STATISTICAL ANALYSIS PLAN	
Study Code	D5161C00017
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The Efficacy and Safety of Osimertinib with Platinum plus Pemetrexed Chemotherapy, as First-line Treatment in Recurrent or Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Patients with Uncommon Epidermal Growth Factor Receptor Mutations (EGFRm): A phase 2, Open Label, Single Arm, Multicenter, Exploratory Study

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ARMS	Amplification Refractory Mutation System
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating Tumour Deoxyribonucleic Acid
DBL	Database Lock
DCO	Data Cut Off
DCR	Disease Control Rate
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FAS	Full Analysis Set
HER2	Human Epidermal Growth Factor Receptor-2
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LSI	Last Subject In
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal Epithelial Transition
MUGA	Multigated Acquisition
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next-Generation Sequencing Technology

Abbreviation or Specialized Term	Definition
NPA	Negative Percent Agreement
NPV	Negative Predictive Value
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
p.o.	Orally
PD	Progression Disease
PFS	Progression Free Survival
PI3K	Phosphatidylinositol 3-kinase
PPA	Positive Percent Agreement
PPV	Positive Predictive Value
PR	Partial Response
PS	Performance Score
PT	Preferred Term
qd	Every Day
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCR	Screened
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TFST	Time to First Subsequent Treatment
TKI	Tyrosine Kinase Inhibitors
TPR	Time Point Response
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	4/25/2022	Initial approved SAP	N/A	N/A

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for study D5161C00017 based on Clinical Study Protocol (CSP) version 1.0 dated June 1, 2021. This plan should be read in conjunction with the CSP and the electronic case report forms(eCRFs).

1.1 Study Objectives

Objectives	Endpoints/Variables
Primary	
To describe the efficacy signals of osimertinib with platinum plus pemetrexed as first-line treatment	● ORR (objective response rate) defined as participants who achieved a complete response(CR) or partial response (PR) as their best overall response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by the investigator;
Secondary	

To further describe the efficacy signals of osimertinib with platinum plus pemetrexed as first-line treatment	● PFS (progression free survival) defined as time from first dose of study intervention until progression (PD) per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PD; ● OS (overall survival) defined as the time from first dose of study intervention until the date of death due to any cause; ● DoR (duration of response) defined as time from first occurrence of a response to a documented PD per RECIST 1.1 as assessed by the investigator or death of any cause; ● Depth of response defined as maximum response of target lesions per RECIST 1.1 as assessed by the investigator; ● DCR (disease control rate) defined as the percentage of participants who achieved CR, PR or stable disease (SD) based on RECIST 1.1 as assessed by the investigator; ● Time to treatment failure (TTF), defined as the time from first dose of study intervention to earlier of the date of last study intervention administration or death due to any cause; ● Time to first subsequent treatment (TFST), defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy start date following study intervention discontinuation or death due to any cause;
Safety	
To describe the safety and tolerability of osimertinib with platinum plus pemetrexed as first-line treatment	● All adverse events (AEs) graded by CTCAE v5 ● Incidence of ≥grade 3 AE/Serious AE (SAE); ● Incidence of all ADR; ● Discontinuation rate due to AEs; ● Clinical chemistry, hematology and urinalysis; ● Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; ● ECOG/WHO Performance Status;
Exploratory	
[redacted]	● [redacted]

a

1.2 Study Design

This is a phase II, open-label, single-arm, multicenter, exploratory study to assess the efficacy and safety of osimertinib plus standard chemotherapy in locally advanced or metastatic or recurrent NSCLC participants with uncommon EGFRm (single or multiple mutations of G719X/L861Q/S768I/de novo T790M without other EGFR mutations including ex19del and L858R). The main assumption is that osimertinib plus chemotherapy could further enhance the ORR in these patients.

Locally advanced or metastatic or recurrent NSCLC patients with uncommon EGFRm who are untreated or received previous adjuvant/neoadjuvant chemotherapy that was completed at least 6 months prior to the development of recurrent disease will be enrolled into the study. Patients should have at least one lesion that can be accurately measured at baseline of study enrolment according to RECIST 1.1. Meanwhile, their mutation status must be confirmed through one of ARMS, Super-ARMS or NGS analysis.

Participants successfully enrolled into the study will be treated The osimertinib will be used to treat participants till treatment discontinuation criteria achieved such as inadequate cycles of platinum and pemetrexed treatment, or discontinuation of pemetrexed maintenance, unacceptable or irreversible toxicities, or confirmed objective disease progression as defined by RECIST 1.1, or symptomatic progression requiring urgent medical intervention (eg, CNS metastases, respiratory failure, spinal cord compression), or death, or study completion, or consent withdrawal. Following treatment discontinuation, subsequent therapy will be at the discretion of the investigator. Patients will be followed till death, or study completion after subsequent treatments for survival analysis.

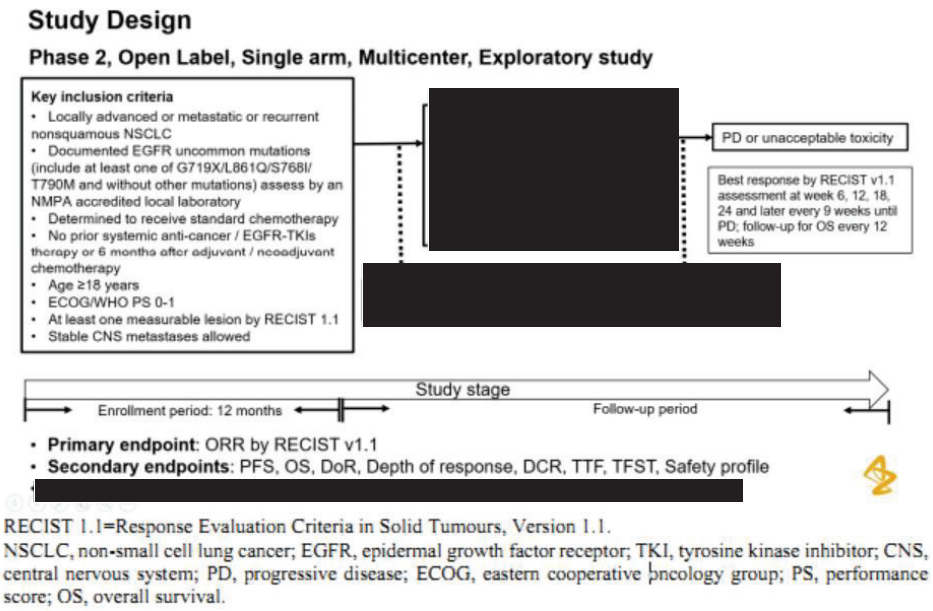
Patients will undergo the efficacy assessments based on RECIST 1.1 assessment criterion at week 6, 12, 18, 24 and later every 9 weeks, until objective disease progression. The survival follow-up will be repeated every 12 weeks after disease progression until study complete. What's more, participants will undergo the safety assessment in the whole

treatment period and 28-day safety follow-up visit after discontinued osimertinib for any reason or study complete.

