Statistical Analysis Plan for Clinical Study I4T-MC-JVCY

A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination with Ramucirumab or Placebo in Previously Untreated Patients with *EGFR* Mutation-Positive Metastatic Non-Small Cell Lung Cancer

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1. Statistical Analysis Plan for Clinical Study: I4T-MC-JVCY: A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination with Ramucirumab or Placebo in Previously Untreated Patients with *EGFR* Mutation-Positive Metastatic Non-Small Cell Lung Cancer

Ramucirumab (LY3009806) Non-Small Cell Lung Cancer

This is a multicenter, randomized, double-blind, Phase 3 study that will compare the efficacy and safety of treatment with erlotin b (150 mg daily) and ramucirumab (10 mg/kg every 2 weeks) versus erlotinib (150 mg daily) and placebo (10 mg/kg every 2 weeks) in previously untreated patients with *EGFR* mutation-positive metastatic NSCLC. Treatment will continue until disease progression, unacceptable toxicity, or another permitted reason for study discontinuation. This Phase 3 part (Part B) is preceded by a Phase 1b part (Part A) to assess the safety and tolerability for the combination of ramucirumab plus erlotin b. In addition, Part C, an open-label, 2-period, single-arm, exploratory cohort is added to the main protocol.

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Protocol I4T-MC-JVCY
Phase 1b/3

Statistical Analysis Plan (SAP) Version 3 electronically signed and approved by Lilly on date provided below.
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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to the first patient visit.

SAP Version 2 was approved 31 May 2018, prior to the primary PFS analysis. The overall changes incorporated in SAP Version 2 were as follows:

1) The number of progression-free survival (PFS) events required to perform the primary analysis was updated from approximately 320 events to approximately 270 events.
2) Removed the interim PFS efficacy analysis that was to occur at approximately 224 PFS events.
3) Exploratory objectives and its analyses plan for Part C were added.
4) Determination of sample size for Part C was described.
5) Analysis populations for Part C were defined.
6) Description of interim analysis related to Part C was added.
7) Updated the rules for determining date of progression or censor for the PFS primary analysis.
8) Updated the PFS sensitivity analyses.
9) Added Part B Per-Protocol population definition.
10) Clearly stated that Interactive Web Response System (IWRS) stratification values will be used for the primary PFS analysis.
11) Changed the terminology of "protocol violation" to "protocol deviation".
12) Added additional age groups.
13) Updated selected concomitant medications.
14) Added progression-free survival 2 (PFS2) and overall survival (OS) analyses for patients who receive osimertinib after disease progression vs. those who do not.
15) Added the following analyses:
    a. time-to-brain metastases analysis.
    b. exposure analyses by months.
    c. summary of treatment-emergent adverse events (TEAEs) by narrow-scope standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) and preferred term (PT).
16) Other minor changes, including editorial changes.

SAP Version 3 was approved prior to the primary PFS analysis. The overall changes incorporated in SAP Version 3 were as follows:

1) Revised the protocol deviation section.
2) Clarified that Part C was conducted in the East Asian region, including Japan.
3) Clarified which analyses will be conducted for Parts A, B, or C.
4) Added liver metastases as a subgroup analysis
5) Added dose modification definitions
6) Defined time to diagnosis of CNS metastases
7) Defined more exposure parameters for each study part
8) Added a sensitivity analysis for primary PFS without censoring for either missed visits or new anticancer therapy
9) Defined immunogenicity-related variables
10) Added 75 age subgroup analyses per EU requirement
11) Added a sensitivity analysis of ORR/DCR/DOR based on independent assessment
12) Other minor changes, including editorial changes

4. Study Objectives

The study is divided into 3 parts. Part A is the Phase 1b single arm safety lead-in portion of the trial and Part B is the randomized double blinded Phase 3 portion of the trial. Part C is an open-label, 2-period, single-arm, exploratory cohort that was added to the main protocol (I4T-MC-JVCY [JVCY]) and is only applicable to sites in the East Asian region, including Japan (see protocol addendum 9.2, approved on 23 May 2018).

4.1. Primary Objective

The objective(s) for each part are as follows:

Part A: The objective of Part A is to assess the safety and tolerability of ramucirumab when administered in combination with erlotinib as therapy in previously untreated patients with epidermal growth factor receptor (*EGFR*) mutation-positive metastatic non-small cell lung cancer (NSCLC).

Part B: The primary objective of Part B is to compare the progression-free survival (PFS) of ramucirumab administered in combination with erlotinib versus placebo in combination with erlotinib in previously untreated patients with *EGFR* mutation-positive metastatic NSCLC.

Part C: All objectives for Part C are exploratory. Please see Section 4.3.

4.2. Secondary Objectives

Part A: There is no secondary objective planned for Part A.

Part B: Secondary objectives of Part B are to compare ramucirumab administered in combination with erlotinib versus placebo administered in combination with erlotinib for:

- safety and toxicity profile
- overall survival (OS)
- objective response rate (ORR) (complete response [CR] + partial response [PR])
- disease control rate (DCR) (CR + PR + stable disease [SD])
- duration of response (DOR)
- pharmacokinetics (PK) and immunogenicity of ramucirumab
- patient-reported outcomes (PROs; using Lung Cancer Symptom Scale [LCSS] and EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L])
- Drug-Drug Interaction (DDI) substudy to assess the pharmacokinetics of erlotinib with and without ramucirumab

4.3. Exploratory Objectives

The exploratory objectives of both Parts B and C are to:

- assess the association between biomarkers and clinical outcome.
- assess progression-free survival 2 (PFS2).
- assess time to deterioration (TtD) in Eastern Cooperative Oncology Group (ECOG) performance status (PS)

- assess time to diagnosis of CNS metastases.
- progression-free survival 2 (PFS2) and overall survival (OS) analyses for patients who receive osimertinib after disease progression vs. those who do not.

