PROTOCOL

Study Number: YH25448-301

Protocol Title: A Phase III, Randomized, Double-blind Study to Assess the Efficacy and Safety of Lazertinib versus Gefitinib as the First-line Treatment in Patients with Epidermal Growth Factor Receptor Sensitizing Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Short Title: Lazertinib vs Gefitinib as First-Line Treatment in Patients with EGFRm+ Locally Advanced or Metastatic NSCLC (LASER301)

Investigational Product:	**Lazertinib**
Phase:	**III**
Protocol Version:	**2**
Date:	**03Sep2020**

YUHAN

SIGNATURE PAGE

SPONSOR SIGNATORY

YUHAN Corporation

Printed Name:

Title:

Signature:

Date:

PPD

INVESTIGATOR SIGNATORY

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Printed Name: _____

Title: _____

Signature: _____

Date: _____

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Ver1	18Oct2019	Not Applicable
Ver2	03Sep2020	• Added the exclusion criteria related to prior/concomitant therapy • Changed the exclusion criteria for brain metastases, the criteria for restart study treatment and the allowed window for PK blood samples at pre-dose • Removed the measurement of metabolite YH26334 • Others including word correction etc.

SYNOPSIS

TITLE OF STUDY: A Phase III, Randomized, Double-blind Study to Assess the Efficacy and Safety of Lazertinib versus Gefitinib as the First-line Treatment in Patients with Epidermal Growth Factor Receptor Sensitizing Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

SPONSOR : Yuhan Corporation (74, Noryangjin-ro, Dongjak-gu, Seoul, Republic of Korea)

PHASE OF DEVELOPMENT: Phase III

OBJECTIVES:

Primary Objective	Endpoint
To assess the efficacy of lazertinib compared with gefitinib as measured by progression-free survival (PFS).	PFS according to RECIST v1.1 by Investigator assessment.
Secondary Objectives	**Endpoints**
To further assess the efficacy of lazertinib compared with gefitinib.	• Objective Response Rate (ORR) • Duration of Response (DoR) • Disease Control Rate (DCR) • Depth of Response • Time to Response All according to RECIST v1.1 by Investigator assessments.
To assess overall survival of lazertinib compared with gefitinib.	• Overall survival (OS)
To characterize the pharmacokinetics (PK) of lazertinib.	• Plasma concentrations of lazertinib at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose • Cerebrospinal fluid (CSF) concentrations of lazertinib
To assess the impact of lazertinib compared with gefitinib on patient's disease-related symptoms and Health Related Quality of Life (HRQoL).	Change from baseline in : • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30) • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13) • Euro-Quality of Life-5 Dimension-5 level (EQ-5D-5L)
Safety Objectives	**Endpoints**
To assess the safety and tolerability profile of lazertinib compared with gefitinib.	• Adverse events graded by Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 • Clinical chemistry, hematology, and urinalysis

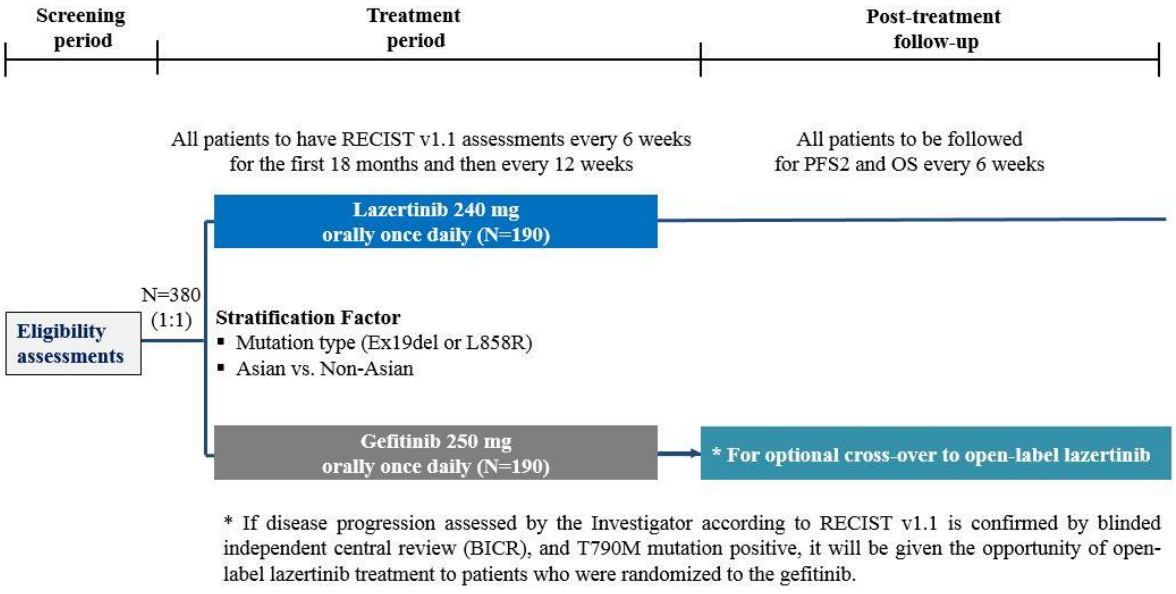
	• Vital signs (pulse, blood pressure, body temperature), physical examination, body weight • Electrocardiogram (ECG) • Left Ventricular Ejection Fraction (LVEF) • World Health Organization (WHO) Performance Status • Ophthalmologic assessment
Exploratory Objectives	**Endpoints**
CCI	CCI
CCI	CCI
	CCI
CCI	CCI
	CCI
	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

CCI	CCI
CCI	CCI

NUMBER OF PATIENTS : Approximately 380 patients

METHODOLOGY:

This study is a randomized, double-blind, multinational phase III to assess the efficacy and safety of lazertinib 240 mg administered once daily orally compared with gefitinib 250 mg administered once daily orally in treatment-naïve patients with EGFR mutation positive (exon 19-deletion [Ex19del] or exon 21 [L858R] substitution), locally advanced or metastatic non-small cell lung cancer (NSCLC).



At screening period, up to 28 days prior to randomization, patients will be assessed for eligibility. Approximately 380 patients will be randomized in a 1:1 ratio to either lazertinib (n=190) or gefitinib (n= 190). Randomization will be stratified by race (Asian vs. non-Asian) and mutation status (Ex19del vs. L858R).

Eligible patients will be administered an investigational product (IP) orally once daily with or without food. A cycle of treatment is defined as 21 days. Patients should continue on their randomized treatment until RECIST v1.1 defined progression or until a treatment discontinuation criterion is met. However, patients may continue to receive their randomized

treatment beyond RECIST v1.1 defined progression as long as patients continue to show clinical benefit, as judged by the investigator.

Efficacy assessments according to RECIST v1.1 are to be performed every 6 weeks for the first 18 months and then every 12 weeks relative to date of randomization using the RECIST v1.1 until objective disease progression. Patients will be followed for survival every 6 weeks following objective disease progression.

Adverse events (AEs) are graded according to National Cancer Institute (NCI) CTCAE v5.0.

For patients who cannot tolerate the protocol-specified dosing schedule due to drug related toxicities, dose interruptions and/or reductions are recommended in order to allow patients to continue the treatment. If, due to study treatment related toxicity, a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment.

Patients who were randomized to the gefitinib arm will have the option to receive treatment with open-label lazertinib 240 mg following objective disease progression according to RECIST v1.1, as per BICR, and a T790M mutation positive result. Determination of T790M mutation positive status may be performed locally, or centrally for those patients unable to be tested locally (plasma or tissue testing).

SAMPLE SIZE DETERMINATION:

To provide 90% power at a two-sided 5% significant level, approximately 207 progression-free survival events will be required to detect a hazard ratio of 0.64 (for median PFS of 16.5 months in lazertinib and 10.5 months in gefitinib). The primary analysis is expected to conduct at around 27 months, assuming approximately 380 patients are randomized over a period of 18 months.

CRITERIA FOR INCLUSION/EXCLUSION

Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male or female patients must be ≥ 18 years of age and satisfy the legal age of consent in the jurisdiction in which the study is being conducted.

Type of Patient and Disease Characteristics

2. Patients with pathologically confirmed adenocarcinoma of the lung (e.g., this may occur as systemic recurrence after prior surgery for early stage disease or patients may be newly diagnosed with Stage IIIB/C or IV disease). Patients with mixed histology are eligible if adenocarcinoma is the predominant histology.
3. Patients with locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.
4. Patients with at least 1 of the 2 common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, assessed in tissue biopsy by an accredited local laboratory based on the Qiagen- Therascreen® EGFR Mutation Detection Kit RGQ (Scorpions ARMS), the

Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit, the PANAGENE-PANAMutyper™ or the Roche Diagnostics-Cobas® EGFR Mutation Test v2, or by central testing in a designated laboratory.

5. Mandatory provision of an unstained, archived tumor tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status for patients.
6. Patients must be treatment-naïve for locally advanced or metastatic NSCLC. (Note: Prior adjuvant and neo-adjuvant therapy (e.g., chemotherapy, radiotherapy, investigational products) for early stage disease is permitted if completed > 12 months prior to randomization provided all other entry criteria are satisfied)
7. Patients must have a WHO performance status score of 0 to 1 with no clinically significant deterioration over the previous 2 weeks before randomization.
8. Patients must have at least 1 measurable lesion, not previously irradiated and not chosen for biopsy during the study Screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), and which is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumor assessment scans are done at least 2 weeks after the screening biopsy is performed.

Male Patients

9. A male patient who has not undergone a vasectomy must agree to follow the contraceptive guidance in Appendix 3 of this protocol during the study treatment period and for at least 24 weeks after the last dose of study treatment and refrain from donating sperm during this period.

Female Patients

10. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP) as defined in Appendix 3.

    OR

    - A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 from the time of screening until 24 weeks after the last dose of study treatment.
    - A WOCBP must have a negative serum pregnancy test (beta human chorionic gonadotropin) at screening.

Informed Consent

11. Patient must sign an informed consent form (ICF) prior to any study specific procedures which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Symptomatic and unstable brain metastases. Patients with asymptomatic and stable brain metastases may participate in this study. If treatment is required, these patients must have completed any planned radiation therapy and/or surgery, are not on steroids, for >2

weeks prior to randomization, and remain asymptomatic. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system (CNS) imaging.

2. Leptomeningeal metastases
3. Symptomatic spinal cord compression. If steroid treatment is not required within at least 2 weeks prior to randomization then the patient may be enrolled.
4. History of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
5. Any medical conditions requiring chronic continuous oxygen therapy.
6. History of any malignancy other than the disease under study within 3 years before randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the medical monitor, is considered cured, or with minimal risk of recurrence within a year from screening).
7. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the study, or which would jeopardize compliance with the protocol.
8. Any cardiovascular disease as follows:
   - History of symptomatic chronic heart failure or serious cardiac arrhythmia requiring active treatment.
   - History of myocardial infarction or unstable angina within 24 weeks of randomization.
9. Positive hepatitis B (HBV) surface antigen (HBsAg), Positive hepatitis C antibody (anti-HCV), other clinically active infectious liver disease or confirmed positive human immunodeficiency virus test results. (Note: Patients with a prior history of HCV, who have completed antiviral treatment and have subsequently documented HCV RNA below the lower limit of quantification per local testing are eligible.)
10. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of study treatment.
11. History of hypersensitivity to active or inactive excipients of investigational product(s), or drugs with a similar chemical structure or class to investigational product(s).

[redacted] CCI

13. Clinically significant chronic infection or significant medical or psychiatric illness.
14. Undergone a bone marrow or solid organ transplant.
15. Any condition which would prevent patient compliance with study procedures, restrictions, and requirements, as determined by the Investigator.

Prior/Concomitant Therapy

16. Prior treatment with any systemic antineoplastic therapy for locally advanced or metastatic NSCLC (Stage IIIB/C or Stage IV) including chemotherapy, biological therapy, immunotherapy, or any investigational drug.

17. Any prior treatment with an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI).
18. Major surgery (excluding placement of vascular access) within 4 weeks of randomization.
19. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomization.
20. Patients currently receiving (or unable to stop use for an appropriate washout period prior to randomization) medications or herbal supplements known to be potent CYP3A4 inhibitors or inducers (Appendix 6).
21. Patients currently receiving the unstable doses of warfarin as an anticoagulant.
22. Patients who have been treated with alternative anti-cancer treatment within 5 half-lives of the treatment or within 4 weeks (whichever is longer) prior to randomization.
23. Any unresolved toxicities from prior therapy, greater than CTCAE grade 1 at randomization, with the exception of alopecia and grade 2, prior chemotherapy-induced neuropathy.

Prior/Concurrent Clinical Study Experience

24. Patients who have been treated with an investigational drug within 5 half-lives of the compound or within 4 weeks (whichever is longer) prior to randomization.

Diagnostic Assessments

25. Patient has any of following cardiac criteria:
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250msec).
    - Mean resting QTc >470 msec obtained from 3 electrocardiograms (ECGs), using the screening ECG machine derived QTc value.
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medications known to prolong QT interval or induce Torsades de Pointes (Appendix 6).
    - Left ventricular ejection fraction <50%
26. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count <1.5 x 10^9/L.
    - Platelet count <100 x 10^9/L.
    - Hemoglobin <90 g/L.
    - Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases, or >5x ULN in presence of liver metastases.
    - Aspartate aminotransferase >2.5x ULN if no demonstrable liver metastases or >5x ULN in the presence of liver metastases.
    - Total bilirubin >1.5x ULN if no liver metastases or >3x ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases.

- Serum creatinine >1.5x ULN concurrent with creatinine clearance < 50 ml/min measured by the study site's standard method (e.g., Cockcroft and Gault equation). Confirmation of creatinine clearance is only required when creatinine is >1.5x ULN.

TREATMENTS:

Investigational products (IPs):

Treatment	Formulation	Dose	Route of administration
Lazertinib	Tablet	240 mg (80 mg x 3 tablets) 160 mg (80 mg x 2 tablets)	Oral
Gefitinib	Capsule[a,b]	250 mg	Oral
Lazertinib-matching placebo	Tablet	Not applicable	Oral
Gefitinib-matching placebo	Capsule[b]	Not applicable	Oral

[a] Gefitinib tablet is over encapsulated.
[b] Appearance of all capsules used for encapsulation is identical.

STATISTICAL METHODS:

The analyses of data will be based on different analysis population according to the purpose of the analyses. Analysis populations are described below:

- Full analysis set (FAS): All randomized patients. The FAS will be the primary analysis set for all efficacy analyses.
- Safety analysis set: All patients who received at least one dose of study treatment
- Pharmacokinetic analysis set: Patients who have at least 1 measurable concentration collected post-dose, supported by the relevant date and time of sample collection; and the relevant dosing date and time on the day of PK sampling and immediately before pre-dose PK sampling.

Efficacy:

Primary Efficacy Analysis:

Progression free survival (PFS)

PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) whichever comes first based on investigator assessment using RECIST v1.1. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

PFS in the FAS will be analyzed using a log rank test stratified by mutation type (Ex19del versus L858R) and race (Asian versus non-Asian) using the Breslow approach for handling ties. PFS will be displayed using Kaplan-Meier plot by treatment group. The number of events, medians and 95% confidence intervals of the medians (calculated from the Kaplan-Meier estimate), and proportion of patients without an event at 12, 18 and 24 months will be summarized for each treatment group. Additionally, the hazard ratio for PFS will be

calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

Secondary Efficacy Analysis:

Objective response rate (ORR)

ORR is defined as the percentage of patients with measurable disease with at least one visit response of complete response (CR) or partial response (PR).

ORR will be analyzed using a logistic regression stratified by mutation type (Ex19del versus L858R) and race (Asian versus non-Asian). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence interval.

Duration of Response (DoR)

DoR is defined as the time from the date of first documented response until the date of documented progression or death whichever comes first.

DoR in responding patients will be summarized and the number of responding patients with a duration of response (>6; >9; >12; >15 months) will be presented by treatment group. A Kaplan-Meier plot and median DoR with 95% CI (calculated from the Kaplan-Meier estimate) will be presented by treatment group. DoR will be analyzed using the same method as the analysis of PFS.

Disease control rate (DCR)

DCR is defined as the percentage of patients who have a best overall response of CR or PR or stable disease (SD).

DCR will be analyzed using the same method as the analysis of ORR.

Depth of response

Depth of response will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of target lesions in the absence of new lesions or progression of non-target lesions compared to baseline. The absolute change and percentage change from baseline in the sum of tumor size at each assessment will be calculated.

The effect of lazertinib on best percentage change in tumor size will be estimated from an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline sum of target lesion diameter as a covariate. The number of patients, unadjusted mean, and least square means for each treatment group will be presented, together with the difference in least squares means, 95% CI and corresponding p-value.

Time to response (TTR)

TTR is defined as the time from the date of randomization until the date of first documented response. A summary statistics will be produced for TTR, by treatment group.

Overall survival (OS)

OS is defined as the time from the date of randomization until the date of death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

OS will be analyzed using the same methodology and model as for the analysis of PFS provided there are sufficient events available for a meaningful analysis (>20 deaths. if not,

descriptive summaries will be provided). As appropriate, summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be presented for each treatment group.

The final analysis of OS will be performed after approximately 45 months survival follow-up from the first patient randomized. Approximately 200 deaths will be anticipated at this time.

HRQoL (Patient Reports Outcomes)

The following variables will be summarized as appropriate and further details will be provided in the statistical analysis plan:

- EORTC QLQ-C30
- EORTC QLQ-LC13
- EQ-5D-5L

Safety:

Safety analysis: All patients who receive at least one dose of IP will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

The safety parameters are AEs, clinical laboratory parameters, vital signs, ECG parameters and physical examination. For each safety parameter, the last non-missing safety assessment made before the date of the first administration of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients, mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency distribution (number and percentage of patients).

All adverse events will be standardized by systemic organ class and preferred term and summarized by each treatment group. Serious adverse events and adverse events with a causal relationship to the study treatment will be described for each treatment group. ECGs, vital signs, physical examinations and clinical laboratory test results at each observed time point will be summarized and listed by each treatment group.

Pharmacokinetics:

Plasma concentrations of lazertinib will be summarized by nominal sampling time. CSF concentrations of lazertinib will also be summarized. The summary statistics will be presented by number of patients, arithmetic mean, standard deviation, arithmetic coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION AND STUDY RATIONALE

1.1. INTRODUCTION

Lung cancer is a leading cause of cancer death worldwide, causing 1.4 million deaths annually ([1]Torre et al, 2015). The discovery of somatic sensitizing epidermal growth factor receptor (EGFR) gene mutations such as exon 19-deletion [Ex19del] or exon 21 [L858R] substitution as targets for tyrosine kinase inhibitors (TKIs) has changed the paradigm of care for advanced non-small cell lung cancer (NSCLC) patients. Based on superior efficacy compared to chemotherapy, first and second generation EGFR TKIs such as erlotinib, gefitinib, afatinib, or dacomitinib are approved for their use in first-line settings for patients with advanced NSCLC harboring sensitizing EGFR mutations. However, patients with advanced NSCLC treated with first and second generation EGFR TKIs invariably develop acquired resistance. The most common mechanism of acquired resistance is a threonine-to-methionine substitution (T790M) secondary mutation at exon 20 in EGFR which develops in 50-60% of treated patients ([2]Pao W et al, 2010; [3]Gazdar AF et al, 2009). This led to the development of third generation EGFR TKIs such as osimertinib, rociletinib, and olmutinib that are specifically designed to target T790M and EGFR TKI sensitizing mutations with more selectivity over the wild type form ([4]Juchum M et al, 2015; [5]Engel J et al, 2016). Recently, osimertinib showed also a significant longer progression-free survival (PFS) compared to standard EGFR-TKI (gefitinib or erlotinib) as first-line treatment in NSCLC patients with EGFR mutations ([6]Soria JC et al, 2018).

In addition, approximately half of patients with EGFR-mutated NSCLC develop brain metastasis (BM) within 3 years of diagnosis. Currently available EGFR TKIs show limited efficacy for the treatment of BM. The hypothesis behind this phenomenon is that due to limited blood-brain barrier (BBB) penetration of first and second generation TKIs, these drugs can neither effectively treat central nervous system (CNS) metastases nor prevent development of CNS metastases ([7]Engel J et al, 2015; [8]Rangachari D et al, 2015).

Lazertinib (YH25448) is an oral, highly potent, mutant-selective and irreversible EGFR TKI that targets both the T790M mutation and activating EGFR mutations while sparing wild type-EGFR. In addition, nonclinical data suggest that lazertinib may be capable of crossing the blood brain barrier and potentially may offer better exposure in this anatomically protected location. Lazertinib will provide clinical benefit to the NSCLC patients with either activating EGFR mutations or T790M mutation based on the non-clinical and clinical results of lazertinib. This phase 3 study is designed to evaluate the efficacy and safety of lazertinib as first-line treatment in locally advanced or metastatic NSCLC patients with EGFR mutations.

1.2. SUMMRY OF NONCLINICAL STUDIES

Lazertinib selectively inhibits EGFR single- or double-mutant kinase activity compared to wild type-EGFR. IC50 of lazertinib was CCI for L858R/T790M, CCI for Ex19del, and CCI CCI for wild type EGFR. In cell proliferation assays, GI50 values for lazertinib were CCI for H1975 cells (L858R/T790M), CCI for PC9 (Ex19del) cells, and CCI for wild type H2073 cells, demonstrating potent and selective activity. Lazertinib inhibited human tumor growth in multiple xenograft mouse models, with more potent activity in models with EGFR mutations compared to models with wild-type EGFR. In a brain metastasis model, in which H1975 cells were implanted into brain parenchyma of nude mice, lazertinib achieved significant, complete tumor growth inhibition. Dose-dependent inhibition of phosphorylated-EGFR (p-EGFR)

expression in both subcutaneous and intracranial tumor tissue by lazertinib treatment was well translated into in vivo efficacy. The subcutaneous tumor to plasma $AUC_{0\text{-last}}$ ratio of lazertinib was CCI indicating high tumor distribution. Lazertinib achieved cerebrospinal fluid (CSF) concentrations exceeding the IC_{50} value for p-EGFR inhibition in vitro. Lazertinib exhibited high BBB penetration and excellent therapeutic efficacy against both primary lung tumors and brain metastases in a T790M mutant NSCLC xenograft model.

In both rat and dog toxicology studies almost all observations and findings were consistent with consequences of the pharmacological inhibition of EGFR by lazertinib or sequelae secondary to primary effects. A wide range of organs and tissues containing epithelial cell lineages were affected with changes spanning from mild epithelial atrophy to degenerative erosions, inflammation and necrosis.