[redacted]

The overall study design is shown in Figure 1 below. The study schedule is detailed in Section 1.3 of the protocol.

Figure 1



RECIST 1.1=Response Evaluation Criteria in Solid Tumours, Version 1.1.
NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CNS, central nervous system; PD, progressive disease; ECOG, eastern cooperative oncology group; PS, performance score; OS, overall survival.

1.3 Number of Patients

[redacted]

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

There will be 3 analyses planned for this study. The data cut-off (DCO) date for primary analysis for ORR will be at 24 weeks after last subject in (LSI). The second analysis DCO for median PFS will be at the point [redacted] The final OS analysis will be performed [redacted]

3.2 Analysis Populations

The screened (SCR) population will include all participants who signed the informed consent form.

Screen failure patients will be defined as patients who signed the informed consent form but who were reported as not fulfilling the inclusion or exclusion criteria according to the final protocol. These patients will be included in the SCR population but will be excluded from all other populations.

The enrolled population will include all participants who enrolled in the study.

The full analysis set (FAS) will include all enrolled participants who have received at least 1 dose of study intervention. The FAS will be used for all efficacy analyses and safety analyses unless specified otherwise.

3.3 General Considerations

All statistical analyses will be conducted using SAS version 9.4 or later.

For continuous variables, the summarization will include the number of subjects with non-missing values, mean, median, standard deviation, minimum and maximum. All means and medians will be reported to one more decimal point than the values being analyzed. Standard deviations will be reported to two more decimal points than the values being analyzed. The minimum and maximum will be reported to the same number of decimal points as the values being analyzed. In general, all descriptive statistics will be rounded to no more than 4 decimal points.

For categorical variables, summary statistics will consist of the number and percentage of subjects in each category. All percentages will be rounded to one decimal point. The number and percentage of subjects will always be presented in the form XX (XX.X) where the percentage is in parentheses. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category. Denominators for each analysis will be based on the population of interest (e.g., FAS population) unless specified otherwise.

For time-to-event variables, the Kaplan-Meier product limit method will be used to estimate the survival curve as well as survival rates at various time points. Kaplan-Meier estimates of medians and quartiles will be reported along with 2-sided 95% CIs using the method of Brookmeyer and Crowley. All medians and quartiles will be rounded to three decimal points.

Results of all statistical analyses will be summarized with descriptive statistics and presented with a 95% confidence interval estimate if applicable. Data will be listed by subject and visit. Subject listings of data will be presented for the FAS population unless otherwise specified.

3.3.1 General Study Level Definitions

3.3.1.1 Study Day

For the purpose of data summary, Study Day 1 is defined as the date of first dose of study intervention (osimertinib). For visits (or events) that occur on or after first dose of osimertinib, study day is defined as (date of visit [event] - date of first dose of osimertinib + 1). For visits (or events) that occur prior to first dose of osimertinib, study day is defined as (date of visit [event] - date of first dose of osimertinib). There is no Study Day 0.

3.3.1.2 Baseline Definition and Change from Baseline Variables

In general, the last non-missing observation prior to the first dose of osimertinib will be considered the baseline measurement unless otherwise specified.

For assessments on the day of first dose of Osimertinib where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose of osimertinib if such procedures are required by the protocol to be conducted before first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. For % change from baseline, calculate as: (post-baseline value-baseline value)/(baseline value)*100%.

3.3.2 Visit Window

For summaries of vital signs, laboratory data, ECG, ECOG/WHO performance status, physical examination and echocardiogram/MUGA, assessments will be assigned to a time-point according to the visit windowing rules defined in Appendix 1 and included in the analysis. If there are multiple assessments within a visit window, then 1) the record closest to the target day will be used; 2) if there are multiple assessments within the same distance from the target day, the latest record will be used; 3) the visit will be missing if no assessment was reported within the specified visit window around the target day; 4)

Treatment Discontinuation Visit and Progression Follow-up Visit will not be windowed, instead, used per nominal visit in relevant analyses.

3.3.3 Handling of Unscheduled Visits

Unscheduled visit assessments will be included in the following: 1) derivations of assessments at scheduled visits for safety analyses per specified visit windowing rules defined in Appendix 1; 2) derivations of baseline; 3) derivations of the maximum/minimum post-baseline values for safety analyses; 4) subject data listings.

3.3.4 Multiplicity/Multiple Comparisons

There is no adjustment for multiplicity of endpoints.

3.3.5 Handling of Missing Data

Missing data will be assumed missing at random or missing completely at random. In general, no imputation will be applied unless otherwise specified.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications. The imputed dates are not advised to be used to calculate durations where the results would be less accurate.

3.3.5.1 Determination of Treatment-Emergent AEs with Partially Missing Dates

If year is missing or the date is completely missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date of AE, assuming year is available. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of osimertinib, then the day and month of the date of the first dose of osimertinib will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of osimertinib, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of osimertinib, then January 1 will be assigned to the missing fields.

Missing Month Only

- The day will remain the same as observed and the month will be replaced according to the same procedure described above for “Missing Day and Month”.

Missing Day Only

- If the month and year of the incomplete start date are the same as those of the date of the first dose of osimertinib, then the day of the date of the first dose of osimertinib will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of osimertinib or if both years are same but the month is before the month of the date of the first dose of osimertinib, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of osimertinib or if both years are same but the month is after the month of the date of the first dose of osimertinib, then the first day of the month will be assigned to the missing day.

The following rules will be applied to impute the incomplete stop date of AE, assuming year is available. If the imputed stop date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using the start date.