The additional exploratory objectives of Part C only are to:

- evaluate the efficacy (for example, 1-year PFS rate) and safety of ramucirumab when administered in combination with gefitinib in previously untreated patients with EGFR mutation-positive metastatic NSCLC, in the East-Asian region including Japan
- evaluate the efficacy and safety of ramucirumab when administered in combination with osimertinib in patients with T790M-positive metastatic NSCLC and who have progressed on ramucirumab plus gefitinib in this study, in the East-Asian region including Japan
- assess pharmacokinetics (PK) and immunogenicity of ramucirumab
- assess patient-reported outcomes (using Lung Cancer Symptom Scale and EuroQol 5 dimension, 5-level questionnaire)

5. A Priori Statistical Methods

5.1. Determination of Sample Size

5.1.1. Part A

At least 12 (6 from Japan and 6 from North America and/or Europe) previously untreated patients with *EGFR* mutation-positive metastatic NSCLC will be enrolled and treated with ramucirumab plus erlotinib.

5.1.2. Part B

The study will enroll approximately 450 patients in 1:1 randomization (that is, approximately 225 patients will be randomly assigned to each treatment arm). The primary PFS analysis will be performed after approximately 270 PFS (approximately 40% censoring rate) events.

An interim futility analysis was conducted at 114 investigator-assessed PFS events (data cutoff date 16 October 2017), and the IDMC recommended the trial continue without modification. A nominal 1-sided alpha <0.00001 was spent in order to maintain type-I error. Assuming an HR of 0.71, this sample size yields at least 80% statistical power to detect superiority of the ramucirumab plus erlotinib arm over the placebo plus erlotinib arm, with the use of a 1-sided log-rank test and a type I error of 0.02499. If the true median PFS for the placebo plus erlotinib arm is 11 months, then the HR of 0.71 amounts to an approximate 4.5-month improvement in median PFS for the ramucirumab plus erlotinib arm under an additional assumption of exponential survival distribution.

Sample size calculation is carried out in EAST Version 6.4 (1994-2016).

5.1.3. Part C

Approximately 80 previously untreated patients with EGFR mutation-positive metastatic NSCLC will be enrolled from East Asia, including Japan, and treated with ramucirumab plus gefitinib in Period 1.

Ichihara et al. (2015) reported a 1-year PFS rate of 56.7% (95% CI: 39.9, 70.5) for bevacizumab plus gefitinib in patients with EGFR mutation-positive metastatic NSCLC. Given an expected 1-year PFS rate of 55% for ramucirumab plus gefitinib, when 80 patients are enrolled, asymptotic 95% confidence interval half-width for expected 1-year PFS rate with normal approximation is approximately 11%.

5.1.4. Drug-Drug Interaction Substudy

Pharmacokinetic parameters of erlotinib will be compared between the ramucirumab plus erlotinib arm and the placebo plus erlotinib arm. Around 15 patients from each treatment arm (approximately 30 patients in total) were deemed sufficient for the initial analysis of PK. Based on an intra-subject coefficient of variation in area under the concentration-time curve (AUC) of 16% obtained from erlotinib PK analyses (Hamilton et al. 2014) and assuming 60% of the total variability (26.7%) contributed by the within-patient variability, a sample size of 15 patients in

each treatment arm will provide a precision of approximately 0.191 in the log scale for the ratio of geometric means of AUC. That is, there is a 90% probability that the half-width of the 90% confidence interval (CI) will be within 0.191 for the estimated ratio of geometric means of AUC of erlotinib in the presence and absence of ramucirumab.

5.2. General Considerations

Part A: The analyses for Part A will be descriptive. Data analyses will be provided separately for study patients in the 2 geographic areas: 1) Japan, 2) European Union (EU) and United States, and 3) total. The list of analyses conducted for the Assessment Committee (AC) review is included in the AC charter.

Part B: All tests of treatment effects will be conducted at a two-sided alpha level of 0.05, and all CIs will be given at a two-sided 95% level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, Version 9.2 or higher).

Part C: This part is only applicable to sites in the East-Asian region, including Japan. The analyses for Part C will be descriptive and conducted separately from Parts A and B. Results of Part C will be included in a separate addendum to the clinical study report (CSR) for Parts A and B. Safety data of Part C will be summarized by each period. Patients who do not enter Period 2 will not be included in summary safety analyses for Period 2.

This document describes the statistical analyses planned prior to final treatment assignment unblinding of the aggregate database. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in this document. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR. The assumptions for each statistical method may be evaluated. If there is violation of assumptions, alternative statistical methods may be used. Additional exploratory analyses of the data will be conducted as deemed appropriate. The SAP will not be updated to reflect post-hoc analyses conducted after unblinding. These will be described in the study report as appropriate.

Statistical analysis of this study will be the responsibility of Lilly or its designee. The study PK scientist will be responsible for designing, conducting, and interpreting the PK analysis and delivering PK parameters. The interpretation of final study results will be the responsibility of the clinical research physician (CRP) and the study statistician. These individuals will also be responsible for the appropriate conduct of an internal review process for both the CSR and any study-related material to be authorized for publication by Lilly.

The following general terms will be used globally in the SAP:

- Unless otherwise specified, **summary statistics** stand for n, mean, standard deviation, median, Q3-Q1, minimum, and maximum for continuous variables; and frequency and percentage for categorical variables.
- Study period

- **Dose-limiting toxicity (DLT) assessment period for Part A: for individual patient** assessment, period begins on the day of the first study drug dose and ends on the day when the patient:
  - completed 2 cycles of treatment, or
  - discontinued from study treatment or study participation before completing 2 cycles due to a DLT.