Further details for non-clinical study results are provided in the investigator brochure (IB).

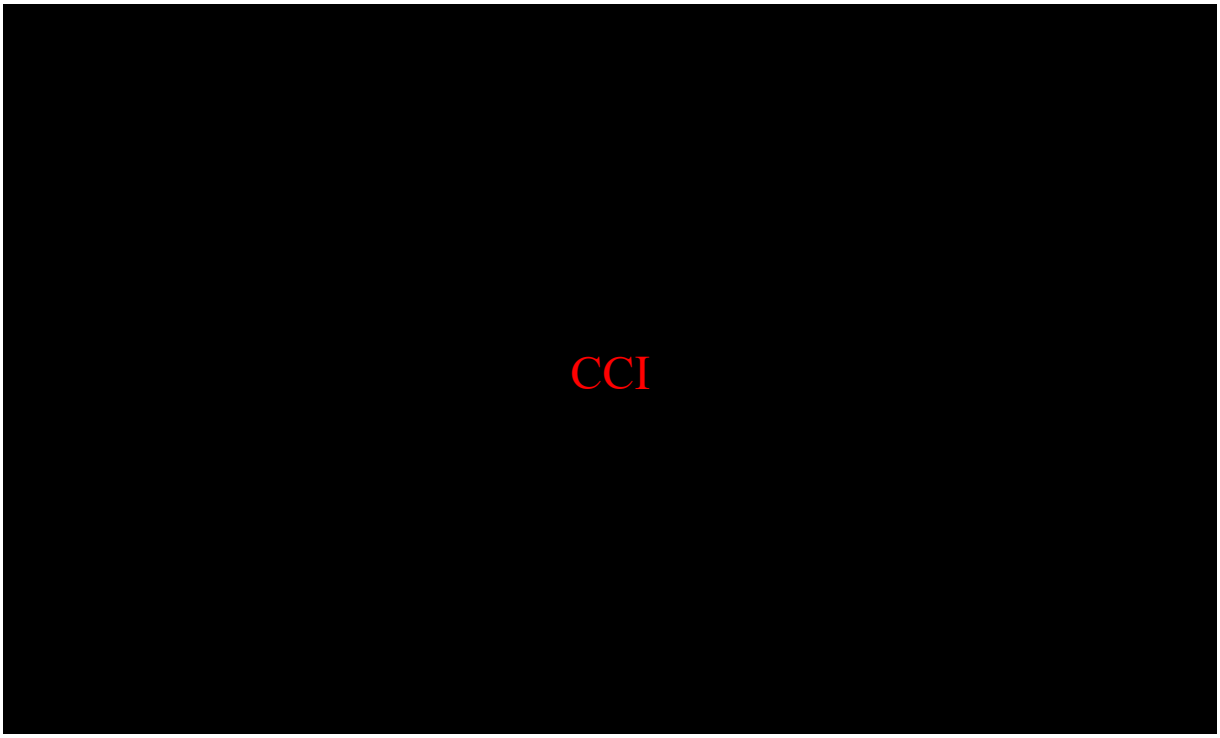
1.3. SUMMARY OF CLINICAL STUDIES

A phase 1/2 study of lazertinib in patients with EGFRm+ advanced NSCLC who had progressed following prior EGFR TKI treatments therapy is ongoing (Study YH25448-201/ 73841937NSC2001). A total of 127 patients were enrolled as of 26 Nov, 2018. Systemic exposure of lazertinib increased in a near dose-proportional manner over the dose range of 20 to 320 mg. At steady state after multiple doses of 20 to 320 mg once daily, the systemic exposure of major metabolite YH26334 was 2 to 4% of the systemic exposure of lazertinib. The confirmed objective response rate (ORR) was 54% across all dose levels by independent central review (ICR) assessment. The ORR for the T790M-positive patients was 57%, and for the T790M-negative patients, ORR was 37%. In patients with measurable brain metastasis at baseline (n=18), the intracranial ORR was 44% across all dose levels. In the overall population, the median duration of objective response was 15.2 months and the median PFS was 9.5 months across all dose levels by ICR assessment. The median PFS was 9.7 months in patients with T790M-positive tumors and 5.4 months in patients with T790M-negative tumors. In patients with T790M-positive tumors who received doses of 120 mg or above, the ORR was 60% and median PFS was 12.3 months according to ICR assessment. There were no dose-limiting toxicities (DLT) up to 320 mg. The most common drug-related adverse events were pruritus (25% of patients), rash (22%), diarrhea (10%), constipation (9%), decreased appetite (9%) and nausea (9%). Drug-related serious treatment-emergent adverse events (TEAEs) were reported in 6 (5%) patients ([9]Ahn MJ et al, 2019)

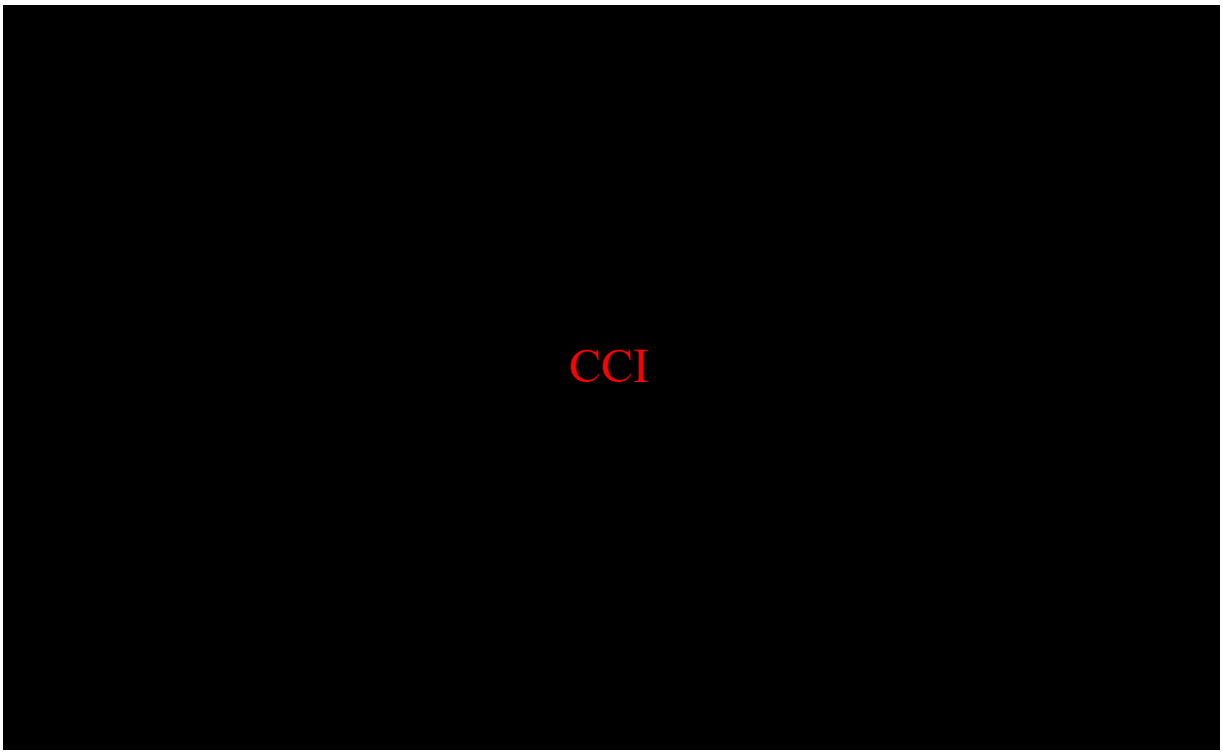
An open-label, single-dose, 2-group, 2-period, single-sequence cross-over study (Study YH25448-101) was performed with CCI Korean and CCI Caucasian healthy volunteers to evaluate the effects of ethnicity and food on PK profile of lazertinib. Results demonstrated that the effect of food was not significant on the systemic exposure of lazertinib, and the systemic exposure of lazertinib in Caucasian subjects was about CCI of Koreans subjects irrespective of food intake. The systemic exposure of YH26334 was CCI of the systemic exposure of lazertinib irrespective of ethnicity and food ingestion. There was no significant difference in safety between Caucasian and Korean subjects.

The details for clinical study results are provided in the IB.

1.4. STUDY RATIONALE



1.5. DOSE SELECTION RATIONALE



1.6. OVERALL RISK/BENEFIT ASSESSMENT

1.6.1. Potential Benefit

CCI

Table 1. Summary of Preliminary Tumor Response (Independent Central Review) from study YH25448-201/ 73841937NSC2001

CCI

1.6.2. Potential Risks

CCI

1.6.3. Overall Benefit-Risk and Ethical Assessment

CCI

CCI

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoint
To assess the efficacy of lazertinib compared with gefitinib as measured by progression-free survival (PFS).	PFS according to RECIST v1.1 by Investigator assessment
Secondary Objectives	**Endpoints**
To further assess the efficacy of lazertinib compared with gefitinib.	• Objective Response Rate (ORR) • Duration of Response (DoR) • Disease Control Rate (DCR) • Depth of Response • Time to Response All according to RECIST v1.1 by Investigator assessments.
To assess overall survival of lazertinib compared with gefitinib	• Overall survival (OS)
To characterize the pharmacokinetics (PK) of lazertinib.	• Plasma concentrations of lazertinib at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose • Cerebrospinal fluid (CSF) concentrations of lazertinib
To assess the impact of lazertinib compared with gefitinib on patient's disease-related symptoms and Health Related Quality of Life (HRQoL).	Change from baseline in : • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30) • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13) • Euro-Quality of Life-5 Dimension-5 level (EQ-5D-5L)
Safety Objectives	**Endpoints**
To assess the safety and tolerability profile of lazertinib compared with gefitinib.	• Adverse events graded by Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 • Clinical chemistry, hematology, and urinalysis • Vital signs (pulse, blood pressure, body temperature), physical examination, body weight • Electrocardiogram (ECG)

	• Left Ventricular Ejection Fraction (LVEF) • World Health Organization (WHO) Performance Status • Ophthalmologic assessment
Exploratory Objectives	**Endpoints**
CCI	CCI
CCI	CCI
	CCI
CCI	CCI
CCI	CCI
	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

CCI	CCI

3. ETHICS

3.1. INDEPENDENT ETHIC COMMITTEES / INSTITUTIONAL REVIEW BOARD

The protocol, protocol amendments, ICF, investigator brochure (IB), and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator, or on the Investigators behalf, and reviewed and approved by the IRB/IEC before the study is initiated. A detailed instruction is provided in Appendix 1.

3.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the protocol, consensus ethical principles (e.g., Declaration of Helsinki), guidelines (e.g., ICH GCP), applicable laws, and regulations. A detailed instruction is provided in Appendix 1.

3.3. PATIENT INFORMATION AND CONSENT

Freely given written informed consent must be obtained from every patient (or in situations where consent cannot be given by patients, their legally acceptable representative) prior to clinical study participation. A detailed instruction is provided in Appendix 1.

4. INVESTIGATIONAL PLAN

4.1. STUDY DESIGN

4.1.1. Overall Design

This study is a randomized, double-blind, multinational phase III to assess the efficacy and safety of lazertinib 240 mg administered once daily orally compared with gefitinib 250 mg administered once daily orally in treatment-naïve patients with EGFR mutations (Ex19del or L858R substitution), locally advanced or metastatic NSCLC.

During screening, a period up to 28 days prior to randomization, patients will be assessed for eligibility. Patients will be enrolled based on either a locally available EGFR mutation result, which has been performed in an accredited local laboratory based on the Qiagen-Therascreen® EGFR Mutation Detection Kit RGQ (Scorpions ARMS), the Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit, the PANAGENE-PANAMutyper™ or the Roche Diagnotics-Cobas® EGFR Mutation Test v2, or by testing performed at a designated central laboratory. All patients who are enrolled based on locally available EGFR mutation results, will be required to provide biopsy tissue and blood for central testing of the two most common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del and L858R).

Approximately 380 patients will be randomized in a 1:1 ratio to either lazertinib (n=190) or gefitinib (n= 190). Randomization will be stratified by race (Asian vs. non-Asian) and mutation

status (Ex19del vs. L858R).

Eligible patients will be administered an investigational product (IP) orally once daily with or without food. A cycle of treatment is defined as 21 days. Patients should continue on their randomized treatment until RECIST version 1.1 (v1.1) defined progression or until a treatment discontinuation criterion is met. However, patients may continue to receive their randomized treatment beyond RECIST v1.1 defined progression as long as patients continue to show clinical benefit, as judged by the investigator.

Efficacy assessments according to RECIST v1.1 are to be performed every 6 weeks for the first 18 months and then every 12 weeks relative to date of randomization using the RECIST v1.1 until objective progression. Patients will be followed for survival every 6 weeks following objective disease progression.

Adverse events (AEs) are graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

For patients who cannot tolerate the protocol-specified dosing schedule due to drug related toxicities, dose interruptions and/or reductions are recommended in order to allow patients to continue the treatment. If, due to study treatment related toxicity, a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose, then the patients must be discontinued from the study treatment.

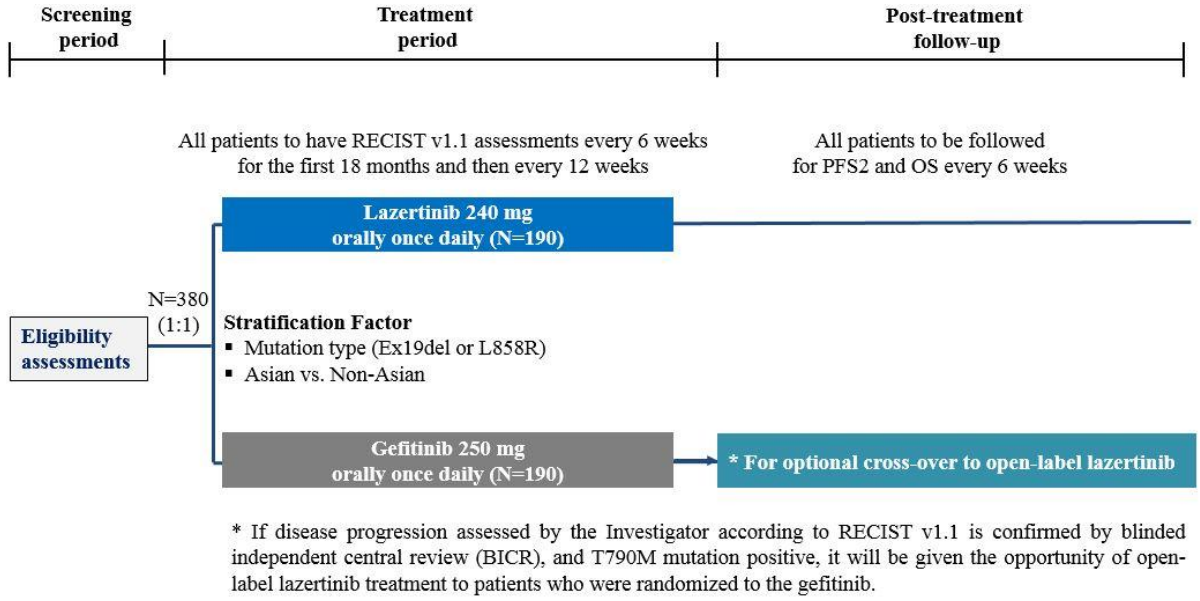
Patients who were randomized to the gefitinib arm may have the option to receive open-label lazertinib following objective disease progression according to RECIST v1.1, as per investigator assessment, provided ALL the following criteria are met, and should the patient wish to do-so:

- Disease progression confirmed by blinded independent central review (BICR) which must be established prior to a patient being unblinded. (Note: if disease progression is not centrally confirmed, the patient is not eligible to be considered for cross-over. Should it be in the patients best interests, they may continue to receive randomized treatment and submit the next scan for central imaging review according to the study schedule.)
- Tumor confirmed as T790M mutation positive by means of plasma or tissue testing (local or central) following disease progression which must be established prior to a patient being unblinded.
- The patient cannot cross-over if they have received intervening therapy following discontinuation of randomized treatment.
- Any unresolved toxicities from prior therapy should be controlled, and be no greater than CTCAE grade 1 (with the exception of alopecia) at the time of starting open-label lazertinib treatment.

Provided all of the above criteria have been met, and the patient was randomized to the gefitinib arm, the patient may commence open-label lazertinib. If the patient has been unblinded and they are not eligible for cross-over or choose not to cross-over, they cannot recommence or continue on their randomized treatment. After IDMC, in consultation with sponsor and regulators determine the primary endpoint of PFS has been achieved, all patients determined to have objective disease progression according to RECIST v1.1 as per Investigator's

assessment and T790M mutation positive will be given the opportunity to begin treatment with open-label lazertinib, if eligible for the criteria above described; central blinded confirmation of disease progression will no longer be required. See Table 6 and Section 6.4 for further details on post progression cross-over to lazertinib.

Figure 1. Study Design



4.1.2. Scientific Rationale for Study Design

The design of this study follows the recommendations of the Food and Drug Administration guidance documents, "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", "Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics", and the European Medicines Agency guidance document, "Guideline on the evaluation of anticancer medicinal product in man". The purpose of this study is to evaluate the efficacy and safety of lazertinib in patients with EGFRm+, locally advanced or metastatic NSCLC as first-line treatment. Eligible patients will be randomized to either lazertinib or gefitinib. Gefitinib is approved for the first-line treatment of EGFRm+ NSCLC in many countries. Gefitinib has been chosen as a comparator as it is the agent most often used in NSCLC patients with activating EGFR mutations in the regions where the present study will be conducted. The primary efficacy endpoint is PFS by Investigator assessment. PFS is a recommended endpoint to support drug approval in the guidelines. PFS is also an acceptable surrogate for overall survival in patients with NSCLC ([10]Laporte S et al, 2013).

Preclinical and clinical data of lazertinib demonstrate promising anti-tumor efficacy and favorable safety profile in patients with EGFRm+ NSCLC.

4.2. STUDY POPULATION

The study population will consist of male and female patients at least 18 years of age with EGFRm+ (Ex19del or L858R) locally advanced or metastatic NSCLC. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.2.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male or female patients must be ≥ 18 years of age and satisfy the legal age of consent in the jurisdiction in which the study is being conducted.

Type of Patient and Disease Characteristics

2. Patients with pathologically confirmed adenocarcinoma of the lung (e.g., this may occur as systemic recurrence after prior surgery for early stage disease or Patients may be newly diagnosed with Stage IIIB/C or IV disease). Patients with mixed histology are eligible if adenocarcinoma is the predominant histology.
3. Patients with locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.
4. Patients with at least 1 of the 2 common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, assessed in tissue biopsy by an accredited local laboratory based on the Qiagen-Therascreen® EGFR Mutation Detection Kit RGQ (Scorpions ARMS), the Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit, the PANAGENE-PANAMutyper™ or the Roche Diagnostics-Cobas® EGFR Mutation Test v2 or by central testing in a designated laboratory.
5. Mandatory provision of an unstained, archived tumor tissue sample in a quantity sufficient to allow for central analysis of EGFR mutation status for patients.
6. Patients must be treatment-naïve for locally advanced or metastatic NSCLC. (Note: Prior adjuvant and neo-adjuvant therapy (e.g., chemotherapy, radiotherapy, investigational products) for early stage disease is permitted if completed > 12 months prior to randomization provided all other entry criteria are satisfied)
7. Patients must have a WHO performance status score of 0 to 1 with no clinically significant deterioration over the previous 2 weeks before randomization.
8. Patients must have at least 1 measurable lesion, not previously irradiated and not chosen for biopsy during the study Screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), and which is suitable for accurate repeated measurements. If only 1 measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumor assessment scans are done at least 2 weeks after the screening biopsy is performed.

Male Patients

9. A male patient who has not undergone a vasectomy must agree to follow the contraceptive guidance in Appendix 3 of this protocol during the study treatment period and for at least

24 weeks after the last dose of study treatment and refrain from donating sperm during this period.

Female Patients

10. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential (WOCBP) as defined in Appendix 3.

    OR

    - A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 from the time of screening until 24 weeks after the last dose of study treatment.
    - A WOCBP must have a negative serum pregnancy test (beta human chorionic gonadotropin) at screening.

Informed Consent

11. Patient must sign an ICF prior to any study specific procedures which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

4.2.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Symptomatic and unstable brain metastases. Patients with asymptomatic and stable brain metastases may participate in this study. If treatment is required, these Patients must have completed any planned radiation therapy and/or surgery, are not on steroids, for >2 weeks prior to randomization, and remain asymptomatic. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system (CNS) imaging.
2. Leptomeningeal metastases
3. Symptomatic spinal cord compression. If steroid treatment is not required within at least 2 weeks prior to randomization then the patient may be enrolled.
4. History of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
5. Any medical conditions requiring chronic continuous oxygen therapy.
6. History of any malignancy other than the disease under study within 3 years before randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the medical monitor, is considered cured, or with minimal risk of recurrence within a year from screening).
7. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the study, or which would jeopardize compliance with the protocol.
8. Any cardiovascular disease as follows:

- History of symptomatic chronic heart failure or serious cardiac arrhythmia requiring active treatment.
- History of myocardial infarction or unstable angina within 24 weeks of randomization.

9. Positive hepatitis B (HBV) surface antigen (HBsAg), Positive hepatitis C antibody (anti-HCV), other clinically active infectious liver disease or confirmed positive human immunodeficiency virus test results. (Note: Patients with a prior history of HCV, who have completed antiviral treatment and have subsequently documented HCV RNA below the lower limit of quantification per local testing are eligible.)
10. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of study treatment.
11. History of hypersensitivity to active or inactive excipients of investigational product(s), or drugs with a similar chemical structure or class to investigational product(s).

[redacted] CCI

13. Clinically significant chronic infection or significant medical or psychiatric illness.
14. Undergone a bone marrow or solid organ transplant.
15. Any condition which would prevent patient compliance with study procedures, restrictions, and requirements, as determined by the Investigators.

Prior/Concomitant Therapy

16. Prior treatment with any systemic antineoplastic therapy for locally advanced or metastatic NSCLC (Stage IIIB/C or Stage IV) including chemotherapy, biological therapy, immunotherapy, or any investigational drug.
17. Any prior treatment with an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI).
18. Major surgery (excluding placement of vascular access) within 4 weeks of randomization.
19. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomization.
20. Patients currently receiving (or unable to stop use for an appropriate washout period prior to randomization) medications or herbal supplements known to be potent CYP3A4 inhibitors or inducers (Appendix 6).
21. Patients currently receiving the unstable doses of warfarin as an anticoagulant.
22. Patients who have been treated with alternative anti-cancer treatment within 5 half-lives of the treatment or within 4 weeks (whichever is longer) prior to randomization.
23. Any unresolved toxicities from prior therapy, greater than CTCAE grade 1 at randomization, with the exception of alopecia and grade 2, prior chemotherapy-induced neuropathy.