Missing Day and Month

- December 31 will be assigned to the missing fields, unless this is after the date of death in which case date of death will be used instead.

Missing Month Only

- The day will be the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

- The last day of the month will be assigned to the missing fields, unless this is after the date of death in which case date of death will be used instead.

3.3.5.2 Determination of Prior and Concomitant Statuses for Medications/Procedures with Partially Missing Dates

If year is missing or the date is completely missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date of prior/concomitant medications/procedures assuming year is available. If the end date is complete and the imputed start date is after the end date, then the start date will be imputed using the end date.

Missing Day and Month

- January 1 will be assigned to the missing fields.

Missing Month Only

- The day will remain the same as observed and the month will be replaced according to the same procedure described above for “Missing Day and Month”.

Missing Day Only

- The first day of the month will be assigned to the missing day.

The following rules will be applied to impute the incomplete end date, assuming year is available. If the imputed end date is before the start date (imputed or non-imputed start date), then the end date will be imputed using the start date.

Missing Day and Month

- December 31 will be assigned to the missing fields, unless this is after the date of death in which case date of death will be used instead.

Missing Month Only

- The day will be the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

- The last day of the month will be assigned to the missing fields, unless this is after the date of death in which case date of death will be used instead.

3.3.5.3 Imputation rules for missing or partial death dates

Missing or partial death dates will be treated or imputed based on the following rules:

- If a patient is known to have died where the death date is missing, then the date of death will be treated missing, i.e. censored at the last known alive date;
- If the day or month is missing, death date will be imputed to the maximum of last contact date+1 and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

The last contact date is defined as the last date the subject was known to be alive up-to the data cut-off date. The date will be the latest complete date among the dates below. Only assessments up-to the data cut-off date will be considered in deriving the last contact date.

- Last non-missing assessment/onset date captured in the following eCRF pages (or if a date of assessment/onset is not available the “Visit Date” for the eCRF page can be used): Vital Signs, Vital Signs_V1, Physical Examination, ECOG/WHO Performance Status, ECG, Non-central Laboratory Test Results, Echocardiography/ MUGA, Tumour Evaluation and biomarker/other specimen sample collection date.
- AE start and stop dates
- Last date of subsequent anti-cancer therapy administered after study treatment discontinuation

- Last dosing date of osimertinib and background treatment, last date of prior and concomitant medications, and last date of concomitant procedures.
- "Date Subject Last Known to be Alive" collected on the eCRF form "Survival Status" page (only used if subject status is 'alive')
- Date of completion/discontinuation from the "Disposition" eCRF page (do not use if status is lost to follow-up)

3.3.5.4 Imputation rules for missing or partial subsequent anti-cancer therapy start dates

Missing or partial subsequent anti-cancer therapy start dates will be imputed as follows:

- If only day is missing, it will be imputed as 1st day of the month or the last dose date+1, which comes later;
- If both day and month are missing, no imputation will be performed.

3.3.5.5 Imputation rules for lab values outside of quantification

Lab values below the lower limit of quantification (LLOQ) that are reported as "<LLOQ" or "≤LLOQ" in the database will be imputed by 0.99*LLOQ for analysis purposes. The original value will be listed.

Lab values above the upper limit of quantification (ULOQ) that are reported as ">ULOQ" or "≥ULOQ" in the database will be imputed by 1.01*ULOQ for analysis purposes. The original value will be listed.

3.3.6 Examination of Subgroups

The following subgroups may be defined for this study if applicable (i.e. with at least 5 observations per level):

- ECOG/WHO Performance Status (0 vs. 1)
- Age at Screening (<65 Years vs. ≥65 Years)
- Sex (Male vs. Female)
- Smoking Status (Never vs. Former/Current)
- CNS metastasis at entry (Yes vs. No)
- EGFR mutation type from accredited laboratory(G719X vs. S768I vs. L861Q vs. T790M vs. Concurrent mutations within EGFR vs. Concurrent mutations other than EGFR)
- Resistance Mechanism (EGFR-dependent vs. EGFR-independent)

4 STATISTICAL ANALYSIS

4.1 Study Population

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

The following disposition information will be derived for each subject:

- Received osimertinib: subject has received at least one non-zero dose of osimertinib
- Ongoing on osimertinib: subject has started osimertinib and osimertinib is not permanently discontinued
- In follow-up: subject has stopped the study treatments and did not die, nor withdrew consent, nor was lost to follow-up and the study is not terminated by sponsor

4.1.1.2 Presentation

The following will be summarized overall for all screened subjects:

- Number of subjects screened (informed consent received)
- Number and percentage of subjects who failed screening overall and grouped by the main reason
- Number of subjects enrolled
- Number and percentage of subjects receiving osimertinib
- Number and percentage of subjects who discontinued from osimertinib and grouped by the main reason for treatment discontinuation
- Number and percentage of subjects who discontinued study treatment but are still in follow-up
- Number and percentage of subjects who completed and discontinued the study and grouped by main reasons for study discontinuation

All subject disposition, treatment discontinuation and study discontinuation will also be listed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The definitions of analysis sets were described in section 3.2.

4.1.2.2 Presentation

The number and percentage of subjects in FAS will be summarized.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

All protocol deviations will be captured and reviewed by study team and identified as important protocol deviation or not. An important protocol deviation is a deviation that significantly affects the safety of participants and efficacy assessments, meeting at least one of the following criteria:

- Affecting the safety and rights of participants;
- Affecting the subject's willingness to continue participating in the trial;
- Affecting the quality and integrity of data.

4.1.3.2 Presentation

All major protocol deviations will be listed and tabulated by deviation category for the FAS.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Baseline body mass index (BMI) and body surface area (BSA) will be derived as:

- Baseline BMI (kg/m^2)=Baseline Weight (kg)/[Baseline Height (cm)/100]^2, rounded to 1 decimal place
- Baseline BSA (m^2)=0.0061×Baseline Height (cm)+0.0128×Baseline Weight (kg)-0.1529, rounded to 1 decimal place

4.1.4.2 Presentation

Demographic data will be listed and summarized for the FAS.