  Note. Two cycles are considered completed on the 14th day from the second dose of ramucirumab.
- **Study treatment period** begins at the first dose of study treatment and ends when the patient and the investigator agree that the patient will no longer continue any study treatment. The date of this agreement is to be reported on the electronic case report form (eCRF) as the Date of Discontinuation from all study treatment.
- **30-day short-term follow-up period** begins the day after the patient and the investigator agree that the patient will no longer continue any study treatment and lasts approximately 30 days (±3 days).
- **Long-term follow-up period** begins the day after short-term follow-up is completed and continues every 6 weeks (±7 days) until progressive disease (PD), thereafter every 3 months (±7 days) until the patient's death, withdrawal of consent to participate or overall study completion, whichever occurs first.

5.3. Definitions of Analysis Variables

Definitions of efficacy, safety, and patient-reported outcome (PRO) analysis variables are listed in Section 5.3.1, Section 5.3.2, and Section 5.3.3, respectively. Other variables are listed below alphabetically.

- **Age (years)**: (Informed Consent Date - Date of Birth + 1)/365.25.
  Note. Average days in a year = 365.25, reflecting the Julian Calendar of 3 years with 365 days each and one leap year of 366 days. Birth month and day are imputed to be 01 July because only birth year is collected through the eCRF.
- **Baseline measurement** is the last non-missing measurement prior to first dose for safety analyses, and the last non-missing measurement prior to randomization for demographic and efficacy analyses.
- **Duration** is calculated as:
  - Duration (days): (End Date – Start Date + 1)
  - Duration (weeks): (End Date – Start Date + 1)/7
  - Duration (months): (End Date – Start Date + 1)/30.4375
    Note. Days in months = (1/12)*average number of days in a year
  - Duration (years): (End Date – Start Date + 1)/365.25
- **Duration of disease** is defined as months from first diagnosis of cancer to randomization.

- **Smoking history (never/ever)** is defined as ever for patients who ≥100 cigarettes, cigars, or pipe-fulls in his/her lifetime by study entry and never otherwise.
- **Study treatment day** indicates the number of days the patient has been receiving study treatment. It is calculated as assessment date - first dose date + 1 day if the assessment is done on or after the first dose day. If the assessment is done prior to the first dose day, study day will be calculated as assessment date - first dose date. Date of first dose is defined as study Day 1.

5.3.1. Efficacy Analysis Variables

Definition of efficacy analysis variables are listed below in order of importance.

Progression-free survival (PFS) is defined as the time from the date of randomization until the date of radiographic documentation of progression (as defined by RECIST v. 1.1) or the date of death due to any cause, whichever is earlier. Table JVCY.5.1 lists rules for determining date of progression or censor for PFS. The censoring is taken in the following order:

- If a patient does not have a baseline disease assessment, then the PFS time will be censored at the randomization date, regardless of whether or not objective PD or death has been observed for the patient; otherwise,
- If a patient is not known to have died or have PD as of the data-inclusion cut-off date for the analysis, the PFS time will be censored at the date of last postbaseline adequate radiological tumor assessment, or at the date of randomization if the patient does not have any postbaseline adequate radiological assessment.

Note. If there are multiple dates associated with one radiological tumor assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise. A radiological tumor assessment is considered adequate if its response is among CR, PR, SD, or PD.

PFS (day) = Date of progression or death / censor - Date of randomization + 1.

Table JVCY.5.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No postbaseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a postbaseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing ≥2 consecutive postbaseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored
8	New anticancer treatment started and no tumor progression or death within 14 days	Date of adequate tumor assessment prior to start of new anticancer treatment +14 days or date of randomization, whichever is later	Censored

Note: PFS and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

Overall survival (OS) is defined as time from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the last date the patient was known to be alive (on or before the data-inclusion cut off date). Contacts considered in the determination of last date include adverse event [AE] date, lesion assessment date, visit date, and last known alive date.

Objective response rate (ORR) is defined as the proportion of randomized patients achieving a best overall response of PR or CR per RECIST v.1.1. Patients who do not have any postbaseline tumor response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate.

Note. Tumor assessments performed after initiation of new anticancer treatment (systemic therapy) will be excluded from evaluating the best overall response and DCR.

Disease Control Rate (DCR) is defined as the proportion of randomized patients achieving a best overall response of complete response (CR), partial response (PR), or stable disease (SD) per Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v.1.1). Patients who do not have any postbaseline tumor response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate.
Note. Best overall response is the best response recorded from the start of treatment until disease progression, in the order of CR, PR, and SD. Refer to Attachment 7 of the protocol for definitions of CR, PR, and SD.

Duration of Response (DOR) is defined from the date of first documented CR or PR (responder) to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression, then the patient will be censored at the date of last evaluable tumor assessment.

5.3.2. Safety Analysis Variables

Definitions of variables for safety analysis are listed by category and alphabetically within each category.

Adverse event-related variables are listed below:

- **Adverse event (AE)** is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship.
- **AEs of special interest (AESIs)** are AEs thought to be potentially associated with the study drug or the disease under study. Therefore, aggregate AE terms for AEs typically associated with anti-angiogenesis or possibly associated with the study drug were developed.
  Adverse events of special interest are listed in the Investigator's Brochure. The Medical Dictionary for Regulatory Activities (MedDRA™) preferred terms (PTs) that are grouped under each of the AESI terms will be provided in the compound-level safety document.
- **Consolidated AEs** Given the high level of granularity of the MedDRA dictionary, clinically identical or synonymous PTs reported under different terms in the database, in addition to being reported separately, will also be consolidated in a separate summary. The list of consolidated AE categories will be reported in the clinical study report.
- **Serious adverse event (SAE)** is any AE that results in one of the following outcomes:
  - death
  - initial or prolonged inpatient hospitalization
  - a life-threatening experience (that is, immediate risk of dying)
  - persistent or significant disability/incapacity
  - congenital anomaly/birth defect
  - considered significant by the investigator for any other reason

- **Treatment-emergent adverse event (TEAE)** is defined as any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.