Prior/Concurrent Clinical Study Experience

24. Patients who have been treated with an investigational drug within 5 half-lives of the compound or within 4 weeks (whichever is longer) prior to randomization.

Diagnostic Assessments

25. Patient has any of following cardiac criteria:
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250msec).
    - Mean resting QTc >470 msec obtained from 3 electrocardiograms (ECGs), using the screening ECG machine derived QTc value.
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medications known to prolong QT interval or induce Torsades de Pointes (Appendix 6).
    - Left ventricular ejection fraction <50%
26. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
    - Absolute neutrophil count <1.5 x 10^9/L.
    - Platelet count <100 x 10^9/L.
    - Hemoglobin <90 g/L.
    - Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases, or >5x ULN in presence of liver metastases.
    - Aspartate aminotransferase >2.5x ULN if no demonstrable liver metastases or >5x ULN in the presence of liver metastases.
    - Total bilirubin >1.5x ULN if no liver metastases or >3x ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases.
    - Serum creatinine >1.5x ULN concurrent with creatinine clearance <50 ml/min measured by the study site's standard method (e.g., Cockcroft and Gault equation). Confirmation of creatinine clearance is only required when creatinine is >1.5x ULN.

4.2.3. Screening Failures

Screening failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment/entered in the study. A minimal set of screening failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any AEs or serious adverse events (SAEs).

If a patient is a screening failure, but at some point in the future is believed to meet all of the eligibility criteria, the patient may be rescreened after a new informed consent has been obtained (only once). Patients who are rescreened will be assigned a new screening number and will start a new screening phase. If the patient already has EGFR sensitizing mutation positive test result at previous screening, the EGFR sensitizing mutation re-test is not required.

4.2.4. Discontinuation of Patient from Study

Refer to the Schedule of Activities (Table 5 and Table 6) for data that are to be collected at the

time of study discontinuation, during follow-up, and for any further evaluations that are to be completed.

4.2.4.1. Discontinuation of Study Treatment

For all patients in the study, discontinuation from study treatment will not result in automatic withdrawal from the study. In the absence of treatment delays, study treatment should continue until one of the following criteria applies:

- Objective disease progression as per RECIST v1.1 or patient is no longer receiving clinical benefit.
  - If there is radiographic evidence of progressive disease by the Investigator, however the Investigator believes the patient is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the patient may remain on study treatment.
  - In the rare event that progressive disease suspected on initial assessment is not confirmed on subsequent scan by the Investigator or central reviewer, the patient may continue in the study.
  - The Investigator should make every effort to immediately submit radiographic assessments for central review when progressive disease is either suspected or confirmed, or uncertainty exists.
  - The central review must provide confirmation of progression prior to discontinuing study treatment for progression.
  - In the case of progressive disease determined by the Investigator that is not confirmed by the central reviewer, and the patient is progressing clinically and requires new anti-cancer treatment immediately, the patient should be discontinued.
- Unacceptable toxicity
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- The patient becomes pregnant
- Intercurrent illness that prevents further administration of study treatment
- Patient refuses further administration of study treatment
- The patient receives concurrent (non-protocol) systemic anticancer treatment
- Severe noncompliance with study treatment or procedure requirements as judged by the Investigator and/or the Sponsor

Where a patient meets one of aforementioned criteria, the Investigator should inform the Sponsor immediately, and a discussion and an agreement should occur between the Sponsor and the Investigator regarding whether to continue or discontinue the patient from treatment.

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 28 days following the last dose of study treatment. Adverse events occurring after 28 days following the last dose of study treatment should also be reported, if considered related to study treatment. All adverse events reported must be followed up until recovery to baseline or Grade ≤ 1 or until deemed irreversible, and must be recorded. (See Section 7.3).

If a clinically significant finding is identified, the Investigator or qualified designee will

determine if the patient can continue in the study and if any change in patient management is needed.

4.2.4.2. Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the treatment period and/or follow-up period of the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons. The reason should be recorded in the patient's medical record/EDC.

The Sponsor may retain and continue to use any data collected before such a withdrawal of consent if the patient withdraws consent for disclosure of future information. If a patient withdraws from the study, he/she may request destruction of any samples taken and not analyzed/tested, and the Investigator must document this in the site study records. If samples are already analyzed/tested, the Sponsor is not obliged to destroy the results of this research.

If the patients wish to withdraw his/her consent to the participation in the study, they should be asked if he/she is willing to continue with both progression follow-up (if applicable) and survival follow-up or only survival follow-up. In addition, they should be also asked if he/she wishes to entirely withdraw his/her consent to any further participation in the study including even survival follow-up. All this should be clearly documented in the patient notes and in the clinical study database.

The status of ongoing, withdrawn (from the study), and lost to follow-up patients at the time of the data cut-off for each analysis of survival (i.e., at the time of primary PFS analysis and final OS analysis) should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients current physician, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Withdrawn patients will not be replaced.

4.2.4.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
The following actions must be taken if a patient fails to return to the study site for a required study visit:

- The study site must attempt to contact the patient and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient. These contact attempts should be documented in the patient's medical record/EDC.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

4.2.4.4. Procedures for Study Treatment Discontinuation

At any time, patients are free to discontinue study treatment or withdraw from the study without prejudice to further treatment. A patient who decides to discontinue study treatment will be asked for the reason(s) for discontinuation and the presence of any AEs. At discontinuation visit, they will be seen and assessed by the Investigator(s). Also, 28-day safety F/U visit will be made via at least a telephone contact. The Investigator will follow up on any AEs that are unresolved at the patient's 28-day safety F/U visit. (See Section 7.3.1 and Appendix 2). The patient or his/her representative will return all unused study treatments.

Any patient who discontinues study treatment for reasons other than objective disease progression should have tumor assessments performed as scheduled in the protocol (See Table 5 and Table 6) until objective disease progression as per RECIST v1.1, unless consent is withdrawn.
Note: Some assessments, e.g., further anti-cancer treatment, should continue beyond first objective progression (according to RECIST v1.1) throughout the survival assessment period (See Table 5 and Table 6).
Upon discontinuation of study treatment, patients will be treated in accordance with the regional standard of care (SoC). Patients who were randomized to the gefitinib arm following objective disease progression according to RECIST v1.1, as per investigator assessment, may have the option to receive open-labeled lazertinib provided the specific criteria are met, should the patient wish to do so. For further details on post-progression cross-over to lazertinib please refer to Table 6 and Section 6.4.

5. TREATMENTS

5.1. STUDY TREATMENT

Study treatment is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

5.1.1. Investigational Product

- Test product: Lazertinib
- Comparator: Gefitinib
- Placebo: Lazertinib-matching placebo, Gefitinib-matching placebo

5.1.2. Non-investigational Product

Not Applicable

5.1.3. Code, Description and Composition of Investigational Products

Table 2. Investigational Products Description

Study treatment	**Test product**	**Comparator**	**Placebo**	
	Lazertinib	Gefitinib	Lazertinib-matching placebo	Gefitinib-matching placebo
Dosage Formulation	Tablet	Capsule[a,b]	Tablet	Capsule[b]
Unit Dose Strengths	80 mg	250 mg	Not applicable	
Dosage Levels	2 levels - 240 mg (3 tablets of lazertinib 80 mg)* - 160 mg (2 tablets of lazertinib 80 mg)	1 level - 250 mg gefitinib (1 capsule of gefitinib 250 mg)*	Not applicable	
Route of Administration	Oral			
Dosing Instructions	Once daily			

*Initial Dose
[a] Gefitinib tablet is over encapsulated.
[b] Appearance of all capsules used for encapsulation is identical.

5.1.4. Packaging and Labeling

Study treatment will be provided in bottle. Each bottle will be labeled as required per country's regulations.

5.1.5. Handling and Dispensing

The Investigator or qualified designee(s) must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, study site, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Study treatment will be dispensed at the study visits summarized in the SoA (See Table 5 and Table 6). Returned study treatment should not be re-dispensed to the patients.

5.2. METHOD OF ASSIGNING PATIENTS TO A TREATMENT

All patients will be centrally randomized using an Interactive Response Technology (IRT). Each patient will be assigned a unique number (randomization number) that encodes the patient's assignment to 1 of the 2 arms of the study, according to the randomization schedule generated by the Sponsor or designated CRO using a validated computer program. Details of the procedure are described in the IRT manual provided to all sites.

Patients will be randomly assigned in a 1:1 ratio to receive study treatment (lazertinib or gefitinib), using permuted blocked randomization. Patients will be stratified at randomization based on EGFR mutation (Ex19del or L858R) and race (Asian or Non-Asian).

5.3. METHOD OF ADMINISTRATION

5.3.1. Treatment in Main Study

At each dispensing visit, sufficient study treatment will be dispensed as follow:

- Cycle 1 to Cycle 4: 21 days plus the quantity covering the duration of visit window
- Cycle 5 onwards: 42 days plus the quantity covering the duration of visit window

Individual bottles of study treatment will be distributed in accordance with the medication identification numbers provided by the IRT.

Patients should swallow 3 tablets and 1 capsule once daily, commencing on Cycle 1 Day 1. Tablets/capsule of study treatment should be taken whole with water. Study treatment (i.e., lazertinib and gefitinib) can be taken with or without food.

The initial dose of lazertinib 240 mg (3 tablets of 80 mg lazertinib) once daily can be reduced to 160 mg once daily (2 tablets of 80 mg lazertinib) under circumstances described in Section 5.4. The initial dose for gefitinib (250 mg once daily) cannot be reduced to a lower dose. The dose of gefitinib may be withheld or discontinued if clinically indicated at the discretion of the Investigator.

On site visit days on which PK samples are scheduled to collect, study treatment should be administered at the study site after pre-dose PK blood samples has been collected. It should be collected dosing date/time and meal consumption on the day of PK sampling; and dosing date/time immediately before pre-dose PK sampling to ensure that an appropriate dosing interval (ideally 24 hours) is reached. For ECGs recorded in parallel with PK sampling, the PK blood samples should be collected subsequently after the triplicate ECGs have been performed.

Study treatments should be taken at a similar time each day, approximately 24 hours apart, if possible. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking his/her study treatment, he/she should not make up for this dose, but should take the next scheduled dose. The time of vomiting should be captured in source document.

Any change from the dosing schedule, dose interruptions, or dose reductions should be recorded

in the EDC.

5.3.2. Open-label Lazertinib Treatment in Cross-Over Study

For the gefitinib arm patients who are eligible and choose to cross-over to open-label lazertinib, lazertinib will be supplied at each visit as tablets for oral administration as a single daily dose of 240 mg sufficient amount for 21 days treatment plus coverage (cycle 1-4) and 42 days treatment plus coverage (cycle 5 and onwards). Individual bottles of study treatment will be distributed in accordance with the medication identification numbers provided by the IRT. Patient in the cross-over study should swallow 3 tablets of lazertinib once daily. Tablets should be taken whole with water. The initial dose of lazertinib 240 mg once daily can be reduced to 160 mg once daily under the circumstances described in Section 5.4.1.

5.4. DOSE MODIFICATION

The initial dose of lazertinib 240 mg once daily can be reduced to 160 mg once daily under the circumstances described in Section 5.4.1. The initial dose of gefitinib 250 mg once daily cannot be reduced to a lower dose. The dose of gefitinib may be withheld or discontinued if clinically indicated, at the discretion of the Investigator.

Where dose modification (e.g., interruption, restart reduced dose or same dose, and discontinuation, etc.) may be considered, the Investigator should inform the Sponsor immediately, and a discussion and an agreement should occur between the Sponsor and the Investigator regarding dose modification.

Table 3. Dose Modification Level

Dose level	Lazertinib	Gefitinib
Starting dose	240 mg/Day (3 tablets of 80 mg lazertinib) / 1 capsule of gefitinib-matching placebo	250 mg/Day (1 capsule of 250mg gefitinib) / 3 tablets of lazertinib-matching placebo
Reduced dose	160 mg/Day (2 tablets of 80 mg lazertinib) / 1 capsule of gefitinib-matching placebo	250 mg/Day (1 capsule of 250 mg gefitinib) [a] / 2 tablets of lazertinib-matching placebo

a No dose reduction for gefitinib is actually possible. Reduced dose for gefitinib is the same as the starting dose as 250 mg are the lowest dose available.

5.4.1. General Dose Adjustments for Adverse Events

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with the study treatment, dosing will be interrupted and supportive therapy will be administered as required in accordance with local practice/guidelines.

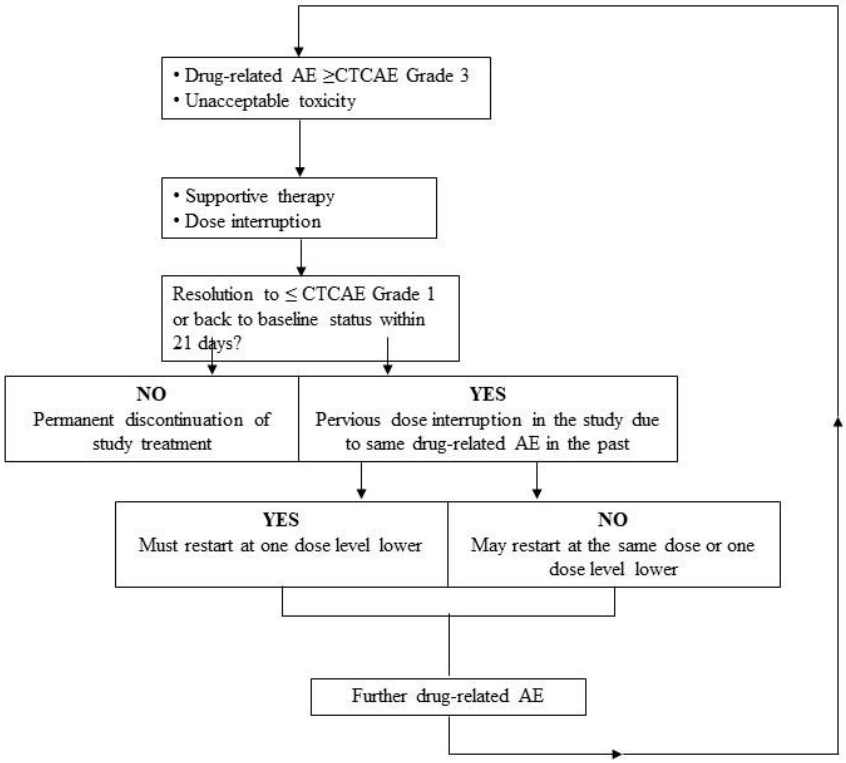
If the toxicity resolves or reverts to ≤CTCAE grade 1 or back to baseline status within 3 weeks

of onset, study treatment may be restarted at the same dose (starting dose) or be reduced using the dose reduction levels in Table 3. Dose modification will follow the rules illustrated in Figure 2 and may be agreed upon between the Investigator and the medical monitor as needed. If restarting at the same dose level, patients should be closely monitored for 3 days following the restart of treatment. If within 3 days there is recurrence of same toxicity, a dose reduction should be considered at the Investigator's discretion.

If the toxicity does not resolve to ≤CTCAE grade 1 or back to baseline status after 3 weeks, then the patient should be withdrawn from the study treatment and the toxicity should be followed (See Section 7.3.1). There will be no individual modifications to treatment schedule in response to toxicity, only potential dose reduction or dose interruption.

If a new as well as recurrent AE subsequently requires dose interruption, study treatment may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the investigator as described above.

Figure 2. Dose Modification for AEs Related to Study Treatment



Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

5.4.1.1. Corneal Ulceration

Any patient developing corneal ulceration will be permanently discontinued from study treatment and should be followed regularly until resolution of the event.

5.4.1.2. Interstitial Lung Disease

Patients with a past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease will be excluded from participation in this study.

Patients with any grade of interstitial lung disease (ILD) will permanently discontinue study treatment and be treated as medically indicated.

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the Sponsor and/or designated CRO should be informed. Investigator will perform a full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters, bronchoscopy with biopsy as needed) to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued. In the absence of a diagnosis of interstitial lung disease, study treatment may be restarted after documentation of radiographic resolution following the agreement with the medical monitor.

5.4.1.3. Cardiac Dysfunction

Patients with confirmed symptomatic cardiac dysfunction (symptoms at rest or with minimal activity) or ≥ Grade 3 left ventricular systolic dysfunction (resting ejection fraction (EF) 39-20%; ≥ 20% drop from baseline) as defined by CTCAE will be discontinued from study treatment.
Asymptomatic declines in LVEF will be handled with the process described in detail in Appendix 5. If the LVEF is reported as a range, the average should be taken. If the Investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. LVEF will be monitored at screening and every 12 weeks (-7 days, +3 days) after randomization, and at discontinuation visit.

Patients with QTc prolongation (i.e., confirmed QTc prolongation to >500 msec absolute or a >60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the QTc prolongation toxicity does not resolve to ≤ grade 1 within 3 weeks, the patient will be permanently withdrawn from study treatment.

5.4.1.4. Rash-related adverse events

Prophylactic treatment
Starting at the initiation of study treatment dosing and continuing during dosing patients are to be instructed to:

- use a thick, alcohol-free emollient cream (e.g., glycerin and cetomacrogol cream) to prevent dry skin and pruritus.
- avoid immersion in hot water / detergent / solvents.
- avoid exposure to sunlight.
- use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 if sunlight exposure cannot be avoided.

Reactive management

The following interventions and the stepwise algorithm shown in Table 4 are to be used for EGFR inhibitor-induced rash

- Topical corticosteroids (e.g., hydrocortisone 2.5% cream)
- Topical antibiotics (e.g., clindamycin 1% gel)
- Topical corticosteroids and systemic antibiotics (minocycline 100 mg bid or first generation cephalosporine (avoid CYP3A4 inhibitors)).
- For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
- For fissuring, the use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is advised.
- For desquamation, thick emollients and mild soap are recommended.
- For paronychia, antiseptic soaks and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.
- For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.
- Consult with a dermatologist if the rash is severe, atypical in appearance, or distribution, or does not improve within 2 weeks of treatment.

Table 4. Stepwise Algorithm for Management of Rash

Step	Rash grading[a]	Management of Rash	Dose Adjustment[b]
1	1	Initiate prophylactic regimen if not already started and add reactive therapies as above. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2	Continue current dose. Reassess after 2 weeks; if rash does not improve, proceed to Step 2
2	2	Initiate prophylactic regimen if not already started, including topical corticosteroids and systemic antibiotics as above.[c] Reassess after 2 weeks; if rash does not improve, proceed to Step 3	Consider reducing dose by one dose level Reassess after 2 weeks; if rash does not improve, proceed to Step 3
3	3 or intolerable Grade 2	Initiate prophylactic regimen if not already started, moderate strength topical corticosteroids and systemic antibiotics as above plus prednisone (0.5 mg/kg) for 7 days. Consider low doses of isotretinoin (20-30 mg/day). Consider obtaining dermatology consultation and manage rash per dermatologist's recommendation.	Temporarily interrupt treatment until rash improves ≤ Grade 2 or resolves, then follow steps outlined for the appropriate grading. Reassess after 2 weeks; if rash worsens or does not improve, permanently discontinue treatment.

[a] Grading per NCI CTCAE (Version 5.0)

[b] Resolution defined as: ≤Grade 1 non-hematologic toxicity or back to baseline

[c] For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream

5.4.1.5. Diarrhea

If patients experience diarrhea, they should be encouraged to drink 8 to 10 large glasses (2 liter (L)) of clear liquids per day while on study in order to maintain adequate hydration. Maintenance of electrolyte balance using electrolyte containing drinks, broth, and clear juices should be considered. If an infectious cause of the diarrhea is suspected, perform stool testing and administer antibiotic therapy (avoid CYP3A4 inhibitors) as appropriate.

General dietary measures to limit impact of diarrhea include:

- Stop all lactose-containing products in patients with evidence of lactose intolerance
- Eat frequent small meals if experiencing increased frequency of stools
- Consider low-fat regimen enriched with bananas, rice, applesauce, and toast

Diarrhea management guideline follows:

CTCAE version 5.0 Grade 1

- Management:
  - Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours).
  - Fluid intake of at least 2 L as described above.
- Study treatment: should be continued at the same dose.

CTCAE version 5.0 Grade 2

- Management:
  - Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours), or consider diphenoxylate and atropine formulations (e.g., Lomotil®).
  - Fluid intake of at least 2 L as described above. Monitor patient closely and consider intravenous hydration.
- Study treatment: If not improved to Grade ≤1 within 24 hours despite use of loperamide, hold treatment until Grade ≤1. If diarrhea of Grade >1 recurs after initial improvement, consider reduction by one dose level

CTCAE version 5.0 Grade 3:

- Management:
  - Oral therapy with diphenoxylate and atropine formulations (eg, Lomotil®), or tincture of opium.
  - Fluid intake of at least 2 L should be maintained as described above, intravenously if necessary.
  - Consider use of octreotide (Sandostatin®) 100-150 microgram (μg) subcutaneously twice daily with escalation to 500 μg three times daily.
  - Consider hospitalization if does not improve to Grade ≤2 within 24 hours, or in presence of fever, abdominal pain, etc.
- Study Treatment: Hold therapy. Upon resolution to Grade ≤1, resume therapy with consideration of reduction by one dose level.

CTCAE version 5.0 Grade 4:

- Management: Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leucocytosis, marked dehydration, etc.
- Study Treatment: Hold until Grade ≤1. Mandatory dose reduction by one dose level.

5.4.1.6. Liver Chemistry Abnormalities

Liver chemistry stopping criteria have been established to provide safety to the patients and to better assess the etiology of a liver event during the development of new investigational products. Liver chemistry should be monitored according to the schedule in SoA (See Table 5 and Table 6). The liver chemistry stopping criteria include any of the following:

1. Patients with AST and ALT and total bilirubin baseline values within the normal range: ALT or AST ≥3x ULN and bilirubin ≥2x ULN (and >35% direct bilirubin) (or ALT ≥3x ULN and

INR >1.5, if INR measured) with no evidence of hemolysis and an alkaline phosphatase ≤ 2x ULN or not available.

2. Patients with pre-existing AST or ALT or total bilirubin values above ULN:
   1) For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥ 2x the baseline value and ≥ 3x ULN, or ≥ 8x ULN (whichever smaller).

   concurrent with

   2) For patients with pre-existing value of total bilirubin above the normal range: Total bilirubin of ≥ 2 times ULN and increased by >1 time the ULN or ≥ 3 times ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times ULN or not available.