The following demographics will be reported as continuous variables and presented as described in section 3.3:

- Age (Years)
- Baseline Weight (kg)
- Baseline Height (kg)
- Baseline BMI (kg/m^2)
- Baseline BSA (m^2)

The following demographics will be reported as categorical variables and presented as described in section 3.3:

- Age group (years) (grouped as <50, ≥50-<65, ≥65-<75, ≥75; <65, ≥65)
- Sex

- Race

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Not Applicable.

4.1.5.2 Presentation

Other baseline characteristics will be listed and summarized for the FAS.

The following baseline characteristics will be reported as continuous variables and presented as described in section 3.3:

- Nicotine consumption (Number of pack years)

The following baseline characteristics will be reported as categorical variables and presented as described in section 3.3:

- Smoking Status (Current, Former, Never)
- ECOG/WHO Performance Status

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Time since primary diagnosis of lung cancer will be derived as:

- Time since primary diagnosis of lung cancer (months) = (Date of first dose of osimertinib – Date of Collection on "Pathology: at Screening" eCRF page+1)/ 30.4375, rounded to 1 decimal place.

Time since recent progression date will be derived as:

- Time since recent progression date (months) = (Date of first dose of osimertinib – Recent Progression Date+1)/ 30.4375, rounded to 1 decimal place.

4.1.6.2 Presentation

Disease characteristics will be listed and summarized for the FAS.

The following disease characteristics will be reported as continuous variables and presented as described in section 3.3:

- Time since primary diagnosis of lung cancer (months)
- Time since recent progression date (months)
- Baseline sum of diameters for target lesions (mm)

The following disease characteristics will be reported as categorical variables and presented as described in section 3.3:

- Histology Type
- Primary Tumor
- Regional Lymph Nodes
- Distant Metastases
- AJCC Stage
- Extent of Disease Upon Entry to Study (Locally Advanced, Metastatic, Both)
- Location of local/metastatic disease
- CNS Metastasis at Entry (No, Yes)
- Recurrence of Earlier Cancer (No, Yes)
- EGFR mutation type from accredited laboratory(G719X, S768I, L861Q, T790M, Concurrent mutations within EGFR, Concurrent mutations other than EGFR)
- EGFR mutation type from Cobas central testing(G719X, S768I, L861Q, T790M, Concurrent mutations within EGFR, Concurrent mutations other than EGFR)
- Baseline sum of diameters for target lesions group (grouped as <40, 40-79, 80-119, ⩾120mm)

4.1.7 Medical History

4.1.7.1 Definitions and Derivations

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.1.7.2 Presentation

Medical history will be listed and the number and percentage of subjects with any medical history events will be summarized for the FAS by system organ class (SOC) and preferred term (PT).

Each subject will be counted only once within each PT or SOC. The summary table will be sorted on decreasing frequency of SOC and decreasing frequency of PT in a given SOC. In case of equal frequency regarding SOC (respectively PT), alphabetical order will be used.

4.1.8 Previous Systemic Anti-cancer Therapy

4.1.8.1 Definitions and Derivations

Previous systemic anti-cancer therapy will be coded using the most current available version of WHO Drug Dictionary.

4.1.8.2 Presentation

The following data entered on the eCRF page "Cancer Therapy_Previous" will be summarized as categorical variables:

- Subjects who received previous systemic anti-cancer therapy. This will also include the number and percentage of subjects by therapy class and treatment status and the number and percentage of subjects by Anatomical Therapeutic Chemical (ATC) classification level 2 and Preferred Term (PT).

Each subject will be counted only once within each ATC class or PT. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

All previous systemic anti-cancer therapy data will also be listed for the FAS.

4.1.9 Previous Anti-cancer Radiotherapy

4.1.9.1 Definitions and Derivations

Previous anti-cancer radiotherapy will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.1.9.2 Presentation

The following data entered on the eCRF page "Radiotherapy_ Previous" will be summarized as categorical variables:

- Subjects who received previous anti-cancer radiotherapy. This will also include the number and percentage of subjects by treatment status and the number and percentage of subjects by SOC and PT.

Each subject will be counted only once within each SOC or PT. The summary tables will be sorted on decreasing frequency of SOC and decreasing frequency of PT in a given SOC. In case of equal frequency regarding SOC (respectively PT), alphabetical order will be used.

All previous anti-cancer radiotherapy data will also be listed for the FAS.

4.1.10 Surgical History

4.1.10.1 Definitions and Derivations

Surgical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.1.10.2 Presentation

Surgical history will be listed and the number and percentage of subjects with any surgical history events will be summarized for the FAS by system organ class (SOC) and preferred term (PT).

Each subject will be counted only once within each PT or SOC. The summary tables will be sorted on decreasing frequency of SOC and decreasing frequency of PT in a given SOC. In case of equal frequency regarding SOC (respectively PT), alphabetical order will be used.

All surgical history data will also be listed for the FAS.

4.1.11 Prior and Concomitant Medications

4.1.11.1 Definitions and Derivations

Prior medications are defined as medications, other than study medications, with an end date occurring before the date of first dose of osimertinib.

Concomitant medications are defined as medications, other than study medications, that (a) started before the date of first dose of osimertinib and ending on or after the date of first dose of osimertinib, or ongoing as indicated on the eCRF; or (b) started on or after the date of first dose of osimertinib.

Prior and concomitant medications will be coded using the most current available version of WHO Drug Dictionary.

4.1.11.2 Presentation

Prior and concomitant medications will be listed and the number and percentage of subjects with any prior and concomitant medications will be summarized for the FAS by Anatomical Therapeutic Chemical (ATC) classification level 2 and Preferred Term (PT).

Each subject will be counted only once within each ATC class or PT. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

4.1.12 Prior and Concomitant Procedures

4.1.12.1 Definitions and Derivations

Prior procedures are defined as procedures with an end date occurring before the date of first dose of osimertinib.

Concomitant procedures are defined as procedures that (a) started before the date of first dose of osimertinib and ending on or after the date of first dose of osimertinib, or ongoing as indicated on the eCRF; or (b) started on or after the date of first dose of osimertinib.

Prior and concomitant procedures will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.1.12.2 Presentation

Prior and concomitant procedures will be listed and the number and percentage of subjects with any prior and concomitant procedures will be summarized for the FAS by system organ class (SOC) and preferred term (PT).

