PPD

YUHAN

YH25448-301

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
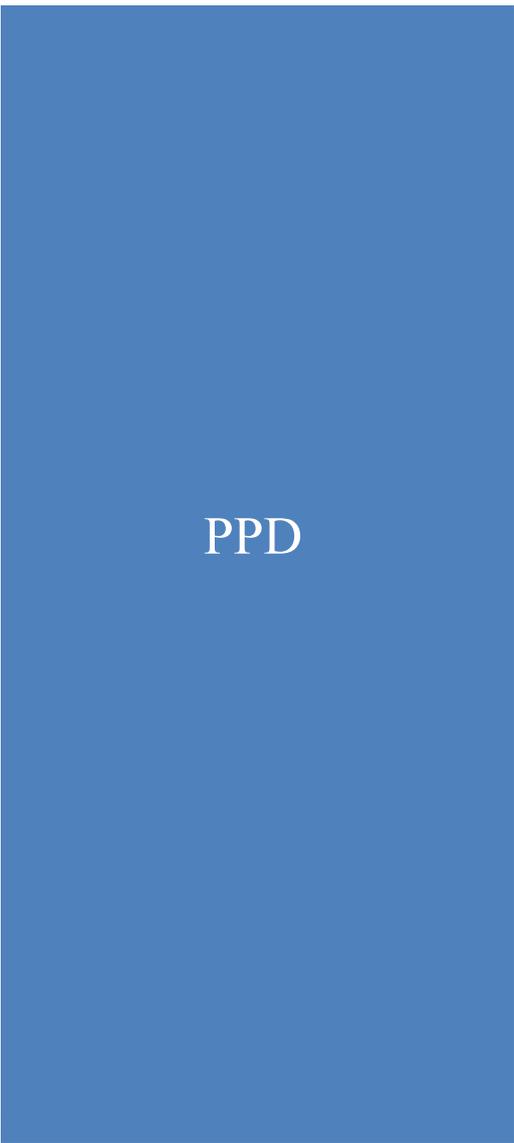
Statistical Analysis Plan

Version: 2.0 16Sep2022

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

Signatory		
Author:		
Reviewer:	PPD	
Reviewer:		

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft V0.1	27Dec2019	New Document
Draft V0.2	16Jan2020	Updated per sponsor comments received by 02Jan2020.
Draft V0.3	05Feb2020	Updated per sponsor comments received by 28Jan2020.
Draft V0.3	11Feb2020	Updated per Biostatistician comments received by 11Feb2020.
Draft V0.4	13Feb2020	Updated per sponsor comments received by 12Feb2020.
Final V1	14Feb2020	SAP V1 finalization.
Draft V1.1	28Apr2020	Updated as programming comments and Full Shell comments.
Draft V1.2	16Nov2020	Updated as DMC dry run programming comments and Full Shell comments.
Draft V1.3	29Apr2021	Updated as DMC2 dry run programming comments and Full Shell comments. • Appendix 3. Hematology Parameters of NCI-CTCAE V5.0 • Appendix 1. Chemistry Parameters of NCI-CTCAE V5.0 • Appendix 5. Other Parameters of NCI-CTCAE V5.0 • Section 4.9.1: treatment exposure definition • Section 4.11.1: TEAE definition
Draft V1.3	18May2021	IDMC analysis for HR boundary is listed as DMC charter revision. • Section 4.11.4.6.1
Draft V1.3	03Aug2021	Protocol deviation • Section 4.4.2 DoR and TTR censoring rule added. • Section 4.10.3.2: Duration of Response (DoR) • Section 4.10.3.5: Time to Response (TTR) Time to Deterioration & PRO Improvement Rate baseline definition added • 4.10.3.7.1: EORTC QLQ-C30 • 4.10.3.7.2: EORTC QLQ-LC13

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Draft V1.3	06Aug2021	• 4.10.3.7.2: MMRM - overall adjusted mean estimate deleted due to not developed in Shell. • ███████████████ CCI ███████████████
Draft V1.3	19Aug2021	DoR and TTR censoring rule revised. • Section 4.10.3.2: Duration of Response (DoR) • Section 4.10.3.5: Time to Response (TTR) DCR definition added. • Section 4.10.3.3: Disease Control Rate (DCR)
Draft V1.3	24Aug2021	Protocol deviation classification categories • Section 4.4.2
Draft V1.3	13Sep2021	Cross-Over study day definition • Section 4.2.4
Draft V1.4	05Nov2021	███████████████ CCI ███████████████
Draft V1.5	05Nov2021	Revised based on sponsor's comments received by 24Nov2021.
Draft V1.5	02Dec2021	Revised based on sponsor's comments received by 26Nov2021.
Draft V1.5	06Jan2022	Section ████████████████ ███████████████ CCI ███████████████

V2.0	19Jan2022	Section of handing dropout of efficacy missing data:
		    Since there will be no missing value imputed for the target lesion calculation, the imputation algorithm is removed.
		    Non responder has been documented in new added BoR section.
		Best objective response: the algorithm of each response is defined for BoR.
		Section DoR: anti-cancer therapy is removed from censor definition.

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		Section Depth of response: no missing value imputed for this endpoint. NE will be documented for patients without post-baseline
		CCI
	25Jan2022	Section 4.7 Updated the population in prior and current concomitant medications from safety set to full analysis set
		Section 4.10.3.8: Added the overall adjusted mean estimate back in MMRM model for quality of life data; updated the visit mapping tables; modified the statements in MMRM model.
	29Jan2022	Section 4.11.1 treatment emergent concept is added to SAE and death summary according to sponsor confirmation on by email 28Jan2022.
		Section 4.5 updated the Number of metastasis organs to locations
		Section 4.10.5 added p-value for subgroup interaction term will be presented in the shell
	07Feb2022	Section 4.10.3.2 ORR the confidence interval method is updated to Wald CI.
	01Mar2022	Section 4.10.3.8 The analysis visit mapping of quality of life data is updated to "Week XX"
		Section 4.11 Safety analysis is summarized to the discontinuation visit
	08 Jun 2022	CCI
	10Jun2022	
		Section 4.8.2 new lesions at the first progression is defined
		CCI
	16Sep2022	CCI
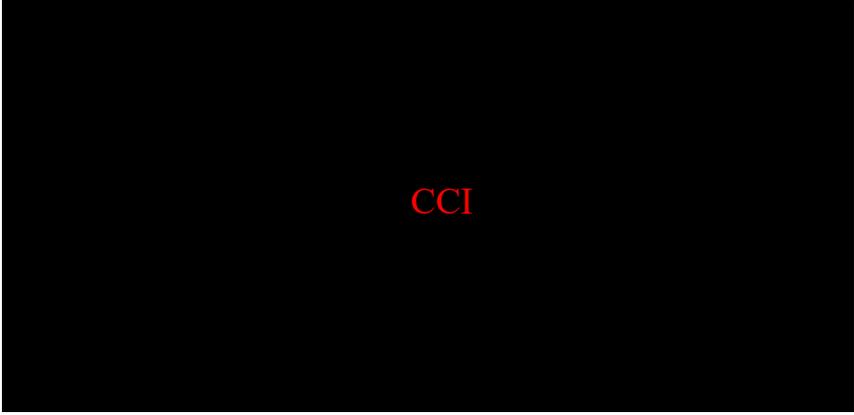
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LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BLQ	Below the limit of quantitation
BM	Brain metastasis
BUN	Blood urea nitrogen
cfDNA	Circulating cell-free deoxyribonucleic acid
CI	Confidence interval
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 Guanosine-5'-triphosphate
HbsAg	Hepatitis B virus surface antigen
hCG	Human chorionic gonadotropin
HCl	Hydrogen chloride
HIV	Human immunodeficiency virus

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Term	Definition
HRQoL	Health-related quality of life
IB	Investigator's brochure
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
iFAS	Intracranial full analysis set
IgM	Immunoglobulin M
iORR	Intracranial objective response rate
iPFS	Intracranial progression-free survival
IRB	Institutional review board
L858R	Leucine-to-arginine substitution in Exon 21
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
m+	Mutation positive
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition
NA	Not applicable
NCI	National Cancer Sites
NCS	Not clinically significant
ND	Not detected
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)
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

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Term	Definition
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
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
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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1 Introduction

This Statistical Analysis Plan (SAP) is applicable to planned statistical analysis at completion of the study and for the preparation of final study report after clinical database lock and general unblinding at the primary analysis. This SAP describes in detail all the planned statistical methodologies used for analyzing the efficacy and safety of Lazertinib versus Gefitinib as the first-line treatment in patients with Epidermal Growth Factor Receptor (EGFR) sensitizing mutation positive, locally advanced or metastatic non-small cell lung cancer. It also details the rules and conventions to be used in the presentation and analyses of efficacy, safety data to meet the different study objectives mentioned in the protocol (Version 2, 03Sep2020) based on the parameters collected from electronic Case Report Form (eCRF, Version2.2, 04Jun2021).

2 Study Objectives

2.1 Primary Objective

Primary Objectives	Endpoints
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.

2.2 Secondary Objectives

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

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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)