Exposure-related variables are listed below:

- **Cumulative dose**
  - For ramucirumab, cumulative dose (mg/kg) is calculated as sum of all calculated dose levels, where calculated dose level (mg/kg) = (actual total dose (mg)) / (closest body weight (kg) prior to the treatment).
  - For erlotinib, cumulative dose (mg) is calculated as sum of all dose levels.
  - For getitinib, cumulative dose (mg) is calculated as sum of all dose levels.
  - For osimertinib, cumulative dose (mg) is calculated as sum of all dose levels.
- **Duration of treatment** (week)
  - For ramucirumab, duration of treatment (week) is calculated as (date of last dose - date of first dose + 14)/7.

    Note. Fourteen days is added because ramucirumab is planned to be administered every 1 cycle (14 days). Last dose stands for planned dose, regardless of whether the actual dose received is 0 or not.
  - For erlotinib, duration of treatment (week) is calculated as (date of last dose- date of first dose + 1)/7, if date of last dose is collected by eCRF.

    Note. If date of last dose is not collected, duration of treatment (week) is calculated as:
    - (date of the discontinuation - date of first dose + 1)/7, if patient discontinues ≤ 14days after the date of the last time when erlotinib is distributed; or
    - (date of the last time when erlotinib is distributed* - date of first dose + 14)/7, if patient discontinues > 14 days after the date of the last time when erlotinib is distributed.
- For gefitinib, duration of treatment (week) is calculated as (date of last dose- date of first dose + 1)/7, if date of last dose is collected by eCRF.

  Note. If date of last dose is not collected, duration of treatment (week) is calculated as:
  - (date of the discontinuation - date of first dose + 1)/7, if patient discontinues ≤ 14days after the date of the last time when gefitinib is distributed; or
  - (date of the last time when gefitinib is distributed* - date of first dose + 14)/7, if patient discontinues > 14 days after the date of the last time when gefitinib is distributed.
- For osimertinib, duration of treatment (week) is calculated as (date of last dose- date of first dose + 1)/7, if date of last dose is collected by eCRF.

  Note. If date of last dose is not collected, duration of treatment (week) is calculated as:

- (date of the discontinuation - date of first dose + 1)/7, if patient discontinues ≤ 14days after the date of the last time when osimrtinib is distributed; or
  (date of the last time when osimrtinib is distributed* - date of first dose + 14)/7, if patient discontinues > 14 days after the date of the last time when osimrtinib is distributed

- **Dose intensity** (mg/kg/week for ramucirumab or mg/week for erlotinib, gefitinib or osimertinib) is calculated as cumulative dose / component-specific duration of treatment in weeks.
- **Relative dose intensity** (%) is calculated as dose intensity / planned dose intensity * 100, where planned dose intensity = 5 mg/kg/week for ramucirumab, 150 mg/day for erlotinib, 250 mg/day for gefitinib, or 80 mg/day for osimertinib (or according to the planned dose recorded in the eCRF).
- **Number of dose reductions for ramucirumab/placebo**: total number of reduction steps considering the intended dose level before each infusion (as entered in the eCRF) as referenced in Table JVCY.5.2.

Table JVCY.5.2. Ramucirumab/Placebo Dose Reduction Schedule

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
10 mg/kg	8 mg/kg	6 mg/kg	5 mg/kg
8 mg/kg	6 mg/kg	5 mg/kg	Not applicable

- **Number of dose reductions for erlotinib:** total number of reduction steps considering the intended dose level. Patients receiving ramucirumab or placebo plus erlotinib can have the erlotinib dose reduced if the toxicity is specifically attributable to erlotinib at the discretion of the investigator per the package insert or SPC. Patients may continue treatment with ramucirumab/placebo if they are discontinued from erlotinib. Patients should be treated following the recommendations, warnings and precautions given for erlotinib in the package insert or SPC of erlotinib.

  The daily dose of erlotinib will be decreased in 50-mg decrements to a minimum dose of 50 mg daily as referenced in Table JVCY.5.3.

Table JVCY.5.3. Erlotinib Reduction Schedule

Starting dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

Re-escalation of erlotinib dosing is allowed at the investigator's discretion. Dose reductions must be documented within the current cycle so that treatment compliance can be determined.

- **Number of dose delays for ramucirumab/placebo:** Total number of treatments reported as delayed in CRF that were administered >3 days but ≤11 days beyond a scheduled infusion where treatment was not given.
    - Dose delays for erlotinib, getifinib, and osimertinib are not captured
- **Number of doses omitted (not administered) for ramucirumab/placebo:** Total number of treatments reported as omitted or delayed in CRF that were administered >11 days beyond a scheduled infusion where treatment was not given.
- **Number of doses omitted (not administered) for erlotinib: gefitinib, or osimertinib:** Total number of doses withheld in CRF as one per omission interval. For example, if subject had to stop taking erlotinib for 5 days due to AE this is counted as one omission.

Patients receiving ramucirumab plus gefitinib can withhold gefitinib for up to 3 weeks if the toxicity is specifically attributable to gefitinib at the discretion of the investigator per the package insert. Patients may continue treatment with ramucirumab if they discontinue gefitinib. For patients whose disease has progressed in Part C Period 1, gefitinib may be continued at the discretion of the investigator, provided that the patient can still benefit from treatment. Patients on gefitinib cannot continue onto Period 2.

Patients should be treated following the recommendations, warnings, and precautions given for osimertinib in the package insert or the user guidance of osimertinib. Patients may also refer to the dose modification guidance in Table JVCY 9.4 of the JVCY Protocol Addenda 9.2.

Immunogenicity-related variables are listed below:

- **Treatment-emergent antidrug antibody (TE ADA) evaluable**: A patient is evaluable for TE ADA if there is at least one non-missing test result for ramucirumab ADA for each of the baseline period and the post-baseline period. All percentages are relative to the total number of subjects evaluable for TE ADA in each treatment arm.