Note: Exception to the bilirubin elevation is made if the subject has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.

This event should be reported as an SAE.

Study treatment should be interrupted, and the medical monitor must be notified as soon as possible if any stopping criterion is met. Liver chemistry should be repeated within 1-3 days. If any of the chemistry stopping criteria are confirmed upon repeat, then assessments listed below should be considered.

Liver Event Follow-Up Requirements

The following follow-up assessments should be considered for any subject meeting liver chemistry stopping criteria:

- Monitor liver chemistries (ALT, AST, ALP, bilirubin, including bilirubin fractions, and INR), creatinine phosphokinase, and lactate dehydrogenase, 1 to 2 times per week until resolution, stabilization, or return to subject's baseline values
- Monitor clinical condition closely
- Draw blood samples for unscheduled PK analysis at timepoints when liver chemistry is assessed
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins
- Record alcohol use in the CRF
- Check the viral hepatitis serology as appropriate and include:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM)
  - Hepatitis C RNA
  - Hepatitis E IgM antibody
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or equivalent test)
- Assess anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Conduct liver imaging (ultrasound, magnetic resonance imaging [MRI], or computerized

tomography [CT]) to evaluate liver disease
- Refer to a specialist as appropriate

Rechallenge Criteria

Resumption of study drug administration may be considered if the following criteria are met:

- A reversible underlying cause not associated with study treatments (eg, alcohol use or concomitant medication) is clearly identified and agreed upon in consultation with the medical monitor
- Liver chemistry abnormalities have resolved or values have returned to baseline

5.5. BLINDING / UNBLINDING

5.5.1. Methods for Ensuring Blinding

Investigational product (IP, also referred to as 'study treatment' in this protocol) will be labelled using a unique material pack code, which is linked to the randomization code. The IRT will assign the bottles of IP to be dispensed to each patient. This is a double-blind study wherein each patient will receive either the active lazertinib plus over encapsulated gefitinib-matching placebo or over encapsulated active gefitinib plus lazertinib-matching placebo. The active and placebo tablets/capsules will be identical and presented in the same packaging to ensure blinding of the medication.

5.5.2. Methods for Unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigators or pharmacists from the IRT. Routine procedures for this will be described in the IRT user manual that will be provided to each site.

The treatment code may be broken in only medical emergencies except for the circumstance where it determined for the patient to receive open-label lazertinib in cross-over arm. The Investigator documents and reports the action to the Sponsor and/or designated CRO, without revealing the treatment given to patient to the Sponsor and/or designated CRO staff.

The Sponsor retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

Should there be a requirement to unblind a patient for reasons other than to determine suitability for cross-over to lazertinib, central confirmation of RECIST v1.1 disease progression is not required. See Table 6 and Section 6.4 for further details of requirements for the post-progression cross-over to lazertinib.

5.6. CONCOMITANT TREATMENTS

All prior medications administered up to 28 days before randomization must be recorded at screening.

Concomitant treatments must be recorded beginning at screening and continuing until 28 days after the last dose of study treatment. Concomitant treatments should be also recorded beyond 28 days after the last dose of study treatment in conjunction with the following situations:

- Adverse events reported after 28 days following the last dose of study treatment, if considered related to study treatment

The sponsor and/or designated CRO should be contacted if there are any questions regarding concomitant or prior treatments. The sponsor and/or designated CRO must be notified immediately if prohibited therapies are administered.

All medications taken by a patient (prescription or nonprescription, including vaccines, vitamins, and herbal/natural supplements) that are not the study treatment must be documented in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a patient into the study. Nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, and exercise regimens should also be recorded in the CRF.

5.6.1. Permitted Treatments

- Symptomatic treatment:
  - Supportive care, such as, antibiotics, analgesics, anticoagulants (e.g., warfarin, etc.), transfusions, diet, etc.
  - Concomitant medications, for the symptomatic treatment of related toxicities (Grade 1-4), may be administered according to the standard of care at the site, and at the treating physician's discretion, as clinically indicated.
- Prophylactic medications:
  - Appropriate prophylactic antiemetic regimens, if required, in accordance with institutional practice and/or current European Society of Medical Oncology guidelines
  - Treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases
    - Patients may also receive palliative radiotherapy for painful bony metastases, as long as it will not affect the target and non-target lesions being assessed.
  - Rash prophylaxis, as described in Section 5.4.1.4 and/or in accordance with institutional practice

Note: Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible. In addition, patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio.

- Localized, limited radiotherapy of short duration (e.g., 5 days) for palliative purposes may be permitted but only after discussion with and approval by the sponsor's medical monitor. Women using hormonal contraceptives as a means of birth control must continue to use the same hormonal contraceptives throughout the study (See Appendix 3).

5.6.2. Prohibited Treatments

The sponsor must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

The following concomitant medications and treatments are prohibited during the study.

- Any chemotherapy, anticancer therapy (other than study treatment[s]), or experimental therapy
- Radiotherapy to target lesions prior to disease progression

In addition, following drugs and/or ingestions of food must have been discontinued for an appropriate period prior to randomization and for a period of 3 weeks after the last dose of study treatment, and should be prohibited during the study (See Appendix 6).

- Medications, herbal supplements and/or foods with known potent inducer or inhibitory effects on CYP3A4 activity or known to or may possibly prolong QT interval or induce Torsades de Pointes

Following concomitant use of medications, herbal supplements and/or foods are not recommended, if possible. However, if medically necessary, these concomitants may be allowed with close monitoring for change in safety (See Appendix 6).

- Substrates of Breast Cancer Resistance Protein (BCRP), P-glycoprotein (P-gp) and/or multi-drug resistance protein 4 (MRP4)
- Drugs affecting gastric pH (e.g., proton pump inhibitors, H2-receptor antagonists, and antacids)

However, patients may receive local standard of care as permitted by protocol for treatment of comorbidities and/or management of adverse events.

5.6.3. Other Restrictions and Precautions

- For WOCBP: Should use reliable methods of contraception from the time of screening until 24 weeks after discontinuing study treatment. In addition, female patients must refrain from donating ovum from randomization until 24 weeks after the last dose of study treatment (See Appendix 3 for more information).
- For male patients who have not undergone a vasectomy: Should use reliable methods of contraception during sex with all partners from randomization until 24 weeks after discontinuing study treatment. Patients should refrain from donating sperm from randomization until 24 weeks after discontinuing study treatment. If male patients wish to father children during aforementioned period, they should be advised to arrange for freezing of sperm samples prior to randomization (See Appendix 3 for more information).

5.7. TREATMENT COMPLIANCE

Patients will be required to return any unused study treatment tablets/capsules at the start of their next cycle of treatment. Unused tablets/capsules will be counted and recorded by study site personnel to assess study treatment compliance. Reason for dose interruption, reduction, or omission will also be recorded in the electronic data capture system. This information plus drug accountability for all study treatments at every cycle will be used to assess compliance with the treatment.

6. STUDY ASSESSMENTS AND PROCEDURES

The overall study duration and procedure will vary for patients due to disease progression, withdrawal, and/or death, but would generally include procedures, as follows:

- Up to 28 days for screening and baseline testing
- 21-day treatment cycles
- Discontinuation visit
- 28-day safety follow-up visit (after last dosing of study treatment)
- Progression follow-up visit (for patients who discontinue study treatment for reasons other than objective disease progression)
- Survival follow-up visits until death or study withdrawal

Study procedures and their timing are summarized in the SoA (See Table 5 and Table 6).

Adherence to the study design requirements, including those specified in the SoA (Table 5, Table 6), is essential and required for study conduct. As protocol waivers or exemptions are not allowed with the exception of immediate safety concerns, these should be discussed with the Sponsor and/or designated CRO immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment. In exceptional circumstances such as COVID-19 pandemic, protocol-specified visits and treatment can be conducted by the local regulation.

Table 5. Schedule of Activities

Activities	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 onward[1]	Unscheduled visit[2]	Discontinuation[3]	28-day Safety F/U[4]	Progression F/U[5]	Survival F/U[6]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[7] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4/ Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[8]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
Informed consent[9]	X												
Demographics & baseline characteristics including current/historical smoking status	X												
Height	X												
Weight	X	X	X	X	X	X	X	X	(X)	X			
Medical and surgical history	X												
Inclusion/Exclusion criteria	X	X											
EGFR mutation test[10] (Tissue biopsy)	X												
Tumor and blood samples for central laboratory[11]	X												
Physical examination[12]	X	X	X	X	X	X	X	X	(X)	X			
WHO Performance Status	X	X	X	X	X	X	X	X	(X)	X			
Vital signs[13]	X	X	X	X	X	X	X	X	(X)	X			
Hepatitis and HIV screen[14]	X												
12-lead ECG[15]	X	X	X	X	X	X	X	X	(X)	X			
Ophthalmologic assessment	X	As clinically required											
Echocardiography/MUGA	X		Every 12 weeks relative to date of randomization							X			

Activities	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 onward[1]**	**Unscheduled visit[2]**	**Discontinuation[3]**	**28-day Safety F/U[4]**	**Progression F/U[5]**	**Survival F/U[6]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[7] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4/ Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[8]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
scan (for LVEF)[16]													
Laboratory tests[17]													
Clinical chemistry	X	X	X	X	X	X	X	X	(X)	X			
Hematology	X	X	X	X	X	X	X	X	(X)	X			
Urinalysis	X	X	X	X	X	X	X	X	(X)	X			
Pregnancy test (WOCBP only)[18]	X	Every 6 weeks relative to date of randomization, if needed by local health authorities-specific requirement or guidance							(X)	X			
PK assessment													
PK blood samples[19]		X			X			X					
cfDNA and blood-borne biomarkers assessment													
Blood samples for cfDNA and blood-borne biomarkers[20]	X		Every 6 weeks for the first 18 months and then every 12 weeks relative to date of randomization										
Tumor assessment													
RECIST v1.1 assessment[21]	X		Every 6 weeks for the first 18 months and then every 12 weeks relative to date of randomization (Per local standard practice following objective disease progression)										
Questionnaires[22]													
EORTC QLQ C-30		X			X	Every 6 weeks relative to date of randomization							
EORTC QLQ LC-13		X			X								
EQ-5D-5L		X			X								
Health resource use module													
Health resource use module		X			X	Every 6 weeks relative to date of randomization							
Other sampling (Optional)													

Activities	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 onward[1]**	**Unscheduled visit[2]**	**Discontinuation[3]**	**28-day Safety F/U[4]**	**Progression F/U[5]**	**Survival F/U[6]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[7] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4/ Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[8]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
Genetic consent	(X)												
Blood samples for genetic assay		(X)								(X)			
CSF (BM only)[23]								(X) (once)					
Tumor or blood samples upon disease progression for confirmation of T790M mutation status[24]			(X)										
Tumor or blood samples upon disease progression for exploratory research			(X)										
Randomization/Study treatment supply/dispensing													
Randomization[25]		X											
Dispense study treatment		X			X	X	X	X	(X)				
Dose with study treatment[26]		Daily dosing											
Study treatment return					X	X	X	X	(X)	X			
Safety assessment													
Adverse events[27]	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)
Survival follow-up													
Survival and anti-cancer therapy survey												X	X

Activities	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 onward[1]	Unscheduled visit[2]	Discontinuation[3]	28-day Safety F/U[4]	Progression F/U[5]	Survival F/U[6]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[7] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4/ Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[8]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
Subsequent response/progression data													X

Abbreviations: BM = brain metastasis; cfDNA = circulating cell-free deoxyribonucleic acid; CSF = cerebrospinal fluid; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, C-30 = Core 30 items, LC-13 = Lung Cancer 13 items; EQ-5D-5L = Euro-Quality of Life-5 Dimension-5 level; F/U = follow-up; HIV = human immunodeficiency virus; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; NA = not applicable; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; T790M = threonine-to-methionine substitution; WHO = World Health Organization; WOCBP = woman of childbearing potential.

1 Study visits will occur on Day 1 of every other cycle from Cycle 5 onwards (C5D1, C7D1, C9D1, C11D1, C13D1, C15D1…).

2 Unscheduled visits can be arranged if necessary. Study procedures will be performed at the discretion of the investigator.

3 All patients will attend a discontinuation visit within 7 days of permanent discontinuation of study treatment, where all procedures for the discontinuation visit will be performed. The discontinuation visit should occur before the start of any new treatment and the reason should be documented on the electronic Case Report Form.

4 28-day safety F/U will be made via at least a telephone contact within 28 days (+7 days) after permanent discontinuation of study treatment.

5 If patients discontinue study treatment for reasons other than objective disease progression, Progression F/U will be made every 6 weeks. Tumor assessment per RECIST v1.1 for the Progression F/U should be continued every 6 weeks for the first 18 months and then every 12 weeks relative to date of randomization until objective disease progression.

6 All patients will be followed for survival, disease progression (per local standard practice) and any post-study anticancer treatment via at least a telephone contact every 6 weeks relative to date of randomization following discontinuation of study treatment, until lost to follow up, the withdrawal of consent, or death (whichever is earlier). However, the patients who discontinue study treatment for reasons other than objective disease progression will conduct survival follow-up following confirmation of objective disease progression.

7 A cycle is defined as 21-day treatment period.

8 Visit window is calculated based on the date of randomization.

9 Signed informed consent must be obtained before the patient undergoes any study-specific procedures.

10 Tumor samples for screening EGFR mutations test should be assessed by an accredited local laboratory, or by central testing in a designated laboratory. If screening EGFR mutations test is performed at an accredited local laboratory, only 4 types of the mutations kits are allowed such as: the Qiagen-Therascreen®

EGFR Mutation Detection Kit RGQ (Scorpions ARMS), the Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit, the PANAGENE-PANAMutyper™ or the Roche Diagnotics-Cobas® EGFR Mutation Test v2.

[11] Collected tumor (Formalin-Fixed Paraffin-Embedded Tissue) and blood samples must be submitted to central laboratory.

[12] May include neurologic examination, if required.

[13] Vital signs (heart rate, blood pressure and body temperature) will be obtained after the patient has rested for 10 minutes. The date and time of the assessment should be recorded.

[14] Hepatitis B (HBV) surface antigen (HBsAg) and hepatitis C antibody (anti-HCV) test will be performed. Additional hepatitis examination could be conducted if required. Evaluation for HIV seropositivity will be performed, and, if positive, further tests can be determined at the discretion of the Investigator, if needed. Appropriate counseling will be made available by the Investigator in the event of a positive finding. Notification of regional and/or national authorities, if required by law, will be the responsibility of the Investigator.

[15] All ECG data will be collected digitally and transferred electronically for central analysis. A set of triplicate 12-lead ECGs, approximately 2 minutes apart, will be performed as scheduled with reading by a cardiologist. For ECGs recorded in parallel with PK sampling at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose on Day 1 of Cycles 1, 2, 5, 9, and 13, the PK blood samples should be collected subsequently after the triplicate ECGs have been performed. Other ECGs will not be time-matched and can be performed regardless of dosing time.

[16] LVEF will be assessed using an echocardiogram or MUGA scan at screening and every 12 weeks (-7 days, +3 days) relative to date of randomization until discontinuation visit. Additional assessments may be performed if clinically indicated. For any patient who has at least one echocardiogram or MUGA that is considered abnormal by local assessment, the Sponsor will collect all echocardiograms or MUGA scans (obtained at Screening and all subsequent assessments) for the purpose of a central read.

[17] Clinical laboratory tests are not required at Cycle 1 Day 1 if acceptable screening is performed within 7 days prior to randomization, unless the patient's clinical condition has changed significantly, otherwise clinical laboratory tests should be performed at Cycle 1 Day 1 before randomization. In addition, clinical laboratory test at Cycle 1 Day 1 can be performed within 7 days prior to randomization. If needed, any clinical laboratory tests may also be performed for safety evaluation of patients.

[18] At screening and discontinuation visit, all WOCBP should complete a serum pregnancy test per the practice of the site. Repeat as necessary during the treatment period if clinically indicated. In addition, it can be performed every 6 weeks relative to date of randomization considering the local health authorities-specific requirement or guidance. At other times during study, a serum or urine pregnancy test may be performed as indicated.

[19] Plasma PK samples will be collected at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose on Day 1 of Cycles 1, 2, 5, 9, and 13.

[20] Blood samples for cfDNA and blood-borne biomarkers analysis will be collected on the same day of any scheduled and unscheduled tumor assessments, if possible.

[21] Baseline tumor assessment during screening must be performed within 28 days before randomization. The patient must have at least 1 lesion, not previously irradiated, that can be accurately measured. If there is only 1 measurable lesion and it is chosen for biopsy, tumor assessment should be performed after at least 14 days following the biopsy. Follow-up tumor assessments will be performed every 6 weeks (-7 days, +3 days) for the first 18 months and then every 12 weeks (-7 days, +3 days) relative to date of randomization using the RECIST v1.1 until objective disease progression.
Tumor assessment will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen (including liver and adrenal glands). Any other sites where disease is suspected or known at baseline must also be imaged. Specifically, patients with confirmed BM at screening should be followed up on study with repeated MRI assessment at the same frequency as the other RECIST v1.1 assessments. The same modality for MRI should be used for a patient throughout the study.
Images will be sent to central reading center timely for BICR. Especially, the Investigator should make every effort to immediately submit radiographic

assessments for central review when progressive disease is either suspected or confirmed, or uncertainty exists.

[22] Questionnaires should be completed prior to any visit-specific procedures. All questionnaires will be performed at Cycle 1 Day 1, Cycle 2 Day 1 (-2 days, +3 days) and then every 6 weeks (-7 days, +3 days) relative to date of randomization until 28-day safety F/U visit or progression F/U visit (whichever is later).

[23] One CSF sample will be collected at any time from Cycle 5 Day 1 onwards. If possible, the CSF sample should be taken on the same day as planned PK samples.

[24] Determination of T790M mutation positive status by means of plasma or tissue testing may be performed locally, or centrally for those patients unable to be tested locally by the discretion of investigator.

[25] Randomization procedures should be performed following completion of **all** eligibility assessments and determination of patient eligibility prior to the initiation of assigned study treatment (i.e., All screening procedures and tests (including Cycle 1 Day 1 procedures and laboratory results for eligibility assessment) must be completed and reviewed before randomization.).

[26] Once randomized, the first dose should be administered on the randomization day. If not possible even though it has made every effort to be taken the first dose on the randomization day, the first dose must be administered within a maximum of 3 days following randomization. Study treatment should be taken orally once daily at approximately the similar time with a glass of water. Patients may continue study treatment following objective disease progression if patient is receiving clinical benefit, as judged by the investigator.

[27] All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 28 days following the last dose of study treatment. Adverse events occurring after 28 days following the last dose of study treatment should also be reported, if considered related to study treatment. Reported all AEs must be followed until recovery to baseline or Grade ≤1 or until deemed irreversible, and all relevant information must be recorded on the eCRF.

Table 6. Schedule of Activities for Post-Progression Cross-Over to Lazertinib from Gefitinib Arm

Activities	Pre-Crossover Screening[1]	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 Onward [2]	Unscheduled visit[3]	Discontinuation[4]	28-day Safety F/U[5]	Progression F/U[6]	Survival F/U[7]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[8] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4 / Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[9]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
Informed consent[10]	X												
Eligibility assessment													
Submit plasma samples for central laboratory with optional tumor tissue sample [11]	X												
Confirmation of T790M mutation positive upon progression[12]	X												
Weight		X	X	X	X	X	X	X	(X)	X			
Physical examination		X	X	X	X	X	X	X	(X)	X			
WHO Performance Status		X	X	X	X	X	X	X	(X)	X			
Vital signs[13]		X	X	X	X	X	X	X	(X)	X			
12-lead ECG[14]		X	X	X	X	X	X	X	(X)	X			
Ophthalmologic assessment		As clinically required											
Echocardiography/MUGA scan (for LVEF)[15]		Every 12 weeks relative to date of lazertinib first-dosing								X			
Laboratory tests[16]													
Clinical chemistry		X	X	X	X	X	X	X	(X)	X			
Hematology		X	X	X	X	X	X	X	(X)	X			
Urinalysis		X	X	X	X	X	X	X	(X)	X			
Pregnancy test (WOCBP	X	Every 6 weeks relative to date of first-dosing, if needed by local health authorities-							(X)	X			

Activities	**Pre-Crossover Screening[1]**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5 Onward [2]**	**Unscheduled visit[3]**	**Discontinuation[4]**	**28-day Safety F/U[5]**	**Progression F/U[6]**	**Survival F/U[7]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[8] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4 / Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[9]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
only)[17]		specific requirement or guidance											
cfDNA and blood-borne biomarkers assessment													
Blood samples for cfDNA and blood-borne biomarkers [18]	X		Every 6 weeks for the first 12 months and then every 12 weeks relative to date of lazertinib first-dosing										
Tumor assessment													
RECIST v1.1 assessment[19]	X		Every 6 weeks for the first 12 months and then every 12 weeks relative to date of lazertinib first-dosing										
Questionnaires[20]													
EORTC QLQ C-30		X			X	Every 6 weeks relative to date of lazertinib first-dosing							
EORTC QLQ LC-13		X			X								
EQ-5D-5L		X			X								
Health resource use module													
Health resource use module		X			X	Every 6 weeks relative to date of lazertinib first-dosing							
Other sampling (Optional)													
Genetic consent	(X)												
Blood samples for genetic assay		(X)								(X)			
Tumor or blood samples upon disease progression for exploratory research			(X)										
Study treatment supply/dispensing													
Dispense lazertinib		X			X	X	X	X	(X)				

Activities	Pre-Crossover Screening[1]	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 Onward [2]	Unscheduled visit[3]	Discontinuation[4]	28-day Safety F/U[5]	Progression F/U[6]	Survival F/U[7]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**After 8**					
Cycle[8] / Day	**NA**	**Cycle 1 / Day 1**	**Cycle 1 / Day 8**	**Cyc1e 1 / Day 15**	**Cycle 2 / Day 1**	**Cycle 3 / Day 1**	**Cycle 4 / Day 1**	**Cycle 5 / Day 1**					
Day	**-28**	**1**	**8**	**15**	**22**	**43**	**64**	**85**					
Visit window[9]		**0**	**± 2**	**± 2**	**-2 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**-7 ~ +3**	**NA**	**+ 7**	**+ 7**	**± 7**	**± 7**
Dose with lazertinib[21]		Daily dosing											
Lazertinib return					X	X	X	X	(X)	X			
Safety assessment													
Adverse events[22]	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)
Survival follow-up													
Survival and anti-cancer therapy survey												X	X

Abbreviations: BM = brain metastasis; cfDNA = circulating cell-free deoxyribonucleic acid; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, C-30 = Core 30 items, LC-13 = Lung Cancer 13 items, EQ-5D-5L = Euro-Quality of Life-5 Dimension-5 level; F/U = follow-up; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition; NA = not applicable; RECIST = Response Evaluation Criteria in Solid Tumors; T790M = threonine-to-methionine substitution; WHO = World Health Organization; WOCBP = woman of childbearing potential.

