancer Network (NCCN). According to the staging criteria of lung cancer by TNM (Version 8), the 5-year survival rate is 80% in NSCLC patients at pathological stage I, 60% in patients at stage II, and 41% in patients at stage IIIA.[8] Compared with small cell lung cancer, non-small cell lung cancer is less sensitive to radiotherapy and postoperative adjuvant chemotherapy, and the overall 5-year survival rate of which is less than 15%.[9]

### 1.3 Current Status on Treatment of Resectable NSCLC

The best treatment for lung cancer is still radical resection, which is indicated for patients at stage I-II and partial patients at stage III. However, the surgery is only applicable to 20-25% of NSCLC patients.[10] In most patients, the cancer may develop into the advanced stage or be found with distant metastasis when it is diagnosed confirmatively, and cannot be resected surgically. More than 60% of patients after surgical resection will develop recurrence, mainly due to micrometastasis. Adjuvant or neoadjuvant chemotherapy is the reasonable method to eradicate micrometastasis and minimize the risk of recurrence. A LACE meta-analysis of adjuvant therapy and neoadjuvant therapy trials, in which cisplatin-based chemotherapy has been analyzed, shows that the patients have a survival benefit of 5% within 5 years from the initiation of adjuvant or neoadjuvant chemotherapy, among which the patients at stage II and IIIA have the greatest survival advantage.[11] In the past 20 years, the systematic therapy has developed from a single empirical method with cytotoxic drugs to a targeting therapy or immunotherapy with multiple options and better tolerance.[12, 13] However, the overall survival rate of NSCLC patients remains very low at present, and the continuous development and improvement of new drugs, technologies and treatment patterns are still needed to overcome the difficulty in treatment of lung cancer.

### 1.4 Gene Mutation and Non-small Cell Lung Cancer

Gene is the genetic information of organisms and determines the structure and functions of cells. Lung cancer is a heterogeneous disease, in which gene mutation plays a vital role with regard to its occurrence and development. The change of tumor genome is extremely complicated. Genetic variation information of genome mainly includes: single nucleotide variation at DNA level, chromosome copy number variation (including gene amplification and large-segment deletion), gene rearrangement, etc.[14-16] transcriptome variation at RNA level, and epigenetic change caused by gene mutation. Driver gene (proposed by Weinstein in 2002 [17]) refers to some molecular changes that play a key role in inducing and maintaining malignant tumors. In recent 10 years, a great progress has been made in studying lung cancer driver genes. In 2015, The Cancer Genome Atlas (TCGA) had fully reported the results of genome landscape on lung adenocarcinoma and squamous cell carcinoma. [14-16] About 60% of the driver genes in lung adenocarcinoma had been identified, including more than 10 genes such as KRAS, EGFR and BRAF. In lung squamous cell carcinoma, the driver genes such as TP53, FGFR and SOX were found. Gene fusion and gene rearrangement had been achieved in genes such as KRAS, EGFR and FGFR, which became the potential therapeutic targets, and brought opportunities for targeted therapeutic interventions. [18-21]

### 1.5 Therapeutic Target for Lung Adenocarcinoma: EGFR

Epidermal growth factor receptor (EGFR) belongs to receptor tyrosine kinases (RTKs) of HER/erbB family, including HER1 (EGFR/erbB1), HER2 (neu, erbB2), HER3 (erbB3) and HER4 (erbB4). EGFR gene is located on the short arm of chromosome 7 (7p11.2) and encodes type I transmembrane growth factor receptor with tyrosine kinase activity. [22] After binding to its ligand, it can induce autophosphorylation of the receptor cytoplasmic domain, [23] and can activate downstream EGFR signal pathways such as RAS-RAF-MEK-MAPK pathway, PI3K-PTEN-AKT pathway, signal transducer and transcriptional activator (STAT), [24] thus promoting effects such as cell proliferation, angiogenesis, metastasis and anti-apoptosis finally. [25] Tyrosine kinase activity of EGFR is regulated by carcinogenic mechanisms such as EGFR mutation, copy number increasing, and EGFR protein overexpression. [26] Receptors and ligands of EGFR family also mediate complex interactions between tumor cells and tumor microenvironment. Inappropriate activation of EGFR tyrosine kinase can inhibit apoptosis of tumor cells and promote tumor progression. [28] EGFR may also interact with integrin pathway, [28,29] activate matrix metalloproteinase, alter cell adhesion, stimulate cell migration and invasion, and promote metastasis. [30] EGFR mutations occur mainly in the coding region of tyrosine kinase, most of which are concentrated in exons 18-21. The most common mutations in lung adenocarcinoma are deletion mutation at exon 19 (about 44%) and L858R mutation at exon 21 (about 41%). [31] Mutation of EGFR tyrosine kinase domain could lead to conformational instability, constitutive activation of kinase activity and activation of downstream signal pathways, [32,33] thus causing the occurrence and development of lung cancer.

### 1.6 EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

EGFR tyrosine kinase inhibitor (TKI) can competitively inhibit the combination of ATP and EGFR tyrosine kinase domain, thus to prevent growth, proliferation, invasion, angiogenesis and metastasis of EGFR activated mutant tumor cells by blocking downstream signal pathways. At present, TKIs include generation-I drugs (gefitinib, icotinib, erlotinib), generation-II drugs (afatinib, dacomitinib), generation-III drugs (osimertinib, aumolertinib) and generation-IV drugs (e.g. EAI045) in preclinical studies.

### 1.7 Aumolertinib

Aumolertinib (trade name: Amele) is a third-generation TKI, researched and developed by Jiangsu Hanson Pharmaceutical Group Co. Ltd, which irreversibly inhibits EGFR sensitive mutations and T790M resistant mutations. Compared with the generation-I and generation-II TKI drugs, aumolertinib has a good benefit in the Chinese population, patients with brain metastases, and patients with 19del/L858R mutations, and the effect is more durable and significantly improves the progression-free survival (PFS) of patients[34]. The efficacy of aumolertinib in the treatment of T790M mutated NSCLC patients is comparable to that of osimertinib, with lower toxicity and no interstitial pneumonia [35].

### 1.8 Current Status of Treatment with EGFR-TKI

According to the latest guidelines of NCCN, TKIs (erlotinib, gefitinib, afatinib and osimertinib) is the first-line therapy for advanced NSCLC with positive EGFR mutation.

It has been found in studies that TKIs therapy can also benefit patients with resectable NSCLC. In a randomized, open-Label, phase III clinical trial (ADJUVANT/CTONG1104), total 222 EGFR mutation-positive patients with NSCLC at stage II-IIIA were enrolled [43] and divided into the experiment group (administrated with gefitinib at a dosage of 250 mg per day for 2 years) and the control group (administrated with vinorelbine at a dosage of 25 mg/m$^2$+ cisplatin at a dosage of 75 mg/m$^2$) at a rate of 1:1, to receive 4 cycles of treatment, with 3 weeks as one cycle. The result showed that in the experiment group, the median disease-free survival (DFS) was significantly higher (36.5 vs. 28.7, P<0.01), and the incidence of toxic and side effects was lower, compared with those in the control group. Another randomized phase II clinical trial showed that IIIA-N2 patients who received postoperative chemotherapy combined with adjuvant gefitinib had got better DFS (39.8 vs. 27.0, P=0.014) and 2-year DFS (78.9% vs. 54.2%) than those who received chemotherapy alone. [44] In addition, there are a number of trials that are ongoing to investigate the TKIs adjuvant therapy for resectable NSCLC (NCT00373425, NCT03983811, NCT01843647, and NCT03656393, etc.).

### 1.9 Neoadjuvant TKI therapy

Neoadjuvant therapy could bring treatment effects such as tumor shrinking, improving the complete resection rate, eliminating micrometastases and reducing the risk of recurrence. It has been reported that the neoadjuvant TKI therapy could achieve the downstaging of tumor or even the complete response in the locally advanced (IIIA-N2) NSCLC patients. [45-48] The results of a neoadjuvant TKI clinical trial, which is the first randomized, controlled study to confirm the application of EGFR-TKI in neoadjuvant and adjuvant phases, were reported in European Society of Medical Oncology (ESMO) Conference. In this EMERGING trial, 72 EGFR mutation-positive patients with NSCLC at stage IIIA-N2 were included and divided into the erlotinib group (administrated with erlotinib at a dosage of 150mg per day for 6 weeks before operation and 1 year after operation) and the chemotherapy group (administrated with gemcitabine at a dosage of 1250mg/m$^2$+ cisplatin at a dosage of 75mg/m$^2$ for two cycles before operation and two cycles after operation, with every 3 weeks taken as 1 cycle). The current results show that in the erlotinib group, the median PFS has been significantly prolonged compared with that in the chemotherapy group (21.5 vs 11.4 months, P<0.001), but the objective response rate (ORR) does not improve significantly (54.1% vs 34.3%, P=0.092). [47] Aumolertinib, as a generation-II TKIs, theoretically has better neoadjuvant effect than the generation-I TKIs. At present, there is only one single-arm phase II clinical trial (ASCENT) on neoadjuvant Aumolertinib in treatment of stage III EGFR mutation-positive NSCLC. The study found that the ORR of neoadjuvant Aumolertinib was as high as 75%, and the median PFS was 34.8 months, but the sample size was small (only 13 cases). [40] However, no more studies are available so far to confirm the efficacy and safety of neoadjuvant Aumolertinib in the treatment of resectable stage III EGFR mutation-positive NSCLC, and there is a lack of studies based on the Chinese population. Given that the neoadjuvant therapy has delayed the operation time and there is a potential risk of cancer progression, more data are needed to perform evaluation.

## 2. Research Objectives

To evaluate the efficacy and safety of induction/neoadjuvant Aumolertinib in the treatment of stage III EGFR-mutant NSCLC.