- **TE ADA positive**: A patient evaluable for TE ADA is considered to be TE ADA+ if the subject has at least one post-baseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment-boosted). If baseline result is ADA Not Present, then the subject is TE ADA+ if there is at least one post-baseline result of ADA Present with titer >= 20 (treatment-induced).

- **TE ADA inconclusive**: A patient evaluable for TE ADA is considered TE ADA Inconclusive if 20% of the subject's post-baseline samples, drawn pre-dose, are ADA Inconclusive and all remaining post baseline samples are ADA Not Present.

- **TE ADA negative**: A patient evaluable for TE ADA is considered TE ADA- if not TE ADA+ and not TE ADA Inconclusive.

5.3.3. Patient-Reported Outcome Analysis Variables

Definitions of variables for PRO analyses are listed below alphabetically.

- **Average Symptom Burden Index (ASBI)** is calculated as the mean of the 6 symptom items of the LCSS. The ASBI will not be computed for a patient if he/she has one or more missing values for the 6 items. Refer to Section 10.2.1 of the protocol for the definition of the LCSS.
- **EQ-5D-5L index score** is calculated as recommended by EuroQol **(**EQ-5D-5L User Guide, www.euroqol.org). Index score and visual analog scale (VAS) will be calculated for each assessment period as per current recommendations (van Hout et al. 2012). The index score is calculated from a set of item weights to derive a score of -0.285 to 1, with 1 representing the best health status. United Kingdom (UK) weights will be applied for the base case. The index score will not be computed for a patient if he/she has one or more missing values for the 5 items.
- **Change from baseline** for each LCSS or EQ-5D item at any postbaseline visit is calculated by subtracting baseline assessment result from the current assessment result.
- **LCSS total score** is calculated as the mean of the 9 LCSS items. The LCSS total score will not be computed for a patient if he/she has one or more missing values for the 9 LCSS items.
- **Maximum change** for each LCSS item is defined as the largest decrease from baseline, which is the smallest (that is, most negative or smallest positive) non-missing value among all change from baseline values.
  Note. Negative values of change from baseline (that is, decreases in the LCSS score towards the lower end of the symptom scale) indicate improvement in symptoms. For a patient and given LCSS item, if all change values are positive, the smallest positive change will be the maximum change; if at least one change value is negative, the most negative value will be the maximum change.
- **Time to deterioration (TtD)** for each of the 9 LCSS items, ASBI, and the LCSS total score is defined as the time from the date of randomization until the date of the first ≥15-mm increase from baseline (de Marinis et al. 2008). Alternative definitions of minimally important differences may be explored as needed. Patients without deterioration will be censored on the date of the patient's last postbaseline LCSS assessment for this item or randomization date, whichever is last.

5.3.4. Exploratory Analyses Variables

- **Time to deterioration (TtD) in Eastern Cooperative Oncology Group (ECOG) performance status (PS)** is defined as the time from the date of randomization to the first date observing a change (that is, deterioration) in ECOG PS to ≥2. Variations of the definition are: 1) a change to ≥3, 2) a change of ≥2 levels from baseline, and 3) a change of ≥1 level from baseline. Censor at time of the last ECOG PS value if no event.

- **Progression-Free Survival 2 (PFS2) (Part B)** is defined as the time from randomization to second disease progression (defined as objective radiological or symptomatic progression after start of additional systemic anticancer treatment), or death from any cause, whichever occurs first.

- **Time to diagnosis of CNS (brain or meninges or spinal cord) metastases** is defined as the time from randomization to CNS metastases. Patients without CNS metastases at the time of data inclusion cut off will be censored at the date of last postbaseline adequate radiological tumor assessment or at randomization if no post-baseline assessment.
- Time to response is defined as time from randomization to response (CR or PR) for those patients that responded only.

The exploratory analyses variables defined below are only applicable for Part C.

- **1-year PFS rate** is defined as the cumulative proportion of patients who survived during the first year (that is, 1 year from enrollment) in the study without disease progression. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment.
- **Progression-free survival in Part C, Period 2** is defined as the duration from the date of last tumor measurement before osimertinib treatment to occurrence of PD or death from any cause, whichever occurs first.
- **PFS2 (Part C)** is defined as the duration from enrollment (assignment to treatment) to the second occurrence of PD or death from any cause, whichever occurs first.
- **Overall survival (OS) in Part C, Period 2** is defined as the duration from the date of last tumor measurement before osimertinib treatment to the date of death. For each patient who is not known to have died as of the data cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data-inclusion cut-off date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

5.4. Handling of Dropouts or Missing Data

Rules for handling dropouts or missing data are listed by type of analysis alphabetically. Unless otherwise specified, observed data will be used and missing data will not be imputed or carried forward.

General rules for imputing dates related to AE or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
    - If only the day is missing, the date will be set to:
        - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.

        - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment.
    - If both the day and month are missing, the complete date will be set to:
        - January 1 of the year of onset, if the onset year is after the year of the first study treatment.
        - The date of the first dose, if the onset year is the same as the year of the first study treatment.
- Resolution date of an AE or end date of a concomitant therapy:
    - If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death if the patient died in the same month.
    - If both the day and month are missing, the date will be set to 31 December of the year of occurrence.

If a date is completely missing, then the AE will be considered treatment emergent. In case of additional therapies, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If the date has no missing year and month but the day is missing, then assign Day 1 to the day
- If the date has no missing year, but has missing month, then assign January to the month.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary. For example, if a visit start date was 10 May 2015 and a tumor assessment date was xx May 2015 (missing day) but it was known that it occurred after that visit, then after imputation, the tumor assessment date became 01 May 2015. In this case, the imputed tumor assessment date should be compared to the visit start date and then corrected to be the visit start date, 10 May 2015.