Each subject will be counted only once within each PT or SOC. The summary tables will be sorted on decreasing frequency of SOC and decreasing frequency of PT in a given SOC. In case of equal frequency regarding SOC (respectively PT), alphabetical order will be used.

4.1.13 Subsequent Anti-Cancer Systemic Therapy

4.1.13.1 Definitions and Derivations

Subsequent systemic anti-cancer therapy will be coded using the most current available version of WHO Drug Dictionary.

4.1.13.2 Presentation

The following data entered on the eCRF page "Subsequent Cancer Therapy" will be summarized as categorical variables:

- Subjects who received subsequent anti-cancer systemic therapy. This will also include the number and percentage of subjects by therapy class and the number and percentage of subjects by Anatomical Therapeutic Chemical (ATC) classification level 2 and Preferred Term (PT).

Each subject will be counted only once within each ATC class or PT. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

All subsequent anti-cancer systemic therapy data will also be listed for the FAS.

4.1.14 Radiotherapy after Treatment Discontinuation

4.1.14.1 Definitions and Derivations

Radiotherapy after treatment discontinuation will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA).

4.1.14.2 Presentation

The following data entered on the eCRF page "Radiotherapy, Post Treatment Discontinuation" will be summarized as categorical variables:

- Subjects who received radiotherapy after treatment discontinuation. This will also include the number and percentage of subjects by treatment status and the number and percentage of subjects by SOC and PT.

Each subject will be counted only once within each SOC or PT. The summary tables will be sorted on decreasing frequency of SOC and decreasing frequency of PT in a given SOC. In case of equal frequency regarding SOC (respectively PT), alphabetical order will be used.

All data of radiotherapy after treatment discontinuation will also be listed for the FAS.

4.2 Endpoint Analyses

4.2.1 Primary Endpoint

4.2.1.1 Definitions and Derivations

The confirmed best overall response (BOR) is defined as the best confirmed response (in the order of CR, PR, SD, PD and NE) among all overall responses recorded after the start of study treatment until disease progression or the start of subsequent anti-cancer therapy, taking requirement for confirmation into account as detailed in Appendix 2. If CR or PR are followed by NE and then by CR or PR, as long as the time between the 2 visits of CR/PR is greater than 4 weeks, then the original CR/PR can be considered confirmed. If a tumor assessment was performed on the same day as start of subsequent anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR.

ORR (per RECIST 1.1 using Investigator assessments) is defined as the proportion of participants in the FAS who achieved a complete or partial response as their best overall response based on RECIST 1.1 as assessed by the investigator, where the response must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

4.2.1.2 Primary Analysis of Primary Endpoint

The number and percentage of subjects in all BOR categories will be summarized. The ORR together with two-sided exact 95% Clopper-Pearson CI will also be presented.

All tumor assessment data and BOR will also be listed for the FAS.

Subgroup Analysis

In each subgroup defined in section 3.3.6, the analysis will be carried out using the same type of methodology and the same analysis set as described for the analysis of ORR, if applicable. Results of the subgroup analyses will be presented using descriptive summaries and the ORR and its corresponding 95% CI of all subgroups will also be presented in a forest plot.

4.2.2 Secondary Endpoint

4.2.2.1 Progression-Free Survival

4.2.2.1.1 Definitions and Derivations

PFS is defined as the time from first dose of study intervention until progression per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PD. PFS will be derived as below:

- PFS(months)=(Date of PD or Death - Date of first dose of Osimertinib+1)/30.4375, rounded to 1 decimal place.

Note that investigators assessment of RECIST will be used for PFS, this will not be derived programmatically. Subjects who have not progressed or died at the time of analysis will have PFS right-censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the subject progresses or dies after 2 or more consecutive missed visits, PFS will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. (Note: NE visit is not considered as missed visit). If the subject has no evaluable visits or does not have baseline data, PFS will be censored at Day 1, unless they die within 2 visits of baseline in which case their date of death will be used as an event. The detailed censoring and event date options to be considered for the PFS analysis are presented in Appendix 3.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For investigator assessments, the date of progression will be determined based on the earliest RECIST assessment/scan dates of the component that indicates progression. If progression is based on unequivocal progression of non-target lesion or a new lesion, the date of PD is the earlier date when PD is detected. If progression is based on target lesions where scans may be obtained at different times, the target lesion PD date is the date of the earliest scan of the component that triggered the progression. For the overall response assessment when PD may be due to target lesions, non-target-lesion, or new lesions, the earliest date when PD is identified from any source is the date of PD.
- When censoring PFS, right-censoring will be at the latest of the scan dates contributing to a particular overall visit assessment.

4.2.2.1.2 Analysis of Progression-Free Survival

The number and percentage of subjects with an event (PD or death) and censoring reasons will be provided.

The distribution of PFS times will be estimated using the Kaplan-Meier product limit method and Kaplan-Meier plots of PFS will be presented. The 25th percentile, median and 75th percentile PFS times and their corresponding two-sided 95% CIs will be estimated.

Confidence intervals for median time to progression or death due to any cause as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley.

The percentage of subjects who had progressed or had died at specific timepoints (e.g. 6, 12 months etc.), and the associated two-sided 95% CIs for each of these outcomes will be provided as well.

The PFS time or censoring time and the censoring reasons will also be presented in a subject listing for the FAS.

Subgroup Analysis

In each subgroup defined in section 3.3.6, the analysis will be carried out using the same type of methodology and the same analysis set as described for the analysis of PFS, if applicable (i.e. with at least 5 observations per level). Results of the subgroup analyses will be presented using descriptive summaries and the median PFS and its corresponding 95% CI of all subgroups will also be presented in a forest plot.

4.2.2.2 Overall Survival

4.2.2.2.1 Definitions and Derivations

OS is defined as the time from the first dose of treatment to the date of death, regardless of the actual cause of the subject's death. OS will be derived as below:

- OS(months)=(Date of Death - Date of first dose of osimertinib+1)/30.4375, rounded to 1 decimal place.

For participants who are still alive at the time of data analysis or who are lost to follow up, OS will be right-censored at Last Contact Date as defined in section 3.3.5.4 prior to or at the data cutoff date for the analysis. The detailed censoring and event date options to be considered for the OS analysis are presented in Appendix 4.

4.2.2.2.2 Analysis of Overall Survival

The analysis of OS will be analogous to that for PFS as described in section 4.2.2.1.2. In addition, a swimmer's plot for survival over time will be presented.