## 3. Trial Content

### 3.1 Design Pattern

A single-arm, open-Label, single-center, phase II clinical trial

### 3.2 Selection of Patients

EGFR-mutant NSCLC patients at stage III (version 8)

#### 3.2.1 Inclusion Criteria

- Non-small cell lung cancer patient with EGFR mutations as confirmed by needle biopsy;
- At stage III (TNM Staging, Version 8) as identified by chest CT, PET-CT or/and EBUS;
- No systemic metastasis (confirmed by head MRI, whole body bone scan, PET-CT, liver and adrenal CT, etc.);
- With the feasibility to receive radical surgery (radical lung lobectomy + systematic lymph node dissection);
- Good pulmonary function that could tolerate surgical treatment;
- Aged 18- 75 years;
- At least one measurable tumor (the longest diameter measured by CT shall be > 10 mm);
- Other major organs shall function well (liver, kidney, blood system, etc.):
  - Hemoglobin ≥9.0 g/dL (which can be maintained or exceeded by means of blood transfusion);
  - Red blood cell count ≥2.0×10^9/L;
  - Absolute neutrophil count (ANC) ≥ 1.0× 10^9/L;
  - Platelet count ≥ 100× 10^9/L;
  - Total bilirubin is within the normal limit;
  - Alanine transaminase, glutamic oxaloacetic transaminase and alkaline phosphatase ≤2.5 times the upper limit of normal value;
  - Creatinine ≤ 2.0 mg/dL; and creatinine clearance rate ≥ 60 ml/min;
  - The international normalized ratio (INR) of prothrombin time and the activated partial thromboplastin time (APTT) of patient who has not received anticoagulant therapy shall be ≤ 1.5 times the upper limit of normal value. The patient who has received full or parenteral anticoagulant therapy shall be allowed to participate in the clinical trial only when the dosage of anticoagulant drugs is stable for at least 2 weeks, and the results of coagulation test are within the limits for local treatment.
- ECOG PS score shall be 0-1;

- The child-bearing female must undergo pregnancy test within 7 days before starting the treatment and the result shall be negative. Reliable contraceptive measures, such as intrauterine device, contraceptive pill and condom, shall be adopted during the trial and within 30 days after completion of the trial. The child-bearing male shall use condom for contraception during the trial and within 30 days after completion of the trial;
- The patient shall sign the Informed Consent Form.

**3.2.2 Exclusion Criteria**

- The patient has undergone any systemic anti-cancer treatment for NSCLC, including surgical treatment, local radiotherapy, cytotoxic drug treatment, targeted drug treatment and experimental treatment, etc.;
- The patient suffered from other cancers besides NSCLC (except cervical carcinoma in situ, cured basal cell carcinoma and bladder epithelial tumor [including Ta and Tis]) within 5 years before the trial;
- The patient suffers from any unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina pectoris, angina pectoris that starts to attack within the last 3 months, congestive heart failure [≥ Grade II specified by New York Heart Association (NYHA)], cardiac infarction (6 months before enrollment), severe arrhythmia and liver, kidney or metabolic diseases that requires drug treatment;
- The patient is a carrier of active hepatitis B, hepatitis C or HIV;
- The patient suffers from severe or new-onset gastrointestinal diseases with diarrhea as the main symptom;
- The patient is receiving the P glycoprotein inhibitor therapy;
- The patient has had or is currently suffering from cardiovascular malformation;
- The patient has had or is currently suffering from interstitial lung disease;
- The patient had undergone other major systemic operations or suffered from severe trauma within 3 months before the trial;
- The patient is allergic to Aumolertinib or its any excipients;
- The patient suffers from nervous system diseases or mental diseases and cannot keep compliance with the trial;
- The patient has any malabsorption condition;
- The female patient is in pregnancy or lactation period;
- There are any conditions under which the investigator considers the patient is not suitable to be enrolled.

**3.2.3 Withdrawal from Trial**

A withdrawal case refers to the patient who have terminated the neoadjuvant therapy due to various reasons during the clinical research. The patient will be withdrawn from the trial under the following conditions:

- The withdrawal is required by the patient himself or his legal representative;

- Continued participation of the patient in the study, as considered by the investigator, will be harmful to his/her health;

The patient must be withdrawn from the trial under any one of the following conditions:

- The patient has formed severe allergic reaction to the chemotherapy drugs, such as exfoliative rash or hypersensitivity of grade 3 to 4;
- There is any other serious adverse reaction that the principal investigator (PI) or the investigator designated by PI believes it will need to suspend the treatment;
- The patient has shown very poor compliance;
- The results of β-HCG test to the patient suggest a pregnancy. The pregnancy event shall be reported in the clinical trial pregnancy report form;
- During the study, the patient has developed other diseases concurrently. It is believed by the investigator that the disease will obviously affect the evaluation of clinical situation to the patient, and it is necessary to terminate the treatment with this regimen;
- The patient has been found with any other malignant tumor that needs treatment;
- The patient gets lost to the follow-up visit;
- The patient has taken prohibited drugs or other substances that may lead to toxic reactions or lead to deviation of research results according to the judgment of the investigator;
- Death of the patient.

The reason for withdrawal shall be recorded in the case report form and the patient's medical record for any patient who has withdrawn from the trial.

It needs to follow up all patients who have withdrawn due to adverse events or abnormal laboratory test results until the adverse events are solved or become stable, and to record the subsequent results of such events. If a patient dies during the trial treatment or within 28 days after the completion of the experiment treatment, the investigator shall notify it to the Sponsor. The cause of death must be recorded in detail in the serious adverse events (SAE) report form and present the report form to the ethics department within 24 hours.

**3.3 Sample Size**

A total of 56 patients will be included in this trial.

**3.4 Study Schedule**

Assuming 3 patients are enrolled each month, it will take about 18 months for all patients to be enrolled. The first patient will be enrolled in Jan of 2021, and the enrollment of all patients is expected to be completed in June of 2022. The first stage will be from the enrollment of patients up to the completion of ORR evaluation to all patients. The primary endpoint, ORR, will be evaluated 3 months after the last patient is enrolled into the group, i.e. in September of 2022 (21st month later), and the preliminary results will be published in December of 2022 (within 6 months after ORR evaluation results are released).

The second stage is from the surgery treatment up to the completion of follow-up procedure. The evaluation of MPR, pCR and R0 resection rate can be completed one month after the operation of the last patient, i.e. in July of 2022. EFS will be basically determined (with reference to EMERGING results) at the 54th month (i.e. June of 2025, 36 months after the last patient has been enrolled in the group). OS follow-up time will be about 60 months. The last patient will complete the survival visit

in June of 2027, and all data statistics, analysis and publication work with regard to secondary endpoints will be completed in December of 2027. Therefore, the total research period will be about 72 months.

### 3.5 Therapy Plan

#### 3.5.1 Therapy Regimen

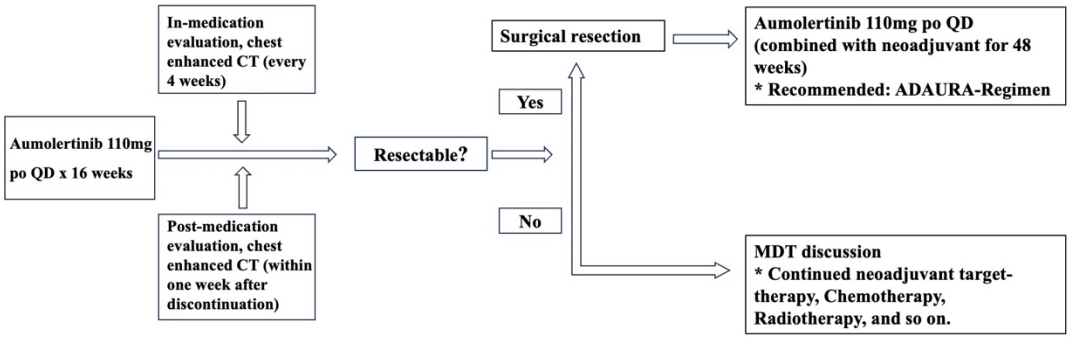
The induction/neoadjuvant therapy stage: the enrolled patients will take Aumolertinib at a dosage of 110mg per day for 16 weeks; and chest CT evaluation will be performed within 1 week after per cycle completion of the therapy.

Surgical treatment stage: the patients who have a response to Aumolertinib therapy (CR, PR, and SD) and can receive surgical treatment will receive radical resection combined with systematic lymph node dissection within 14th post-therapy day.

Adjuvant treatment stage: the patients with CR, PR or SD who have undergone the operation will take Aumolertinib at a dosage of 110mg per day for 48 weeks (combined with neoadjuvant). *Meanwhile, we strongly recommend that surgical treated patients undergo adjuvant target-therapy for at least three years, in accordance with the ADAURA-regimen.

The patients assessed as inoperable after four cycles of targeted neoadjuvant therapy will undergo a multidisciplinary team (MDT) discussion to determine the next phase of treatment. This discussion will involve experts from thoracic surgery, oncology, radiation therapy, and respiratory medicine. The specific decisions are as follows: Patients with Partial Response (PR): If it is anticipated that continuing the original treatment plan will benefit the patient, the original treatment plan will be maintained. Patients with Stable Disease (SD) or Progressive Disease (PD): For patients assessed as SD or PD after neoadjuvant therapy, as well as those who develop PD after surgery, they will be transferred to the oncology department for comprehensive treatment. *The specific treatment plan will be determined through multidisciplinary discussion and may include, but is not limited to: continued neoadjuvant target-therapy (for some SD patients); chemotherapy; and/or radiotherapy.