2.3 Safety Objectives

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

2.4 Exploratory Objectives

Exploratory Objectives	Endpoints
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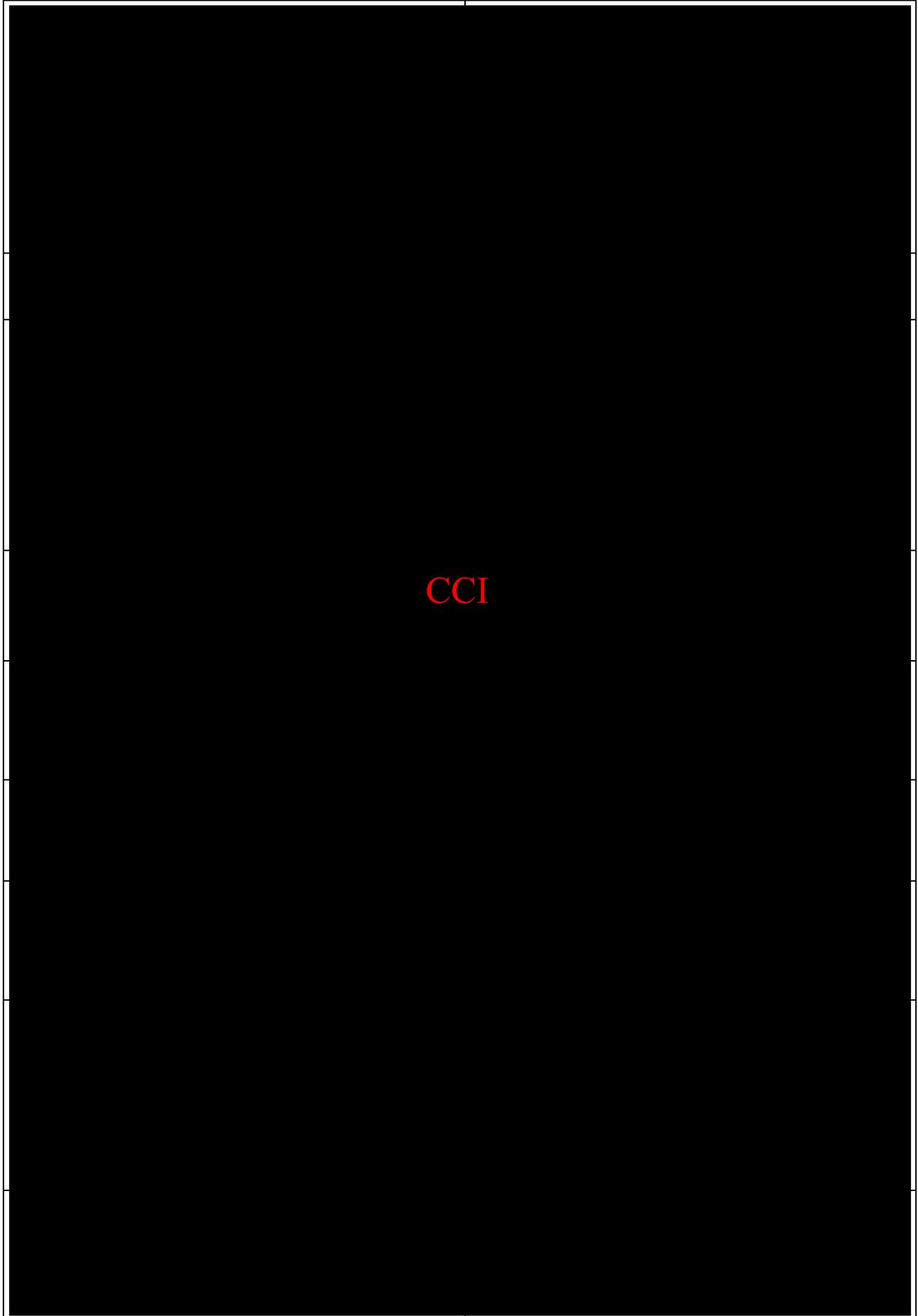
3 Investigation Plan

3.1 Overall Study Design and Plan

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). See Figure **1.** for study design and **Appendix.** for Schedule of Assessment.

Figure 1. Study Design
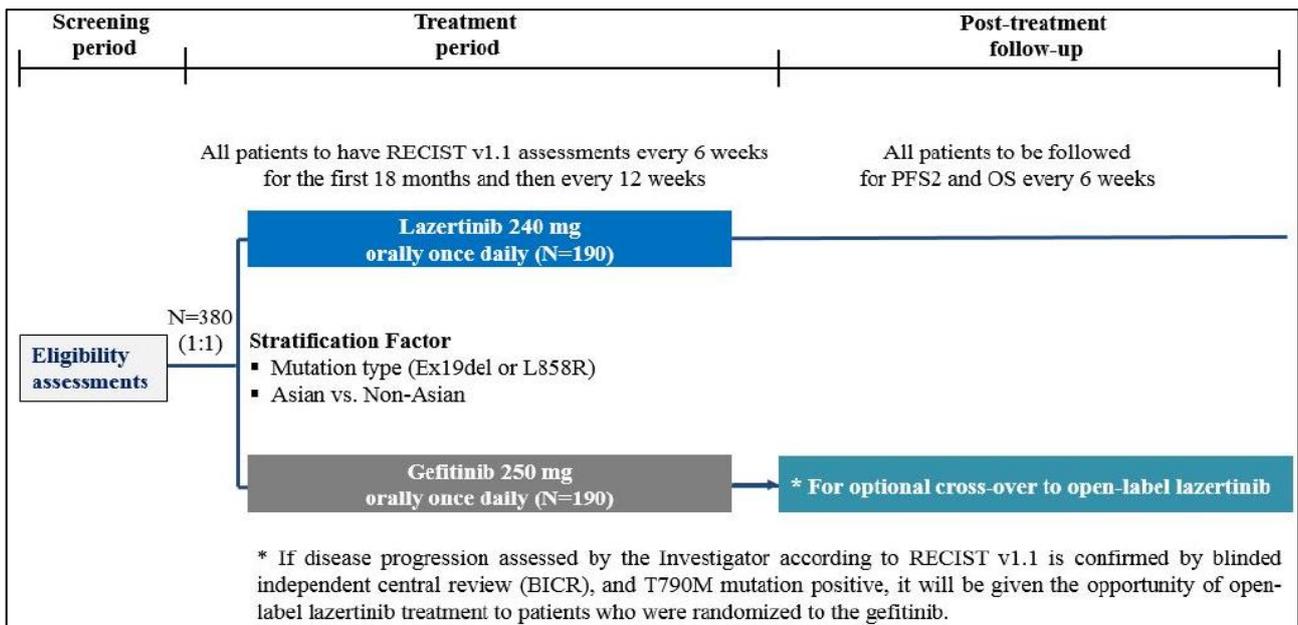
Eligible patients will be administered an investigational product (IP) orally once daily with or without food. A cycle of treatment is defined as 21 days. Patients should continue on their randomized treatment until RECIST version 1.1 (v1.1) defined progression or until a treatment discontinuation criterion 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.

Number of Participants:

Approximately 380 patients will be randomized in a 1:1 ratio to either Lazertinib (n=190) or Gefitinib (n= 190) in this study as follows:

- Test product: Lazertinib (n=190)

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- Comparator: Gefitinib (n=190)

Randomization:

Subject will be randomized and stratified by:

- Race (Asian vs. Non-Asian)
- Mutation status (Ex19del vs. L858R).

Treatment Duration

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

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

Table 1. 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.

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.

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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.

Open-label Lazertinib Treatment in Cross-Over Study:

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 patient's 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 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 diseases progression will no longer be required. See **Appendix .** for further details on post progression cross-over to Lazertinib.

3.2 Endpoints

3.2.1 Efficacy Variables

Primary efficacy endpoint

The primary efficacy endpoint is 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.

Secondary efficacy endpoints

Secondary efficacy endpoints include the following:

- Objective response rate (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).

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- Duration of response (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.

- Disease control rate (DCR) is defined as the percentage of patients who have a best overall response of CR or PR or stable disease (SD at $\geq$ 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).

- 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.

- Time to response (TTR) is defined as the time from the date of randomization until the date of first documented response.

- Overall survival (OS) is defined as the time from the date of randomization until the date of death due to any cause.

- The EORTC QLQ-C30 consists of 30 items and measures cancer patient's functioning (health-related quality of life (HRQoL)) and symptoms (Aaronson NK et al, 1993) for all cancer types.

- The EORTC QLQ-LC13 is a well-validated complementary module measuring lung cancer associated symptoms and side effects from conventional chemotherapy and radiotherapy (Bergman B et al, 1994).

- 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 (EuroQol Group, 1990).

3.2.2 Safety Variables

The safety endpoints will include the following:

- 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

3.2.3 Pharmacokinetic Variables

- 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.

- Cerebrospinal fluid (CSF) concentrations of Lazertinib.

No PK parameters will be calculated as there are only two post-dose PK sampling time points on each day.

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3.2.4   Exploratory Variables
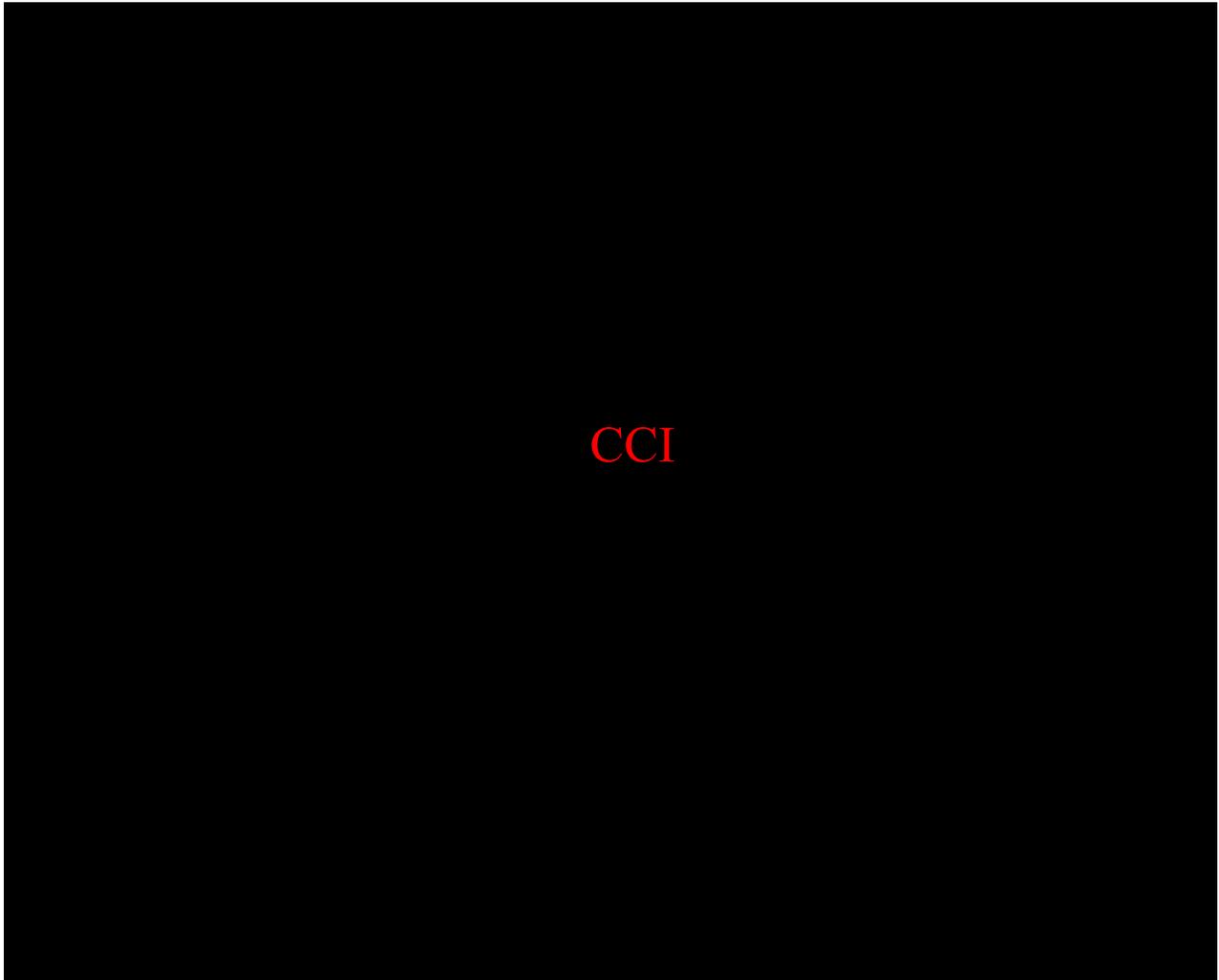
4   Statistical Methods

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.

4.1   Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PPD procedures.

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4.2 General Presentation 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.