4.2.2.3 Duration of Response (DoR)

4.2.2.3.1 Definitions and Derivations

DoR is defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. DoR will be derived as below:

- DoR(months)=(Date of PD or Death - Date of First be Confirmed CR/PR+1)/30.4375, rounded to 1 decimal place.

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of PR or CR. The end of response should coincide with the date of

progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then his/her duration of response will use the PFS censoring time as the end point for their DoR calculation. The detailed censoring and event date options to be considered for the DoR analysis are presented in Appendix 3.

4.2.2.3.2 Analysis of DoR

The analysis of DoR will be based on the responding subjects. Analysis method of DoR will be the same as PFS.

4.2.2.4 Disease Control Rate

4.2.2.4.1 Definitions and Derivations

DCR is defined as the percentage of subjects who have a best overall response of CR or PR or SD by RECIST 1.1 as assessed by the investigator. For participants with a best overall response of SD, a RECIST assessment of SD must have been observed at least 6 weeks following enrolment to be included in the numerator of the calculation for disease control rate.

4.2.2.4.2 Analysis of DCR

The analysis of DCR will be analogous to that for ORR as described in section 4.2.1.2.

4.2.2.5 Depth of Response

4.2.2.5.1 Definitions and Derivations

The percent change from baseline in sum of diameters for target lesions at week XX will be derived as:

- [(Sum of diameters for target lesions at week XX - sum of diameters for target lesions at baseline)/sum of diameters for target lesions at baseline]×100%.

Depth of response is defined as maximum response of target lesions per RECIST 1.1 as assessed by the investigator and will be derived across all the post-baseline assessments until disease progression, excluding assessments after start of subsequent anti-cancer therapy, as

- Minimum of [(Sum of diameters for target lesions at week XX - sum of diameters for target lesions at baseline)/sum of diameters for target lesions at baseline]×100%.

4.2.2.5.2 Analysis of Depth of Response

Descriptive statistics will be used to summarize absolute and percentage change in sum of diameters for target lesions from baseline at each scheduled post-baseline tumor assessment visit. In addition, the best absolute change in sum of diameters for target lesions from baseline, and best percentage change in sum of diameters for target lesions from baseline will be summarized using descriptive statistics.

A waterfall plot of best percentage change in sum of diameters for target lesions from baseline for each subject will be presented with vertical lines representing the sorted values

of percent changes. A spider plot of the percent change in sum of diameters for target lesions from baseline for each subject will be presented as well.

4.2.2.6 Time to Treatment Failure or Death

4.2.2.6.1 Definitions and Derivations

Time to treatment failure(TTF) or death is defined as the time from first dose of study intervention (osimertinib) to earlier of the date of last study intervention administration or death due to any cause. TTF will be derived as below:

- TTF(months)=(Date of last dose of osimertinib or Death - Date of first dose of osimertinib+1)/30.4375, rounded to 1 decimal place.

Any subject not known to have permanently discontinued study intervention and not known to have died at the time of the analysis will be censored at Last Contact Date as defined in section 3.3.5.4. The detailed censoring and event date options to be considered for the TTF analysis are presented in Appendix 5.

4.2.2.6.2 Analysis of TTF

The analysis of TTF will be analogous to that for PFS as described in section 4.2.2.1.2.

4.2.2.7 Time to First Subsequent Therapy or Death

4.2.2.7.1 Definitions and Derivations

Time to first subsequent therapy (TFST) is defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy (except cisplatin or carboplatin or pemetrexed) start date following study intervention discontinuation or death due to any cause. TFST will be derived as below:

- TFST(months)=(Date of first subsequent anti-cancer therapy or death - Date of first dose of osimertinib+1)/30.4375, rounded to 1 decimal place.

Any participant not known to have had a subsequent therapy or not known to have died at the time of the analysis will be censored at the last known time to have not received subsequent therapy (obtained from the eCRF pages “Time to Subsequent Cancer Therapy”). The detailed censoring and event date options to be considered for the TFST analysis are presented in Appendix 6.

4.2.2.7.2 Analysis of TFST

The analysis of TFST will be analogous to that for PFS as described in section 4.2.2.1.2.

4.2.3 Other Endpoint

4.2.3.1 Definitions and Derivations

Concordance of Local and Central Testing

[redacted]

[redacted]

4.2.3.2 Presentation

[redacted]

4.3 Pharmacodynamic Endpoint(s)

Not Applicable.

4.4 Pharmacokinetics

Not Applicable.

4.5 Immunogenicity

Not Applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG. Tables, figures and listings are provided for the FAS.

4.6.1 Exposure and Drug Compliance

4.6.1.1 Definitions and Derivations

Duration of Exposure/Treatment

The following durations will be defined:

- [redacted]
- [redacted]
- [redacted]

Cumulative Dose

The overall cumulative dose is the sum of the actual dose that the subject received.

Dose Intensity

The dose intensity will be calculated for each subject across all cycles.

- [redacted]
- [redacted]
- [redacted]

Relative Dose Intensity

The relative dose intensity is defined as the actual dose intensity divided by the planned dose as specified in the protocol per day/cycle.

4.6.1.2 Presentation

Treatment exposure and compliance will be summarized for the following categories:

- Osimertinib
- Pemetrexed
- Carboplatin/Cisplatin

And the following parameters will be summarized:

- Total exposure

- Actual exposure(for osimertinib only)
- [redacted]
- [redacted]
- Relative dose intensity(%)
- Relative dose intensity categories: <80%, 80%-<90%, 90%-<110%, ≥110%
- Number and percentage of subjects with at least one dose reduction/interruption/ discontinuation as well as a categorical breakdown of adjustment reason(for osimertinib only)
- total number of cycles initiated([redacted]

All study drug administration data will be listed by subject.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

AEs will be coded using the latest available version of MedDRA at the time of DBL.

TEAEs are defined as AEs that started or worsened in severity on or after the date of first dose of osimertinib, up to 28 days after the date of last dose of osimertinib or the start of subsequent anti-cancer therapy, whichever occurred first.

Related Adverse Events: adverse events with relationship to osimertinib (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, Reasonable Possibility AE Caused by Osimertinib=Yes) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Reasonable Possibility AE Caused by Osimertinib").