#### 3.5.2 Treatment Flow Chart




#### 3.5.3 Dosage Adjustment and Disposal of Missed Dose

Dosage adjustment due to adverse reactions

The symptomatic drug-related adverse reactions (such as those accompanied by severe/persistent diarrhea or skin-related adverse reactions) can be controlled by suspending the treatment and reducing the dosage of the test drug as listed in Table 1. (Please see the section “Adverse Reactions” in the Investigator Brochure or Instruction; and for more details on disposal of specific drug-related adverse event (AE), please refer to the section “Precautions” in the Investigator Brochure or Instruction.)

Table 1 – Dosage Adjustment for Adverse Reactions

| **CTCAE[a] Drug-related Adverse Events** | **Recommended Dosage of Aumolertinib** | |
|---|---|---|
| Grade 1 or 2 | No suspension [b] | No dosage adjustment |
| Grade 2 (prolonged [c] or intolerant) or ⩾ Grade 3 | To suspend medication up to restoration to grade 0/1 [b] | To reduce the dosage progressively by 55 mg [d] |

[a] Common Terminology Criteria Adverse Events (Version 4.0) of The American National Cancer Institute (NCI).

[b] When diarrhoea occurs, the anti-diarrhoea drugs (such as loperamide) shall be used immediately, and in the event of persistent diarrhoea, the medication shall be kept up to the cessation of diarrhoea.

[c] Diarrhea has lasted for more than 48 hours and/or rash has lasted for more than 7 days.

[d] If the patient cannot tolerate the dosage of 55mg per day, permanent termination of the medication shall be considered.

Missed Dose

If the dose is missed once, the patient shall take the test drug as soon as possible when he/she remembers on the same day. However, if less than 8 hours have been left before the next administration, there will be no need to supplement the missed dose.

**3.5.4 Concomitant Therapy and Smoking**

All concomitant medications and treatments (including start/end dates and indications) must be recorded in the patient's original data and the Case Report Form (CRF). It is recommended that all patients give up smoking during treatment.

**3.5.5 Concomitant Medication**

3.5.5.1 Drugs Not Allowed to be Used

- Bevacizumab, other TKIs and any drugs targeting VEGF, VEGFR, etc. (including those registered or under study).
- Research drugs (e.g. antibiotics, antiemetics and other drugs under research).
- Any Chinese herbal medicine treatment indicated with anti-tumor efficacy.

3.5.5.2 Drugs Allowed to be Used

- Unconventional therapy (e.g. non-anticancer Chinese herbal medicine therapy or acupuncture) and vitamin/trace elements are also allowed to be used provided that they cause no effect on the observation of the research endpoints, depending on decision of the investigator.
- The patients are allowed to receive palliative treatment and supportive treatment for the original diseases.
- Folic acid, vitamin B12 and corticosteroids are allowed to be used preventively to reduce toxic reactions.

**3.5.6 Treatment Compliance**

A record shall be made in the Case Report Form with regard to the dosage and administration time of Aumolertinib, for each participant in each course of treatment, as well as the reasons for delayed administration, dosage reduction or missed dose.

The compliance of a participant with the treatment and protocol includes his/her voluntary compliance with all aspects of the protocol. If the participant fails to make visits or take drugs on time, he or she could be withdrawn from the study according participant to the opinion of the principal investigator.

### 3.6 Research Process

#### 3.6.1 Screening Period and Baseline Period

Screening period: within 14 days before commencement of neoadjuvant/induction therapy

- To record/confirm the pathological type, mutation type and clinical tumor stage of the patient;
- To get the informed consent form signed.

Baseline period: within 7 days before the experiment group starts the neoadjuvant/induction therapy

- To record demographic information, complete medical history and smoking history, including previous anti-cancer treatment.
- To perform complete physical examination (PE), including ECOG performance status score, height, weight and detailed systematic examination.
- To check vital signs (including heart rate, blood pressure, respiratory rate and body temperature).
- To record all concomitant diseases, concomitant drugs and their indications.
- Blood routine examination: hemoglobin, hematocrit, platelet count, white blood cell count and classification, including absolute counts of neutrophils and lymphocytes.
- Whole blood biochemical examination: including blood sugar, calcium, phosphorus, sodium, potassium, chlorine, creatinine, blood urea nitrogen (BUN), total protein, albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, total bilirubin, etc.
- Tumor biomarkers.
- To perform serum pregnancy tests for all female patients of child-bearing age, including those whose partners have undergone sterilization operation. Pregnancy tests are not required for postmenopausal female patients who have been menopausal for at least one year and for the female patients who have undergone sterilization operation.
- Routine urine examination: including urine specific gravity, pH value, urine sugar, urine protein and occult blood.

#### 3.6.2 Neoadjuvant/Induction Treatment Period

The enrolled patients will take Aumolertinib at a dosage of 110mg per day for 16 weeks. Adverse events and concomitant medication of patients will be recorded during the period. The blood routine examination results, blood biochemical examination results and tumor biomarkers of the patients will be evaluated at the end of per neoadjuvant cycle (4 weeks per cycle).

#### 3.6.3 Imaging Evaluation after Neoadjuvant/Induction Therapy

Chest CT examination will be performed within 1 weeks after completion of treatment to assess the response of patient (according to RECIST1.1) and to determine whether surgical resection is feasible.

#### 3.6.4 Surgical Treatment Period

The patients who have a response to Aumolertinib therapy (CR, PR, and SD) and could receive the surgical treatment (SD and PD) will receive radical lobectomy and systematic lymph node dissection within two weeks after Aumolertinib discoutinued.

#### 3.6.5 Adjuvant Treatment Period

The patients with CR, PR and SD who have undergone the operation will take Aumolertinib at a dosage of 110mg per day for 48 weeks (combined with neoadjuvant);

The patients with SD or PD who cannot receive operation and the patients with PD who have undergone the operation will be transferred into medical oncology and receive comprehensive therapy. The regimen is designed by MDT discussion, which includes but is not limited to: continued neoadjuvant target-therapy (for some SD patients); chemotherapy; and/or radiotherapy.

### 3.6.6 Follow-up after Treatment

After surgery, the patients will be followed up in the outpatient 3 months later. If the patient has no recurs, the patients will be followed up in the outpatient every 6 months until the disease recurs or 5 years later. The outpatient follow-up examination includes symptom check, physical examination, chest CT scan, tumor marker examination, upper abdominal ultrasound examination, systemic ECT in case of bone pain, and cranial MRI in case of headache, vomiting, bilateral limb inequality, and walking instability, etc. In addition, the telephone follow-up will be made every 3 months from 3 to 5 years after treatment to obtain the data on disease recurrence and overall survival of patients.

### 3.6.7 Unscheduled Visits

Unscheduled visits shall be made according to the clinical needs, and relevant information shall be recorded in CRF and original data, including laboratory examination abnormalities and adverse events of clinical significance. If multiple laboratory tests have been carried out within the same day, only the latest results need to be recorded in CRF. However, all abnormal values found in the repeated laboratory tests shall be recorded in CRF.

### 3.6.8 Follow-up of Patients with Relapse or No Relapse after Study (5 Years after Operation)

The patients will be contacted once every 3 months (by on-site visit or phone call) to obtain the information about the overall survival and postoperative treatment of the patients. The follow-up visit shall be made every 3 months until the patient dies. The following information should be obtained during each follow-up visit:

- Survival status.
- If dead, the date and cause of death shall be recorded in detail.
- Disease status and relapse, in the event of relapse, the relapse date shall be recorded in detail (for those patients who have not got relapse in the last follow-up).
- The subsequent postoperative anti-cancer treatment (including reoperation, chemoradiotherapy and immunotherapy after relapse) shall be recorded in detail.

### 3.6.9 Flow Sheet of Research

| | Screening period and Baseline period | Neoadjuvant treatment period | | | | Evaluation | Operation | Adjuvant treatment period | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of days | -14~0 | 28 ±3 | 56 ±3 | 84 ±3 | 112 ±3 | 57-63, 85-91,113-119 | 120-133 | | Monthly assessment(A) | Security visit | (1). After surgery, the patients will be followed up in the outpatient 3 months later. If the patient has no |
| Informed Consent Form | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical history (including smoking) | X | | | | | | | | | | recurs , the patients will be followed up in the outpatient every 6 months until the disease recurs or 5 years later. (2). the telephone follow-up will be made every 3 months from year 1 to 5 after treatment to obtain the data on disease recurrence and overall survival of patients.( If the patient dies, information such as cause of death and date of death should be collected) |
| Physical examination | X | | | | | X | | | | X | |
| Needle biopsy | X | | | | | | | | | | |
| Vital signs | X | | | | | X | | | | X | |
| ECOG score | X | | | | | | | | | X | |
| ECG | X | | | | | | | | | | |
| Chest enhanced CT | X | | | | | X | | | | X(D) | |
| Radionuclide bone scan | X | | | | | | | | | | |
| Abdominal ultrasonography | | | | | | | | | | | |
| Heart color ultrasound | X | | | | | | | | | | |
| Pulmonary function | X | | | | | | | | | | |
| Cranial CT or MRI | X | | | | | | | | | | |
| HIV test | X | | | | | | | | | | |
| Hepatitis index | X | | | | | | | | | | |
| Blood routine | X | X | X | X | X | | | | X | X | |
| Blood biochemistry | X | X | X | X | X | | | | X | | |
| Urine routine | X | | | | | | | | | | |
| Thyroid function | X | | | | | | | | | | |
| Coagulation function(E) | X | | | | | | | | | | |
| Tumor biomarker | X | X | X | X | X | X | | | | | |
| Pregnancy test (if applicable) | X | | | | | | | | | | |
| Concomitant disease | X | X | X | X | X | | | | | | |
| Concomitant medication | | X | X | X | X | | | | | | |
| Aumolertinib | | X | X | X | X | | | X | | | |
| Comprehensive therapy(B) | | | | | | | | X# | | | |
| Tumor assessment (RECIST) | X | | | | | X | | | | | |
| Surgery | | | | | | | X | | | | |
| Safety Assessment/Record(C) | | X | X | | | X | X | | X | X | |
| EORTC-QLQ-C30&LC13 | | | X | | | | | | X | | |
| Postoperative follow-up and survival follow-up | | | | | | | | | | X | |

(A). The patients who take Aumolertinib will be evaluated according to the clinical symptoms.