- 'Baseline' is defined as the last available pre-treatment assessment.

- 'End of Study' is defined as the last available post-treatment assessment.

- 'Treatment Day' will be calculated relative to the date of randomization i.e., Treatment Day = Assessment Date -Randomization Date + 1.

4.2.1 Continuous Data Presentation

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, upper quartile, lower quartile, minimum, maximum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

4.2.2 Categorical Data Presentation

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place along with 95% confidence interval (CI) where applicable. Percentages will not be presented for zero counts. Percentages will be calculated using n (the total number of patients providing data at the relevant time point) as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

4.2.3 Other Considerations

In general, listings will be sorted and presented by treatment group and subject number across all sites. P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Any analyses requiring significance testing will use a 2-sided test at 5% level of significance, unless otherwise stated. Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, the normal approximation methods will be employed unless otherwise specified. Confidence intervals (2-sided and 95%) will be presented to one more decimal place than the raw data.

The convention of Treatment labels in tables, figures and listings will be as follows:

- Lazertinib

- Gefitinib

Where analysis models are stratified by the randomization stratification factors race and mutation status, the strata obtained at randomization will be used.

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4.2.4   Study Day and Study Cycle

Main Study Period Study Day

A treated cycle for a specific drug is defined as a cycle in which the subject received any amount of the specific drug. The cycle number will be named according to the sequence of every 21-day cycle for study drug administration.

Assessments will be presented chronologically by study day or cycle day as described below:

   · Reference date (Day 1) = Randomization date (for efficacy data except for PRO questionnaires data), or first dose date of study treatment (for safety data and PRO questionnaires data).

   · Study day = Assessment date – Reference date + 1 (for assessment performed on or after the reference date).

   · Study day = Assessment date – Reference date (for assessment performed before the reference date).

   · Cycle day = Assessment date – Date of the first day of the cycle +1.

The full study screening period is 28 days before the randomization. There is no 'Day 0'.

In case that the event date is partial or missing, the date will appear partial or missing in the listings. And study day will be calculated after proper imputation has been carried out as described in 4.2.8.

Cross-Over Period Study Day

   · Cross-over ICF date = the start of Cross-over stage for all Cross-over patients.

   · Cross-over Reference date (Day 1) = Cross-over first dose date (for Efficacy & Safety analysis).

4.2.5   Baseline Measurements

For efficacy analysis, a baseline value will be defined as the last non-missing measurement value prior to the randomization.

For PRO questionnaires analysis, a baseline value will be defined as follows:

   • Patients who had been randomized and treated: First dosing date

   • Patients who had been randomized but not treated: Randomization date

Also, for all safety analyses, baseline is defined as the last non-missing measurement collected on or before first study drug administration. However, if there is evidence that measurements are taken on the same day as administration of first IP, then only those values taken strictly prior to the time of IP administration or previous day(s) (closest to first study drug administration) should be used as baseline value.

4.2.6   Discontinuation Visit Measurements

Patients who discontinue the study treatment (either during the double-blind period or during the open-label treatment period) will perform Discontinuation Visit and the corresponding assessments as per the study protocol will be performed.

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4.2.7 Visit Windows

For summaries of vital signs, laboratory data, ECG, HRQoL, and patient reported outcomes (PROs) etc., assessments will be assigned to calculated visit windows (using study day).

The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the visit window should be based on the actual date and not the intended date of the visit. For summaries at a subject level, all values should be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a subject level statistic such as a maximum.

The window for the visits following baseline (including unscheduled visits) will be constructed in such a way that the upper limit of the interval falls halfway between the two visits.

For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval). Values from scheduled and unscheduled visits will be included. Listings should display all values contributing to a time point for a subject; they should also highlight the value for that subject that was used in the summary table, wherever feasible.

For visit-based summaries:

- If there is more than one value per subject within a visit window then the closest to the planned study day value should be summarized, or the later in the event the values are equidistant from the planned study day. The visit will be missing if no assessment was reported within the specified visit window around the planned study day.

- To prevent very large tables or plots being produced that contain many cells with meaningless data, summary statistics will be presented where at least 10 patients in either treatment group have data recorded at a particular visit.

4.2.8 Common Calculations

For quantitative measurements, changes from baseline at Visit will be calculated as follows:

- Change at Visit = Measurement value at Visit – Baseline Value (Baseline)

- Percentage Change at Visit = (Measurement value at Visit – Baseline Value) / Baseline Value x 100 %

Changes from baseline in categorical data will be summarized using shift tables, where appropriate.

Duration is calculated as (excluding treatment duration):

- Duration (days) = (End Date – Start Date + 1)

- Duration (weeks) = (End Date – Start Date + 1) / 7

- Duration (months) = (End Date – Start Date + 1) / 30.4375

4.2.9 Handling Missing Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing with the exceptions specified for certain efficacy variables

4.2.9.1 Imputation of Partial Dates

Birth Date

- If year is missing (or completely missing), do not impute.

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- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as July 1st or Jul.

- If year and month are present and day is missing, impute day as the day "15th" of the month.

Concomitant Medication and Adverse Events Start Dates

- If year is missing (or completely missing), do not impute.

- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st .

- If year and month are present and day is missing, impute day as first day of the month.

Concomitant Medication and Adverse Events End Dates

- If year is missing (or completely missing), do not impute.

- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31st , unless this is after the date of death in which case date of death will be used instead.

- If year and month are present and day is missing, impute day as last day of the month, unless this is after the date of death in which case date of death will be used instead.

In addition, for AEs and CMs if, for a partial start date, the start date could (when also considering the end date) potentially be on the first study medication date, the start date will be imputed with the first study medication date to assume a "worst case" scenario; e.g. AE from UN-Feb-2020 to 23-Mar-2020 with first study medication date 21-Feb-2020, then the AE start date will be imputed to 21-Feb-2020.

4.2.10 Software

All tables, figures and listings for clinical study report (CSR) will be produced using SAS® version 9.3 or a later version in a secure and validated statistical computing environment. The version of SAS actually used for the analysis will be specified in the Clinical Study Report.

4.3   Analysis Sets

The analyses of data will be based on different analyses populations according to the purpose of the analyses. Patients without valid written informed consent will be excluded from all analysis populations. While every effort will be made to blind both the patient and the investigator to the identity of the treatment, the inadvertent unblinding of a patient may occur. This unblinding will not be sufficient cause (in and of itself) for that patient to be excluded from any safety or efficacy analyses.

4.3.1   Screened Set

Screened set will include all patients who signed the ICF (including 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.

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4.3.2 Full Analysis Set (FAS)

The FAS will include all randomized patients. The patients will receive the study treatment as soon as they are getting randomized. Statistical analyses will be based on study treatment groups as per randomization, irrespective of the study treatment received.

The FAS will be the primary analysis set for all efficacy analyses.

If a subject is allocated the incorrect study treatment and not as per the study randomization list, patients will be summarized and analyzed 'as randomized' i.e., by planned randomized treatment group. If a subject is stratified incorrectly, 'randomized stratum' will be used rather than 'actual stratum'.

4.3.3 Safety Analysis Set (SAF)

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.

If a subject is randomized to the incorrect study treatment and not as per the study randomization list, patients will be summarized and analyzed 'as treated' i.e. by actual treatment received for the safety analysis. If a patient receives both treatments, they will be summarized according to the treatment they were randomized to.

4.3.4 Pharmacokinetic (PK) 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. All adverse events, protocol deviations or incomplete dosing interval (i.e., within 14 hour- or over 34 hour-interval between two dosing on the day of PK sampling and immediately before pre-dose PK sampling) that occur during the PK evaluation period will be considered for their severity and impact on PK when patients are assigned to the PK analysis set.

4.3.5 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.

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4.4   Study Patients

4.4.1   Disposition of Patients

The analysis set summary will include the screened set, Full analysis set (FAS), Safety analysis sets (SAF), Pharmacokinetic (PK) analysis set, centrally confirmed EGRF analysis set (cEAS), intracranial Full analysis set (iFAS), and Cross-over analysis set. The screened set will only be summarized overall. The number of patients in the Full analysis set (FAS) and Cross-over analysis set will be summarized by treatment and by sites/countries. Screening failures (i.e., patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment/entered in the study) and the associated reasons for failure will be tabulated overall.

The disposition of all patients who enter the study will be provided, from enrolment to study completion. The subject disposition summaries include the following (overall and by treatment group where applicable) summaries based on associated analysis populations:

Patients screened: A summary of the number of patients screened, the number of screen failures and reasons for screen failure.

Patients randomized: A summary of number of patients who satisfied eligibility criteria for enrolment and randomized to one of the two study treatment groups.

Patients treated and ongoing the study/withdrawing including withdrawal reason: A summary of the number of patients who received treatment, and who discontinued treatment, the primary reasons of discontinuation including the study day of treatment discontinuation, disease progression, adverse events, death, withdrawal by patient, lost to follow-up, physician's decision and other reasons will be summarized by treatment group and overall.

Patients randomized to receive Gefitinib who crossed over to Lazertinib: A summary of the number and percentage of patients who crossed over to Lazertinib will be provided.

Patients in each analysis population: A summary of the number and percentage of patients in each analysis population by treatment group and overall will be provided.

Patients enrolled by countries: The similar summary statistics for subject disposition will be performed by countries, treatment group and overall (Analysis set: FAS).

A by-patient listing of analysis populations will be provided. This listing will be presented by treatment group and overall and will include countries, subject identifier, inclusion/exclusion flag for each analysis population and reason for exclusion from each population, if any. All patients screened will be included in this listing.

4.4.2   Protocol Deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a patient, and include the following:

- Inclusion/exclusion criteria deviations
- Disallowed medication
- Informed consent
- IP admin/study treatment
- Visit schedule
- Procedure/test

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- AE/SAE

- Withdraw criteria

- Other

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviation specification (PDS) document.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for primary analysis. Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to un-blinding and closure of the database to ensure all important deviations are captured and categorized. The final determination of major protocol deviations and the exclusion of patients from each of the analysis populations will be made prior to database lock. Please refer to the study protocol deviation specification for more information.

Major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification. The final determination of major protocol deviations and the exclusion of patients from each of the analysis populations will be made prior to database lock where protocol deviations and analysis sets will be reviewed and confirmed through the two or more.

Protocol deviations with action to be taken for analysis

Protocol Deviation	Action to be Taken for Analysis
Patient did not receive any study medication	Exclude from the Safety analysis set
Patient was given incorrect study medication	Analyzed "As-randomized" for the FAS. Analyzed "As-treated" for the Safety analysis set. If only the incorrect study medication was taken for the whole study, then analyzed according to treatment taken. If patient received both Lazertinib and Gefitinib then analyzed according to randomized treatment.

Protocol deviations including those deviations from the protocol that will be assessed as "Major", "Major COVID-19", "Minor" or "Minor COVID-19" in collaboration with Sponsor.