1 Pre-crossover screening visit may occur on the same day of discontinuation visit of main study.
2 Study visits will occur on Day 1 of every other cycle from Cycle 5 onwards (C5D1, C7D1, C9D1, C11D1, C13D1, C15D1…).
3 Unscheduled visits can be arranged if necessary. Study procedures will be performed at the discretion of the investigator.
4 All patients will attend a discontinuation visit within 7 days of permanent discontinuation of open-label lazertinib, where all procedures for the discontinuation visit will be performed. The discontinuation visit should occur before the start of any new treatment and the reason should be documented on the electronic Case Report Form.
5 28-day safety F/U will be made via at least a telephone contact within 28 days (+7 days) after permanent discontinuation of lazertinib.
6 If patients discontinue lazertinib for reasons other than objective disease progression, Progression F/U will be made every 6 weeks. Tumor assessment per RECIST v1.1 for the Progression F/U should be continued every 6 weeks for the first 12 months and then every 12 weeks relative to date of lazertinib first-dosing until objective disease progression.
7 All patients will be followed for survival and any post-study anticancer treatment via at least a telephone contact every 6 weeks relative to date of lazertinib first-

dosing following discontinuation of open-label lazertinib, until lost to follow up, the withdrawal of consent, or death (whichever is earlier). However, the patients who discontinue open-label lazertinib for reasons other than objective disease progression will conduct survival follow-up following confirmation of objective disease progression.

[8] A cycle is defined as a 21-day treatment period.

[9] Every visit window is calculated based on the date of first dose of open-label lazertinib.

[10] Signed informed consent for optional cross-over study must be obtained before the patient undergoes any new study-specific procedures.

[11] Plasma sample at progression must be submitted to central laboratory for central testing of T790M mutation. Tumor (Formalin-Fixed Paraffin-Embedded Tissue) sample collected at progression may be submitted for central testing of T790M mutation (Optional).

[12] Confirmation of T790M mutation test result is required. The sample that is used to test for the mutation to be eligible to go on to the cross-over arm, can be the same as the optional sample at progression.

[13] Vital signs (heart rate, blood pressure, and body temperature) will be obtained after the patient has rested for 10 minutes. The date and time of the assessment should be recorded.

[14] All ECG data will be collected digitally and transferred electronically for central analysis. A set of triplicate 12-lead ECGs, approximately 2 minutes apart, will be performed as scheduled with reading by a cardiologist.

[15] LVEF will be assessed using an echocardiogram or MUGA scan at pre-crossover screening and every 12 weeks (-7 days, +3 days) relative to date of first-dosing until discontinuation visit. Additional assessments may be performed if clinically indicated. For any patient who has at least one echocardiogram or MUGA that is considered abnormal by local assessment, the Sponsor collects all echocardiograms or MUGA scans (obtained at pre-crossover screening and all subsequent assessments) for the purpose of a central read.

[16] If needed, any clinical laboratory tests may also be performed for safety evaluation of patients.

[17] At pre-crossover screening and discontinuation visit, all WOCBP should complete a serum pregnancy test per the practice of the site. Repeat as necessary during the treatment period if clinically indicated. In addition, it can be performed every 6 weeks relative to date of first-dosing considering the local health authorities-specific requirement or guidance. At other times during study, a serum or urine pregnancy test may be performed as indicated.

[18] Blood samples for cfDNA and blood-borne biomarkers analysis will be collected on the same day of any scheduled and unscheduled tumor assessments, if possible.

[19] Baseline tumor assessment during pre-crossover screening must be performed within 28 days before first-dosing of open-label lazertinib. Follow-up tumor assessments will be performed every 6 weeks (-7 days, +3 days) for the first 12 months and then every 12 weeks (-7 days, +3 days) relative to date of first-dosing of open-label lazertinib using the RECIST v1.1 until objective disease progression. Tumor assessment will be performed using computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen (including liver and adrenal glands). Any other sites where disease is suspected or known at baseline must also be imaged. Images will be sent to central reading center timely for BICR.

[20] Questionnaires should be completed prior to any visit-specific procedures. All questionnaires will be performed at Cycle 1 Day 1, Cycle 2 Day 1 (-2 days, +3 days) and then every 6 weeks (-7 days, +3 days) relative to date of first-dosing until 28-day safety F/U visit or progression F/U visit (whichever is later).

[21] Lazertinib should be taken orally once daily at approximately the similar time with a glass of water. Patients may continue lazertinib following objective disease progression if patient is receiving clinical benefit, as judged by the investigator.

[22] All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 28 days following the last dose of lazertinib. Adverse events occurring after 28 days following the last dose of lazertinib should also be reported, if considered related to lazertinib. Reported all AEs must be followed until recovery to baseline or Grade ≤1 or until deemed irreversible, and all relevant information must be recorded on the eCRF.

Table 7. Blood Sample Volumes

The estimated volume of blood samples required in screening and the first 15 weeks is 248 mL in maximum. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Visit	Safety (mL)[1]	PK analysis (mL)[2]	Others (mL)[3]	PGx (mL)
Screening	15	NA	40	NA
Cycle 1	45 (3 * 15 mL)[4]	6 (3 * 2 mL)	20	10 (optional)[5]
Cycle 2	15	6 (3 * 2 mL)	NA	NA
Cycle 3	15	NA	20	NA
Cycle 4	15	NA	NA	NA
Cycle 5	15	6 (3 * 2 mL)	20	NA
Subtotal at Cycle 5	120	18	100	10

Abbreviations: NA = not applicable; PGx =pharmacogenetics; PK=pharmacokinetics.
[1] Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.
[2] Only taken at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose on Day 1 of Cycles 1, 2, 5, 9, and 13.
[3] Included samples for mutation confirmation, cfDNA and blood-borne biomarkers.
[4] Patients attend visits every week within Cycle 1. A cycle is defined as a 21-day treatment period.
[5] If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit.

6.1. SCREENING PERIOD

The screening period starts at the time of the signing of the informed consent form, and continues until randomization. The duration of the screening period cannot exceed 28 days. The screening period will include items listed in the SoA (Table 5), including signing of the informed consent, a review of medical history to determine eligibility for the study, and the completion of all assessments required to verify eligibility before randomization.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA (See Table 5).

It is recommended that the screening assessments be performed in a stepwise process beginning with the confirmation of EGFR mutation status either from mutation testing results available locally where testing has been performed by an accredited or determined by the designated central laboratory. However, screening assessments may be done in parallel to the EGFR mutation assessment, as appropriate. Tumor assessments and other clinical data obtained prior to consent may be used for the study, provided the assessments fall within the protocol specified period prior to randomization.

6.1.1. Written informed consent

Each potential patient will provide written informed consent prior to starting any study specific procedures (See Appendix 1).

All patients will be required to provide consent to supply a tumor biopsy sample taken during the Screening period or a pre-study tumor biopsy sample for entry into this study. Patient will also be required to provide consent for collection of blood samples both during the Screening period and during study treatment period. This consent is included in the main patient informed consent form (ICF). Additionally, patient will be given the option to consent to the [redacted]CCI[redacted], and the host pharmacogenetics research component of the study.

6.1.2. Assignment of Patient Screening/Randomization Number

A screening number will be assigned to each patient when the Principal Investigator or delegate performs the screening. For randomization, each patient will receive a randomization number via the IRT (See Section 5.2).

6.2. TREATMENT PERIOD

Once randomized, the first dose should be administered on the randomization day. If not possible even though it has made every effort to be taken the first dose on the randomization

day, the first dose must be administered within a maximum of 3 days following randomization.

A cycle of treatment is defined as 21 days. Patients will be randomized and receive once daily treatment with either lazertinib or gefitinib. Patients will continue study treatment until objective disease progression or beyond RECIST v1.1 defined progression if patient is receiving clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria. Patients who continue to receive treatment following objective progression due to clinical benefit will have tumor assessments as per standard local practice.

Detailed study treatment schedule is shown in the SoA (See Table 5).

If disease progression assessed by the Investigator according to RECIST v1.1 is confirmed by BICR, and T790M mutation positive, it will be given the opportunity of open-label lazertinib treatment to the patient who randomized to the gefitinib. For further details on post-progression cross-over to open-label lazertinib please refer to Section 6.4 and Table 6.

6.3. FOLLOW-UP PERIOD

Post study treatment assessment will be initiated at the time study treatment is permanently discontinued (See Table 5). This may include:

6.3.1. Discontinuation Visit

A Discontinuation visit will be performed at the time the study treatment is permanently stopped. Refer to the SoA for details (See Table 5).

6.3.2. 28-Day Safety Follow-up Visit

28-Day safety follow-up should be made with the patient 28 + 7 days following the discontinuation of study treatment to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Appendix 2 for full details on AE recordings during follow up.

6.3.3. Progression Follow-up Visit

If patients discontinue study treatment for reasons other than objective disease progression, Progression F/U will be made every 6 weeks. Tumor assessment per RECIST v1.1 for the Progression F/U will be continued every 6 weeks for the first 18 months and then every 12 weeks (relative to randomization) until objective progression (See Table 5).

6.3.4. Survival Follow-up Visit

All patients will be followed for survival, disease progression (per local standard practice) and any post-study anticancer treatment via at least a telephone contact every 6 weeks relative to date of randomization following discontinuation of study treatment, until lost to follow up, the withdrawal of consent, or death (whichever is earlier). However, in the case which patients who discontinue study treatment for reasons other than objective disease progression will conduct survival follow-up following confirmation of objective disease progression.

In addition to the survival status, the following assessments are also required post progression:

- Anti-cancer therapy and surgery collected every 6 weeks.
- Subsequent response/progression data every 6 weeks until the first confirmed disease progression on a subsequent treatment.

Patient should be contacted in the week following the data cut-off for each analysis of survival (i.e., at the time of primary PFS analysis and final OS analysis) to provide complete survival data.

6.4. CROSS-OVER TO OPEN-LABEL LAZERTINIB

Following objective disease progression according to RECIST v1.1, as per investigator assessment, patients who were randomized to gefitinib arm may have the option to receive open-label lazertinib. The following steps must be performed as specified for a patient to be able to receive open-label lazertinib.

6.4.1. Central Confirmation of Disease Progression

Should the investigator determine the patient to have progressed according to RECIST v1.1, images must be sent for central confirmation of disease progression. Progression must be confirmed centrally in order for a patient to be eligible to receive open-label lazertinib. If progression is not confirmed centrally, the patient may continue to receive randomized treatment (should it be in their interests to do so) and have progression assessed by BICR at a future time point.

After IDMC in consultation with sponsor and regulators determine the primary endpoint of PFS has been achieved, all patients determined to have objective disease progression as per Investigator's assessment and have T790M mutation positive, will be given the opportunity to begin treatment with open-label lazertinib, if eligible; central confirmation of disease progression will no longer be required.

6.4.2. T790M Testing

In order to be eligible to receive open-label lazertinib, the patient's tumor must have been confirmed as T790M mutation positive by means of plasma or tissue collected post-progression. Determination of tumor T790M mutation positive status may be performed locally (without the requirement for a central test), or centrally for those patients unable to be tested locally.

- For local determination of T790M status, a laboratory report confirming tumor T790M status performed in an accredited, certified or quality assured clinical laboratory as required by country-specific guidelines, using an appropriately validated test must be provided.
- For central determination, patients are required to provide tumor tissue or blood from a sample taken at progression (Specific instructions regarding the preparation and shipment of these tumor samples will be provided in the Laboratory manual).

6.4.3. Unblinding

Following central confirmation of objective disease progression according to RECIST v1.1 and T790M mutation positive, the patient may then be unblinded to establish randomized treatment. If randomized to the gefitinib treatment arm, the patient may be a candidate to receive open-

label lazertinib. Patients who have been unblinded prior to central confirmation of progression are not able to receive open-label lazertinib.

6.4.4. Open-label Treatment with Lazertinib

Any unresolved toxicities from prior therapy should be controlled, and be no greater than CTCAE grade 1 (with the exception of alopecia) at the time of starting open-label lazertinib treatment. The patient cannot cross-over if they have received intervening therapy following discontinuation of randomized treatment. The disease assessment which documents progression will serve as the new baseline for the cross-over portion of the study. The investigator will reevaluate the patient for target and non-target lesions, according to RECIST v1.1, based on the disease assessment scans showing the initial progression. A cross-over patient need not repeat imaging assessments before cross-over Cycle 1, Day1, unless the disease assessment is incomplete, or occurred >28 days prior to cross-over Cycle 1, Day 1 (in which case, disease assessments must be repeated and will serve as the new baseline). If the disease assessment is incomplete, the site will obtain any missing radiographic imaging (e.g. MRI of the brain) prior to initiation of treatment with lazertinib.

Patients who are eligible and choose to cross-over to open-label lazertinib treatment will be dispensed bottles of lazertinib. For details on lazertinib please refer to Section 5.1.3.

6.5. End of Study Definition

The end of the study is defined as ‘the last visit of the last patient undergoing the study.’
The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if recruitment is slow. The Sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with lazertinib.

6.6. STUDY MATERIALS

Study specific guidelines (e.g., Study reference manual) and materials (e.g., laboratory kit) will be provided by the Sponsor or designated CRO/third party.

6.7. SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (See Table 5 and Table 6). Adverse events will be reported throughout the study as described in Appendix 2.

6.7.1. Adverse Events (AEs)

6.7.1.1. Adverse Events of Special Interest (AESI)

Not Applicable

6.7.1.2. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The definitions and other details of AEs and SAEs can be found in Section 7 and Appendix 2.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the

patient's legally authorized representative).

The Investigator and any qualified designee(s) are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up the AE or SAE. (See Section 7.3).

Care will be taken not to introduce bias when detecting AEs/SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence.

6.7.2. 12-lead Electrocardiograms

- Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. For each time point, the ECG should be taken three times at about 2 minutes-interval.
- ECGs should be obtained immediately before PK blood sampling at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose on Day 1 of Cycles 1, 2, 5, 9, and 13. Other ECGs will not be time-matched and can be performed regardless of dosing time.
- A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study if possible. Triplicate 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT intervals and QTc.
- All ECG data will also be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. Heart rate, PR, RR, QRS and QT intervals will be determined and reviewed by an external cardiologist. (Central confirmed ECG results at screening will not be used in eligibility assessment).
- After paper ECGs have been recorded, the Investigator or designated physician will review each ECGs and may refer to a local cardiologist if appropriate for immediate management of the patient. Each ECGs review should be performed before the next cycle of treatment is administered. A paper copy and centrally confirmed results should be filed in the patient's medical records. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

6.7.3. Physical Examinations

- Height (at screening only) and weight will be measured and recorded.
- The physical examination includes an assessment of general appearance and a review of systems (e.g., dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems, etc.).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.7.4. Vital Signs

- Assessment and measurement of vital signs (seated systolic and diastolic blood pressure, pulse rate, and body temperature) will be performed at the time points indicated in the SoA (See Table 5 and Table 6).
- Measurement of vital signs should be made in the same arm of the patient at each visit.
- The method used to measure body temperature at screening should be maintained

throughout the study for each patient, and should be indicated (e.g., ear, mouth, or armpit, etc.).

6.7.5. Laboratory Test Assessment

- Refer to the SoA for the timing and frequency of all protocol-required laboratory assessments (See Table 5 and Table 6).
- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 4.2.1 and Section 4.2.2 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- The Investigator must review the laboratory test report, document this review, and record any clinically relevant changes occurring during the study in EDC. The laboratory reports must be filed with the source documents. Clinically relevant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- If laboratory values from laboratory assessments not specified in the protocol and performed at the institution’s local laboratory result in the need for a change in patient management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification, etc.), then the results must be recorded in EDC.
- Laboratory values that meet the criteria for CTCAE grade 3 or higher and/or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.
- If a patient demonstrates a concomitant elevation of AST or ALT and total bilirubin that meet the liver chemistry stopping criteria in Section 5.4.1.6 (which may be an indicator of Hy’s law or potential hepatotoxicity), it must be reported to the Sponsor and/or designated CRO within 24 hours (see Section 7. 4.1). The Investigator will need to follow liver studies more frequently, may need to perform additional examinations, and confirm the results with the medical monitor. Investigators must document their review of each laboratory safety report. Details of identification of potential Hy’s Law cases and actions to take are detailed in Section 5.4.1.6.

Table 8. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Platelet Count RBC Count WBC Count	RBC Indices: %Reticulocytes	WBC differential count: Basophils Eosinophils Lymphocytes Neutrophils Monocytes
Clinical Chemistry	Albumin BUN Creatinine Potassium Sodium Magnesium Total and direct bilirubin Total Protein Uric acid	ALT AST Alkaline phosphatase Calcium γGTP Glucose, fasting	
Routine Urinalysis	Protein (albumin) Glucose Blood (RBC) WBC by dipstick		
Other Tests	Serum hCG pregnancy test at screening and discontinuation. Additional testing may be performed if needed in WOCBP. At other times during study, a serum or urine pregnancy test may be performed as indicated Serology (anti-HIV, HBsAg, and hepatitis C antibody) (Screening Visit only)		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; γ-GTP = gamma guanosine-5'-triphosphate; HbsAg = hepatitis B virus surface antigen; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; RBC = red blood cell; WBC= white blood cell; WOCBP = women of childbearing potential.

6.7.6. Other Safety Assessments

6.7.6.1. Ophthalmologic Assessment

An ophthalmic assessment, including slit lamp examination, fundoscopic examination, visual acuity test and other tests at the discretion of the Investigator will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for review by the medical monitor if necessary. Ophthalmology examination results should be recorded in EDC.

6.7.6.2. Echocardiography or Multiple Gated Acquisition Scan

Echocardiography (or multiple gated acquisition scan) to assess left ventricular ejection fraction

will be conducted at screening, every 12 weeks (-7 days, +3 days) after randomization, and at discontinuation visit. Additional assessments can be conducted at the discretion of the Investigator. The modality of the cardiac function assessments must be consistent within a patient (i.e., if echocardiography is used for the screening assessment then echocardiography should also be used for subsequent scans). The patients should also be examined using the same machine and operator whenever possible. For any patient who has at least one echocardiogram or MUGA scan that is considered abnormal by local assessment, the Sponsor and/or designated CRO will collect all echocardiograms or MUGA scans (obtained at Screening and all subsequent assessments).

6.8. EFFICACY ASSESMENTS

6.8.1. RECIST v1.1 Assessments

The imaging modalities used for RECIST v1.1 assessments will be CT or MRI scans of the chest and abdomen (including liver and adrenal glands). The methods used at baseline for assessment of tumor burden (CT or MRI) must be used at each subsequent follow-up assessment. Any other sites where disease is suspected or known at baseline must also be imaged, and additional sites of disease, confirmed at baseline not covered by the protocol-specified anatomy, should be followed at the same scheduled visits as the other RECIST v1.1 assessments.

Specifically, patients with confirmed BM at screening should be followed up on study with repeated CT or MRI assessment at the same frequency as the other RECIST v1.1 assessments. The same modality for MRI should be used for a patient throughout the study.

Baseline assessments should be performed within 28 days prior to randomization. Subsequent assessments are to be performed every 6 weeks (-7 days, +3 days) for the first 18 months and then every 12 weeks (-7 days, +3 days) relative to randomization until objective disease progression as per RECIST v1.1. Patients who discontinue study treatment for reasons other than objective disease progression will continue RECIST v1.1 assessments every 6 weeks (-7 days, +3 days) for the first 18 months and then every 12 weeks (-7 days, +3 days) relative to randomization until objective disease progression, even if a patient receives other anti-cancer treatment. It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled timepoint and the patient has not progressed, every attempt should be made to perform the subsequent scans at the next scheduled time points, relative to the date of randomization. Any other sites at which new disease is suspected should also be appropriately imaged during the study. In general, scans should be performed after PRO assessments, when possible.

Imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to the designated CRO or third party to enable independent central analyses. Following objective disease progression, per RECIST v1.1, patients should have tumor assessments performed as per standard local practice to assess time to second progression. These post RECIST v1.1 progression local-practice scans should not be sent to the designated CRO or third party which is performing the independent RECIST v1.1 assessments. However for patients that discontinue study treatment due to reasons other than objective disease progression should have tumor assessment performed according to RECIST v1.1 and the images submitted to the

designated CRO or third party to enable independent central analyses until objective disease progression.

For Investigator assessment, RECIST v1.1 criteria will be used to assess each patient's tumor response to treatment and allow calculation of PFS, ORR, DoR, DCR, depth of response and time to response. Measurable, non-measurable, target and non-target lesions, and the objective tumor response criteria (complete response, partial response, stable disease, or progression of disease) are followed the RECIST v1.1 guidelines ([11]Eisenhauer et al, 2009).

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions (NTLs) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment (or sooner if clinically indicated) and reassess the patient's status. If the repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall substantial worsening in NTLs such that, even in the presence of stable disease or partial response in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Categorization of objective tumor response assessment at each visit will be based on the RECIST v1.1 criteria of response: complete response, partial response, stable disease, and progression of disease. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (complete response, partial response, or stable disease) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

The primary analysis for this study will be based on the tumor assessments using investigator assessment according to RECIST v1.1 and the management of patients will be based solely upon the results of the RECIST v1.1 assessment conducted by the Investigator.

6.8.2. Blinded Independent Central Review

All protocol required imaging assessments, including unscheduled visit scans, will be duplicated and collected on an ongoing basis and sent to the designated CRO or third party to enable central analysis for BICR. The results of this independent central review will not be communicated to the investigational site and the management of patients will be based on the result of RECIST v1.1 assessments conducted by the investigator.

However, in case of patients whose tumor have progressed, as assessed by the Investigator, the central review must provide confirmation of progression, prior to cross-over receiving open-label lazertinib, or prior to discontinuing study treatment for progression.

6.8.3. Assessment of PFS after Next-line treatment (PFS2)

Following objective disease progression per RECIST v1.1, patients will have their progression status recorded every 6 weeks to assess second progression (PFS2). Second progression is considered as an event of subsequent progressive disease, post initiation of subsequent anti-cancer therapy, or death. A patient's progression status is defined according to the local standard clinical practice and may involve any of the following: objective radiological progression (preferred), symptomatic progression, or death. Scans will be performed according to the local practice and formal RECIST v1.1 measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and Investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in EDC.