(B). The patients with SD or PD who can not receive operation and the patients with PD who have undergone the operation will be transferred into medical oncology or/and radiation oncology and receive comprehensive therapy (chemotherapy or/and radiotherapy, the regimen is designed by oncologist and radiologist.

(C). All adverse events shall be collected from the signature of ICF by participants up to 30 days after the last administration of Aumolertinib or platinum-doublet chemotherapy. Then only SAE related to Aumolertinib will need to be collected up to the completion of study.

(D) Chest enhanced CT was reviewed 3 months after surgery, and every 6 months thereafter if the results were good.

(E) If warfarin or heparin is necessary, clotting function should be closely tested.

### 3.7 Indicators of Research

#### 3.7.1 Primary Endpoint

Objective response rate (ORR)

According to RECIST1.1, ORR refers to the proportion of patients who have achieved a tumor shrinkage to certain an extent and had it maintained for a certain period of time, including patients with complete response (CR) and partial response (PR). Complete response: all target lesions disappear, and the short diameter of any pathological lymph node (including target nodules and non-target nodules) must be reduced to a length of <10 mm. Partial response: the sum of target lesion diameters is reduced by at least 30% from baseline level. In this study, ORR is defined as the proportion of patients who have completed the 16-week treatment with Aumolertinib before operation and have achieved CR or PR as confirmed by CT evaluation after 1 week in all patients.

#### 3.7.2 Secondary Endpoints

Pathological downstaging rate: It is defined as the proportion of patients who have completed the 16-week treatment with Aumolertinib before operation and have achieved a T stage downing of the tumor as confirmed by CT evaluation after 1 week in all patients who have completed the treatment.

Major pathological response (MPR) rate: It is defined as the proportion of patients with no more than 10% residual viable tumor cells in primary tumor lesions and lymph nodes under microscope with HE staining in all patients who received radical surgery.

Pathological complete response (pCR) rate: It is defined as the proportion of patients with no residual carcinoma in primary tumor lesions and lymph nodes under microscope with HE staining in all patients who received radical surgery.

R0 resection: It is defined as the proportion of patients with negative surgical margin and no residual found under microscope after resection in all patients who have completed the treatment.

Event-free survival (EFS): It is defined as the time from the first administration of Aumolertinib in this study to the any progression of disease before surgery, disease recurrence after surgery, disease progression in the absence of surgery, or death from any cause.

Overall survival (OS): It is defined as the time from random enrollment to death of participant due to any cause.

Treatment-related adverse events: It refers to the number of adverse events related to Aumolertinib monotherapy or platinum-based chemotherapy as evaluated according to CTCAE v4.0.

**Exploratory endpoints:** Potential biomarkers, tumor microenvironment dynamics.

### 3.8 Termination of Study

This study may be terminated or suspended ahead of schedule if there is a sufficient reason, which includes but are not limited to the cases when:

- It is infeasible to evaluate the treatment plan since a major error has been found in the protocol of clinical trial.
- The Sponsor who has initiated the project requires to terminate the study (e.g. due to management reasons, and serious safety issues, etc.).

## 4. Ethical and Legal Matters

### 4.1 Independent Ethics Committee (IEC) or Institutional Review Committee (IRB)

According to GCP, Chinese laws and regulations and requirements of relevant organizations, all participating research centers shall obtain the approval from the corresponding ethics committee/institutional review committee prior to commencement of the study. When necessary, the approval from the ethics committee shall be extended, amended or reviewed, and transferred to the investigator.

### 4.2 Ethical Guidance for the Study

This study complies with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (IHC)/Quality Management Standards for Drug Clinical Trials, other relevant regulatory requirements, and Jiangsu Hanson Pharmaceutical Group Co. Ltd's policies on bioethics and human samples.

The procedures for operation, evaluation and documentation included in this research protocol are to ensure that the investigators will follow the guidelines of GCP and the guiding principles specified in the Declaration of Helsinki. The implementation of this research protocol will also follow the applicable laws and regulations of our country.

The investigators shall not modify the research protocol with no prior consent. However, in the event of emergency, the investigator may deviate from or change the research protocol in order to remove the risk factors for the participants, without the prior consent/support from the ethics committee/institutional review committee/Sponsor. The report on deviations or changes made thereby and their causes shall be submitted to the ethics committee/institutional review committee/Sponsor as soon as possible, and the proposals for modification of the protocol shall also be submitted if appropriate. The investigator must completely describe and explain all deviations or changes made to the research protocol.

### 4.3 Instructions to Participants and Informed Consent

The participants should be provided with the main information on the study and the Informed Consent Form (ICF). The investigator must provide the participants with written approval/agreement on the ICF from the ethics committee/institutional review committee as well as all other written information before the study starts. The approval documents from the ethics committee/institutional review committee, the approved instructions to participants and the Informed Consent Form must be filed together into the research document.

The ICF must be obtained before implementing any specific research steps. The date when a patient participates in the study and signs the ICF shall be recorded in the corresponding document of the participant.

### 4.4 Privacy Protection

All records that may identify the patients shall be kept confidential and will not be made public to the extent permitted by relevant laws and/or regulations.

Only the number and initials of a participant' name rather than his/her real name will be recorded in the Case Report Form (CRF). If the participant's name appears in any other document (e.g. pathological report), it must be covered in the copy of the document. The research report stored in the computer must comply with local laws on data protection. When the results of the study are published, the participant's identity will still be kept confidential.

The investigator will keep a list of names to identify participants' records.

### 4.5 Researcher Training

Before the first patient is included into the study, the representatives of Jiangsu Hanson Pharmaceutical Group Co. Ltd will review and discuss the research protocol and relevant documentation requirements with the working staff of research center, and provide training to them for any specific process of the protocol. The research institution shall ensure that all research staff involved in the study will receive appropriate training.

## 5. Research Supervision

If the protection to the privacy of patients meets the local requirements, the responsible supervisor (or designated personnel) will contact and visit the research institution regularly, and shall be allowed to check various test records (including Case Report Form and other relevant data) as required.

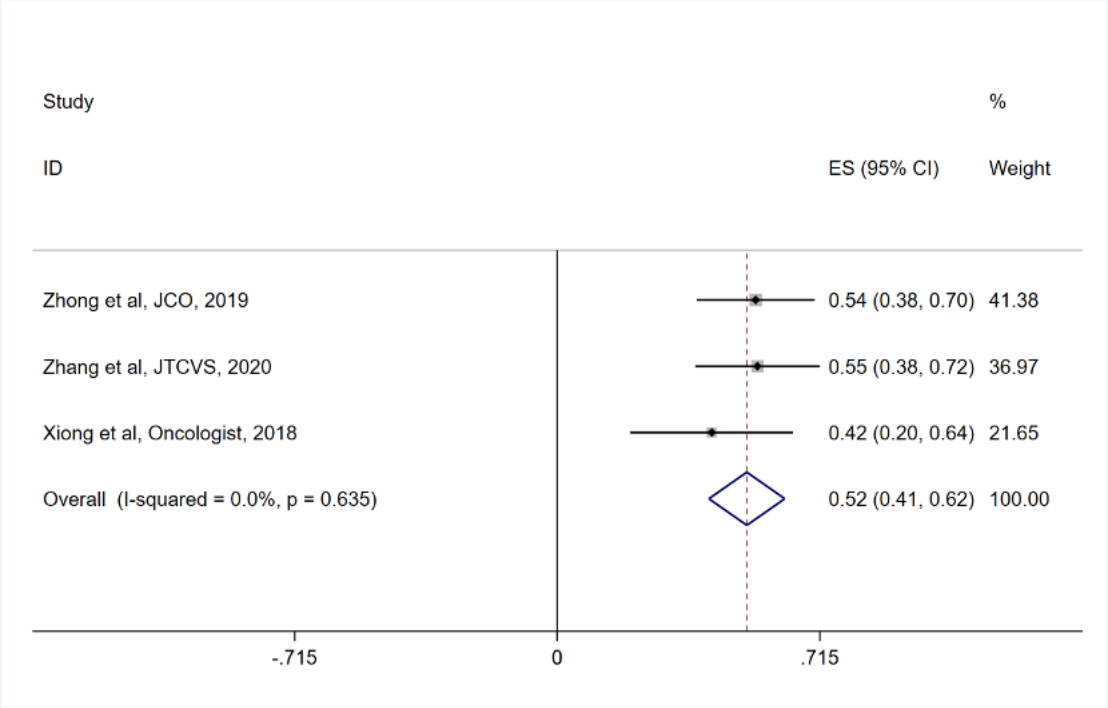
During the study, the supervisor (Jiangsu Hanson Pharmaceutical Group Co. Ltd representative) shall contact the research center regularly according to local regulations, including the requirements on the follow-up. If the investigators or other personnel of the center need information and suggestions on the implementation of the study, the representative of Jiangsu Hanson Pharmaceutical Group Co. Ltd shall be available. The research center shall maintain the original data according to GCP or local regulations. The investigators in each center must abide by all terms and obligations in the research agreement or related documents of this research, and they must also comply with the filing requirements specified in the research agreement. The study is expected to start in December of 2019 and the last patient is expected to be enrolled in April of 2022.