All protocol deviations will be discussed at the Blinded data review meeting (BDRM) prior to database hard lock to define the Analysis Population for the study. Decisions regarding the exclusion of patients and/or subject data from the specific analysis set will be made prior to treatment code unblinding and will be documented and approved. Protocol deviations will be handled in accordance with PPD SOPs.

A summary of the number and percentage of patients with protocol deviations by protocol deviations classification i.e. "Major", "Major COVID-19", "Minor" or "Minor COVID-19" will be presented by treatment group and overall. Percentages will be based on Full Analysis Set.

A by-subject listing will be provided including subject identifier, protocol deviation classification, protocol deviation description and exclusion from specific analysis population.

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4.5 Demographic and Other Baseline Characteristics

Demographics, baseline characteristics, extent of disease, WHO performance status, and smoking status of the patients will be listed for each patient and summarized by treatment for the FAS (eCRF: Demographics; EGFR Mutation Result(central/local); Smoking/Drinking History; WHO Performance Status; NSCLC Diagnosis; Serology; Ophthalmologic Assessment; Vital Signs; Imaging assessments). Following demographic and baseline characteristics measured before randomization as stated below will be listed by subject and summarized by treatment group and overall, for the FAS.

Demographics Characteristics

- Age (years).

- Age group ($<$ 65 and $\geqslant$ 65).

- Gender: Male; Female; Unknown; Undifferentiated.

- Ethnicity: Hispanic or Latino; Neither Hispanic nor Latino ; Unknown; Not Reported.

- Race: Asian (Korean, Chinese, Other Asians); American Indian or Alaska Native; Black or African American; Native Hawaiian or Other Pacific Islander; White.

- Height,Weight and Body Mass Index (BMI) at baseline.

- WHO performance status: 0; 1; 2; 3; 4; 5.

- Smoking status: Never; Former; Current; Not reported.

- Nicotine consumption (pack years): Packs smoked per day* Years as a smoker.

- Drinking status: Never; Former; Current; Not reported.

- Frequency of drinking in the last 4 weeks: Every day; 4-5 times a week; 2-3 times a week; once a week; 2-3 times a month; once a month; None; Unknown.

- Ophthalmologic abnormal findings: Normal, Abnormal.

- Clinically significant for ophthalmologic: Not clinically significant; Clinically significant.

- Corneal Ulceration: Yes, No.

Baseline EGFR Mutation Status & Serology

- EGFR mutation type: Positive (L858R; EX19DEL; T790M; L861Q; G719X; S768I; Ex20Ins; Other); Negative; Invalid; Unknown ; Not Done.

- Type of mutation kits: Qiagen-Therascreen® EGFR Mutation Detection Kit RGQ (Scorpions ARMS); Amoy Diagnostics-the AmoyDx® EGFR Mutation Test Kit; PANAGENE-PANAMutyper™; Roche Diagnostics-Cobas® EGFR Mutation Test v2; Other

- Hepatitis B surface antigen (HBsAg): Positive; Negative; Not done; Not Evaluable.

- Hepatitis C antibody (anti-HCV): Positive; Negative; Not done; Not Evaluable.

- Human immunodeficiency virus antibody (anti-HIV): Positive; Negative; Not done; Not Evaluable.

Baseline NSCLC History

- NSCLC Histology: Adenocarcinoma; Squamous cell carcinoma; Large cell carcinoma; Adenosquamous cell carcinoma; Not classified; Others.

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- Disease status at enrollment: Advanced/metastatic NSCLC at the first diagnosis; Recurrence after treated NSCLC

- Histopathological grade: Unknown; Well differentiated; Moderately differentiated; Poorly differentiated; Undifferentiated; Other

- Time since first NSCLC diagnosis (years): (Randomization date - First date of NSCLC confirmed +1)/ 365.25.

- Age at NSCLC diagnosis (years): (First date of NSCLC confirmed - Date of birth +1)/ 365.25. Since the eCRF only recorded the Year and Month of the birth date, the "Day" of birth date will be imputed by "15th" day of each month for the age of NSCLC diagnosis. If the Month of age is missing, "July" of the year will be imputed.

- Target lesions: Lymph node only; Non-lymph node only; Both.

- Non-target lesions: Yes; No.

- Cancer stage at enrollment.

- TNM staging (Primary Tumor/T).

- TNM staging (Regional Lymph Nodes/N).

- TNM staging (Distant Metastasis/M).

- Location of metastasis at enrollment: Adrenal Gland; Bone; Brain; Liver; Lung; Lymph Node; Pleura; Other.

Number of metastasis locations involved. By-subject listings of demographics as well as baseline characteristics and stratification factors will be provided (Listing analysis set: FAS).

4.6   Medical History

Medical conditions will be coded by the medical dictionary for regulatory activities (MedDRA). The final MedDRA version to be used will be decided prior to database lock (for both primary and final analysis).

Medical and surgical history/conditions present at screening will be summarized and listed (eCRF: Medical History). They will be summarized by primary system organ class (SOC) and preferred term. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the condition was ongoing at the time of first study drug administration. The number and percentage of patients with each medical condition will be provided in terms of decreasing frequency for SOC, and PT within SOC, in Lazertinib, and then similarly by decreasing frequency in Gefitinib, and then alphabetically for SOC, and PT within SOC treatment

for the FAS.

Additionally, the by-subject listing of medical and surgical history will also include SOC, PT, verbatim term, start date, end date and status etc. as provided in eCRF.

4.7   Prior, Concomitant and Post-treatment Medication

Prior and concomitant medications will be presented for the FAS and summarized by treatment group (eCRF Form: Prior and Concomitant Medication). 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. Concomitant treatments must be recorded beginning at screening and continuing

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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:

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 eCRF. 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 eCRF.

Medication start and stop dates will be compared to the date of first dose and last dose date of study medication to allow medications to be classified as either Prior, Concomitant or Post-treatment medications .

- **Prior medications** - those taken prior to study treatment with a stop date prior to the first dose of study treatment.

- **Concomitant medications** - those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).

- **Post-treatment medications** - those with a start date after the last dose date of study treatment.

Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as Concomitant. Medications will be classified as Concomitant if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medication partial date imputation guideline is listed in section 4.2.9. Medications will be assumed to be Concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication and stopped prior to the first dose of study medication, the medication will be assumed to be Prior.

A summary of the number of patients with prior, current concomitant and post medications by treatment group and overall will be generated for FAS. The numbers (n) and percentage will be provided by anatomical therapeutic chemistry (ATC) term level 1 and level 2 separately, coded by World Health Organization-Drug Dictionary (WHO-DD) will be provided and each subject will be counted once only under each category. (Analysis set: FAS) The final WHO DD version to be used will be decided prior to database lock (for both primary and final analysis).

A by-subject listing of prior/current concomitant/post-treatment medication will be generated using FAS, including start/end date of medication taken, dose information (dose name, unit, total dose, route and frequency), indication /reason for treatments, and any anti-cancer therapies/ radiotherapies/ surgeries taken during the study.

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4.8   Anti-Cancer History and Lesion Assessment

4.8.1   Anti-Cancer History

Anti-cancer procedures, therapy and radiotherapy will be collected for following information (eCRF: Prior Cancer-related Surgery/Procedures; Anti-Cancer Surgical Therapy; Prior Anti-Cancer Drug Therapy; Anti-Cancer Drug Therapy; Prior Radiotherapy; Anti-Cancer Radiotherapy).

- **Prior Cancer-related Surgery/Procedures:** Surgery/Procedure Term; Surgery/Procedure Date; Location; Type of Surgery/Procedure; Time from the latest cancer-related surgery prior to study entry (months): (Randomization date - Date of latest cancer-related surgery +1)/ 30.4375.

- **Anti-Cancer Surgical Therapy:** Surgical Term; Surgery Date; Location; Indication.

- **Prior Anti-Cancer Drug Therapy:** Drug Name; Purpose; Start Date; End Date; Dose; Dose Unit; Frequency; Route; Duration of last therapy (months): (End date - Start date of the last cancer-related drug therapy +1)/ 30.4375; Time from end of last cancer-related drug therapy prior to study entry (months): (Randomization date - End date of the last cancer-related drug therapy +1)/ 30.4375.

- **Anti-Cancer Drug Therapy:** Regimen number; Drug Name; Start Date; End Date; Best Response;.

- **Prior Radiotherapy:** Radiotherapy site; Purpose; Start Date; End Date; Total cumulative dose; Unit; Time from last radiotherapy prior to study entry (months) : (Randomization date - End date of the last radiotherapy +1)/ 30.4375.

- **Anti-Cancer Radiotherapy:** Radiotherapy site; Purpose; Start Date; End Date; Total cumulative dose; Unit, Best Response.

Overall summary tables will be summarized between treatment groups by SOC and PT of MedDRA in the order of frequency for the FAS separately for the above surgery and procedure history with corresponding listings (Listing analysis set: FAS). Analysis for cancer drug therapies will be summarized by WHO-DD by ATC level 1 and level 2 for FAS with corresponding listings (Listing analysis set: FAS). The final version of MedDRA and WHO-DD to be used will be decided prior to database lock (for both primary and final analysis).

4.8.2   Target Lesion /Non-Target Lesion Assessment /New Lesion Assessment

Target Lesion Assessment

Target lesion assessments will be collected for following information (eCRF: Tumor Assessment - Target Lesions): Anatomic site; Location of lesion; Timepoint of Tumor Assessment; Lesion number; Progression F/U or Unscheduled Visit number; Date of Procedure; Method of Assessment; Longest diameter for non-nodal/Short axis for lymph node (mm).

Non-Target Lesion Assessment

Non-target lesion assessments will be collected for following information (eCRF: Tumor Assessment - Non-Target Lesions): Anatomic site; Location of lesion; Timepoint of Tumor Assessment; Lesion number; Progression F/U or Unscheduled Visit number; Date of Procedure; Method of Assessment; Status.

New Lesion Assessment

New lesion assessments will be collected for following information (eCRF: Tumor Assessment - New Lesions): Anatomic site; Location of lesion; Timepoint of Tumor Assessment; Lesion number;

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Progression F/U or Unscheduled Visit number; Date of Procedure; Method of Assessment; Status; Measurable or Not; Longest diameter for non-nodal/Short axis for lymph node (mm).

The new lesions at the time of first progression are the new lesions assessed when the first disease progression occurs. The assessment visit of new lesion should be in the same visit with the disease progression. The lesions sites at the first progression will be summarized.

The overall listings will be summarized between treatment group separately for Target lesion, non-target lesion and new lesion assessments in FAS.

4.9   Treatment Exposure & Compliance

4.9.1   Treatment Exposure

Study treatment (Lazertinib vs. Gefitinib) exposure, including the following parameters will be summarized with descriptive statistics in SAF. The number of missed doses will also be displayed.

- **The total duration of exposure (week)** is defined as the duration from the first dosing date to the last dosing date at the end of treatment regardless the dose interruptions.