6.8.4. Mandatory Tumor Biopsy Sample for Central Mutation Analysis

Tumor tissue sample must be formalin-fixed and paraffin embedded (Specific instructions regarding the preparation and shipment of these tumor samples will be provided in the Laboratory manual). Biopsy samples taken from bone metastasis and cytology samples are unsuitable for testing and should not be provided. Samples may be collected from primary or metastatic tumor deposits. Study sites personnel should ship the tumor sample to the sponsor-designated testing laboratory following patient consent. Blocks must be provided wherever possible. Mandatory provision of an unstained, archived tumor tissue sample in a sufficient quantity to allow for central analysis of EGFR mutation status should be required.
The mandatory screening tumor biopsy sample must not be taken from a previously irradiated lesion. The biopsy must not be taken from the lesion(s) selected for Inclusion criterion # 8 (unless only 1 measurable lesion exists, in which case the baseline tumor assessment scans are to be done at least 14 days after the screening biopsy). This biopsy sample is not subject to the 28-day screening window; for patients with systemic recurrence after prior surgery for early stage disease, any fresh tumor tissue taken since such recurrence will be acceptable; for newly diagnosed patients with locally advanced or metastatic NSCLC, any tumor tissue since the initial diagnosis will be acceptable as long as no chemotherapy or radiotherapy (adjuvant or neo-adjuvant) are intercalated between the biopsy and screening; if tissue is already available from a biopsy sample taken since confirmation of disease progression to Stage IIIB/C or Stage IV, then there is no need for a further biopsy as this sample can be submitted for EGFR mutation status including Ex19del , L858R, T790M testing. If the first biopsy submitted for central testing is not confirmed as EGFR mutation positive (i.e., due to test failure), a further biopsy sample may be submitted for central testing. Central re-tests on a new sample can only be performed if the original testing failed; re-tests are not permitted if the central EGFR testing result is EGFR mutation negative, or does not report an EGFR eligible mutation (Ex19del or L858R). Patients who have been locally tested as EGFR mutation negative may submit their tissue biopsy sample for testing at the central laboratory at the discretion of the Investigator.

6.9. OTHER ASSESSMENTS

6.9.1. WHO Performance Status

Performance status will be assessed at the scheduled visits indicated in the SoA according to WHO criteria as follows (See Table 5 and Table 6):

- 0 = Fully active, able to carry out all pre-disease activities without restrictions.

- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework, office work).
- 2 = Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.
- 5 = Death

6.9.2. Concomitant Medication Use

Information on any treatment within the 4 weeks prior to randomization and all concomitant treatments given up to 28 days after discontinuation of study treatment with reasons for the treatment, will be recorded in EDC. For additional information, refer to Section 5.6.

6.9.3. Anti-cancer and Surgical Treatments

All prior and concomitant anti-cancer and surgical therapies will be collected at screening and throughout the study. Subsequent regimens of anti-cancer therapy will be recorded in EDC.

6.9.4. Patient-Reported Outcomes (PROs)

Patient-reported outcomes, an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical trials.

The following PROs will be administered (Appendix 8, 9 and 10):
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) Core 30 items (EORTC QLQ-C30);
- EORTC QLQ-Lung Cancer 13 items (EORTC QLQ-LC13);
- Euro-Quality of Life-5 Dimension-5 level (EQ-5D-5L)

PROs will be collected for all patients throughout the study period. See Table 5 and Table 6 for the timing of collection. PROs should be completed prior to any visit-specific procedures. In general, the PRO instruments should be administered prior to any and all treatment assessment (i.e., including scans for tumor assessment).

6.9.4.1. EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group in 1993. It consists of 30 items and measures cancer patients' functioning (health-related quality of life (HRQoL)) and symptoms ([12]Aaronson NK et al, 1993) for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, nausea/vomiting); a 2-item global HRQoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, diarrhea) and 1 item on the financial impact of the disease. The EORTC QLQ-C30 is a valid and reliable PRO instrument in this patient population.

The EORTC QLQ-LC13 is a well-validated complementary module measuring lung cancer

associated symptoms and side effects from conventional chemotherapy and radiotherapy ([13]Bergman B et al, 1994). The EORTC QLQ-LC13 includes questions assessing cough, hemoptysis, dyspnea, site specific pain (symptoms), sore mouth, dysphagia, peripheral neuropathy, and alopecia (treatment-related side effects), and pain medication.

The items on both measures were scaled and scored using the recommended EORTC procedures ([14]Fayers PM et al, 2001). Raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. Provided at least half of the items in the scale were completed, the scale score was calculated using only those items for which values existed.

Both EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be administered in those countries where a linguistically validated version exists. EORTC QLQ-C30 and EORTC-QLQ LC13 will be performed at Cycle 1 Day 1, Cycle 2 Day 1 (-2 days, +3 days) and then every 6 weeks (-7 days, +3 days) relative to date of randomization until 28-day Safety F/U visit or progression F/U visit (whichever is later).

Note: Signs and symptoms assessed with the EORTC QLQ-C30 and EORTC QLQ-LC13 will not be considered AEs.

6.9.4.2. EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([15]EuroQol Group, 1990). The EQ-5D is a disease generic instrument that has been widely used and has been found to capture HRQOL changes in NSCLC ([16]Trippoli S et al, 2001; [17]Belani CP et al, 2006). The EQ-5D comprises the following two questionnaires:

- The EQ-5D comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises five levels (no problems, slight problems, moderate problem, severe problem, unable/extreme problems).
- The EQ VAS records the patients self-rated health status on a vertical graduated (0-100) visual analogue scale. The patient's self-rated health is assessed on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state) by the EQ-VAS.

The EQ-5D-5L will be administered in those countries where a linguistically validated version exists. EQ-5D-5L will be also performed at Cycle 1 Day 1, Cycle 2 Day 1 (-2 days, +3 days) and then every 6 weeks (-7 days, +3 days) relative to date of randomization until 28-day safety F/U visit or progression F/U visit (whichever is later).

6.9.5. Health Resource Use Module

The Healthcare Resource Use Module will be completed by the investigational site for any healthcare resource use between visits. The site will ask patients for any health resource use between visits (i.e., excluding routine follow-up clinic visits associated with the clinical trial but including both planned and unplanned admissions) at Cycle 1 Day 1, Cycle 2 Day 1 (-2 days, +3 days) and then every 6 weeks (-7 days, +3 days) relative to date of randomization until 28-day safety F/U visit or progression F/U visit (whichever is later).

For the purposes of economic evaluation, it is necessary to capture healthcare resource use related to the treatment and the underlying disease. Within the study, the following resource use will be captured:

- Hospital episodes including the type of contact (hospitalizations, outpatient, day case), reason, length of stay (including intensive care unit), and concomitant medications and procedures.
- Symptoms for admission.

The above resource use data will mainly come from the patient's medical record and will be captured by site staff using EDC.

6.10.PHARMACOKINETIC ASSESSMENTS

6.10.1. Collection of PK Samples

Venous blood samples (2 mL each) will be obtained at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose on Day 1 of Cycles 1, 2, 5, 9, and 13. A blood samples taken at pre-dose on Day 1 of Cycle 1 can be collected at any time before first dosing on the day, but a -1-hour window will be allowed for blood samples taken at pre-dose on Day 1 of Cycles 2, 5, 9, and 13. The pre-dose PK blood sample should be taken prior to the administration of study treatment on each PK sampling day. Optionally, 1 CSF sample (at least 1-2 mL) will be obtained at any time from Cycle 5, Day 1 onwards. If possible, the CSF sample should be taken on the same day as planned PK blood samples.

Dosing date/time and meal consumption on the day of PK sampling and dosing date/time immediately before pre-dose PK sampling should be collected. In addition, the date and time of collection of each sample (blood and CSF samples) will be collected. The dosing date and time, meal consumption and the date and time of collection of each sample will be recorded in the EDC.

Details of PK sample collection, labeling, storage and shipment will be provided in the Laboratory manual.

6.10.2. Determination of Drug Concentration in PK Samples

Lazertinib concentrations in plasma and CSF will analyzed using an appropriate bioanalytical method by the Sponsor's designated bioanalytical laboratory. Full details of the analytical method used will be described in a separate bioanalytical report. All samples within the known stability of the analyses of lazertinib at the time of receipt by the bioanalytical laboratory will be analyzed.

In addition, the residual PK samples may be subjected to further analyses by the Sponsor in order to future exploratory biomarker research and/or further investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report.

Details on sample processing, handling, shipment, and storage will be provided in the Laboratory manual.

6.10.3. Storage and Destruction of PK Samples

PK samples will be retained for a maximum of 5 years following the finalization of the Clinical Study Report.

Any residual PK samples may be used for future exploratory biomarker research and/or further investigate the presence and/or identity of additional drug metabolites. In this case, the residual PK samples will be shipped to the Sponsor or the designated bioanalytical laboratory or third party, and the residual PK samples will be retained for a maximum of 5 years following the finalization of the final Clinical Study Report.

6.11. PHARMACODYNAMICS ASSESSMENTS

Not applicable

6.12. PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

6.12.1. Pharmacogenetics: Collection and Processing

If a patient agrees to participate in the Sponsor's pharmacogenetics research component of the study, a blood sample will be collected (See Appendix 4).

The 10 mL blood sample for genetic research will be obtained from patients immediately prior to randomization. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias by excluding patients who may withdraw due to an AE. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. The samples will be retained for a maximum of 15 years following the finalization of the final Clinical Study Report or other period as per local regulations. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory manual.

6.12.2. Pharmacogenetic Sample Analyses

The results of this pharmacogenetic research will be reported separately and will not be part of the Clinical Study Report. Detailed information is provided in Appendix 4.

6.13. EXPLORATORY ASSESSMENT

[redacted] CCI

[redacted] CCI

[redacted] CCI

CCI

7. ADVERSE EVENTS

7.1. DEFINITIONS

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study patient, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product. A detailed explanation is provided in Appendix 2.

7.1.2. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is or results in a congenital anomaly/birth defect
- Is medically important*

  * Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or new malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, a concomitant elevation of AST or ALT and total bilirubin that meet the liver chemistry stopping criteria in Section 5.4.1.6 (which may be an indicator of Hy's law or potential hepatotoxicity).

A detailed explanation is provided in Appendix 2.

7.1.3. Adverse Events of Special Interest

Not Applicable

7.2. INTENSITY AND CAUSALITY

The investigator will assess intensity and causality for each adverse event, and answer 'yes (Certain, Probable/Likely, Possible, Unassessable/Unclassifiable)' or 'no (Unlikely, Not related)' to the following question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?' A detailed instruction is provided in Appendix 2.

For SAEs causal relationship will also be assessed for other medication and study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

7.3. COLLECTION AND REPORTING

7.3.1. Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 28 days following the last dose of study treatment. All adverse events should be followed until recovery to baseline or Grade ≤1 or until deemed irreversible.

Adverse events occurring after 28 days following the last dose of study treatment should also be reported, if considered related to study treatment. Aforementioned all adverse events also must be followed until recovery to baseline or Grade ≤1 or until deemed irreversible.

Patients may receive local standard of care as permitted by protocol for treatment of comorbidities and/or management of adverse events.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The method of recording, evaluating, and assessing causality of AEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

7.3.2. Serious Adverse Events

The Investigator must report any SAEs to the Sponsor and/or designated CRO within 24 hours of becoming aware of the event. A detailed instruction is provided in Appendix 2.

- Prompt notification (within 24 hours, see Appendix 2) by the Investigator to the Sponsor and/or designated CRO of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- The Sponsor will report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB

that approved the protocol unless otherwise required and documented by the IEC/IRB.

7.3.3. Adverse Events of Special Interest

Not Applicable

7.4. ADVERSE EVENTS BASED ON EXAMINATIONS AND TESTS

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfill any of the following criteria unless clearly due to progression of disease under study or underlying disease:

- Test results associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
- Test results that require additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
- Test results that lead to a change in study treatment dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Test results considered to be an AE by the Investigator or Sponsor.

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

7.4.1. Adverse events based on Potential Hy's Law Criteria

If a patient demonstrates a concomitant elevation of AST or ALT and total bilirubin that meet the liver chemistry stopping criteria in Section 5.4.1.6 (which may be an indicator of Hy's law or potential hepatotoxicity), it must be reported to the Sponsor and/or designated CRO within 24 hours as an SAE. Prompt reporting of cases meeting potential Hy's Law criteria is required for compliance with regulatory guidelines. Details of identification of potential Hy's Law cases and actions to take are detailed in Section 5.4.1.6.

7.5. ADVERSE EVENTS BASED ON DISEASE PROGRESSION

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the study treatment is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Progression of the malignancy under study, including signs and symptoms progression, should not be reported as a serious adverse event. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event.

7.6. ADVERSE EVENTS BASED ON NEW CANCERS

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

7.7. OVERDOSE

For this study, any greater dose than intended will be considered an overdose.
No specific treatment for overdose is known. The treatment given to the patient in case of overdose should be symptomatic and supportive.
In the event of an overdose, the Investigator/treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the patient for AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in EDC.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

7.8. PREGNANCY

All pregnancies occurred throughout the study, from date of randomization until 24 weeks following last dosing of study treatment in female patients and female partners of male patients should be reported to the medical monitor. A detailed instruction is provided in Appendix 3.
If a pregnancy is reported, the Investigator should inform the Sponsor and/or designated CRO within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered to be SAEs.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

The Investigator must follow-up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor and/or designated CRO on the pregnancy outcome report form within 30 days after he/she has gained knowledge of normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study treatment) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

7.9. STANDARD TREATMENT AFTER STUDY COMPLETION

Upon discontinuation of study treatment, patients will be treated in accordance with the regional standard of care (SoC).

7.10.OTHER SAFETY CONSIDERATION

Not Applicable

8. STATISTICAL CONSIDERATIONS

The statistical considerations summarized in this section outline the plan for data analysis of this study. Any deviations from the planned analyses will be described and justified in the final integrated study report.

The aim of the study is to compare the efficacy and safety of lazertinib with gefitinib.

The primary analysis will be performed when approximately 207 PFS events have occurred.

The key secondary endpoints of OS in the overall population will be tested after the primary PFS analysis in a hierarchical procedure at the time of the PFS analysis. Other secondary efficacy endpoints will be analyzed at the time of the PFS analysis, including ORR, DoR, DCR, depth of response and time to response at a 2-sided significance level of 5%.

In addition, a final analysis of OS will be performed at approximately 50% maturity, when approximately 200 death events (across both arms) have occurred. The alpha will be split between the two analyses to provide strong control of the family-wise error rate (See Section 8.7.10 for further detail).

8.1. SAMPLE SIZE DETERMINATION

The median PFS for gefitinib from the previous conducted randomized phase III study were 9.2 to 10.9 months ([18]Mok TS et al, 2009; [19]Mitsudomi T et al, 2010; [20]Maemondo M et al, 2010; [21]Wu YL et al, 2017). A median PFS of 10.5 months for the gefitinib arm has been assumed.

To provide 90% power at a two-sided 5% significant level, approximately 207 progression-free survival events will be required to detect a hazard ratio of 0.64 (for median PFS of 16.5 months in lazertinib and 10.5 months in gefitinib). The primary analysis is expected to conduct at around 27 months, assuming approximately 380 patients are randomized over a period of 18 months with 1:1 ratio.

In order to randomize 380 patients, approximately 670 EGFRm+ patients will need to be screened. Sample size estimates have been calculated using PASS version 16.

8.2. POPULATIONS FOR ANALYSES

The analyses of data will be based on different analyses populations according to the purpose of the analyses.
For purposes of analysis, the following analysis sets are defined:

- Screened set: All patients who signed the ICF (including screening failures).
- Full analysis set (FAS): The FAS will include all randomized patients. Statistical analyses will be based on study treatment groups as per randomization, irrespective of the study treatment actually received. Safety analysis set: The safety analysis set will consist of all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment they actually received. A precise definition of "as actually received" will be added in the statistical analysis plan.
- Pharmacokinetic analysis set: Patients who have at least 1 measurable concentration collected post-dose, supported by the relevant date and time of sample collection; and the relevant dosing date and time on the day of PK sampling and immediately before pre-dose PK sampling.
- Centrally confirmed EGFR analysis set (cEAS): The cEAS will be a subset of the FAS and comprises all patients who have centrally confirmed EGFRm+ with either Ex19del or L858R substitution mutations.
- [redacted]
- [redacted] CCI [redacted]

The FAS will be the primary analysis set for all efficacy analyses. Further details will be provided in the Statistical Analysis Plan (SAP).

8.3. PATIENT DISPOSITION

The number of patients in the FAS, safety analysis sets, pharmacokinetic analysis set, cEAS, iFAS, and cross-over analysis set will be summarized by treatment and by institute. The screened set will only be summarized overall. Screening failures (i.e., patients who signed the ICF but are not received at least 1 dose of study treatment) and the associated reasons for failure will be tabulated overall.

All randomized patients will be accounted for in the patient disposition table. The number and percentage of patients will be presented for discontinued patients, and for each reason for discontinuation by treatment. Reasons for discontinuation of study treatment will be listed including the study day of treatment discontinuation and will be summarized by treatment.

8.4. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics, baseline characteristics, extent of disease, WHO performance status, and smoking status of the patients will be listed for each patients and summarized by treatment for the FAS.

Baseline information (e.g., medical and surgical history), prior chemotherapy, prior radiotherapy and concomitant medications (baseline and post first dose) will also be listed individually for each patient and summarized by treatment.

8.5. PRIOR AND CONCOMITANT MEDICATION AND CONSERVATIVE TREATMENT

Prior and concomitant medications will be presented for the safety analysis set and summarized by treatment.

Prior medication is defined as any medication taken within the period from 28 days before first dose of study treatment. Concomitant medication is defined as any medication taken during the treatment and until 28 days following the last dose of study treatment.

Prior and concomitant medications will be coded using latest version of World Health Organization Drug Dictionary (WHO-DD).

Prior and concomitant medications will be summarized separately by ATC level 1, ATC level 2, and preferred name. A listing will be provided with relevant information for prior and concomitant medications for the safety analysis set.

8.6. ASSESSMENT OF TREATMENT COMPLIANCE

Exposure to study treatment (i.e., total amount of study treatment received) will be listed for all patients.

Total exposure and total time on study (date of last dose minus date of first dose) will be summarized by the following: mean, standard deviation, minimum, maximum, median, and number of observations. In addition, the number and percentage of patients with at least 1 dose interruption/dose delay and at least 1 dose reduction will be presented separately for the initial period defined as 21 days (Cycle 1) and for any time following this initial period of the study.

8.7. ANALYSES

The SAP will be developed and finalized around the time of first patient in. Below is a summary of planned statistical analyses of the primary and secondary endpoints. Further details are presented in the SAP.

8.7.1. Calculation or Derivation of Variables

8.7.1.1. Investigator RECIST v1.1-based Assessments

From the investigator review of the imaging scans, the RECIST tumor response data will be used to determine each patient visit response according to RECIST v1.1.

At each visit, patient will be programmatically assigned a RECIST v1.1 visit response of complete response, partial response, stable disease, or progressive disease depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumor assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable unless there is any evidence of progression, in which case the response will be

assigned as progressive disease.

The data from the investigator's RECIST v1.1 assessment will be used as a primary analysis.

8.7.1.2. BICR of RECIST v1.1-based Assessments

The BICR of radiological imaging data will be carried out using RECIST v1.1. All radiological scans for all patients (including those at unscheduled visits or outside visit windows) will be provided to the BICR. All imaging scans will be reviewed by 2 independent radiologists using RECIST v1.1 criteria and will be adjudicated if required. The independent reviewers will be blinded to treatment.

Tumor assessment will be performed using CT or MRI of the chest and abdomen (including the liver and adrenal glands) and other regions as clinically indicated. For each patient, the BICR will define the overall visit response date (complete response, partial response, stable disease, progressive disease, or not evaluable) and the relevant scan dates for each timepoint (i.e., for visits where response or progression is not identified). If a patient has had a tumor assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (unless there is any evidence of progression in which case the response will be assigned as progressive disease). Progression-free survival will be derived from the overall visit response date and the scan dates. A sensitivity analysis of PFS will be performed based on data assessed by BICR for all patients.

Further details of BICR will be documented in the independent review charter.

8.7.2. Efficacy Analyses

8.7.2.1. Primary Efficacy Analysis

Progression free survival (PFS)

The primary efficacy endpoint is PFS. PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) whichever comes first based on investigator assessment using RECIST v1.1. Patients who have not progressed or have not died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.
If the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the last evaluable RECIST v1.1 assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at Day 1 unless they die within 2 visits of baseline.
The PFS time will always be derived based on scan/assessment dates not visit dates.

The primary efficacy endpoint will be analyzed based on the FAS according to the treatment group patients were randomized and the strata they were assigned to at randomization.
PFS in the FAS will be analyzed using a log-rank test stratified by mutation type (Ex19del versus L858R) and race (Asian versus non-Asian) using the Breslow approach for handling ties. PFS will be displayed using Kaplan-Meier plot by treatment group. The number of events, medians, and 95% confidence intervals of the medians (calculated from the Kaplan-Meier estimate), and proportion of patients without an event at 12, 18, and 24 months will be

summarized for each treatment group. Additionally, the hazard ratio for PFS will be calculated, along with its 95% confidence intervals, from a stratified Cox model using the same stratification factors as for the log-rank test.

8.7.2.2. Secondary Efficacy Analyses

Objective response rate (ORR)

ORR is defined as the percentage of patients with measurable disease with at least one visit response of complete response (CR) or partial response (PR).

A visit response of CR is defined when all target lesions (TLs) and non-target lesions (NTLs) present at baseline have disappeared (with the exception of lymph nodes which must be <10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response which occurred after a further anticancer therapy was received will not be included in numerator of the ORR calculation (where the FAS will be the denominator).

ORR will be analyzed a logistic regression stratified by mutation type (L858R vs ex19del) and race (Asian vs non-Asian). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence intervals.

A summary of all responses will also be presented by treatment group.

ORR will also be summarized by each stratification factor.

Duration of Response (DoR)

DoR is defined as the time from the date of first documented response (CR or PR) until the date of documented progression or death, whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

If a patient does not progress following a response, then his/her duration of response will use the PFS censoring time.

The analysis of DoR will be stratified by the same covariates as the primary analysis.

DoR in responding patients will be summarized and the number of responding patients with a duration of response (>6; >9; >12; >15 months) will be presented by treatment group. A Kaplan-Meier plot and median DoR with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented by treatment group.

Disease control rate (DCR)

DCR is defined as the percentage of patients who have a best overall response of CR or PR or stable disease (SD at ≥ 6 weeks, prior to any PD event). The 6 week time point will allow for a visit window and be defined as on or after study day 35 (allowing for the visit window).