## 6. Statistical Analysis

### 6.1 Sample Size

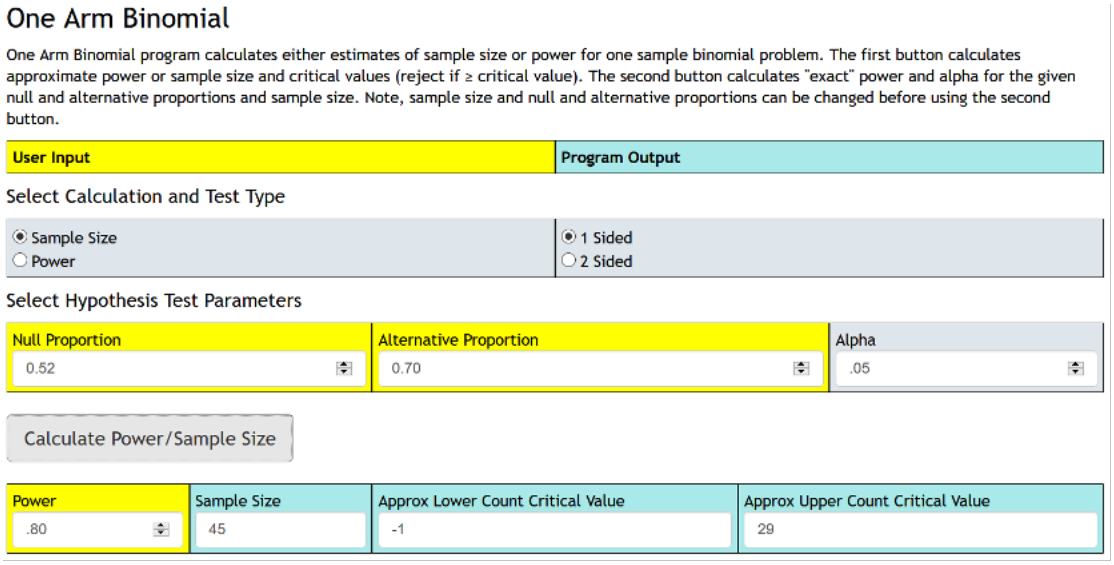
The primary endpoint of this research is ORR, which is taken to calculate the sample size.

Referring to three reported clinical trials of targeted neoadjuvant therapy for EGFR mutations, the ORR of CTONG1103 (erlotinib) was 54.1% (20/37), and that of NCT01833572 (gefitinib) was 54.5% (18/33). The ORR of NCT01217619 (erlotinib) was 42.1% (8/19), and the overall ORR of the generation-I TKI combined by single-arm meta-analysis was 52% (figure below).




The Phase II clinical study of aumolertinib for second-line treatment of advanced EGFR mutations (NCT02981108) resulted in a total ORR of 68.9%, it is expected that the ORR of aumolertinib for first-line neoadjuvant therapy in this study will be 70%.

Based on the sample size calculation, at the end of binary classification to reported from the generation-I of TKI results of neoadjuvant therapy for historical control group, alpha = 0.05 (unilateral), test effectiveness (1 - beta) = 80%, using binomial precise inspection (http://stattools.crab.org/) method to calculate sample size 45, Considering the 20% shedding rate, the total sample size was 56 patients, and no less than 29 patients were required to respond.




### 6.2 Description on Outcome Variables Related to Purpose and Assumptions

The following information in CRF will be evaluated through analysis:

EGFR mutation status, history of related diseases, body weight, disease characteristics, cancer treatment history, related concomitant medication, disease evaluation, progress follow-up, survival status, adverse events, laboratory evaluation, etc.

### 6.3 Description on Analysis Set

Full Analysis Set (FAS): it will include all patients who have been administrated with at least one dose of test drug.

### 6.4 Statistical Analysis Methods

All analyses will be conducted for FAS population. No statistical test will be conducted and all statistical analyses will be descriptive.

Efficacy analysis will be repeated according to the cohort defined by the number and category of previous treatment lines.

Descriptive statistical summary data will be used as appropriate. Continuous variables will be summarized by the number of observed values (n), average value, standard deviation (SD), median, quartile (Q1 and Q3), minimum, and maximum. Categorical variables will be summarized by frequency count and percentage for each category.

All statistical tests will give test statistics and their corresponding P values, and in Fisher's exact probability test, P values will be given directly. In the comparison between groups, it is considered that the difference tested is statistically significant when the P value is less than or equal to 0.05 by two-tailed test.

The difference analysis for qualitative data will be conducted by using chi-square test, Fisher exact probability test and Wilcoxon rank sum test. Quantitative data will be analyzed by t test, corrected t test, Wilcoxon rank sum test or covariance analysis.

Log-rank test will be used to compare survival time, and K-M method will be used to estimate median survival time.

#### 6.4.1 Evaluation on Primary Endpoint

Objective Response Rate (ORR): It refers to the proportion of patients who have completed the 16-week treatment with Aumolertinib before operation and have had a complete response or partial response (according to RECIST1.1) as confirmed by CT evaluation after 3 weeks in all patients who have completed the treatment. Only patients with measurable lesions at baseline will be analyzed.

#### 6.4.2 Evaluation on Secondary Endpoints

Pathological downstaging rate: It is defined as the proportion of patients who have completed the 16-week treatment with Aumolertinib before operation and have achieved a T stage downing of the tumor as confirmed by CT evaluation after 1 week in all patients who have completed the treatment.

Major pathological response (MPR) rate: It is defined as the proportion of patients with no more than 10% residual viable tumor cells in primary tumor lesions and lymph nodes under microscope with HE staining in all patients who received radical surgery.

Pathological complete response (pCR) rate: It is defined as the proportion of patients with no residual carcinoma in primary tumor lesions and lymph nodes under microscope with HE staining in all patients who received radical surgery.

R0 resection: It is defined as the proportion of patients with negative surgical margin and no residual found under microscope after resection in all patients who have completed the treatment.

Event-free survival (EFS): It is defined as the time from the first administration of Aumolertinib in this study to the any progression of disease before surgery, disease recurrence after surgery, disease progression in the absence of surgery, or death from any cause.

Overall survival (OS): It is defined as the time from random enrollment to death of participant due to any cause.

Treatment-related adverse events: It refers to the number of adverse events related to Aumolertinib monotherapy or platinum-based chemotherapy as evaluated according to CTCAE v4.0.

**Exploratory endpoints:** Potential biomarkers, tumor microenvironment dynamics.

### 6.4.3 Safety Analysis

The information will be collected from all patients for safety and tolerability tests based on AEs:

Adverse events: SAEs and adverse events leading to study drug discontinuation will be summarized by MedDRA preferred terminology (PT) and CTCAE grade.

The AE summary will include adverse events occurring up to 30 days after study drug discontinuation (last administration of Aumolertinib) or until disease progression, whichever occurs later.

## 7. Adverse Events

### 7.1Considerations/Precautions

Please refer to the detailed prescription information in the locally approved package of the related drugs or in the Investigator Brochure for research of Aumolertinib for the potential adverse reactions caused by Aumolertinib and/or platinum-doublet chemotherapy.

### 7.2Monitoring of Adverse Events

Adverse events of participants must be closely monitored, for example, through clinical related examinations. Assessment shall be made according to the importance, severity and relationship with test drug of adverse events.

The investigators shall be responsible for evaluating the relationship between all adverse events and the study drugs. The principal investigator can entrust other investigators participating in this study to make a judgment, but will still need to be responsible for it. The investigators must provide a list of qualified persons who accept the entrustment.

### 7.3 Definition of Adverse Event

### 7.3.1 Adverse Event

An adverse event refers to any adverse medical events that occur to the patients or participants who have received the treatment with study drugs. The adverse event is not necessarily causally related to the treatment. Therefore, the adverse event can be any adverse and meaningless sign (including abnormality in laboratory examination), symptom or disease temporarily associated with the study drugs used, regardless of whether the event is considered to be related to drugs.

The adverse events occurring in human body (whether related to drugs or not) include:

- Adverse events occurred during the use of drugs by professionals;
- Adverse events caused by overdose (intentionally or unintentionally);

- Adverse events caused by drug abuse;
- Adverse events caused by discontinuation of medication;
- The adverse event that may be caused solely by the patient's participation in the study (e.g. adverse events or serious adverse events due to discontinuation of antihypertensive drugs during elution period) must be reported as an adverse event even if it is not related to the study medication.

The event with no clinical pharmacological effect or with a clinical pharmacological effect that does not achieve the expected level, which has been recorded in the corresponding part of CRF, will not be taken as an adverse event.

**7.3.2 Serious Adverse Event**

A serious adverse event refers to any adverse medical event that meets one of the following conditions under any medication condition:

- Causing death;
- Life-threatening;
- Causing the patient to be hospitalized or prolonging the hospitalization time;
- Causing permanent or obvious loss of working ability or disability;
- Causing congenital malformation or congenital defect;
- Causing major medical events.

Death from disease progression was not considered a serious adverse event.

**Life-threatening:** The term "life threatening" is defined as "serious" and means that the participant is at the risk of death when such an adverse event occurs. It does not refer to any adverse event that may lead to death on condition that the situation gets worse.

**Hospitalization:** Any adverse event that results in hospitalization of a patient or prolongs the hospitalization time of patient will be considered serious unless one of the following conditions is met.

– The patient stays in hospital for observation for no more than 12 hours;

or

– The hospitalization is scheduled in advance (i.e. the surgery or elective surgery has been scheduled before commencement of this study);

or

– The hospitalization is not due to the adverse event (e.g. hospitalization for convalescent purposes).