  Total exposure (weeks) = [(Date of last dose - Date of first dose) + 1] / 7

- **The actual duration of exposure (week)** is defined as the duration from the first dosing date to the last dosing date at the end of treatment and the interruption days will not be counted. Actual duration of exposure (in weeks) will be calculated as:

  Actual exposure (weeks) =

  ([(Date of last dose - Date of first dose) + 1] – [Sum of interruption periods])/ 7

  Sum of Interruption periods (weeks) =

  [(Date of the first dose interruption end date - Date of the first dose interruption start date +1)

  + ... + (Date of the last dose interruption end date - Date of the last dose interruption start date +1)]/ 7.

- **The actual cumulative total dose received (mg)** of study treatment (Lazertinib vs. Gefitinib) is defined as the summation of all actual total dose administrated from the first dosing date to the last doing date at the end of treatment.

- **Plan dose intensity (PDI) (mg/week)** of study treatment (Lazertinib vs. Gefitinib) will be calculated as:

$$PDI = \frac{\text{Planned cumulative total dose received}}{\text{Planned duration of exposure}}$$

- **Actual dose intensity (ADI) (mg/week)** of study treatment (Lazertinib vs. Gefitinib) will be calculated as:

$$ADI = \frac{\text{Actual cumulative total dose received}}{\text{Actual duration of exposure}}$$

- **Relative dose intensity (RDI) (%)** of study treatment (Lazertinib vs. Gefitinib) will be calculated as

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$$RDI = \frac{\text{Actual dose intensity}}{\text{Planned dose intensity}} \times 100\%$$

- **Number of doses actual received (n)**

- **Number of cycles actual received (n)**

- **Planned dose**

  - Lazertinib: initial dose 240 mg once daily can be reduced to 160 mg once daily.
  - Gefitinib: initial dose 250 mg once daily cannot be reduced to a lower dose.

4.9.2   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 (eCRF: Drug accountability; Overdose). 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. Exposure to study treatment (i.e., total amount of study treatment received) will be listed for all patients based on the Safety analysis set. Total exposure (obtained as the total amount of drug taken in mg. from the Study Drug Accountability page of the eCRF). 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 (eCRF: Study Drug Administration).

Treatment compliance will be calculated as follows and will be summarized using the safety population:

Study drug compliance (%)
= [(Total actual dose administrated (mg) /Total planned dose administrated (mg)] *100 %.

If subject who discontinues early in the study, then only the actual dose administered and planned dose till the time of discontinuation will be considered for compliance calculation.

A summary of the treatment compliance measures by treatment group, overall and visit, including the number and percentage of compliant and non-compliant patients, percentages of patients with dose delays beyond 21 days, and the percentage of patients with treatment reduction, interruption, discontinuation, overdose, maximum duration of dose interruption (days) and frequency of dose interruptions will be provided by treatment period. A by-patient listing of study drug administration including starting and end date and time, intended dose, actual dose administered, actual administered, reason for interruption, reduction or discontinuation, AE details that lead interruption, reduction or discontinuation will also be provided.

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4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

4.10.1.1 Multi-center Studies

Since this is a multinational study, for the following sections of safety and efficacy analysis, the term 'Center' in this SAP will be defined as a nation.

4.10.1.2 Adjustments for Covariates

During the time of randomization, the patients will be stratified based on mutation type (Ex19del or L858R) and Race (Asian and Non-Asian).

The primary efficacy analysis (PFS) will be stratified for the following covariates:

- Mutation type (stratification variable)
- Race (stratification variable)

4.10.1.3 Multiple Comparisons/Multiplicity

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

Two analyses of OS are planned; one interim at the time of PFS and a final analysis. 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. 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. 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%.

A 2-sided α = 0.05 will be used in all testing, except for 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.

The significance level for the two OS analyses will be calculated using the statistical software package SAS 9.3 or later version by specifying the information fraction for each analysis. The information fraction is calculated as the number of OS events at the analysis time-point divided by the total number of events at the final analysis time-point. For example, assuming a median OS on the gefitinib of 30 months and a median OS of 40 months for Lazertinib, that 137 OS events were observed at the first analysis, the information fraction would be entered as 0.685 (137/200 events) for the first analysis since 137 events are expected at the first analysis. This would result in a significance level for the first analysis of 0.0389 (2-sided) and a significance level for the final

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analysis of 0.02448 (2-sided). Any non-statistically significant OS analyses at the time of the primary analysis of PFS will not preclude further testing of OS.

4.10.1.4 Interim Analyses

No interim analysis will be performed.

4.10.2 Primary Efficacy Variable

The primary efficacy endpoint is PFS. PFS is defined as the number of months 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 regardless of whether the patient withdraws from randomized therapy or receives the new anti-cancer therapy prior to progression. 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.

The primary efficacy endpoint, which is calculated as *date of death - date of randomization +1* or *date of progression – date of randomization+1*, whichever is smaller, will be analyzed based on the FAS according to the treatment group patients were randomized by the strata they were assigned to at randomization. PFS in the FAS will be analyzed using a log-rank test stratified by randomized stratification factor mutation type (Ex19del versus L858R) and race (Asian versus non-Asian) using the Breslow approach for handling ties.

Additional supportive analyses include K-M and Cox modelling approaches. PFS will be displayed using Kaplan-Meier plot by treatment group. If data warrant, 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 along with its 95% LOGLOG confidence intervals will be summarized for each treatment group. The Brookmeyer-Crowley method will be used to calculate the standard error of the estimates of these percentiles which is further used for their confidence interval calculation. The Greenwood formula would be used to calculate the standard error of the proportion of patients without an event at 12, 18, and 24 months based on the Kaplan-Meier estimate.

A stratified Cox proportional hazard regression model will be used including treatment in order to provide an estimate of the treatment effect expressed as hazard ratio (Lazertinib vs. Gefitinib), as well as a 95% Wald confidence interval using the same stratification factors as for the log-rank test.

The proportional hazards assumption may be assessed both graphically from the Kaplan-Meier plot as well as by adding a treatment by time interaction term to the Cox regression model. This assumption would also be checked by the plot of the Schoenfeld residuals against each of the predictors in the Cox model. If the proportional hazards assumption is not met, alternative appropriate methods may be used.

By patient listing will be provided for PFS by treatment group and overall will be provided by investigator assessment and central review.

Handling of Censoring for PFS Analysis

Censoring considered here is generalized Type I right censoring. Here the entry of the patient is staggered with complete follow-up until the end of the study. 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 radiological tumor 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

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baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline. Given the scheduled visit assessment scheme (i.e., six-weekly for the first 78 weeks then twelve-weekly thereafter) the definition of 2 missed visits will change.

If the previous RECIST assessment is less than study day 497 (i.e., week 71) then two missing visits will equate to 13 weeks since the previous RECIST assessment, allowing for early and late visits (i.e., 2 x 6 weeks + 3 days for an early assessment + 3 days for a late assessment = 13 weeks).

If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from six-weekly to twelve-weekly (i.e., between days 497 and 553) this will equate to 19 weeks (i.e., take the average of 6 and 12 weeks which gives 9 weeks and then apply same rationale, hence 2 x 9 weeks + 3 days for an early assessment + 3 days for a late assessment = 19 weeks). From week 79 onwards (when the scheduling changes to twelve weekly assessments), two missing visits will equate to 25 weeks (i.e., 2 x 12 weeks + 3 days for an early assessment + 3 days for a late assessment = 25 weeks).

The PFS time will always be derived based on assessment dates which will be collected during the time of tumor assessment as per the eCRF.

Table 2. PFS Censoring Rules

Situation	Date of Censoring/Progression	Outcome
No evaluable baseline or post-baseline disease assessment	Censored at the date of randomization	Censored
No documented disease progression or death	Censored at the date of last RECIST v1.1 assessment	Censored
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last RECIST v1.1 assessment before the missed/unevaluable visits	Censored
PD or death between scheduled assessment	Date of the last RECIST v1.1 assessment, or date of death whichever comes first, regardless of new anticancer treatment started	Progression
Death before first PD assessment	Date of death	Progression

*If no evaluable disease assessment before the consecutive missed/unevaluable visits, patients will be censored at the date of randomization.

4.10.3 Secondary Efficacy Variables

4.10.3.1 Best objective response (BoR)

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment. It is the best response a patient has had following randomisation but prior to starting any

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new anti-cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

The following categories of BoR will be derived based on the RECIST 1.1 criteria.

- Complete response (CR): Patients with an overall visit response of CR. This will be defined at the latest of the dates contributing to the first overall visit assessment that showed CR.
- Partial response (PR): Patients with an overall visit response of PR. This will be defined at the latest of the dates contributing to the first overall visit assessment that showed PR.
- Stable disease (SD): Stable disease recorded on or after the first scheduled post-baseline RECIST assessment (SD at ≥ 6 weeks) after randomisation. This will be defined at the earliest of the dates contributing towards the overall visit assessment that showed SD. 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).
- Progressive disease (PD): Progression in the absence of CR, PR or SD.
- Not evaluable (NE): Patient did not satisfy any of the above categories (i.e. patient did not qualify for CR, PR or SD, and had not progressed according to RECIST).

4.10.3.2 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 the new anti-cancer therapy was received will not be included in numerator of the ORR calculation (where the FAS will be the denominator).

ORR will be analyzed based on a fitted logistic regression stratified by mutation type (L858R vs ex19del) and race (Asian vs non-Asian). The fitted logistic regression model would use the proportion of patients with measurable disease with at least one visit response of complete response (CR) or partial response (PR) as the response variable and use a logit link function as its canonical link to model the treatment effects on the ORR. The results of the analysis will be presented in terms of an estimated odds ratio for treatment effects together with its associated 95% Wald confidence intervals.

A summary of all responses will also be presented by treatment group. ORR will also be summarized by each stratification factor.

A by patient listing will be provided for ORR by treatment group and by stratification factors.

4.10.3.3 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 mutation type and race as in primary analysis.

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DoR in responding patients will be summarized and the estimated proportion of responding patients with a duration of response (>6; >9; >12; >15 months) will be presented by treatment group along with its 95% Wald confidence interval. A Kaplan-Meier plot and median DoR with 95% Wald confidence interval (calculated from the Kaplan-Meier estimate) will be presented by treatment group. The Brookmeyer-Crowley method will be used to calculate the standard error of the estimates of the median DoR which is further used for its confidence interval calculation. The Greenwood formula would be used to calculate the standard error of the estimated proportion of responding patients with a duration of response (>6; >9; >12; >15 months).

A by patient listing will be provided for DoR by treatment group and overall.

4.10.3.4 Disease Control Rate (DCR)

DCR is defined as the percentage of patients who have a best objective response of CR or PR or stable disease (SD at $\geq$ 6 weeks). 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).

- Any CR, PR or SD occurred after PD, will not be included in numerator of the DCR calculation (where the FAS will be the denominator).
- Any CR, PR or SD occurred after a new anticancer therapy was received will not be included in numerator of the DCR calculation (where the FAS will be the denominator).

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

A by patient listing will be provided for DCR by treatment group and overall.