DCR will be analyzed using the same method as the analysis of ORR.

Depth of response

Depth of response will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of target lesions in

the absence of new lesions or progression of non-target lesions compared to baseline. The absolute change and percentage change from baseline in the sum of tumor size at each assessment will be calculated.
The best change in tumor size (defined as the maximum reduction from baseline or the minimum increase from baseline, in the absence of a reduction) will include all assessments prior to progression or start of subsequent anti-cancer therapy. Missing target lesion data at visits may be imputed using appropriate imputation rules.
Depth of response will be examined by summarizing the absolute change in target lesion tumor size from baseline, and percentage change in target lesion tumor size from baseline using descriptive statistics and presented at each timepoint and by randomized treatment group.
The effect of lazertinib on best percentage change in tumor size will be estimated from an analysis of covariance model with treatment group as a fixed effect and baseline sum of target lesion diameter, mutation type (L858R versus Ex19del) and race (Asian versus non-Asian) as a covariate. The number of patients, unadjusted mean, and least squares means for each treatment group will be presented, together with the difference in least squares means, 95% confidence interval, and corresponding p-value.

Time to response (TTR)
TTR is defined as the time from the date of randomization until the date of first documented response.
A summary statistics will be produced for TTR, by treatment group.

Overall survival (OS)
OS is defined as the time from the date of randomization until the date of death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.
OS will be analyzed using the same methodology and model as for the analysis of PFS provided there are sufficient events available for a meaningful analysis (>20 deaths; if not, descriptive summaries will be provided). The number of events, median (calculated from the Kaplan Meier estimate), and proportion of patients without an event at 6, 12, 18, 24 and 36 months will be summarized by treatment group. As appropriate, summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up, and have withdrawn consent will be presented for each treatment group.
The analysis of OS will be conducted at 2 time points:

- At the time of the primary analysis of PFS
- After approximately 45 months survival follow-up from the first patient randomized. Approximately 200 deaths will be anticipated at this time.

[redacted]
CCI

Additional analysis of overall survival adjusting for the impact of patients randomized to gefitinib, who subsequently receive lazertinib would be completed if this treatment sequence occurs in a significant proportion of patients. Further detail will be provided in the SAP.

Health-Related Quality of Life (PROs)

EORTC QLQ-C30, EORTC QLQ-LC13:
An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/items, the functional scales and the global health status scale in the EORTC QLQ-C30, and for each of the symptom scales/items in the EORTC QLQ-LC13 according to the EORTC QLQ-C30 scoring manual and EORTC QLQ-LC13 instructions.
Higher scores on the global health status and functioning scales indicate better health status/function. Higher scores on the symptoms scales indicate greater symptom burden.
Changes in score compared to baseline will be evaluated. A minimum clinically meaningful change is defined as a change in the score from baseline of ≥5 for scales/items from the EORTC QLQ-LC13 and ≥10 for scales/items from the EORTC QLQ-C30 ([22]Osoba D et al, 1998).
At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable or worsening. Further details will be provided in the SAP.
The PRO questionnaire data will be analyzed using a mixed model for repeated measure (MMRM) analysis of the change from baseline in PRO score for each visit. The MMRM model will include patient as a random effect, treatment, visit, treatment by visit interaction as a fixed effects, baseline PRO and baseline PRO score by visit interaction as a covariate. The within-patient correlation will be modeled using the unstructured covariance matrix in the mixed model. The restricted maximum likelihood method will be used. Adjusted mean estimates per treatment group and corresponding 95% confidence intervals will be presented along with an estimate of the treatment difference, and 95% confidence interval. No p-values will be presented. The treatment-by-visit interaction will remain in the model regardless of significance.

Time to symptom deterioration:
For each of the symptom scales/items in EORTC QLQ-C30 and EORTC QLQ-LC13 as well as global health status, time to symptom deterioration will be defined as the time from randomization until the date of first clinically meaningful symptom deterioration or death (by any cause) in the absence of a clinically meaningful symptom deterioration.
Patients whose symptoms have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data, they will be censored at Day 1.

Symptom Improvement Rate:
The symptom improvement rate will be defined as the percentage of patients with 2 consecutive assessments which showed a clinically meaningful improvement in that symptom from baseline. The denominator will consist of a subset of the FAS who have a baseline symptom score ≥5 (EORTC QLQ-LC13) or ≥10 (EORTC QLQ-C30).

EQ-5D-5L

The EQ-5D VAS scale will be analyzed using the same method as the analysis of global health status in EORTC QLQ-C30. For the EQ-5D health status profiles, descriptive statistics including the proportions of patients reported having each response level at each time point will be reported.

8.7.3. Exploratory Analyses

CCI

CCI

CCI

CCI

CCI

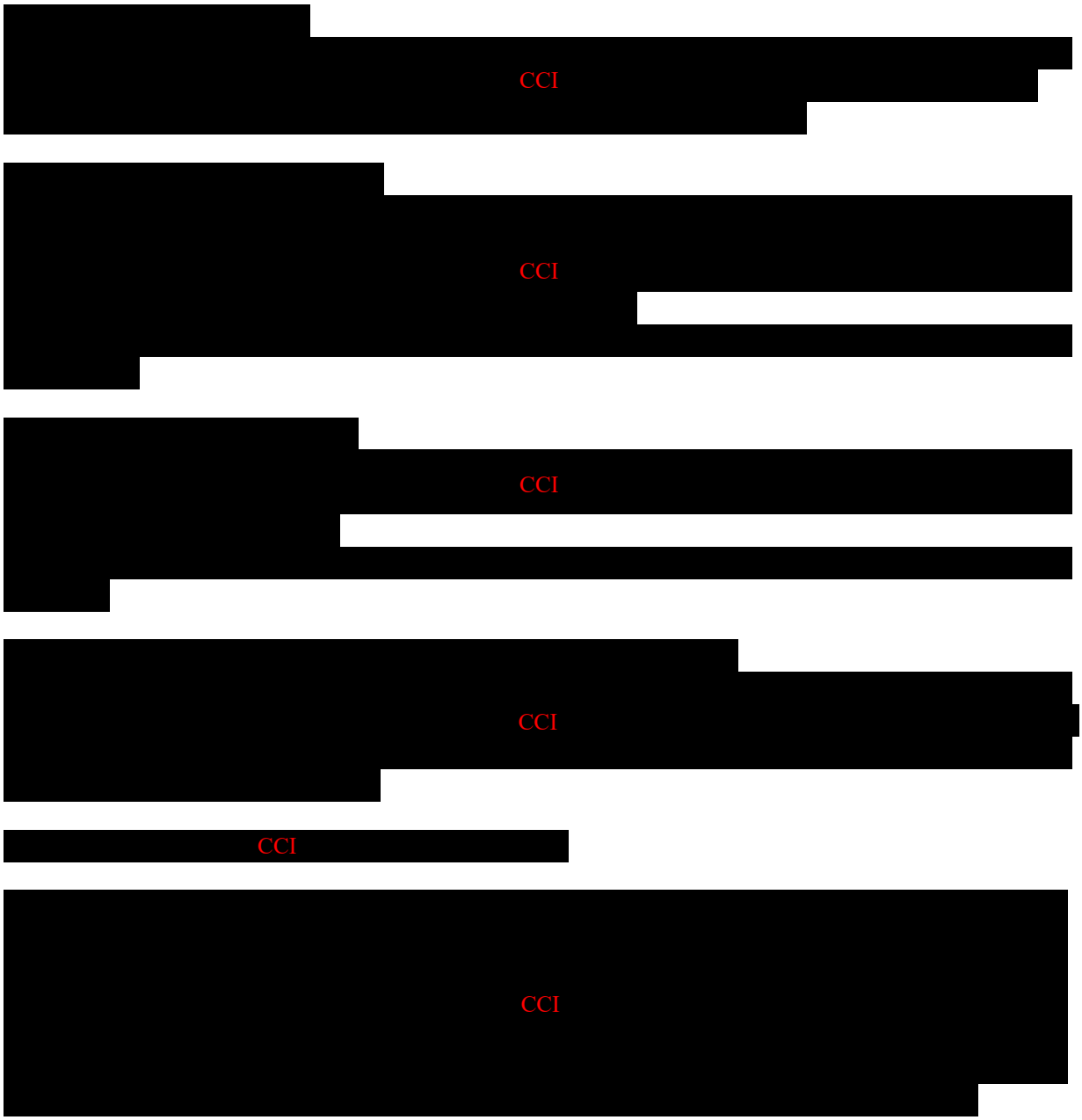
CCI

CCI

CCI

CCI

CCI



8.7.4. Pharmacokinetic Analyses

Pharmacokinetic analysis of the plasma and CSF concentration data for lazertinib will be performed by the designated bioanalytical laboratory or third party. For each patient, the following concentrations will be listed.

- Plasma concentrations of lazertinib at pre-dose, 1 to 3 hours, and 4 to 6 hours post-dose on Day 1 of Cycles 1, 2, 5, 9, and 13
- CSF concentrations of lazertinib

Plasma concentrations of lazertinib will be summarized by nominal sampling time. CSF concentrations of lazertinib will also be summarized. The summary statistics will be presented by number of patients, arithmetic mean, standard deviation, arithmetic coefficient of variation,

median, minimum, maximum, geometric mean, and geometric coefficient of variation. Further details will be provided in the SAP.

Pharmacokinetic data from this study will be analyzed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allow. PK data collected in this study may also be combined with similar data from other lazertinib studies and explored using population PK and/or pharmacokinetic-pharmacodynamic approach. The results of any such analyses will be reported separately from the final Clinical Study Report.

8.7.5. Pharmacodynamic Analyses

Not Applicable

8.7.6. Pharmacogenomic / Pharmacogenetic Analyses

Refer to Appendix 4.

8.7.7. Biomarkers Analyses

The data collected from biomarkers will be analyzed and reported separately.

8.7.8. Safety Analyses

All patients who receive at least one dose of study treatment will be included in the assessment of the safety profile. All safety analyses will be performed on the safety analysis set. At the end of the study, appropriate summaries of all safety data will be produced.
The safety parameters are AEs, clinical laboratory parameters, vital signs, ECG parameters and physical examination. For each safety parameter, the last non-missing safety assessment made before the date of the first administration of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients, mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency distribution (number and percentage of patients).

8.7.8.1. Adverse Events

AEs will be coded using MedDRA. The CTCAE grade will be assigned by the Investigator. Severity of all AEs will be graded according to the CTCAE, v5.0.

Any AE occurring before study treatment will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring until 28 days following the last dose of study treatment will be included in the AE summaries. Any AEs in this period that occur after a patient has received further anticancer therapy (following discontinuation of study treatment) will be flagged in the data listings. AEs occurring after 28 days following the last dose of study treatment will be listed separately, but not included in the summaries.

The number and percentage of patients reporting AEs, SAEs including deaths, AEs considered related to study treatment, and AEs leading to discontinuation from study treatment will be tabulated by treatment, systemic organ class, and preferred term by each treatment group.

The AEs by maximum severity and relationship will also be tabulated by treatment group, system organ class and preferred term. If more than one AE is coded to the same preferred term for the same patients, the patients will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study treatment.

Listings of AEs, SAEs, deaths, and AEs leading to discontinuation will be produced by patients.

8.7.8.2. Clinical Laboratory Parameters

Descriptive statistics for laboratory test results (hematology, clinical chemistry, and urinalysis) will be provided for the observed values and changes from baseline and each observed time point by treatment group.

For all laboratory variables, which are included in the CTCAE v5.0, the CTCAE grade will be calculated.

Any qualitative assessments will be summarized for all patients using the number of patients with results of negative, trace, or positive.

A shift table (abnormal low/normal/abnormal high) will be provided for laboratory tests. In addition, shifts in toxicity grade from baseline to the worst toxicity grade will be provided for safety analysis set. A supportive listing of patients with clinical significant changes in post-baseline values will be provided, including the patient number, study site and baseline and post baseline values.

8.7.8.3. Vital Signs

Descriptive statistics by treatment group will be provided for the observed values and changes from baseline at each observed time point with vital signs assessment.

8.7.8.4. 12-lead Electrocardiogram

ECG parameters will be summarized by observed time point using appropriate descriptive statistics by treatment group. For all ECG variables, which are included in the CTCAE v5.0, the CTCAE grade will be calculated.

A shift table (abnormal NCS/normal/abnormal CS) will be provided for ECG overall evaluation. In addition, shifts in toxicity grade from baseline to the worst toxicity grade will be provided for safety analysis set. A supportive listing of patients with clinically significant changes in post baseline 12 lead ECG findings will be provided, including the patient number, study site, and baseline and post-baseline findings.

8.7.8.5. Physical Examination

Results of the physical examinations will be summarized by observed time point using appropriate descriptive statistics by treatment group.

The number and percentage of patients with clinically significant changes in post baseline

physical examination findings will be tabulated by treatment group. A supportive listing of patients with clinically significant changes in post baseline physical examination findings will be provided, including the patient number, study site, and baseline and post baseline findings. A listing of physical examination findings at screening will be provided as part of the medical history listing.

8.7.9. Subgroup Analyses

The subgroup analysis will be performed by baseline potential prognostic factors by comparing PFS between treatment group (i.e., using a Cox-Proportional Hazards Model) including the following groups.

- Mutation type (Ex19del versus L858R)
- Race (Asian versus Non-Asian)
- Brain metastatic at entry
- Gender (Male versus Female)
- Age at screening (<65 versus ≥65)
- Smoking history
- WHO Performance Status (0 versus 1)

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events per level in a subgroup), the relationship between that subgroup and PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

No adjustment to the significance level for testing will be made since the subgroup analysis may only be supportive of the primary analysis of PFS. Further details will be provided in the SAP.

8.7.10. Multiple Testing Strategy

In order to provide strong control of the type I error rate, α=0.05 (two-sided), the primary endpoint of PFS and secondary endpoints of OS, will be tested in this sequential order. If any previous analysis in the sequence is not statistically significant, the alpha will not be transferred to subsequent analyses.

Sequential order of endpoints

1. PFS
2. OS

One analysis of the primary endpoint (PFS) is planned.

Two analyses of OS are planned; one interim at the time of PFS and a final analysis. The final OS analysis is planned to be conducted when the OS data is approximately 50% mature (approximately 200 deaths).

A 2-sided 5% alpha will be used in all testing, with the exception of OS endpoint. Since two analyses of OS are planned, the Lan-DeMets approach with the Pocock-type spending function will be used to maintain an overall 2-sided 5% type I error across the two planned analyses of

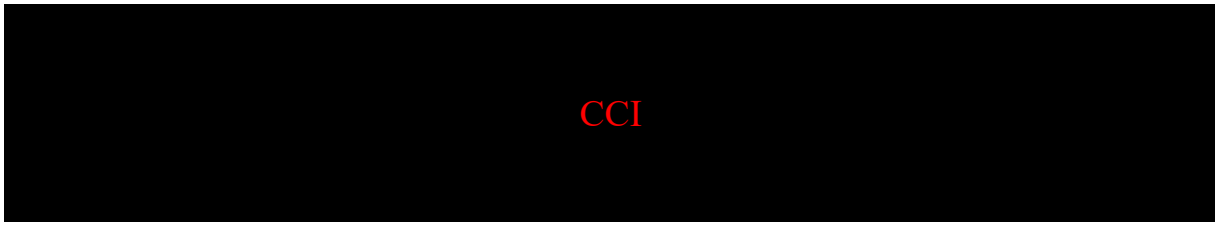
OS.

8.7.11. Independent Data Monitoring Committee (IDMC)

An IDMC will be convened, and will meet initially when approximately 100 patients have been randomized and followed up for 3 months (estimated to be 6 months from the first patient randomized). Thereafter, the IDMC will conduct further reviews of safety data, for example, when global recruitment ends (estimated to be approximately 18 months from first patient randomized). Further meetings for review of safety data and supportive efficacy data from all patients may be convened at the discretion of the IDMC to evaluate whether the trial should be stopped due to potential harm to patients.

The IDMC will review safety and supportive efficacy assessments and make recommendations to continue, amend, or stop the study based on findings. SAEs, AE, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. Note no alpha adjustment is required for the IDMC data assessment as the stopping boundary would allow for ruling out harm only. Full details of the number of progression events, number of patients and boundary hazard ratio to determine stopping for harm will be documented in the IDMC Charter prior to the first IDMC safety review meeting. The boundary will not be considered binding and will be used in addition to the accumulating available safety data to decide whether to continue the trial as planned, stop, or modify the trial.

8.7.12. Sensitivity Analyses



9. ADMINISTRATIVE SECTION

9.1. COMPLIANCE

9.1.1. Compliance with the Protocol and Protocol Revisions

This study will be conducted in accordance with the protocol. A detailed instruction is provided in Appendix 1.

9.1.2. Monitoring

Representative(s) of the Sponsor and/or designated CRO must be allowed to visit all study sites periodically to assess the data quality and study integrity. On the site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by auditors from the Sponsor and/or designated CRO and the Institutional Review Board (IRB) or regulatory authorities' inspectors who must be allowed access to EDC system, source documents, other study files, and study facilities. The audit reports will be kept confidential.

The investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

9.1.3. Investigational Site Training

Site study personnel involved in the conduct of this study must be qualified by education, training, and experience for the appropriate performance of their respective task(s).

The Sponsor and/or designated CRO will provide appropriate investigational staff training prior to study initiation. Training topics will include but are not limited to: ICH-GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrollment method.

For study sites using the EDC system including electronic CRF system provided by The Sponsor and/or designated third party, each individual making entries and/or corrections on EDC system and/or each individual electronically signing electronic CRFs must meet the training requirements offered by the Sponsor and/or designated CRO and must only access the EDC system using the unique user account provided by the Sponsor and/or designated third party. User accounts are not to be shared or reassigned to other individuals.

For EDC system, corrections are made through the EDC system provided by the Sponsor and/or designated third party that generates an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The system also prompts the user to document the reason for the change which is also recorded in the audit trail.

9.2. RECORD RETENTION

Records and documents pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. A detailed instruction is provided in Appendix 1.

9.2.1. Data on Electronic Data Capture System

All patient data relating to the study will be recorded on EDC unless transmitted to the Sponsor or designee electronically (e.g., ECG result data). A detailed instruction is provided in Appendix 1.

9.2.2. Investigational Product Records

It is the responsibility of the principal investigator to ensure that a current record of investigational product disposition is maintained at each study center where investigational product is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- quantity received and placed in storage area
- quantity currently in storage area
- label ID number or batch number and use by date or re-test date
- dates and initials of person responsible for each investigational product inventory entry/movement
- quantity dispensed to and returned by each patient, including unique patient identifiers
- quantity transferred to another areas/centers for dispensing or storage

- any details of non-study use (e.g., lost, wasted, broken, etc.)
- quantity returned to the sponsor

The Sponsor and/or designated CRO will provide forms to facilitate inventory control if the staff at the investigational center does not have an established system that meets these requirements.

9.3. RETURN AND DESTRUCTION OF INVESTIGATIONAL PRODUCT

9.3.1. Return of Investigational Product

All unused and/or partially used investigational product must be returned to the Sponsor and/or designated CRO. After receiving approval of the Sponsor and/or designated CRO in writing, the designated CRO is responsible for returning all unused or partially used study treatment to the Sponsor and/or designated third party or for preparing the study treatment for destruction via incineration. If required, destruction of study treatment following completion of Sponsor confirmed accountability can be proceeded in the site according to the regulation of jurisdiction which the study being conducted.

9.3.2. Destruction of Investigational Product

The Sponsor and/or designated third party will destroy all used and unused study treatment as per their SOP and relative regulation.

9.4. RETENTION AND DESTRUCTION OF HUMAN BIOLOGIC MATERIALS

Human biological materials will be stored at The Sponsor and/or designated third party during a specified period as described in the informed consent. At the end of the period, they will be destroyed in accordance with their SOP and relative regulation.

9.5. PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor. Any publications or abstracts arising from this study require prior written approval from the Sponsor and must adhere to the Sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). A detailed instruction is provided in Appendix 1.

10. GLOSSARY OF TERMS

Term	Definition
Adverse Event	Any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient for clinical investigation administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory findings, for example), symptom, or disease temporally associated with the use of an investigational product.
Adverse Drug Reaction	In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Suspected Unexpected Serious Adverse Reactions	Any Unexpected Adverse Drug Reaction that at any dose: • Results in death • Is life-threatening • Requires inpatient hospitalization or prolongation of existing hospitalization • Results in persistent disability/incapacity or substantial disruption of the ability to conduct normal life functions. • Is or results in a congenital anomaly/birth defect • Is medically important* * Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or new malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, a concomitant elevation of AST or ALT and total bilirubin that meet the liver chemistry stopping

	criteria in Section 5.4.1.6 (which may be an indicator of Hy's law or potential hepatotoxicity).
Unexpected Adverse Drug Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

11. LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BBB	Blood-brain barrier
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BM	Brain metastasis
BUN	Blood urea nitrogen
cfDNA	Circulating cell-free deoxyribonucleic acid
CFR	Code of Federal Regulation
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CS	Clinically significant
CSF	Cerebrospinal fluid
CT	Computerized tomography
CTA	Clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DGR	Dangerous Goods Regulations
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
(e)CRF	(Electronic) case report form(s)
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	Euro-Quality of Life-5 Dimension-5 level
Ex19del	Exon 19-deletion
FAS	Full analysis set
F/U	Follow-up
GCP	Good Clinical Practice
γ–GTP	Gamma-glutamyl transpeptidase
HbsAg	Hepatitis B virus surface antigen
hCG	Human chorionic gonadotropin
HCl	Hydrogen chloride
HCTZ	Hydrochlorothiazide
HIV	Human immunodeficiency virus

HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IATA	International Airline Transportation Association
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICR	Independent central review
iDCR	Intracranial disease control rate
IDMC	Independent data monitoring committee
iDoR	Intracranial duration of response
IEC	Independent ethics committee
iFAS	Intracranial full analysis set
IgM	Immunoglobulin M
ILD	Interstitial lung disease
IM	Intra-muscular
IND	Investigational new drug
iORR	Intracranial objective response rate
iPFS	Intracranial progression-free survival
IRB	Institutional review board
IRT	Interactive response technology
L858R	Leucine-to-arginine substitution in Exon 21
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
m+	Mutation positive
MRI	Magnetic resonance imaging
MRP4	Multidrug resistance-associated protein 4
MUGA	Multiple gated acquisition
NA	Not applicable
NCI	National Cancer Institute
NCS	Not clinically significant
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PD	Progression of disease
PFS	Progression-free survival
PFS2	Time to second progression
PK	Pharmacokinetic(s)
P-gp	p-glycoprotein
PR	Partial response
PRO	Patient-reported outcome(s)
QD	Quaque die (daily)
QTc	Corrected QT interval

RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SoA	Schedule of activities
SoC	Standard of care
SOP	Standard operational procedure
SUSAR	Suspected unexpected serious adverse reaction
T790M	Threonine-to-methionine substitution
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TTR	Time to response
ULN	Upper limit of normal
UN number	United Nations numbers
US	United States
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

12. REFERENCES LIST

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.