**Note:** Any invasive treatment during hospitalization may meet the criteria of a "major medical event", so it may need to be reported as a serious adverse event according to clinical judgment. Moreover, if the local regulatory authority has proposed a stricter requirement in definition of such an event, the local regulations shall prevail.

**Disability:** It means that one's ability to engage in daily life is seriously impaired.

**Major medical event:** Any adverse event that may endanger the participants and may require intervention to prevent more serious cases can be considered as a serious adverse event. Please refer to the "World Health Organization Adverse Reaction Terms-Main Terminology" to determine a major medical event. These terms refer to or describe the status of a serious disease.

The reason why such an event shall be reported as a serious adverse event is that they may be related to a serious disease status, and special concern may be caused for the event reported as a SAE, which could promote necessary actions to be carried out.

### 7.3.3 Unexpected Adverse Event

An unexpected adverse event refers to any adverse drug-related event with the characteristics or severity inconsistent with criteria specified in the Investigator Brochure (or in the instructions supplied with the marketed products). The report of unexpected adverse events is also made partially for the purpose of supplementing important information on the characteristics or severity of known and recorded adverse events. For example, the event with more specialty or severity compared with that described in the Investigator's Brochure shall be considered "unexpected". Specifically, for example, it may include: (a) acute renal failure that has been marked as an adverse event and followed by a complication of interstitial nephritis; and (b) the hepatitis reported initially as acute liver necrosis.

### 7.3.4 The Relationship between Adverse Events and Study Drugs

The evaluation on the relationship between an adverse event and study drugs is a comprehensive clinical judgment based on all the information obtained when completing the Case Report Form.

It could be evaluated as "Unrelated" under following conditions:

1. There are other clear explanations, such as traumatic hemorrhage at the surgical site;

or

2. It is considered as unreasonable, for example, a participant is hit by a car, but there is no evidence indicating that the drug-induced disorientation has caused the incident; or a cancer occurs only a few days after commencement of medication.

The affirmative result of the evaluation indicates that there are reasonable reasons to confirm the adverse events may be related to the study drugs.

Factors to be considered when evaluating the relationship between adverse events and study drugs include:

– Occurring in the short term after drug use: such an adverse event shall occur after drug administration. The time span between medication and occurrence of the event shall be considered in clinical evaluation of the event.

– The event disappears after discontinuation of medication (stimulation discontinued) and occurs again after resuming medication (stimulation resumed): when analyzing the clinical process of suspicious events, the reaction of the participant after discontinuation of medication (stimulation discontinued) or the reaction of the participant after resuming medication (stimulation resumed) shall be fully considered.

– Basic diseases, concomitant diseases and sporadic diseases: the evaluation shall be made to the natural course, treatment process and all other diseases that the patient may suffer from shall

be made in each report;

– Concomitant medication or treatment: other drugs taken by the participant or other treatments received by the participant shall be checked to determine whether one of them is the cause of the adverse event;

– Known response patterns of certain a drug: clinical/preclinical;

– Pharmacology and pharmacokinetics of the study drugs: the pharmacokinetic characteristics (absorption, distribution, metabolism and excretion) of the study drugs shall be considered in combination with the individual pharmacodynamic response of each participant.

### 7.3.5 Record of Adverse Events

All adverse events shall be collected from the signature of ICF by participants up to 30 days after the last administration.

Records must be supported by original data. Any abnormality in laboratory examination that is considered with clinical correlation (for example, those causing participants to withdraw from the study ahead of schedule, requiring treatment or causing obvious clinical manifestations, or those considered clinically relevant by investigators) shall be reported as an adverse event. Each event shall be described in detail, including the start and end dates, severity, relationship with the test drug, measures taken and outcome of the event.

## 7.4 Report of Serious Adverse Events/Pregnancy

All serious adverse events (SAEs) that meet the criteria of definition and occur during the safety reporting period of this study, including laboratory examination abnormalities, must be reported to the personnel designated in the study documents immediately (within 24 hours after the investigators learn about the events). Any serious adverse event discovered by the investigators or working staff of the research center during the research process, whether it is related to the study drugs or not, must be recorded in the serious adverse event report form immediately after it has been known and reported to the ethics department of the research center, Research representative of Jiangsu Hanson Pharmaceutical Group Co. Ltd and Patient safety department of Jiangsu Hanson Pharmaceutical Group Co. Ltd within 24 hours. The serious adverse event related to the research treatment must be collected and reported, regardless of how long it has been since the last administration, even if the trial has been completed. Disease progression in this study was not reported as SAE.

All serious adverse events shall be followed up until they are resolved or become stable, and an update report shall be submitted to the designated personnel. A simple level 4 laboratory examination abnormality (according to the CTCAE 4.0) will not be reported as a serious adverse reaction unless the investigators believe that the abnormality has met the standard proposed by the International Conference of Harmonization for serious adverse events (seeing the definition in section 7.3.2). The Level 4 laboratory examination abnormality that is found in the baseline period as the manifestation of diseases shall not be reported as a serious adverse event, though it meets the criteria in CTCAE 4.0, especially when the patient has been allowed into the trial or not excluded from the trial. If there is a doubt about whether the abnormality shall be reported as a serious adverse event or not, the investigators may consult the research inspector. The laboratory examination abnormalities of level 4 as specified in CTCAE shall be recorded in the "Laboratory Information" page and checked regularly by medical inspectors. If it is uncertain whether an adverse event is caused by the disease research, it shall be reported as an AE or SAE.

If a female participant gets pregnant during the study, her medication of study drugs must be discontinued according to the instructions, and a report shall be sent immediately to the investigators. The investigators shall give the patients medical advice and discuss the risks of continuing pregnancy and the possible impact on the fetus. The patients shall be monitored until the pregnancy

issue has been resolved. The pregnancies that occur within 90 days after the completion of study medication shall also be reported to the investigators. And the patients shall be monitored continuously until the pregnancy issue has been resolved.

### 7.5 Non-Serious Adverse Reactions to Drugs

A non-serious adverse reaction refers to the adverse event related to treatment but not meeting the severity criteria as evaluated by the investigators. The severity criteria are detailed in section 7.3.2 of the protocol.

The non-serious adverse reactions that occur during the safety reporting period of this study must be reported to Jiangsu Hanson Pharmaceutical Group Co. Ltd within 7 natural days after being learnt.

## 8. Data Processing and Preservation

### 8.1 Case Report Form (CRF)

A Case Report Form (CRF) must be completed and signed by the principal investigator or the representative authorized by the principal investigator for each patient selected. This also applies to the recording of CRF for patients who fail to complete the trial (even during the screening period prior to randomization, provided that the case report form has been filled in). In the event that a patient withdraws from the study treatment, the reason for withdrawal must be recorded on CRF. If the patient withdraws from the study due to treatment-limited adverse events, comprehensive efforts shall be made to clearly record the results.

All forms shall be printed or recorded with indelible ink and must be legible. The errors can be crossed out instead of being removed, and the revised contents can be inserted accordingly. The investigators or their authorized representatives shall sign and date the revisions.

### 8.2 Preservation of Research Documents, Case Report Forms and Records

#### 8.2.1 Preservation of Investigators' Folders/Files

The investigators must keep comprehensive and accurate records during the implementation of the research, in order to ensure that the implementation of the research is fully recorded and the research data can be verified subsequently. These documents should be divided into two different types:

(1) Research documents of the investigators;

(2) Original clinical records of the patients.

The research documents of investigators include the trial protocol and revisions, approvals from the Independent Ethics Committee/Institutional Review Committee and the government, ICF sample, drug records, personnel resumes, power of attorney and other relevant documents/correspondence, etc.

Original clinical records of the patients (generally referring to the key effectiveness/safety parameters, defined before the start of the project and recorded outside the medical record form) usually include patient hospitalization/outpatient records, doctors' and nurses' records, appointment forms, original laboratory reports, electrocardiogram, electroencephalogram, X-ray, pathology and special evaluation reports, signed informed consent forms, consultation letters, patient screening and recruitment forms.

### 8.3 Archiving

The data to be entered into the CRF must be consistent with the original documents, or they may be recorded directly into the CRF. In the case of directly recording into CRF, the recorded content will be taken as the original data. The parameters of the original data must be verified and the information of the data source must be recorded. The research documents and all the original materials shall be kept until the notification for destruction from the Sponsor is received(also a researcher at IIT).

### 8.4 Establishment of Database

After receiving the CRFs, the statisticians will propose the questions to the investigators for verification through the clinical inspector, and the investigators shall make a response as soon as possible. The statisticians shall establish the database in time. After the database is verified, the data will be locked by the principal investigator, Sponsor, statisticians and clinical inspectors. In consideration of data safety, the unauthorized person cannot access and modify the data, and the data must be backed up.