4.10.3.5 Depth of Response

Depth of response will be determined for patients with measurable disease at baseline (last non-missing assessment before randomization date) 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 new anti-cancer therapy. Missing target lesion data at visit will be documented as not evaluable (NE).

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 ANCOVA model with treatment group as fixed effect and baseline sum of target lesion target, mutation type (L858R & Ex19del) and race (Asian Vs 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. The best percentage change from baseline in target lesion tumor size will also be and presented graphically using waterfall plots, with each patient's best percentage change in tumor size represented as a separate bar and the bars ordered from the largest increase to the largest decreases. Reference lines at the +20% and -30% change in tumor size levels will be added to the plots, which correspond with the definitions of progression and partial response respectively. A waterfall plot will also be produced by each stratification factor.

A by patient listing will be provided for Depth of response by treatment group and overall.

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4.10.3.6 Time to Response (TTR)

TTR is defined as the time from the date of randomization until the date of first documented response (CR or PR) prior to any disease progression and new anti-cancer therapy, for patients who have PR or CR as their response.

A summary statistic will be produced for TTR by treatment group. A by patient listing will be provided for TTR by treatment group.

4.10.3.7 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.

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. Updated analyses of data collected post progression and safety may also be performed at this time.

The alpha will be split between the two analyses to provide strong control of the family-wise error rate (See 4.10.1.4)

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, and 24 months will be summarized by treatment group for the analysis of OS at the primary PFS analysis, and the proportion of patients without an event at 12, 18, 24 and 36 months will be summarized by treatment group for the analysis of OS at the final survival follow-up. 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.

Assuming a median OS of 30 months in the Gefitinib arm, 200 deaths will provide approximately 50% power to demonstrate a 33% improvement (median OS of 40 months in the Lazertinib arm), and approximately 26% power to demonstrate a 20% improvement (median OS of 36 months in the Lazertinib arm) after 45 months survival follow-up from the first patient randomized with 2-sided 5% significance level.

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. Method such as the inverse probability of censing weighting (IPCW) approach and other methods in development may be explored. The decision to adjust and final choice of methods will be based on the plausibility of the underlying assumption.

A by patient listing will be provided for OS by treatment group.

Handling of Censoring for OS Analysis

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact. For example, if information of death is still pending or unknown under clinical operation and could not be obtained this information during the dry run analysis, then the last contact date will be considered as censored date of overall survival analysis.

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4.10.3.8 Health-Related Quality of Life (HRQoL) / Patient Reported Outcomes (PROs)

PRO questionnaire data will be analyzed using a mixed model of repeated measure (MMRM) analysis of the change from baseline in PRO score for each visit. The change from baseline will be calculated as: (score at post baseline- score at baseline).

The MMRM model will include patient as a random effect, treatment, visit, treatment by visit interaction as a fixed effect, 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. A by patient listing will be provided by treatment group.

4.10.3.8.1 EORTC QLQ-C30

European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) is a cancer health-related quality-of-life questionnaire that has been widely used in clinical trials and investigations using PROs for individual patient management.

The EORTC QLQ-C30 v3 questionnaire is an established measure of health-related quality of life (HRQoL) and is commonly used as an endpoint in oncology clinical trials. The questionnaire assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, nausea and vomiting), and 1 global health and QoL (quality of life) scale. The 6 individual symptom measures include: dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties. For the 15 domains described above, the total score is standardized to a range from 0 to 100, where higher scores indicate stronger functioning, higher HRQoL or higher symptom levels.

For ease of presentation and interpretation, all scale and item scores are linearly transformed to a 0 to 100 scale. 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. Note that the global health status scale is based on only the two specific HRQoL items (Item 29, 30) and not the entire questionnaire.

 The transformed score for a subject and missing data handling can be expressed asError! Reference source not found. **Appendix 6. Scoring the QLQ-C30 Version 3.0.**

EORTC-QLQ-C30 scores during treatment period and changes from baseline will be summarized by visit and treatment arms for FAS. A summary statistics table will be provided for all 5 function domains and self-estimated health score by FAS population with a corresponding listing (Listing analysis set: FAS).

4.10.3.8.2 EORTC QLQ-LC13

The EORTC-QLQ-LC13 is a 13-item self-administered questionnaire for lung cancer disease that will be used along with the EORTC QLQ-C30. The scale includes both multiple and single lung cancer-related symptom parameters (i.e., cough, haemoptysis, dyspnea and pain), as well as side effects of conventional chemotherapy and radiotherapy (i.e., alopecia, neurological disorders, oral pain and dysphagia). Similar to the EORTC QLQ-C30, all questions (except one) are on a 4-point scale: "not at all", "a little", "quite a bit", and "very much". Only 1 question (43rd question "Did you take any medicine for pain?") is with response options of "yes" or "no". The QLQ-LC13 are scored similarly to the EORTC-QLQ-C30.

For ease of presentation and interpretation, all scale and item scores are linearly transformed to a 0 to 100 scale, with higher scores representing increasing symptom levels.

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$$\text{Transformed QLQ-LC13 score} = \frac{\text{Sum of item scores} - \text{Number of items}}{3 \times \text{Number of items}} \times 100$$

The observed values and changes from baseline for overall score, sub-scores and individual scores for each visit will be statistically described (Analysis set: FAS). The overall score is defined as the sum of all item scores except pain medication. The sub-scores are Lung cancer related symptoms including cough, haemoptysis and dyspnea; Treatment related side-effects including sore mouth or tongue, dysphagia, hair loss, tingling hands and feet; Pain.

The summary statistics for the overall score, sub-scores and individual scores and the changes from baseline will be tabulated by study treatment and visit.

Statistical analyses including baseline, post baseline, change from baseline are the same as the EORTC-QLQ-LC13 score. A by-subject listing of EORTC-QLQ-LC13 will be provided (Listing analysis set: FAS).

EORTC QLQ-C30 and EORTC QLQ-LC13 Compliance Rates

Summary measures of overall compliance and compliance over time will be derived for both EORTC QLQ-C30 and EORTC QLQ-LC13. These will be based upon:

- Received questionnaire = a questionnaire that has been received and has a completion date and at least one individual item completed.

- Expected questionnaire = a questionnaire that is expected to be completed at a scheduled assessment time e.g., a questionnaire from a patient who has not died, is not lost to follow-up or withdrawn from the study at the scheduled assessment time but excluding patients in countries with no available translation. For patients that have progressed, the latest of progression and safety follow-up will be used to assess whether the patient is still under PRO follow-up at the specified assessment time. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected forms.

- Evaluable questionnaire = a questionnaire with a completion date and at least one subscale that is non-missing.

- Overall PRO compliance rate is defined as: Total number of evaluable questionnaires across all time points, divided by total number of questionnaires expected to be received across all time points multiplied by 100.

- Overall patient compliance rate is defined for each randomized treatment group as: Total number of patients with an evaluable baseline and at least one evaluable follow-up questionnaire (as defined above), divided by the total number of patients expected to have completed at least a baseline questionnaire multiplied by 100.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable questionnaire at the time point (as defined above), divided by number of patients still expected to complete questionnaires. Similarly, the evaluable rate over time will be calculated separately for each visit, including baseline, as the number of evaluable questionnaires (per definition above), divided by the number of received questionnaires.

Mixed Models Repeated Measures of Change from Baseline in Primary PRO Symptoms

The analysis population for PRO data will be the FAS. Change from baseline in the primary PRO symptom scores of dyspnea (EORTC QLQ-LC13), cough (EORTC QLQ-LC13), pain in chest (EORTC QLQ-LC13), fatigue (EORTC QLQ-C30) and appetite loss (EORTC QLQ-LC30) will be regarded as the primary analysis of the PRO questionnaire data and will be analyzed using a mixed

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model for repeated measures (MMRM) analysis of the change from baseline in PRO score for each visit.

The primary analysis will be to compare the average treatment effect from the point of randomization for the first nine months (which will include visit data obtained at protocol scheduled time-points of day 1, days 22, every six weeks after randomization and the discontinuation and follow-up visits if occurring within the first nine months) unless there is excessive missing data (defined as >75% missing data in either arm).

It is acknowledged that patients will discontinue treatment at different timepoints during the study and that this is an important time with regards to PRO data collection. To account for this and in order to include the discontinuation and follow up visits, a visit variable will be derived for each subject in order that the average treatment effect can be analyzed using the above method. Each visit will be assigned a sequential number.

As an example, say a patient (X) attends the first four scheduled visits and then discontinues treatment, whilst another patient (Y) discontinues treatment after the first two scheduled visits, the generic visits would be as follows, which are supposed to be all visits within the first 9 month (ie. Week 36):

Sequential Number	Generic visit	Days since Randomization		
		Patient X	Patient Y	Comment
1	Baseline	1	1	
2	Week 3	22	22	
3	Week 3		29 (Discontinuation)	The discontinuation visit won't be analyzed in MMRM because Day22 visit is the closet to the target day 22.
4	Week 6	43	57 (28-day safety follow-up)	
5	Week 12	85	99 (Progression Follow-Up 1)	
6	Week 18	127 (Discontinuation)		
7	Week 24	155 (28-day safety follow-up)		
8	Week 30	200 (Progression follow up 1)		
9	Week 36			

For Patients X and Y the first six and four visits respectively could be used in the analysis of deriving the average treatment effect (change from baseline in PRO score) as they are within the first nine months of randomization. Time windows will be exhaustive so that data recorded at any time point has the potential to be summarized and included in the model. If there are two or more values potentially allocated to the same visit, the post baseline assessment closest to the scheduled visit date will be included in the summaries and in the MMRM.

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The MMRM model will include patient, treatment, visit (generic) and treatment by visit interaction as explanatory variables, the baseline PRO score as a covariate along with the baseline PRO score by visit interaction. Treatment, visit and treatment-by-visit interaction will be fixed effects in the model; patient will be included as a random effect. Restricted maximum likelihood (REML) estimation will be used. An overall adjusted mean estimate will be derived that will estimate the average treatment effect over visits giving each visit equal weight. For this overall treatment comparison, adjusted mean estimates per treatment group and corresponding 95% CIs will be presented along with an estimate of the treatment difference, 95% CI. No p-values will be presented. The treatment-by-visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: compound symmetry (CS), variance components (VC), toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive.

The visits included in the MMRM model will be within the first nine months (within week 36 mapped in the table above) and at least 20 patients per visit per arm.

Time to Deterioration

For each of the symptom scales/items in EORTC QLQ-C30 and EORTC QLQ-LC13 will be defined as the time from randomization until the date of first clinically meaningful symptom deterioration (an increase from baseline score ≥10 points for symptom scales/item; an decrease from baseline score ≥10 points for functional scales and global health status for EORTC QLQ-C30; an increase from baseline score ≥5 for EORTC QLQ-LC13) 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 (in Cycle 01 Day 1), they will be censored at Day 1. The population for analysis of time to deterioration will include a subset of the FAS population as follow:

EORTC-QLQ-C30

- For symptom scales, only patients who have baseline score ≤90 will be included in time to deterioration analysis.