Serious Adverse Events (SAE): serious adverse events (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, Serious AE=Yes).

Adverse Events Leading to Dose Reduction: adverse events leading to dose reduction of osimertinib (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, "Action Taken, Osimertinib"=Dose Reduced).

Adverse Events Leading to Treatment Interruption: adverse events leading to interruption of osimertinib (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, "Action Taken, Osimertinib"=Drug Interrupted).

Adverse Events Leading to Treatment Discontinuation: adverse events leading to permanent discontinuation of osimertinib (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, "Action Taken, Osimertinib"= Drug Permanently Discontinued).

Adverse Events Leading to Death: adverse event leading to death (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, Outcome of AE=Fatal, as well as AEs of Grade 5).

Adverse Events Leading to Withdrawal from Study: adverse event leading to withdrawal from study (as recorded on the "Adverse Event & Serious Adverse Event Report" eCRF page, "AE Caused Subject to Withdraw from Study"=Yes).

A subject with more than one occurrence of the same AE in a particular SOC/PT will only be counted once under the SOC/PT. If a subject experiences the same AE at more than one CTCAE grade level, or with more than one relationship to osimertinib, the most severe rating or the stronger causal relationship to osimertinib will be given precedence. Any missing CTCAE grade, causality, or outcome will not be imputed and classed as unknown.

4.6.2.2 Presentation

The number and percentage of subjects within each of the following categories will be presented overall and by SOC and PT:

- TEAEs
- Related TEAEs
- TEAEs, CTCAE grade≥3
- Related TEAEs, CTCAE grade≥3
- Treatment emergent SAEs (TESAEs)
- Related TESAEs
- TEAEs leading to dose reduction
- Related TEAEs leading to dose reduction
- TEAEs leading to treatment interruption
- Related TEAEs leading to treatment interruption
- TEAEs leading to treatment discontinuation
- Related TEAEs leading to treatment discontinuation
- TEAEs leading to death
- Related TEAEs leading to death
- TEAEs leading to withdrawal from study
- Related TEAEs leading to withdrawal from study

In addition, a truncated AE table of most common TEAEs, showing all events that occur in at least 5% of subjects overall will be summarised by PT, by decreasing frequency.

The number and percentage of subjects with TEAEs and related TEAEs will be provided by maximum CTCAE grade, SOC and PT.

All reported AEs will be listed along with the start date, stop date, investigator's assessment of maximum CTCAE grade and relationship to study treatment, etc. Related TEAEs, SAEs, TEAEs leading to death, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to treatment interruption and TEAEs leading to withdrawal from study will be listed as well.

4.6.3 Deaths

4.6.3.1 Definitions and Derivations

Not Applicable.

4.6.3.2 Presentation

The following summary of deaths for the FAS will be provided:

- The number and percentage of subjects who died
- The number and percentage of subjects by cause of death. In the case of deaths reported due to an AE, the number and percentage by PT will be presented.
- The number and percentage of subjects who died within 28 days after last dose of osimertinib.

A corresponding listing will also be produced.

4.6.4 Clinical Laboratory, Blood Sample

4.6.4.1 Definitions and Derivations

Applicable hematology and chemistry laboratory results will be graded according to the NCI-CTCAE criteria version 5.0 as outlined in Appendix 7. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: low (below range), normal (within range) and high (above range) based on project-specific reference ranges. As applicable, all laboratory data will be converted to the International System of units (SI).

For calcium, CTCAE grading is based on corrected calcium. Corrected calcium is calculated from albumin and calcium as follows:

- Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02*(40 - serum albumin [g/L])

4.6.4.2 Presentations

The following summaries for the hematology and chemistry data will be produced:

- Absolute values and change from baseline summarized by laboratory parameter and visit

- Box-Whisker plots of absolute values and change from baseline for all hematology and chemistry parameters
- Shift from baseline to worst post-baseline value according to NCI-CTCAE grade (for parameter with NCI-CTCAE grade defined). Bi-dimensional parameters will be split and presented in both directions.
- Shift from baseline to worst post-baseline value according to clinical significance

In addition, data listings of all hematology and chemistry data collected will be presented by subject.

4.6.5 Clinical Laboratory, Urinalysis

4.6.5.1 Definitions and Derivations

Not Applicable.

4.6.5.2 Presentations

The following summaries for the urinalysis data will be produced:

- Absolute values and change from baseline summarized by laboratory parameter and visit (for quantitative urinalysis parameter)
- The number and percentage of categorical results by laboratory parameter and visit (for qualitative urinalysis parameter)
- Shift from baseline to worst post-baseline value according to clinical significance

In addition, data listings of all urinalysis data collected will be presented by subject.

4.6.6 Other Laboratory Evaluations

4.6.6.1 Definitions and Derivations

Not Applicable.

4.6.6.2 Presentations

The results of pregnancy tests will be listed by subject.

4.6.7 Vital Signs

4.6.7.1 Definitions and Derivations

Not Applicable.

4.6.7.2 Presentations

All vital sign parameters will be summarized using descriptive statistics of absolute values and changes from baseline for each visit over time. Data listings of all vital signs collected during the study will be presented by subject as well.

4.6.8 Electrocardiogram

4.6.8.1 Definitions and Derivations

Not Applicable.

4.6.8.2 Presentations

For quantitative parameters, the absolute values at each visit as well as changes from baseline will be summarized using descriptive statistics. For the overall evaluation of ECG, the counts and percentages at each visit and shift table from baseline to worst post-baseline evaluation according to clinical significance will be presented. Box-Whisker plots for observed ECG parameters and change from baseline in ECG parameters over time will be presented.

All data from ECG will also be presented in the data listings.

4.6.9 Other Safety Assessments

4.6.9.1 Definitions and Derivations

Not Applicable.

4.6.9.2 Presentations

Echocardiography/MUGA

The following summaries for the echocardiography/MUGA data will be produced:

- LVEF values and change from baseline summarized by visit
- Box-Whisker plots of LVEF values and change from baseline
- Shift from baseline to worst post-baseline value according to NCI-CTCAE grade.
- Shift from baseline to worst post-baseline value according to clinical significance

In addition, data listings of echocardiography/MUGA data collected will be presented by subject.