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## 10. Appendixes

**Appendix I ECOG Scoring Criteria**

| Score | Performance Status |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction<br>(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 selfcare 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 selfcare, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40 points) |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair (Karnofsky 10-20 points) |

**Appendix II TNM Classification – International Lung Cancer Staging Standard (8th Edition)**

| Primary lesions (T staging) | |
|---|---|
| **Tx** | Size of primary tumor immeasurable; cancer cell in sputum/bronchial washings but tumor not be assessed in imaging or bronchoscopy. |
| **T0** | No evidence of tumor |
| **Tis** | Carcinoma in situ |
| **T1** | Primary tumors≤3 cm surrounded by lung/visceral pleura, not involving main bronchus (some rare superficial tumors limited to bronchial wall are classified as T1 regardless of size even if they involve the part above the main bronchus.) |
| **T1a mi** | Minimally invasive carcinoma |
| **T1a ss** | Superficial spreading tumor of any size, but limited in the airway wall or main bronchus |
| **T1a** | Maximum diameter of tumor ≤1cm |
| **T1b** | 1cm<maximum diameter of tumor≤2cm |
| **T1c** | 2cm<maximum diameter of tumor≤3cm |
| **T2** | 3cm<maximum diameter of tumor≤5cm， or involvement of main bronchus without carina (distance from carina≥2cm), or invasion visceral pleural, or atelectasis or post obstructive pneumonitis extending to hilum but not the whole lung. |
| **T2 Visc Pl** | invasion of visceral pleural * |
| **T2 Centr** | Invasion of main bronchus (excluding carina); obstructive pneumonia, partial or complete atelectasis *. |
| **T2a** | 3cm<maximum diameter of tumor≤4cm. |
| **T2b** | 4cm<maximum diameter of tumor≤5cm. |
| | *In the case of of 3cm<maximum diameter of tumor≤4cm, T2a；in the case of 4cm<maximum diameter of tumor≤5cm, T2b. |
| **T3** | 5cm<maximum diameter of tumor≤7cm, or directly invade one of the following: chest wall (including superior sulcus tumor of lung); diaphragm; phrenic nerve; mediastinal pleura; pericardium; or the tumor is located in the main bronchus <2 cm away from the carina, but the carina is not involved; causing atelectasis or obstructive pneumonia; satellite nodules appear in the same lobe of the primary tumor. |
| **T3** | 5cm<maximum diameter of tumor≤7cm |
| **T3 Inv** | Direct invasion of chest wall, phrenic nerve and pericardium. |
| **T3 Satell** | Solitary cancer nodule appears in the same lobe. |
| **T4** | 7 cm < maximum diameter of tumor; tumors of any size invade any of the following organs, including mediastinum, heart, large blood vessels, carina, recurrent laryngeal nerve, main trachea, esophagus, vertebral body and diaphragm; solitary cancer nodules in different lung lobes on the same side. |
| **T4** | 7cm<maximum diameter of tumor |
| **T4 Inv** | Regardless of size, invasion of specific organs. |
| **T4 Ipsi Nod** | Solitary cancer nodules in different lung lobes on the same side. |

| | | | |
|---|---|---|---|
| Regional lymphnode (N staging) | | | |
| **Nx** | Regional lymphnodes cannot be evaluated. | | |
| **No** | No regional lymph node metastasis. | | |
| **N1** | Metastasis to ipsilateral peribronchial lymphnodes and/or ipsilateral hilar lymphnodes, and primary tumor directly involving pulmonary lymphnodes. | | |
| **N2** | Metastasis to ipsilateral mediastinum and/or subtrochanteric lymph nodes. | | |
| **N3** | Metastasis to contralateral mediastinal lymphnodes, contralateral hilar lymphnodes, ipsilateral or contralateral scalene muscle lymphnodes, or supraclavicular lymphnodes. | | |
| Distant metastasis (M staging) | | | |
| **Mx** | It is impossible to evaluate whether there is any distant metastasis. | | |
| **M0** | No distant metastasis. | | |
| **M1** | Distant metastasis. | | |
| **M1a Pl Dissem** | Pleural dissemination (malignant pleural effusion, pericardial effusion or pleural nodule), pleural effusion of lung cancer is caused by tumor, and pleural effusion of a few patients is negative in multiple cytological examinations, neither bloody nor exudative. If it is believed that exudation has nothing to do with tumor based on various factors and clinical judgment, pleural effusion should not be included in staging factors. | | |
| **M1a Contr Nod** | Solitary cancer nodules appear in the contralateral lobe. | | |
| **M1b** | Distant single-organ metastasis. | | |
| **M1c** | Distant single-organ metastasis or multiple-organ metastases. | | |
| **Clinical stage** | | | |
| **Delitescence stage** | TX | N0 | M0 |
| **Stage 0** | Tis | N0 | M0 |
| **StageI A1** | T1a(mi) | N0 | M0 |
| | T1a | N0 | M0 |
| **Stage I A2** | T1b | N0 | M0 |
| **Stage I A3** | T1c | N0 | M0 |
| **Stage I B** | T2a | N0 | M0 |
| **Stage II A** | T2b | N0 | M0 |
| **Stage II B** | T1a-c | N1 | M0 |
| | T2a | N1 | M0 |
| | T2b | N1 | M0 |
| **Stage III A** | T1a-c | N2 | M0 |
| | T2a-b | N2 | M0 |
| | T3 | N1 | M0 |

| | | | |
|---|---|---|---|
| | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| **Stage III B** | T1a-c | N3 | M0 |
| | T2a-b | N3 | M0 |
| | T3 | N2 | M0 |
| | T4 | N2 | M0 |
| **Stage III C** | T3 | N3 | M0 |
| | T4 | N3 | M0 |
| **Stage IV A** | Any T | Any N | M1a |
| | Any T | Any N | M1b |
| **Stage IV B** | Any T | Any N | M1c |

**Appendix III NYHA Functional Classification**

| | **HYHA Functional Classification** |
|---|---|
| **Class I** | Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain. |
| **Class II** | Patients with cardiac disease resulting slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results fatigue, palpitation, dyspnea or anginal pain. |
| **Class III** | Patients with cardiac disease resulting in marked limitation of physical activity. There are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain. |
| **Class IV** | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases. |

**Appendix IV Common Terminology Criteria for Adverse Events of NCI (CTCAE v4.0)**

| Blood/Marrow | | | | | | |
|---|---|---|---|---|---|---|
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Bone marrow hypocellular | Bone marrow hypocellular | Mildly hypocellular or <=25% reduction from normal cellularity for age | Moderately hypocellular or >25-<=50% reduction from normal cellularity for age | Severely hypocellular or >50-<=75% reduction cellularity from normal for age | — | Death |
| CD4 Cell Count | CD4 Cell Count | <LLN-500/$mm^3$<br><LLN-0.5 $\times 10^9$/L | <500-200/ $mm^3$<br><0.5-0.2$\times 10^9$/L | <200-50/$mm^3$<br><0.2$\times$0.05-$10^9$/L | <50/$mm^3$<br><0.05$\times 10^9$/L | Death |
| Haptoglobin | Haptoglobin | <LLN | — | None | — | Death |
| hemoglobin | hemoglobin | <LLN-10.0g/dL<br><LLN-6.2mmol/L<br><LLN-100g/L | <10.0-8.0g/dL<br><6.2-4.9mmol/L<br><100-80g/L | <8.0-6.5g/dL<br><4.9-4.0mmol/L<br><80-65g/L | <6.5g/dL<br><4.0mmol/L<br><65g/L | Death |
| Hemolysis (e.g. immune hemolytic anemia, drug-induced hemolysis) | Hemolysis | Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin) | Evidence of hemolysis and >=2 gm decrease in hemoglobin. | Transfusion or medical intervention indicated (e.g., steroids) | Consequences caused by hemolysis (e.g. renal failure, hypotension, bronchospasm, emergency splenectomy) | Death |
| White blood cells (total WBC) | White blood cells | <LLN-3000/$mm^3$<br><LLN-3.0$\times 10^9$/L | <3000-2000/$mm^3$<br><3.0-2.0$\times 10^9$/L | <2000-1000/$mm^3$<br><2.0-1.0$\times 10^9$/L | <1000/$mm^3$<br><1.0$\times 10^9$/L | Death |
| Lymphocytopenia | Lymphocytopenia | <LLN-800/$mm^3$<br><LLN$\times$0.8-$10^9$/L | <800-500/$mm^3$<br><0.8-0.5$\times 10^9$/L | <500-200/$mm^3$<br><0.5-0.2$\times 10^9$/L | <200/$mm^3$<br><0.2$\times 10^9$/L | Death |
| Myelodysplasia | Myelodysplasia | — | — | Genetic variation of bone marrow cells (bone marrow bud cells < 5%) | RAEB or RAEB-T (bone marrow bud cells <5%) | Death |
| Neutrophil / granular cells (ANC/AGC) | Neutrophil | <LLN-1500/$mm^3$<br><LLN-1.5$\times 10^9$/L | <1500-1000/$mm^3$<br><1.5-1.0$\times 10^9$/L | <1000-500/$mm^3$<br><1.0-0.5$\times 10^9$/L | <500/$mm^3$<br><0.5$\times 10^9$/L | Death |
| Platelet | Platelet | <LLN-75,000/$mm^3$<br><LLN-75.0$\times 10^9$/L | <75,000-50,000/$mm^3$<br><75.0-50.0$\times 10^9$/L | <50,000-25,000/$mm^3$<br><50.0-25.0$\times 10^9$/L | <25,000/$mm^3$<br><25.0$\times 10^9$/L | Death |
| Splenic function | Splenic function | Incidental findings (e.g., HowellJolly bodies) | Prophylactic antibiotics indicated | — | Life-threatening | Death |
| Blood/bone marrow-other situations (specify, —) | Blood-other situations (specify) | Mild | Moderate | Severe | Life-threatening; disabling | Death |

| Arrhythmia | | | | | | |
|---|---|---|---|---|---|---|
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Conduction abnormality/atrioventricular heart block – select | Conduction abnormality – select | Asymptomic, intervention not indicated | Non-urgent medical intervention indicated | Incompletely controlled medically or controlled with device (e.g., pacemaker) | Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) | Death |
| Palpitations | Palpitations | Present | With associated symptoms (e.g., lightheadedness, shortness of breath) | — | — | — |
| Cardiac Arrhythmia – Other | Cardiac Arrhythmia | Mild | Moderate | Severe | Life-threatening; disabling | Death |
| Cardiac | | | | | | |
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Cardiac ischemia/infarction | Cardiac ischemia/infarction | Asymptomatic arterial narrowing without ischemia | Asymptomatic and testing suggesting ischemia; stable angina | Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated | Acute myocardial infarction | Death |
| Cardiac troponin T | cTnT | 0.03 – <0.05 ng/mL | 0.05 – <0.1 ng/mL | 0.1 – <0.2 ng/mL | 0.2 ng/mL | — |
| Hypertension | Hypertension | Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated | Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg from normal blood pressure at above condition; monotherapy may be indicated | Requiring more than one drug or more intensive therapy than previously | Life-threatening consequences (e.g., hypertensive crisis) | Death |
| Remark: There are different grading standards for pediatric patients, which are not involved in this study and are not listed here. | | | | | | |