- For functional scales and global health status, only patients who have baseline score ≥10 will be included in time to deterioration analysis.

EORTC-QLQ-LC13

- For symptom scales, only patients who have baseline score ≤95 will be included in this analysis.

PRO Improvement Rate

The PRO 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 (a decrease from baseline score ≥10 points for symptom scales/item; an increase from baseline score ≥10 points for functional scales and global health status; a decrease from baseline score ≥5 for EORTC QLQ-LC13).

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The population for analysis of PRO improvement rate will include a subset of the FAS population as follow:

EORTC-QLQ-C30

- For symptom scales, only patients who have baseline score ≥10 will be included in PRO improvement rate analysis.

- For functional scales and global health status, only patients who have baseline score ≤90 will be included in PRO improvement rate analysis.

EORTC-QLQ-LC13

- For symptom scales, only patients who have baseline score ≥5 will be included in PRO improvement rate analysis.

Descriptive statistics and graphs will be reported for the primary PRO symptom scores by visits as well as change in these scores from baseline. These will also be reported for the other EORTC QLQ-C30 and EORTC QLQ-LC13 reported symptoms and scales.

Definition of clinically meaningful changes

Changes in EORTC score compared to baseline will be evaluated as the following

Table 3.

Table 3. Visit response for health-related quality of life and disease-related symptoms

EORTC Score	Change from baseline	Clinically meaningful changes	Deterioration / Improvement
EORTC-QLQ-C30 symptom scales/items	≥ +10	Worsened	Deterioration
	≤ -10	Improved	Improvement
	Otherwise	Stable	
EORTC-QLQ-C30 functional scales and Global health status	≥ +10	Improved	Improvement
	≤ -10	Worsened	Deterioration
	Otherwise	Stable	
EORTC-QLQ-LC13 symptom scales/items	≥ +5	Worsened	Deterioration
	≤ -5	Improved	Improvement
	Otherwise	Stable	

4.10.3.8.3 EQ-5D-5L

The EQ-5D comprises the following two sections:

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).

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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 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 (as collected in the eCRF) at each time point will be reported. A summary statistics table and listing will be provided for all 5 dimensions' health scores and self-estimated health score by FAS population with a corresponding listing (Listing analysis set: FAS).

4.10.4 Exploratory Variables

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4.10.5 Examination of Subgroups

The subgroup analysis will be performed by baseline potential prognostic factors by comparing PFS between treatment group using a Cox-Proportional Hazards Model including the following groups:

- EGFR Mutation type (Ex19del vs. L858R) at randomization
- EGFR Mutation (Positive vs. Negative) from central lab
- Race (Asian vs. Non-Asian)
- Brain metastatic at entry (Yes vs. No)

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- Gender (Male vs. Female)

- Age at screening (<65 vs. ≥65)

- Smoking history (Yes vs. No)

- WHO Performance Status (0 vs. 1)

The estimated HR between the treatment groups including its 95% Wald Confidence Interval will be presented separately for each level of the categorical variables.

For each subgroup, the HR and 95% CI will be calculated from a single cox proportional hazards model that contains a term for treatment, the subgroup covariate of interest and the treatment by subgroup interaction term. The treatment effect HR will be obtained for each level of the subgroup from this model. The cox models will be fitted using SAS PROC PHREG with the Efron method to control for ties. The p-value for interaction term TRT*SUBG will also be presented, to be assessed at a 10% level for the purpose of hypothesis generation.

These HRs and associated two-sided 95% CIs will be summarized and presented on a forest plot, along with the results of the overall primary analysis. In addition, a cox proportional hazard model that contains a term for treatment will be fitted and the treatment effect HR and the two-sided 95% CIs will also be presented on the forest plot.

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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.

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.4. All safety summaries except AE/SAE/Death will be summarized until treatment discontinuation visit.

4.11.1 Adverse Events

AEs will be coded using MedDRA. The final MedDRA version to be used will be decided prior to database lock (for both primary and final analysis). The NCI-CTCAE grade will be assigned by the Investigator. Severity of all AEs will be graded according to the CTCAE v5.0.

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

Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of study treatment and until 28 days following the last dose of study treatment, or the day before the first administration of cross-over treatment, whichever is sooner. Any TEAE will be included in the AE summaries. Any AEs in this period that occur after a patient has received further anti 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. For cross-over patients, all AEs that occurred after the start of cross-over treatment up until the 28 days following the last dose of cross-over treatment will be summarized separately.

Multiple Observations for One Adverse Event

Changes in toxicity grade, severity or outcome of AE are recorded as separate entries in the eCRF with the associated end and start dates. Such entries reporting the same event in such immediately consecutive periods are to be considered as one event in the analysis.

If an AE is reported for a given subject more than once for a period, the worst severity and the strongest relationship to study treatment will be used for that period.

All the records belonging to the same AE set will be kept in the analysis datasets as separate records

- If an AE started before treatment starting and **improved** during treatment, it should not be counted as TEAE.

- If an AE started before main study discontinuation and a corresponding sequential AE **improved** after 28 days of the last dose in main study treatment and cross-over treatment started (no matter within 28 days or beyond), it should be also counted as the same sub-sequential/ TEAE. Not cross-over TEAE.

- If an AE **worsened** during the treatment period, it is counted as TEAE even if there was an observation with start date before treatment period.

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.

Adverse events with relationship "Certain"; "Probable/Likely"; "Possible" and "Unassessable/ Unclassifiable" will be classified as "Related" with the study drug. If an AE relationship is missing, it would be also classified as related as the conservative relationship.

An overall summary table including the above specified AEs will describe number of patients with incidence rate.

$$\text{Incidence} = \frac{(\text{Number of Subject with AE})}{\text{Number of patients in the Safety analysis set}}$$

An overview table of TEAEs will be provided detailing the number and percentage of patients along with the incidences with:

- TEAEs

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- TEAEs by Severity (CTCAE Grade 1, 2, 3, 4 and 5)

- Related TEAEs

- CTCAE Grade ≥ 3 TEAEs

- Related CTCAE Grade ≥ 3 TEAEs

- Treatment emergent SAE

- Related treatment emergent SAE

- TEAEs leading to interruption of study drugs (Lazertinib / Gefitinib)

- TEAEs leading to dose reduction of study drugs (Lazertinib / Gefitinib)

- TEAEs leading to withdrawn of study drugs (Lazertinib / Gefitinib)

- Related TEAEs leading to withdrawn of study drugs (Lazertinib / Gefitinib)

- TEAE with outcome of death

- Related TEAE with outcome of death

- Other treatment-Related TEAEs: Overdose of study medication

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in Lazertinib, and then similarly by decreasing frequency in Gefitinib, and then alphabetically for SOC, and PT within SOC treatment (Analysis set: Safety set).

A by-patient listing of all AEs will be provided (Listing analysis set: Safety set).

4.11.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

All AEs that meet any one or more of the following situations during the clinical trial should be considered serious adverse events (SAEs):

1. Results in death

2. Is life-threatening

3. Requires inpatient hospitalization or prolongation of existing hospitalization

4. Results in persistent disability/incapacity or substantial disruption of the ability to conduct normal life functions.

5. Is or results in a congenital anomaly/birth defect

6. Is medically important

The treatment emergent SAE and treatment emergent related SAE will be tabulated by study treatment, SOC and PT treatment (Analysis set: Safety set):

- SAEs

- Related SAEs

Treatment emergent AEs leading to dose modifications (dose reductions or dose interruptions and withdrawn of study drugs) will be summarizes by study treatment, SOC and PT treatment (Analysis set: Safety set).

Treatment emergent AE leading to death will be tabulated by study treatment, SOC and PT treatment (Analysis set: Safety set).

The following listings will be provided (Listing analysis set: Safety set):

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- A by-subject listing of all SAEs

Listings of SAEs, deaths and other significant adverse events will be provided along with SAEs and AEs that led to withdrawal. A summary of death and primary cause of death will be summarized by the number and percentage of patients experiencing events by treatment group and overall. A by-patient listing of death will be provided.

4.11.3 Clinical Laboratory Evaluation

The clinical laboratory tests include the following tests:

- Hematology (eCRF: Local Lab-Hematology)
- Clinical Chemistry (eCRF: Local Lab-Chemistry)
- Urinalysis (eCRF: Local Lab-Urinalysis)
- Serum Pregnancy test (eCRF: Pregnancy test)

Descriptive statistics for laboratory test results (hematology, 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 NCI-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 (normal/abnormal ncs/abnormal cs) will be provided for laboratory tests A supportive listing of patients with clinically significant changes in post-baseline values will be provided, including the patient number, study site and baseline and post baseline values.

NCI-CTCAE Grades Available

The laboratory toxicities will be tabulated by the worst on-treatment NCI-CTCAE grade or the shift of NCI-CTCAE grade from baseline to worst grade during on-treatment period using descriptive statistics (count and percentage). The highest NCI-CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

- The worst grade during the on-treatment period will be summarized considering only patients with post baseline laboratory samples: Laboratory tests by NCI-CTCAE grade (0, 1, 2, 3, 4, and missing).

The shift table will summarize baseline NCI-CTCAE grade vs. the worst on-treatment CTCAE grade (grade = 0, 1, 2, 3, 4). The above analyses apply to the following hematology and chemistry parameters which can be graded per NCI-CTCAE:

- Hematology: Hemoglobin, Leukocytes, Lymphocytes, Neutrophils, Eosinophils, Platelets.
- Chemistry: Creatinine, Alanine Aminotransferase, Aspartate Aminotransferase, Total Bilirubin, Albumin, Alkaline Phosphatase, Glucose, Sodium, Potassium, Calcium, Magnesium, gamma-GTP, Uric-acid.

Tables will summarize, separately for hematology (**Appendix**) and chemistry parameters

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Appendix), the shift from baseline grade to worst on-treatment grade by parameters and study treatment.

4.11.4 Vital Signs, Physical Findings and Other Observations Related to Safety

4.11.4.1 Vital Signs

The vital sign variables include height, weight, systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, assessment location for body temperature, and respiratory rate (eCRF: Vital Sign).

The following summaries will be provided:

- A summary of each vital sign by visit and study treatment (Analysis set: Safety Set).

- A summary of change from baseline in each vital sign by visit and study treatment (Analysis set: Safety Set).

- A by-subject listing of all vital signs will be provided (Listing analysis set: Safety set).

4.11.4.2 12-Lead Electrocardiogram

ECG parameters (Heart Rate; PR; RR; QRS; QT Interval; QTcF) will be summarized by observed time point using appropriate descriptive statistics by treatment group (eCRF: 12-lead ECG). The CTCAE grade 1 - grade 3 of QTcF will be calculated (**Appendix.**) by program. The Grade 4 of QTcF (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia) cannot be calculated quantitatively in the summary.

Box plots for observed ECG parameters and change from baseline in ECG parameters over time will be presented. Shift plots of the value corresponding to the maximum absolute change from baseline versus the baseline value for QTcF, with reference lines for 450 ms, ±30 ms and ±60 ms change, will be presented.