[2] Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer. 2010;10(11):760-774.

[3] Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009;28 Suppl 1:S24-31.

[4] Juchum M, Günther M, Laufer SA. Fighting cancer drug resistance: opportunities and challenges for mutation-specific EGFR inhibitors. Drug Resist Updat. 2015;20:12-28.

[5] Engel J, Becker C, Lategahn J, Keul M, Ketzer J, Mühlenberg T, et al. Insight into the inhibition of drug-resistant mutants of the receptor tyrosine kinase EGFR. Angew Chem Int Ed. 2016;55(36):10909-10912.

[6] J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125.

[7] Engel J, Lategahn J, Rauh D. Hope and disappointment: covalent inhibitors to overcome drug resistance in non-small cell lung cancer. ACS Med Chem Lett. 2015;7(1):2-5.

[8] Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, Uhlmann EJ, Wong ET, Dahlberg SE, Huberman MS, Costa DB. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer. 2015;88(1):108-111.

[9] Ahn MJ, Han JY, Lee KH, Kim SW, Kim DW, Lee YG, Cho EK, Kim JH, Lee GW, Lee JS, Min YJ, Kim JS, Lee SS, Kim HR, Hong MH, Ahn JS, Sun JM, Kim HT, Lee DH, Kim SH, Cho BC. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1–2 study. Lancet Oncol. 2019 Oct 3. pii: S1470-2045(19)30504-2. doi: 10.1016/S1470-2045(19)30504-2.

[10] Laporte S, Squifflet P, Baroux N, Fossella F, Georgoulias V, Pujol JL, Douillard JY, Kudoh S, Pignon JP, Quinaux E, Buyse M. Prediction of survival benefits from progression-free survival benefits in advanced non-small-cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomised trials. BMJ Open. 2013 Mar 13;3(3). pii: e001802. doi: 10.1136/bmjopen-2012-001802.

[11] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D,

Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

[12] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

[13] Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

[14] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

[15] EuroQol Group, EuroQol-a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

[16] Trippoli S, Vaiani M, Lucioni C, Messori A. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life Study Group of the Master 2 Project in Pharmacoeconomics. Pharmacoeconomics. 2001;19(8):855-63.

[17] Belani CP, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Fossella F; TAX 326 study group. Effect of chemotherapy for advanced non-small cell lung cancer on patients' quality of life. A randomized controlled trial. Lung Cancer. 2006 Aug;53(2):231-9.

[18] Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M; Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. New England Journal of Medicine 361.10 (2009): 947-957.

[19] Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M; Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. The lancet oncology 11.2 (2010): 121-128.

[20] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T; Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. New England Journal of Medicine 362.25 (2010): 2380-2388.

[21] Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, Migliorino MR, Pluzanski A, Sbar EI, Wang T, White JL, Nadanaciva S, Sandin R, Mok

TS; "Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial." The Lancet Oncology 18.11 (2017): 1454-1466.

[22] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.

Appendix 1. Regulatory, Ethical, and Study Oversight Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
  - Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor and/or designated CRO with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor and/or designated CRO to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and sub-Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized

representative.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor and/or designated CRO. Any patient records or datasets that are transferred to the Sponsor and/or designated CRO will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor and/or designated CRO in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor and/or designated CRO, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

Committees will be organized and operated. Full details regarding committees (e.g., IDMC, Steering Committee, BICR, etc.) will be documented in the specific charter prior to the first review meeting.

Dissemination of Clinical Study Data

When the final Clinical Study Report is completed, the Sponsor and/or designated CRO will provide the major findings of the study to the Investigator. A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinicalTrials.gov). The results may also be submitted for publication.

Data Quality Assurance

- All patient data relating to the study will be recorded on EDC unless transmitted to the Sponsor or designated third party electronically (e.g., ECG result data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing EDC.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in EDC.
- The Investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designated CRO is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into EDC by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study

agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor or designated CRO. No records may be transferred to another location or party without written notification to the Sponsor or designated CRO.
- All data generated by the site personnel will be captured electronically at each study center using EDC. Data from external sources (e.g., ECG result data) will be imported into the database. Once EDC clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the EDC page.
- The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in EDC that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the Sponsor at the earliest practicable time for review, but in any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. The Sponsor retains the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for purposes of filing a patent application.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

Major Protocol Violations Reporting

All potential major violations must be reported to the Sponsor and/or designated CRO immediately. A major violation is a violation of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Liability and Insurance

The Sponsor and/or designated CRO will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor and/or designated CRO with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of EDC entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit/inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor and/or designated CRO of the necessary support at all times.

Appendix 2. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study patient, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements) fulfill any of the following criteria unless clearly due to progression of disease under study or underlying disease: o Test results associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator. o Test results that require additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention. o Test results that lead to a change in study treatment dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. o Test results considered to be an AE by the Investigator or Sponsor. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be considered as an AE/SAE. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads

to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease under study).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death Disease progression can be considered as the worsening of a patient's condition attributable to NSCLC. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastases from the primary cancer under study should be considered as disease progression and not an AE. Death which are unequivocally due to disease progression should not be reported as an AE during the study. SAE term should be recorded as immediate cause of death, not "Death".
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. NOTE: The following hospitalizations are not considered SAEs in Sponsor clinical studies: • hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an "important medical event" or event life threatening) • elective surgery, planned prior to signing consent • admissions as per the protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission for purposes other than remedying ill health state and that are planned prior to entry into the study. Appropriate documentation is required in these cases • admission due to another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

Results in persistent disability/incapacity or substantial disruption of the ability to conduct normal life functions. • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is or results in a congenital anomaly/birth defect
Is medically important • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or new malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, a concomitant elevation of AST or ALT and total bilirubin that meet the liver chemistry stopping criteria in Section 5.4.1.6 (which may be an indicator of Hy's law or potential hepatotoxicity).

Recording and Follow-up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in EDC. • It is not acceptable for the Investigator to send photocopies of the patient's medical records in lieu of completion of the AE/SAE EDC page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor and/or designated CRO. In this case, all patient identifiers, with the exception of the patient number, will be blinded on the copies of the medical records before submission to the Sponsor and/or designated CRO. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Grade 1: Mild; Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Grade 2: Moderate; Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
AEs will be graded according to NCI-CTCAE v5.0.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

The investigator will assess causality for each adverse event, and answer 'yes (Certain, Probable/Likely, Possible, Unassessable/Unclassifiable)' or 'no (Unlikely, Not related)' to the following question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factor exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any Dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is there a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor and/or designated CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor and/or designated CRO with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- All AEs and special reporting situations, whether serious or non-serious, should be reported from the time a signed and dated ICF is obtained until 28 days following the last dose of study treatment. All adverse events should be followed until recovery to baseline or Grade ≤1 or until deemed irreversible.
- AEs occurring after 28 days following the last dose of study treatment should also be reported, if considered related to study treatment. Aforementioned all AEs also must be followed until recovery to baseline or Grade ≤1 or until deemed irreversible.
- The Investigator will submit any updated SAE data to the Sponsor and/or designated CRO.

SAE Reporting

SAE Reporting to the Sponsor and/or designated CRO

- The Investigator must submit the completed SAE form and any supporting documentation to the Sponsor and/or designated CRO within 24 hours of becoming aware of the event according to the Study reference manual.
- The Investigator and the Sponsor and/or designated CRO will review each SAE report and the Sponsor and/or designated CRO will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor and/or designated CRO will evaluate the expectedness according to the reference documents (Investigator's Brochure or package insert/summary of product characteristics for an approved product for gefitinib). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.
- SAE reporting process and contact information of the medical monitor can be found in the Study reference manual.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any AE that is serious, associated with the use of the study treatment, and unexpected (not listed in the investigator brochure) (SUSAR) has additional reporting requirements, as described below.

- Regulatory authorities, the Investigators and IEC/IRB (if required) will be notified

within 7 calendar days after the Sponsor and/or designated CRO learns of the event, if the SUSAR is fatal or life-threatening, associated with study treatment, and unexpected. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

- Regulatory authorities, the Investigators and IEC/IRB (if required) will be notified within 15 calendar days after the Sponsor and/or designated CRO learns of the event, if the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study treatment, and unexpected.
- The Sponsor and/or designated CRO will also provide annual safety updates to the regulatory authorities, the Investigators and IEC/IRB (if required) responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

Appendix 3. Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1.1. Premenarchal

1.2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- Documented bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations]

NOTE: Documentation can come from the site personnel's review of the patient's med ical records, medical examination, or medical history interview.

1.3. Post-menopausal female

- A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

Contraception Guidance:

Male Patients:

Male Patients who have not undergone a vasectomy should use reliable methods of contra ception from randomization until 24 weeks after discontinuation of study treatment.

Male Patients with female partners of childbearing potential are eligible to participate i f they agree to ONE of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male Patients must refrain from donating sperm from randomization until 2 4 weeks after the last dose of study treatment.

Male Patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from randomization until 24 weeks after the last dose of study treatment.

Female Patients

Female Patients should use reliable methods of contraception from the time of screening until 24 weeks after discontinuation of study treatment.

Female Patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

In addition, female Patients must refrain from donating ovum from randomization until 24 weeks after the last dose of study treatment.

Highly Effective Contraceptive Methods That Are User Dependent[1] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[2] • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent[1]
Implantable contraceptive method[2] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

NOTES:

[1] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

[2] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized from the time of screening until 24 weeks after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed a negative serum pregnancy test.
- Additional pregnancy testing may be repeated during the treatment period as necessary if clinically indicated.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male Patients with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in the study period, from randomization until 24 weeks following last dosing of study treatment.
- This applies only to male patients who are randomized.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor and/or designated CRO within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor and/or designated CRO. Generally, the follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who become pregnant

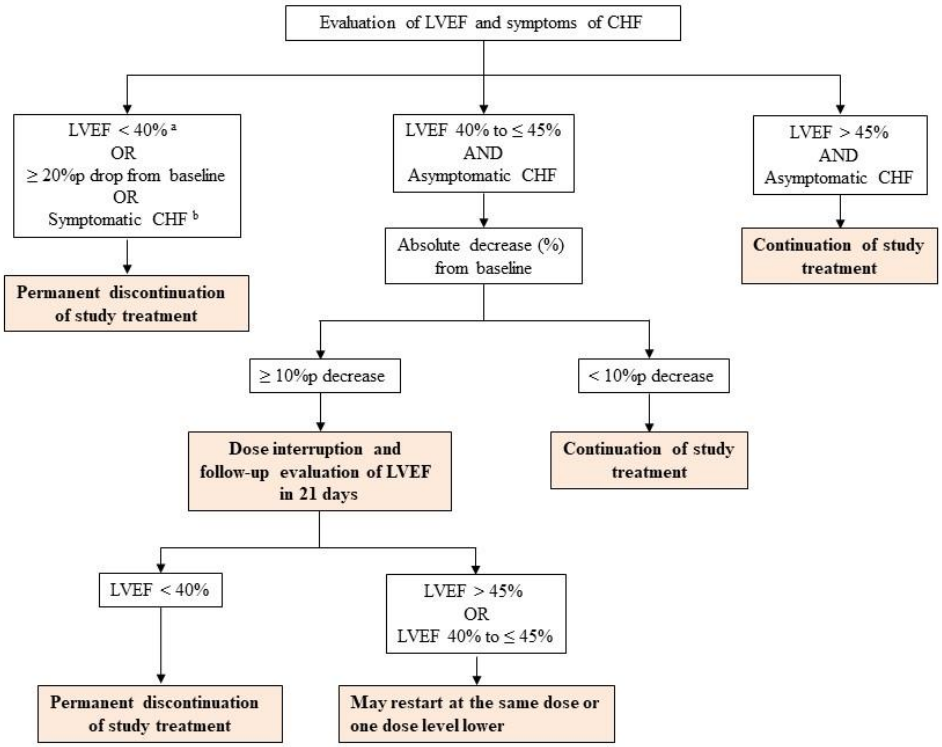
- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study, from randomization until 24 weeks following last dosing of study treatment.
- Information will be recorded on the appropriate form and submitted to the Sponsor and/or designated CRO within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect any follow up information on the patient and the neonate and the information will be forwarded to the Sponsor and/or designated CRO. Generally, follow up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to study treatment by the Investigator will be reported to the Sponsor and/or designated CRO. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will be withdrawn from the study treatment.

Appendix 4. Pharmacogenetic Research

Use/Analysis of DNA

- Genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to lazertinib or NSCLC with EGFR mutation status and related diseases. They may also be used to develop tests/assays related to lazertinib and NSCLC with EGFR mutation status. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to lazertinib.
- DNA samples will be analyzed for exploratory genetic research. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to lazertinib or drug of this class to understand study disease or related conditions.
- The results of genetic analyses will be reported separately and will not be part of the Clinical Study Report.
- The Sponsor or designated CRO/third party will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained for a maximum of 15 years following the finalization of the final Clinical Study Report or other period as per local regulations.

Appendix 5. Algorithm for Continuation, Dose Modification, or Discontinuation of Study Treatment Based on Decreases of LVEF Assessment



CHF = congestive heart failure; LVEF = left ventricular ejection fraction

[a] LVEF < 40% can be repeated within 21 days, and study treatment should be discontinued if LVEF < 40% is confirmed. Study treatment should be held while the repeat LVEF is obtained.

[b] Class ≥ 3 as defined by New York Heart Association (NYHA) classification (2014)

Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF)
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF)

Appendix 6. Guidance on Concomitant Medications regarding Drug Interaction with Study Treatment

LAZERTINIB

Lazertinib is an investigational product that currently has no available data on clinical drug interactions. Use of any other medications, folk remedies, natural/herbal products (e.g. Ginseng and other Traditional Chinese Medicine) should be discouraged in this study. Use of these folk remedies or products, as well as use of all nutritional supplements, vitamins, and all other concomitant medications should be recorded in the electronic case report form (eCRF).

Potent CYP3A4 inhibitors/inducers are prohibited for co-administration with lazertinib

According to *in vitro* data, the principal cytochrome P450 (CYP) enzyme involved in the metabolism of lazertinib is CYP3A4. Therefore, the following concomitants of medications, herbal products and/or ingestions of foods with known potent inhibitors/inducers of CYP3A4 should not be used for any patient receiving lazertinib (Table 1, Table 2). However this list is not meant to be exhaustive, and similar restrictions should be applied to other drugs known to potently modulate CYP3A4 activity. Appropriate medical judgment is required.

Table 1. Examples of potent CYP3A4 inhibitor

Contraindicated drugs	**Washout period prior to randomization**
boceprevir, clarithromycin[2], cobicistat, conivaptan, danoprevir, dasabuvir, diltiazem, elvitegravir, indinavir, ketoconazole, nelfinavir, paritaprevir, ritonavir[1,3], saquinavir[1,3], tipranavir,	2 days
grapefruit juice, lopinavir[1,3], telaprevir, telithromycin[3], troleandomycin	4 days
atazanavir, darunavir, mibefradil, nefazodone, ombitasvir ,voriconazole	1 week
itraconazole, posaconazole	2 weeks

[1]also see Table 3.
[2]also see Table 4.
[3]also see Table 5.

Table 2. Examples of potent CYP3A4 inducer

Contraindicated drugs	**Washout period prior to randomization**
phenytoin, rifapentine, St. John's wort	2 weeks

Table 2. Examples of potent CYP3A4 inducer

Contraindicated drugs	Washout period prior to randomization
carbamazepine, phenobarbital, rifabutin, rifampin (rifampicin)[1]	3 weeks

[1]also see Table 3.

BCRP/P-gp/MRP4 substrates may be allowed with caution

According to *in vitro* data, lazertinib has potent inhibitory effect on breast cancer resistance protein (BCRP) and weak inhibitory effect on p-glycoprotein (P-gp) and multidrug resistance protein 4 (MRP4). Therefore, the bioavailability of BCRP, P-gp or MRP4 substrate may increase by lazertinib. Co-administration of the following substrates is allowed with caution, and possible drug interaction should be closely monitored for any patient receiving lazertinib (Table 3). Please refer to their label before co-administration with lazertinib. However this list is not meant to be exhaustive, and similar restrictions should be applied to other drugs known to BCRP, P-gp or MRP4 substrate. Appropriate medical judgment is required.

Table 3. Examples of BCRP, P-gp or MRP4 substrate

Transporter	Drugs to use with caution
BCRP	abacavir, ciprofloxacin, coumesterol, daidzein, estrone-3-sulfate, 17β-estradiol sulfate, 17β-estradiol 17-(β-D-glucuronide), folic acid, genistein, nitrofurantoin, norfloxacine, ofloxacin[4], pitavastatin, pravastatin, quercetin, resveratrol, rosuvastatin, sulfasalazine, warfarin, zidovudine
P-gp	aliskiren, ambrisentan, bunitrolol, carvedilol, celiprolol, colchicine, cyclosporine A, dabigatran etexilate, digoxin, diltiazem, erythromycin[3], fentanyl, fexofenadine, ivermectin, loperamide, maraviroc, methadone[3], morphine, nelfinavir[1], posaconazole, ranitidine, ranolazine, rifampin (rifampicin)[2], ritonavir[1,4], saquinavir[1,4], saxagliptin, sirolimus, sitagliptin, tacrolimus[4], talinolol, tolvaptan
MRP4	acyclovir, adefovir, cefazolin, ceftizoxime, furosemide, hydrochlorothiazide[4], olmesartan, ritonavir[1,4], tenofovir

[1]also see Table 1.
[2]also see Table 2.
[3]also see Table 4.
[4]also see Table 5.

Drugs that are known to or may possibly prolong QT interval or induce Torsades de Pointes are prohibited for co-administration with lazertinib

The following drugs are known to or may possibly prolong QT interval or induce Torsades de Pointes should not be used for any patient receiving lazertinib (Table 4, Table 5). However this

list is not meant to be exhaustive, and similar restrictions should be applied to other drugs known to prolong QT interval or induce Torsades de Pointes. Appropriate medical judgment is required.

Table 4. Examples known to prolong QT interval or induce Torsades de Pointes

Contraindicated drugs	**Washout period prior to randomization**
anagrelide, ciprofloxacin, clarithromycin[1], cocaine (only medical use), domperidone, droperidol, erythromycin[2], ibutilide, levofloxacin, ondansetron, papaverine HCl (intra-coronary), procainamide, quinidine, sulpiride, sultopride, terlipressin, thioridazine	2 days
chlorpromazine, cilostazol, disopyramide, dofetilide, dronedarone, ibogaine, levosulpiride, moxifloxacin, sotalol	4 days
citalopram, escitalopram, flecainide, fluconazole, levomepromazine (ethotrimeprazine), roxithromycin, sevoflurane	1 week
methadone[2], pimozide, terodiline	2 weeks
azithromycin, donepezil, propofol	15 days
halofantrine, pentamidine	2 months
haloperidol	4 months
amiodarone, chloroquine	10 months

[1]also see Table 1.
[2]also see Table 3.

Table 5. Examples that may possible prolong QT interval or induce Torsades de pointes

Contraindicated drugs	**Washout period prior to randomization**
apomorphine, benperidol, clotiapine, dexmedetomidine, dolasetron, eliglustat, encorafenib, gemifloxacin, granisetron, hydrocodone-ER, isradipine, melperone, nicardipine, ofloxacin[2], oxytocin, perflutren lipid microspheres, pilsicainide, primaquine phosphate, prothipendyl, risperidone, saquinavir[1,2], telavancin, tetrabenazine, tiapride, tolterodine, tramadol, tropisetron, vardenafil	2 days

Table 5. Examples that may possible prolong QT interval or induce Torsades de pointes

Contraindicated drugs	**Washout period prior to randomization**
alfuzosin, clozapine, cyamemazine (cyamepromazine), deutetrabenazine, dextromethorphan/quinidine, ezogabine (retigabine), lacidipine, lopinavir[1,2]/ritonavir[1,2], mifepristone, moexipril/HCTZ[2], pasireotide, perphenazine, promethazine, telithromycin[1], venlafaxine	4 days
asenapine, atomoxetine, betrixaban, felbamate, imipramine (melipramine), ketanserin, nortriptyline, paliperidone, pipamperone, trimipramine, valbenazine, zotepine, zuclopenthixol (zuclopentixol, oral)	1 week
buprenorphine, delamanid, desipramine, iloperidone, lithium, maprotiline, mirabegron, mirtazapine, palonosetron, rilpivirine, tacrolimus[2], tizanidine	2 weeks
aripiprazole, clomipramine, efavirenz, memantine	3 weeks
artemether/lumefantrine, sertindole	1 month
fingolimod, flupentixol, pimavanserin	1.5 months
zuclopenthixol (zuclopentixol, IM injection)	3.5 months
artenimol/piperaquine	6 months
clofazimine	12 months
nusinersen	15 months
bedaquiline	28 months

[1]also see Table 1.
[2]also see Table 3.

GEFITINIB

Gefitinib is an approved drug indicated for the treatment of patients with advanced or metastatic non-small-cell lung cancer whose cancer cells have a mutation in the genes that make a protein called epidermal-growth-factor receptor (EGFR). In addition to the restrictions imposed by lazertinib, the following restrictions apply as prescribed by gefitinib in this study;

Drugs affecting gastric pH

Drugs that elevate gastric pH (e.g., proton pump inhibitors, H_2-receptor antagonists, and antacids) may reduce plasma concentrations of gefitinib. Patients should avoid concomitant use

of gefitinib with proton pump inhibitors, if possible. If treatment with a proton-pump inhibitor is required, Patients could take gefitinib 12 hours after the last dose or 12 hours before the next dose of the proton-pump inhibitor. Patients could take gefitinib 6 hours after or 6 hours before an H_2-receptor antagonist or an antacid.

Hemorrhage in Patients taking Warfarin

International normalized ratio elevations and/or hemorrhage have been reported in some patients taking warfarin while on gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or International normalized ratio.

Appendix 7. International Airline Transportation Association (IATA) Guidance Document

Labeling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg. Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix 8. EORTC QLQ C-30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9. EORTC QLQ LC-13

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 10.Euro-Quality of Life-5 Dimension-5 Level (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