| General | | | | | | |
|---|---|---|---|---|---|---|
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Fatigue (lethargy, malaise, asthenia) | Fatigue | Mild fatigue over baseline | Moderate or causing difficulty performing some ADL | Severe fatigue interfering with ADL | Disabling | — |
| Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x $10^9$/L) | Fever | 38.0-39.0°C<br>(100.4-102.2°F) | >39.0-40.0°C<br>(102.3-104.0°F) | >40.0°C<br>(>104.0°F)<br>≤24hrs | >40.0°C<br>(>104.0°F)<br>>24hrs | Death |
| Hypothermia | Hypothermia | — | 35->32°C<br>95->89.6°F | 32->28°C<br>89.6->82.4°F | ≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation) | Death |
| Insomnia | Insomnia | Occasional difficulty sleeping, not interfering with function | Difficulty sleeping, interfering with function but not interfering with ADL | Frequent difficulty sleeping, interfering with ADL | Disabling | — |
| REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia. | | | | | | |
| Rigors/chills | Rigors/chills | Mild | Moderate, narcotics indicated | Severe or prolonged, not responsive to narcotics | — | — |
| Sweating (diaphoresis) | Sweating | Mild and occasional | Frequent or drenching | — | — | — |
| Weight gain | Weight gain | 5 – <10% from baseline | 10 – <20% from baseline | ≥20% from baseline | — | Death |
| Weight loss | Weight loss | 5 to <10% from baseline; intervention not indicated | 10 – <20% from baseline; nutritional support indicated | ≥20% from baseline; tube feeding or TPN indicated | — | — |
| General Symptoms – Other (Specify, __) | General Symptoms – Other (Specify) | Mild | Moderate | Severe | Life-threatening; disabling | Death |

| Gastrointestinal | | | | | | |
|---|---|---|---|---|---|---|
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| NOTE: Abdominal pain or cramping is graded as Pain – Select in the PAIN CATEGORY. | | | | | | |
| Anorexia | Anorexia | Loss of appetite without alteration in eating habits | Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated | Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated | Life-threatening | Death |
| Constipation | Constipation | Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema | Persistent symptoms with regular use of laxatives or enemas indicated | Symptoms interfering with ADL; obstipation with manual evacuation indicated | Life-threatening (e.g., obstruction, toxic megacolon | Death |
| ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – Select. | | | | | | |
| Dehydration | Dehydration | Increased oral fluids indicated; dry mucous membranes; diminished skin turgor | IV fluids indicated <24 hrs | IV fluids indicated ≥ 24hrs | Life-threatening (e.g., hemodynamic collapse) | Death |
| ALSO CONSIDER: Diarrhea; Hypotension; Vomiting. | | | | | | |
| Diarrhea | Diarrhea | Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL | Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL | Life-threatening (e.g., hemodynamic collapse) | Death |
| REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea.<br>ALSO CONSIDER: Dehydration; Hypotension. | | | | | | |
| Distension | Distension | Asymptomatic | Symptomatic, but not interfering with GI function | Symptomatic, interfering with GI function | — | Death |
| ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – Select. | | | | | | |
| Flatulence | Flatulence | Mild | Moderate | — | — | — |
| Gastritis (including bile reflux gastritis) | Gastritis | Asymptomatic, radiographic or endoscopic findings only | Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs | Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs | Life-threatening ; operative intervention requiring complete organ resection (e.g., gastrectomy) | Death |
| ALSO CONSIDER: Hemorrhage, GI – Select; Ulcer, GI – Select. | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – Select in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY. | | | | | | |
| Heartburn/dyspepsia | Heartburn | Mild | Moderate | Severe | — | — |
| Mucositis/stomatitis (functional/symptomatic) | Mucositis (functional/ symptomatic) – Select | Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function | Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL | Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL | Symptoms associated with life-threatening consequences | Death |
| Nausea | Nausea | Loss of appetite without alteration in eating habits | Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs | Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs | Life-threatening consequences | Death |
| Vomiting | Vomiting | 1 episode in 24 hrs | 2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs | ≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs | Life-threatening | Death |
| Hepatic | | | | | | |
| Alkaline phosphatase | WNL | >ULN ~ 2.5×ULN | >2.5×ULN ~ 5.0×ULN | >5.0×ULN ~ 20.0×ULN | >20.0×ULN | |
| Bilirubin | WNL | >ULN ~ 1.5×ULN | >1.5×ULN ~ 3.0×ULN | >3.0×ULN ~ 10.0×ULN | >10.0×ULN | |
| GGT (γ-Glutamyl transpeptidase) | WNL | >ULN ~ 2.5×ULN | >2.5×ULN ~ 5.0×ULN | >5.0×ULN ~ 20.0×ULN | >20.0×ULN | |
| Liver enlargement | Absent | - | - | Present | - | |
| | Note: Grading should only be performed when liver enlargement is caused by treatment-related adverse reactions, including venous occlusion diseases. | | | | | |
| Hypoalbuminemia | WNL | <LLN ~ 3 g/dL | ≥2 ~ <3 g/dL | <2 g/dL | - | |
| Liver dysfunction/ Liver failure (clinical) | Normal | - | - | Asterixis | Encephalopathy or coma | |
| Portal vein blood flow | Normal | - | Decreased | Portal vein countercurrent | - | |
| SGOT (AST) (serum glutamic oxaloacetic transaminase) | WNL | >ULN ~ 2.5×ULN | >2.5×ULN ~ 5.0×ULN | >5.0×ULN ~ 20.0×ULN | >20.0×ULN | |
| SGPT (ALT) (serum glutamic pyruvic transaminase) | WNL | >ULN ~ 2.5×ULN | >2.5×ULN ~ 5.0×ULN | >5.0×ULN ~ 20.0×ULN | >20.0×ULN | |
| Hepatic – Other (Specify, ___) | Absent | Mild | Moderate | Severe | Life-threatening or disabling | |

| Neurology | | | | | | |
|---|---|---|---|---|---|---|
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Apnea | Apnea | — | — | Present | Intubation indicated | Death |
| ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10 9/L); Infection – Select; Pain – Select; Vomiting | | | | | | |
| Ataxia (incoordination) | Ataxia | Asymptomatic | Symptomatic, not interfering interfering with ADL | Symptomatic, interfering with ADL; mechanical assistance indicated | Disabling | Death |
| REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention. | | | | | | |
| Dizziness | Dizziness | With head movements or nystagmus only; not interfering with function | Interfering with function, but not interfering with ADL | Interfering with ADL | Disabling | Death |
| Memory impairment | Memory impairment | Memory impairment not interfering with function | Memory impairment interfering with function, but not interfering with ADL | Memory impairment interfering with ADL | Amnesia | — |
| Mood alteration —Select:<br>—Agitation<br>—Anxiety<br>—Depression | Mood alteration —Select: | Mild mood alteration not interfering with function | Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated | Severe mood alteration interfering with ADL | Suicidal ideation; danger to self or others | Death |
| Personality/behavioral | Personality | Change, but not adversely affecting patient or family | Change, adversely affecting patient or family | Mental health intervention indicated | Change harmful to others or self; hospitalization indicated | Death |
| Psychosis (hallucinations/ delusions) | Psychosis | — | Transient episode | Interfering with ADL; medication, supervision or restraints indicated | Harmful to others or self; life-threatening | Death |
| Neuropathy: sensory | Neuropathy-sensory | Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function | Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL | Sensory alteration or paresthesia interfering with ADL | Disabling | Death |
| Somnolence/depressed level of consciousness | Somnolence | — | Somnolence or sedation interfering with function, but not interfering with ADL | Obtundation or stupor; difficult to arouse; interfering with ADL | Coma | Death |
| Pain | | | | | | |
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Pain – Select: 'Select ' AEs appear at the end of the CATEGORY. | Pain – Select: | Mild pain not interfering with function | Moderate pain; pain or analgesics interfering with function, but not interfering with ADL | Severe pain; pain or analgesics severely interfering with ADL | Disabling | Death |
| Pain – Other (Specify, __) | Pain – Other (Specify) | Mild pain not interfering with function | Moderate pain; pain or analgesics interfering with function, but not interfering with ADL | Severe pain; pain or analgesics severely interfering with ADL | Disabling | Death |

| Hemorrhage/Bleeding | | | | | | |
|---|---|---|---|---|---|---|
| Coagulation-related | | | | | | |
| | | Grade | | | | |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Human Fibrinogen | Human Fibrinogen | <1.0 – 0.75 x LLN or <25% decrease from baseline | <0.75 – 0.5 x LLN or 25 – <50% decrease from baseline | <0.5 – 0.25 x LLN or 50 – <75% decrease from baseline | <0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL | Death |
| INR | INR | >1-1.5×ULN | >1.5-2×ULN | >2×ULN | — | — |
| PTT | PTT | >1-1.5×ULN | >1.5-2×ULN | >2×ULN | — | — |
| Adverse Event | Short Name | 1 | 2 | 3 | 4 | 5 |
| Hemorrhage/Bleeding | Hemorrhage | Mild without transfusion | — | Transfusion indicated | Massive bleeding, requiring major intervention | Death |