Physical Examination

A shift table from baseline to worst post-baseline value according to clinical significance will be provided for physical examination. All data from physical examination will also be presented in the data listings.

ECOG/WHO Performance Status

The ECOG shift from baseline to post-baseline highest score will be summarized. All ECOG/WHO performance status will also be listed.

5 INTERIM ANALYSIS

There will be 3 analyses planned for this study. The data cut-off (DCO) date for primary analysis for ORR will be at 24 weeks after last subject in (LSI). The second analysis DCO for median PFS will be at the point when approximately 21 progression events (60% of maturity of PFS events) achieved. The final OS analysis will be performed when at approximately 21 death events (60% maturity of OS events) achieved.

6 REFERENCES

Clopper, C. J. & Pearson, E. S., 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, Volume 26, pp. 404-413.

Brookmeyer, R. & Crowley, J., 1982. A Confidence Interval for the Median Survival Time. Biometrics, Volume 28, pp. 29-41.

7 APPENDIX

7.1 Appendix 1 Analysis Visit Windows for Safety Assessments

Assessments	Visit	Analysis Visit	Target Study Day	Visit Window (in study days)
Physical Examination, ECOG/WHO Performance Status, clinical chemistry, hematology, urinalysis, 12-lead ECG, Vital Signs	Visit 2	Baseline	1	Prior to first dose of osimertinib on Day 1
	Visit 3	Week 3	22	[2,32]
	Every 3 weeks up to Visit 7	Week 3*i,i=2,3,4,5	1+21*i,i=2,3,4,5	[21*i-9,21*i+11]
	Visit 8	Week 18	127	[117,158]
	Every 9 weeks thereafter	Week {18+9*j},j=1,2,…	127+63*j,j=1,2,…	[96+63*j,158+63*j]
	Treatment Discontinuation	EOT	NA	Remain as the nominal visit
	Progression Follow-up 1	Progression Follow-up 1	NA	Remain as the nominal visit
	Progression Follow-up 2	Progression Follow-up 2	NA	Remain as the nominal visit
	Progression Follow-up X	Progression Follow-up X	NA	Remain as the nominal visit
Echocardiogram/MUGA	Visit 2	Baseline	1	Prior to first dose of osimertinib on Day 1
	Visit 6	Week 12	85	[2,127]
	Every 12 weeks thereafter	Week {12+12*k},k=1,2,…	85+84*k,k=1,2,…	[44+84*k,127+84*k]
	Treatment Discontinuation	EOT	NA	Remain as the nominal visit

7.2 Appendix 2 Best Overall Response When Confirmation of CR/PR Is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

7.3 Appendix 3 Outcome and Event Dates for PFS and DOR Analyses

Situation	Date of Event or Censoring	Outcome	Censoring Reason
No baseline assessment	Date of First Dose of Osimertinib	Censored*	No baseline assessment
No adequate post-baseline assessment	Date of First Dose of Osimertinib	Censored*	No adequate post-baseline assessment
PD or death - After at most one missing post-baseline tumor assessment, OR ≤13 weeks after date of first dose of Osimertinib	Date of progression or death	Event	
PD or death after 2 or more consecutive missing post-baseline tumor assessments	Date of the latest evaluable tumor assessment prior to the 2 or more consecutive missed tumor assessments	Censored	Event after 2 or more consecutive missing post-baseline tumor assessments
No PD or death	Date of the latest evaluable tumor	Censored	No PD or death

	assessment		

*However if the subject dies≤13 weeks after the date of first dose of osimertinib the death is an event with date on death date.

7.4 Appendix 4 Outcome and Event Dates for OS Analysis

Situation	Date of Event or Censoring	Outcome
Subjects died	Date of death	Event
Subjects alive or lost to follow-up	Last Contact Date	Censored

7.5 Appendix 5 Outcome and Event Dates for TTF Analysis

Situation	Date of Event or Censoring	Outcome
Subjects permanently discontinued from osimertinib or died	min(Date of Last dose of Osimertinib, Date of Death)	Event
Subjects alive or not known to permanently discontinued from osimertinib	Last Contact Date	Censored

7.6 Appendix 6 Outcome and Event Dates for TFST Analysis

Situation	Date of Event or Censoring	Outcome
Subjects received subsequent anti-cancer therapy or died	min(Date of first subsequent anti-cancer therapy, Date of Death)	Event
Subjects alive or not known to have had a subsequent therapy	last known date to have not received subsequent therapy	Censored

7.7 Appendix 7 Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Parameter	CTCAE v5.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemoglobin	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hemoglobin	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2-4 g/dL	Increase in >4 g/dL	-	-
Leukocyte count	White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L	-
Leukocyte count	Leukocytosis	-	-	>100 x 10e9 /L	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Platelet count	Platelet count decreased	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9 /L	-
Absolute neutrophil count	Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L	-
Absolute lymphocyte count	Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L	-
Absolute lymphocyte count	Lymphocyte count increased	-	>4-20 x 10e9 /L	>20 x 10e9 /L	-	-
Albumin	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alanine transaminase (ALT)	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Aspartate transaminase (AST)	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Alkaline phosphatase (ALP)	Alkaline phosphatase increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 – 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Bilirubin, total	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Calcium, total*	Hypercalcemia	Corrected serum calcium of >ULN - 2.9 mmol/L; Ionized calcium >ULN	Corrected serum calcium of >2.9 - 3.1 mmol/L; Ionized calcium >1.5	Corrected serum calcium of >3.1 - 3.4 mmol/L; Ionized calcium >1.6	Corrected serum calcium of >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening	Death

		- 1.5 mmol/L	- 1.6 mmol/L; symptomatic	- 1.8 mmol/L; hospitalization indicated	consequences	
Creatinine	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Glucose	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L; life-threatening consequences; seizures	Death
Magnesium	Hypermagnesemia	>ULN - 1.23 mmol/L	-	>1.23 - 3.30 mmol/L	>3.30 mmol/L; life-threatening consequences	Death
Magnesium	Hypomagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L; life-threatening consequences	Death
Potassium	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Potassium	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
Sodium	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Sodium	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
Left Ventricular Ejection Fraction	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%	-

* For grading of calcium, corrected calcium (mmol/L) is used and calculated as total calcium (mmol/L) + 0.02*[40 - serum albumin(g/L)]

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