Patient-reported outcome analysis: For percentage compliance of the LCSS and EQ-5D-5L, instruments with at least one item completed will be considered as having been completed. No other adjustment or imputation for missing data will be performed.

Safety analysis: The following rule for missing data processing will apply for safety analysis:

- Missing classifications concerning study medication relationship will be considered as related to study medication.
- If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication when determining whether or not the AE is present at baseline. In this case, the AE will be assumed to be treatment emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study medication.

Time-to-event analysis: All censored data will be accounted for using appropriate statistical methods. See Sections 5.3.1 and 5.11 for details.

5.5. Multicenter Studies

Part A is a multicenter, open-label study.

Part B is a multicenter, randomized, double-blind study. Investigative center was not a stratification factor because the large number of investigative centers would break down the intended balance within each combined stratification level by the stratified randomization method. It will not be included as a covariate in any covariate-adjusted analysis because the large number of investigative centers in this study cannot be practically incorporated into such analysis.

Part C is a multicenter, open-label study.

5.6. Adjustments for Covariates

As supportive analysis, the primary PFS and secondary efficacy endpoint OS of Part B will also be analyzed adjusting for prespecified potential prognostic factors chosen from the variables listed below, with * indicating the reference level. Detailed description as for which factors to be used will be provided for relevant analyses in later sections.

- Randomization stratification factors:
  - *EGFR* mutation (exon 19 deletion or exon 21 [L858R] substitution mutation*)
  - Gender (male or female*)
  - Region (East Asia or other*)
  - *EGFR* testing method (*Therascreen*® [Qiagen] and *Cobas*® [Roche] or other PCR and sequencing-based methods*)
- Other factors of interest:
  - age (<65 years or ≥65 years*)
  - age (<70 years or ≥70 years*)
  - age (<75 years vs. ≥75 years)
  - smoking history (ever or never smoker*)
    Note. The definition of "ever smoker" includes those who smoked ≥100 cigarettes, cigars, or pipe-fulls in his/her lifetime and the definition of "never smoker" is one who smoked <100 cigarettes, cigars, or pipe-fulls in his/her lifetime.
  - performance status (0 or 1*)
  - initial stage at diagnosis (Stage IV or other)
  - liver metastases (yes vs no)

5.7. Study Patients

The following summaries (frequency and percentage) and listings for patient disposition will be performed:

- Patient disposition by cohort/treatment and overall: patients entered (that is, signed informed consent), entered but not enrolled (that is, screen failure), enrolled (that is, randomized, intent-to-treat (ITT) population), enrolled but not treated, treated (that is, safety population), completed, and discontinued, DLT-evaluable (Part A only), DLT-non-evaluable (Part A only)
- Reasons for discontinuation for:
    - all treated patients as well as patients continuing on the study
    - screen fail patients (that is, patients who entered by not enrolled)
    - enrolled patients who did not receive any study treatment for Part A and C, or randomized patients who did not receive any study treatment for Part B
- Listings of:
    - primary reason for all study treatment discontinuation
    - PFS, PFS2, OS for Part B only
    - PFS, PFS2, OS for Part C, Periods 1 and 2
    - date of randomization for Part B only

5.7.1. Analysis Populations

The following populations will be defined for this study:

Part A Safety Population: all patients enrolled in Part A and received at least 1 dose of any study treatment. Demographics, baseline disease characteristics, dosing/exposure and AE analyses will be presented for part A safety population.

Part A DLT-Evaluable Population: patients who either completed first 2 cycles of treatment (approximately 28 days + 3 days) or discontinued from study treatment or study participation before completing first 2 cycles due to a DLT would be considered DLT-evaluable. Refer to Section 9.4.1 of the protocol for detailed DLT definitions.

Part B Intention-to-Treat (ITT) Population: This population is defined as all patients who will be randomized (enrolled) to study treatment during Part B. Patients will be grouped according to randomized treatment. This population will be used for demographics and baseline disease characteristics, study treatment disposition, efficacy, and PRO analyses.

Part B Per-Protocol (PP) population: includes all patients who are randomized and treated and do not have any major protocol deviations that could potentially affect the efficacy conclusions of the study. The PP population is a subset of the ITT population that will be defined and finalized prior to database lock for the primary PFS analysis. The PP population will be used for sensitivity analyses of OS and PFS.

Part B Safety Population: all enrolled (randomized) patients that received at least 1 dose of any study treatment in Part B. Patients will be grouped according to treatment received in Cycle 1.

The Part B safety population will be used for all dosing/exposure, AEs, and resource utilization analyses.

All the analyses for Parts A and B will be conducted separately, unless otherwise stated.

Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset of ITT population in Part B from whom a valid assay result (according to laboratory guideline) has been obtained. These analyses will be included in a separate SAP or LOA.

Compliance for the PRO instruments will be reported for the ITT population. All other PRO analyses will be on the ITT population and will include those from whom a completed PRO instrument was obtained at baseline and at least one postbaseline (either during study treatment period or 30-day short-term postdiscontinuation follow-up period); thus, the actual patients included for each analysis will depend on the instrument and response variable.

A patient listing of analysis population details will be provided. This listing will be presented by treatment arm and will include: investigator site, patient identifier, inclusion/exclusion flag for each population, and reason for exclusion from each population. All patients screened will appear on this listing.

Part C ITT Population: All patients who will be enrolled to study treatment during Part C. ITT population will be used for demographic, baseline disease characteristics, and 1-year PFS rate and PFS2.

Part C Period 1 Safety Population: All enrolled patients who received at least 1 dose of any study treatment in Part C Period 1.

Part C Period 2 Safety Population: All enrolled patients who received at least 1 dose of any study treatment in Part C Period 2.

The Part C safety populations will be used for all dosing/exposure, AEs, and resource utilization analyses. The safety summaries may be provided by period.

Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset ITT population in Part C from whom a valid assay result (according to laboratory guideline) has been obtained.

5.7.2. Important Protocol Deviations

The TIMP (trial issue management plan) stored in the eTMF documents the list of important protocol deviations identified for this study. These violations were selected from the major protocol deviations listed in the Study Specific Monitoring Requirements. Only the ones that could potentially affect efficacy conclusions were selected for exclusion of the per protocol population.

The list of patients (except for patients with incorrect study medication) excluded in the per protocol population will be identified prior to unblinding for the primary PFS analysis.

Non-programmable protocol deviations will be evaluated and summarized by the study Clinical Trial Manager(s). The study statistician will then combine them with the programmable ones. All programmable and non-programmable protocol deviations will be reported.

Number and percentage of patients with important protocol deviations will be reported by treatment arm and by type of deviation for Part A, B and C separately. A patient listing of important protocol deviations will also be generated.

Discrepancies between the local and central laboratory that may have an impact on treatment decisions will not be considered protocol deviations.

5.8. Demographic and Baseline Characteristics

The following patient demographic and other baseline characteristics will be summarized for each part of the study:

- Patient demographics: age (years), age group (<65 vs. ≥65 years; <70 vs. ≥70 years, <75 vs. ≥75 years; and <65, 65-74, 75-84, ≥85, gender, race, ethnicity, height (cm), weight (kg)
- Potential prognostic factors for NSCLC as listed in Section 5.6
- Baseline disease characteristics:
    - at study entry only: duration of disease (months), number of metastatic sites, tumor burden size (sum of target lesions in cm), anatomical sites of metastasis
      Note. Number of sites and anatomical sites of metastasis will be derived from radiographic assessment data collected at baseline.
    - at initial diagnosis and at study entry: disease stage, basis for pathological diagnosis (histopathological versus cytological), pathological diagnosis, histopathological diagnosis grade
- Prior cancer therapies: type of prior surgery, type of prior radiotherapy, type of prior systemic therapy
- Historical illness by MedDRA PT, presented in decreasing frequency
  Note. Patients reporting more than one condition/diagnosis within a PT will be counted only once for that PT

Comparison between the eCRF and IWRS values of the stratification factors corresponding to Part B will be performed in terms of a sensitivity analysis. Patient listings of demographic data and baseline characteristics will be provided. Patient listings of prior cancer therapies (surgery, radiotherapy, and systemic therapy) will be provided.

5.9. Concomitant Medications

A medication will be regarded as concomitant if:

- the medication was started on or after the date of first dose of study treatment and before the end of short-term follow-up;

- the medication was started prior to first dose of study treatment but was ongoing at the time of the first dose of study treatment.

The following concomitant medications used in study treatment period or the 30-day short-term postdiscontinuation follow-up period will be summarized by numbers and percentages by treatment arm, presented in decreasing frequency of the World Health Organization (WHO) drug term across treatment arms:

- All concomitant medications
- Best supportive care and select concomitant medications, including antidiarrheal agents, antiemetic agents, analgesic agents, antibiotics, antihypertensives, antifungals, antivirals, appetite stimulants, granulocyte-colony stimulating factor, erythroid growth factors, rash treatment and bisphosphonates.
  Note. Such drugs to be used for programming will be identified through reviewing of the unique drug terms collected in the study.
- Premedication for ramucirumab/placebo.

The proportions of patients receiving at least one concomitant medication and the proportion reporting use of concomitant medications will be compared between the treatment arms using the Chi-square test for Part B. The concomitant medications will be summarized for Parts A and C. Patient listing of all concomitant therapies and premedications will be provided.

5.10. Treatment Compliance

The number of tablets taken relative to the number expected to be taken will be summarized for erlotinib for Part B, for gefitinib for Part C Period 1, and for osimertinib for Part C Period 2, respectively. Note that treatment compliance can only be checked for those sites where study drug was received at the site.

Ramucirumab/placebo will be intravenously administered only at the investigational sites. As a result, patient compliance is ensured.

5.11. Efficacy Analyses

There is no efficacy analysis planned for Part A. This section is applicable for Part B, unless otherwise specified.

5.11.1. Primary Efficacy Analyses

The primary efficacy analysis will be performed in the Part B ITT population. For the primary comparison of investigator-assessed PFS between the 2 assigned study treatment arms, a stratified log-rank test at alpha level of 0.04998 (2-sided) will be performed to test the following statistical hypotheses about the PFS HR for ramucirumab plus erlotinib over placebo plus erlotinib:

H_0: PFS HR $\geq$ 1.00

H_a: PRS HR $<$ 1.00

The stratification will be the same as that used for randomization in the IWRS. An unstratified log-rank test will also be performed.

The following analyses of PFS will also be performed:

- Summary of PFS events (number and percentage), censoring rate, and reasons for censoring
- Kaplan-Meier survival curve (Kaplan and Meier 1958) by treatment arm will be provided.
- Restricted mean difference in PFS between the treatment arms and its 95% CI, while the restriction time is defined by the latest time where the standard error of the PFS estimates are ≤ 0.075 months.
- The Kaplan-Meier method will be used to estimate parameters (medians, quartiles, and percentages), difference of percentages and associated 95% CI and p-values for landmark analyses on each treatment group at 3 month intervals, based on a normal approximation. Patients who did not have the event at the corresponding time point will be considered right-censored observations.
- HR for treatment effect will be estimated using Cox proportional hazards (PH) model (Cox 1972) stratified identically to the primary log-rank test with assigned treatment as the only covariate, reported with 2-sided 95% CIs. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. This Cox PH model will be referred to as the primary Cox PH model henceforth.