QTc outliers are defined as QTcF values following dosing that are greater than 450 ms or are increases from baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarized using the following categories:

- Values >450 ms, >480 ms, >500 ms,

- Increase from baseline of >30 ms,

- Increase from baseline of >60 ms,

- Increase from baseline of >90 ms,

- Values >450 ms and increases of >30 ms.

- Values >500 ms and increases of >60 ms.

The number and percentage of patients who meet the ECG outlier criteria at any assessment post-date of first dose will be summarized. Triplicate 12-ECG will be analyzed by the mean of the 3 time-points.

A shift table in CTCAE Grade of QTcF will be provided. 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

4.11.4.3 Physical Examination

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

The following summaries will be provided:

- A summary of each physical examination by body system, visit and study treatment (Analysis set: Safety set).
- A summary of change from baseline using shift table in each physical examination by visit and study treatment (Analysis set: Safety set).
- A by-subject listing of all physical examination will be provided (Listing analysis set: Screened set).

4.11.4.4 Left Ventricular Ejection Fraction (LVEF) Assessment

Plots of absolute LVEF values and change from baseline in LVEF values over time will be presented. LVEF outliers are defined as LVEF values following dosing that are:

- $\geq$10 percentage points decrease from baseline and <50%, or
- $\geq$15 percentage points decrease from baseline and $\geq$50%.

The number of patients with the following LVEF values for the maximum post-baseline change will be displayed:

- LVEF increase:
  - $\geq$30%
  - $\geq$20 - <30%
  - $\geq$10 - <20%
- LVEF change <10%
- LVEF decrease
  - $\geq$10 - <20% and absolute value <50%
  - $\geq$10 - <20% and absolute value $\geq$50%
  - $\geq$20 - <30% and absolute value <50%
  - $\geq$20 - <30% and absolute value $\geq$50%
  - $\geq$30% and absolute value <50%
  - $\geq$30% and absolute value $\geq$50%

For the maximum change, patients with a maximum increase $\geq$10% and a maximum decrease <10% will be summarized under their maximum increase, and patients with a maximum decrease $\geq$10% and a maximum increase <10% will be summarized under their maximum decrease. CTCAE grade of LVEF is shown as **Appendix.**

A summary table by treatment group for displaying the number and percentage of LVEF result and NYHA classification class will be provided as per the data collected in eCRF (Analysis set: Safety set). Along with this a by-subject listing of LVEF assessment will be provided (Listing analysis set: Safety set) as per the eCRF.

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4.11.4.5 Liver Event Follow-Up

A summary table by treatment group for displaying the number and percentage of liver event follow-up results will be provided as per the data collected in eCRF (Analysis set: Safety set).

Along with this a by-subject listing of liver event follow-up will be provided (Listing analysis set: Safety set) as per the eCRF.

4.11.4.6 Safety Monitoring (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.

4.12 Pharmacokinetic Evaluation

4.12.1 Listing of PK Concentration Data

Plasma and CSF concentration data are used as supplied by the bioanalytical laboratory. The units and decimal place of the concentrations will be presented as they are received from the bioanalytical laboratory. 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 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 as per the assessment schedule.

4.12.2 Analysis of PK Concentration Data

Plasma concentrations of Lazertinib will be summarized by nominal sampling time. CSF concentrations 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 for the PK analysis set. In the summary statistics for the concentration data, BLQ values will be treated as half of the lower limit of quantification ($\frac{1}{2}$LLOQ) with the exception of the value for 'not detected (ND)', which is set to zero. If all the values are BLQ in all patients by each nominal sampling time, then the arithmetic mean, standard deviation, median, minimum, maximum and geometric mean are presented as zero, and the arithmetic and geometric coefficient of variation are denoted as NA. Missing values of the

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concentration will be excluded from the summary statistics. All summary statistics will be performed using data collected after the administration of Lazertinib 240 mg without dose reduction of Lazertinib.

The PK data collected in this study may be combined with data from other Lazertinib studies for Lazertinib and analyzed using population PK approach, which may include exploring the influence of covariates on PK, if the data allow. The results of any such analyses will be reported separately from the CSR.

4.13 Other Analyses

4.13.1 Sensitivity Analyses

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4.14 Determination of Sample Size

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.

4.15 Changes in the Conduct of the Study or Planned Analysis

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Appendix 1. Schedule of Assessments

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[14] and HIV screen	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			

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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	Cycle 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)													

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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	Cycle 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 and blood samples upon disease progression for confirmation of T790M mutation status[24]			(X)										
Tumor and 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

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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 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®

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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.

[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

22 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.
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.

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Appendix 2. 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	Cycle 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								
EORTC QLQ LC-13		X			X	Every 6 weeks relative to date of lazertinib first-dosing							
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 and blood samples upon disease progression for exploratory research					(X)								
Study treatment supply/dispensing													
Dispense lazertinib		X			X	X	X	X	(X)				

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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 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 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

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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.

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Appendix 3. Hematology Parameters of NCI-CTCAE V5.0

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology								
Hemoglobin - Low	Decrease	Blood and lymphatic system disorders	Anemia	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.								
Hemoglobin - High	Increase	Investigations	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL		-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal.								
Leukocytes/ White blood cell	Decrease	Investigations	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.								
Leukocytes/ White blood cell	Increase	Blood and lymphatic system disorders	Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.								
Lymphocyte - Low	Decrease	Investigations	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.								
Lymphocyte - High	Increase	Investigations	Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.								
Neutrophils	Decrease	Investigations	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.								

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Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count (PLT)	Decrease	Investigations	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.								
Eosinophils	Increase	Blood and lymphatic system disorders	Eosinophilia	>ULN and >Baseline Baseline grade: (>ULN)	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood.								

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Appendix 4. Chemistry Parameters of NCI-CTCAE V5.0

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chemistry								
Albumin	Decrease	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.								
Alkaline phosphatase (ALP)	Increase	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal (Baseline grade: >ULN - 2.5 x ULN)	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal (Baseline grade: >2.5 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.								
Alanine aminotransferase (ALT)	Increase	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal (Baseline grade: >ULN - 3.0 x ULN)	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal (Baseline grade: >3.0 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.								

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Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase (AST)	Increase	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal (Baseline grade: >ULN - 3.0 x ULN)	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal (Baseline grade: >3.0 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.								
Bilirubin (total)	Increase	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal (Baseline grade: >ULN - 1.5 x ULN)	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal (Baseline grade: >1.5 - 3.0 x ULN)	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal (Baseline grade: >3.0 - 10.0 x ULN)	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal. (Baseline grade: >10.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.								
Creatinine	Increase	Investigations	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN (Baseline grade: >1.5 - 3.0 x ULN)	>3.0 x baseline; >3.0 - 6.0 x ULN (Baseline grade: >3.0 - 6.0 x ULN)	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.								
Potassium - Low	Decrease	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.								
Potassium - High	Increase	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.								

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Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium - Low	Decrease	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood. **Specified for programming use:** Grade 1: <LLN - ≥130 mmol/L; Grade 2: ≥ 125 - < 130; Grade 3: ≥ 120 - < 125; Grade 4: < 120 mmol/L.								
Sodium - High	Increase	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.								
Magnesium - Low	Decrease	Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.								
Magnesium - High	Increase	Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.								

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Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Calcium - Low	Decrease	Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.								
Calcium - High	Increase	Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.								
Glucose - Low	Decrease	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.								

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Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gamma GTP	Increase	Investigations	GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal. (Baseline grade: >ULN - 2.5 x ULN)	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal. (Baseline grade: >2.5 - 5.0 x ULN)	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal. (Baseline grade: >5.0 - 20.0 x ULN)	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal. (Baseline grade: >20.0 x ULN)	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.								
Uric Acid	Increase	Metabolism and nutrition disorders	Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	-
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.								

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Appendix 5. Other Parameters of NCI-CTCAE V5.0

Lab Test Name	Direction toxicity	CTCAE v5.0 SOC	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Others								
QTcF	Increase	Investigations	Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia.	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.								
LVEF	Decrease	Investigations	Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >=20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.								

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Appendix 6. Scoring the QLQ-C30 Version 3.0

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score.*

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Technical Summary

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $\qquad S = \left\{1 - \dfrac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $\quad S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $\; S = \{(RS-1)/range\} \times 100$

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

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	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)[†]	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)[†]	PF2	5	3	1 to 5	F
Role functioning (revised)[†]	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore, RS,* is the mean of the component items:
$$RawScore = RS = \left(I_1 + I_2 + ... + I_n\right)/n$$

For all scales, the *RawScore, RS,* is the mean of the component items:
$$RawScore = RS = \left(I_1 + I_2 + ... + I_n\right)/n$$

Then for **Functional scales**:
$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL**:
$$Score = \left\{(RS - 1)/range\right\} \times 100$$

Examples:

Emotional functioning
$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$EF\,Score = \left\{1 - (RawScore - 1)\,\beta\right\} \times 100$$

Fatigue
$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$FA\,Score = \left\{(RawScore - 1)\,\beta\right\} \times 100$$

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Summary – Missing items

- Have at least half of the items from the scale been answered?
- If *Yes*, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.
- If *No*, set scale score to missing.
- For single-item measures, set score to missing.

Example:

Emotional functioning if
Q_{23} *is missing*
(3 items not missing)

$$RawScore = (Q_{21} + Q_{22} + Q_{24})/3$$
$$EF\, Score = \{1 - (RawScore - 1)/3\} \times 100$$

For example, role functioning (RF) and cognitive functioning (CF) each contain 2 items, and so these scales can be estimated whenever one of their constituent items is present; physical functioning contains 5 items, and so at least 3 need to have been completed. Using this method, none of the single-item measures can be imputed.

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Appendix 7. Scoring the QLQ-LC13

Scoring of the lung cancer module

The lung cancer module incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis.

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single items of the QLQ-C30.

Scale name	Scale	Number of items	Item range*	QLQ-LC13 Item numbers	†
Symptom scales / items					
Dyspnoea†	LCDY	3†	3	3,4,5	X
Coughing	LCCO	1	3	1	
Haemoptysis	LCHA	1	3	2	
Sore mouth	LCSM	1	3	6	
Dysphagia	LCDS	1	3	7	
Peripheral neuropathy	LCPN	1	3	8	
Alopecia	LCHR	1	3	9	
Pain in chest	LCPC	1	3	10	
Pain in arm or shoulder	LCPA	1	3	11	
Pain in other parts	LCPO	1	3	12	

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

† The dyspnoea scale should only be used if all three items have been answered. Some respondents ignore question 5 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 5 is missing then items 3 and 4 should be used as single-item measures.

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PPD

Approval Signatures

Document Name: Statistical Analysis Plan 26 Sep 2022 YH25448-301

Document Number: VV-TMF-2080833

PPD

System Version Number: 1 .0

Document Approvals

Reason for signing: Approved	
Reason for signing: Approved	PPD
Reason for signing: Approved	
Reason for signing: Approved	