5.11.2. Secondary Efficacy Analyses

5.11.2.1. Key Secondary Efficacy Analyses

For OS, the same analyses used for the analyses of the primary PFS endpoint (except sensitivity analyses based on PFS censoring rule) will be performed. One interim analysis and a final analysis for OS may be performed in this study. A hierarchical testing procedure will be employed to test OS. The OS will be tested only if PFS is significant. If PFS is not significant after the primary analysis for PFS is performed, OS will not be statistically evaluated. This comparison of OS using the same method as that for the primary analysis of PFS will be considered inferential only in case of significant results for PFS analysis (that is, a gate keeping approach was used so as not to inflate the overall type I error rate).

The OS interim analysis may be performed at the time of primary PFS analysis (approximately 270 PFS events) and the final OS analysis may be conducted later with the aim of providing as much information as possible on OS. This final analysis of OS will be performed when OS data are relatively mature (approximately 300 OS events and 35% censoring). The 1-sided type I error rate will be controlled at 2.5% by using a Haybittle Peto type spending function (p-value bound 0.0001 at the interim analysis) (Jennison and Turnbull 1999).

5.11.2.2. Analyses of Other Secondary Efficacy Endpoints

The ORR and DCR (investigator and independent assessment) of each treatment arm will be calculated as defined by RECIST v1.1. Tumor response (CR+PR) rate and disease control (CR+PR+SD) rate will be reported along with exact confidence intervals (CI: 95%) and compared using the Cochran-Mantel-Haenszel test adjusting for the stratification variables.

Duration of response (investigator and independent assessment) will be compared between both treatment arms using unstratified log-rank test and Kaplan-Meier estimates. The DoR analysis is for responders only.

Patient listings of tumor assessments (target and non-target lesion assessments and tumor response) and DOR will also be provided.

5.11.3. Exploratory Efficacy Analyses

Time to deterioration in ECOG PS and its variations will be analyzed using the Kaplan-Meier method and compared using an unstratified log-rank test. The association between PFS event and ECOG PS deterioration will be assessed through an analysis of change from baseline in ECOG PS by objective progression (yes versus no) by tumor measurement period.

Time to diagnosis of CNS metastases will be analyzed using the Kaplan-Meier method and compared using an unstratified log-rank test for Part B only. For Part C, time to diagnosis of CNS metastases will be analyzed using the Kaplan-Meier method.

A waterfall plot of the (best) percent change from baseline in target lesion measurement will be generated for each study arm in Part B and Part C period 1.

Regarding PFS2 in Part B and PFS in Part C Period 2, the median with 95% CI, and progression free survival rates at various time points will be estimated using Kaplan-Meier method (Kaplan and Meier 1958).

A 1-year PFS rate of Part C, i.e., a cumulative proportion of patients who survived during the first year (that is, 1 year from enrollment) in the study without disease progression, will be estimated using Kaplan-Meier method (Kaplan and Meier 1958) in addition to PFS curves, the median with 95% CI, and survival rates at various time points, for Part B and C, respectively.

For PFS2 and OS in Part C Period 2, the median with 95% CI will be estimated using Kaplan-Meier method (Kaplan and Meier 1958) for patients that receive osimertinib after disease progression.

5.11.4. Subgroup Analyses

Subgroup analyses will be performed for PFS, the primary endpoint, and OS. Only unstratified analysis will be performed on each subgroup. Each analysis will use the similar methodology as for the primary analysis. A Forest plot of the estimated HRs with 95% CIs will be provided for subgroups with sufficient number of events (≥15).

- all baseline stratification factors
- age (<65 years vs. ≥65 years)

- age (<70 years vs. ≥70 years)
- age (<75 years vs. ≥75 years)
- smoking history (ever vs. never smoker)
- performance status (0 vs. 1)
- initial stage at diagnosis (Stage IV vs. other)
- liver metastases (yes vs no)

Tobacco product smoking history will be collected. The definition of 'ever smoker' includes those who smoked ≥100 cigarettes, cigars, or pipe-fulls in his/her lifetime and the definition of 'never smoker' is one who smoked <100 cigarettes, cigars, or pipe-fulls in his/her lifetime.

Tests within each subgroup and tests for subgroup-by-treatment interaction terms will use an unstratified test and unstratified Cox PH model.

Additional subgroup analyses may be performed as deemed appropriate. If any safety analyses described in Section 5.15 identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

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The goal of subgroup analyses is to assess internal consistency of study results, and whether there is significant treatment heterogeneity across any of the subgroups. Appropriate interpretation is important since, even if all patient subgroups benefit to exactly the same extent in truth, smaller or larger estimated effects, even negative effects, may be seen for some subgroups simply by chance alone. Without appropriate interpretation, this can lead to erroneous conclusion in one or more subgroups, in particular where differential treatment effects are not expected across any of the factors assessed. In order to assist with interpretation of the subgroup results, the methodology of Fleming (1995) may be followed to provide background information on the extent of variability that might be expected by chance alone.

5.11.5. Sensitivity Analyses

The following sensitivity analyses will be performed:

- An analysis of PFS based on Blinded Independent Radiological Review. Discordance statistics, such as those defined by the Pharmaceutical Research and Manufacturers of America methodology (Amit et al. 2011) will also be calculated. These analyses will be conducted on all reviewed patients for Part B only.
- Comparison between the eCRF and IWRS values of the stratification factors corresponding to Part B will be performed.

- An analysis of investigator PFS will be estimated using an multivariate Cox PH model to be constructed by selecting variables among all the variables listed in Section 5.6 using stepwise selection method (for age, only include 65 as cut-off). The stepwise selection will use p-value <0.05 as the criterion for adding a variable and p-value ≥0.10 for dropping a variable. The treatment factor will be kept out of the model throughout the covariate selection process and only added into the final model. Hazard ratio for treatment effect and corresponding 95% CI will be estimated from the final model. **Note.** A covariate may be removed from the analysis if the number of patients representing one level of that variable is insufficient or data collected on that variable are incomplete. If a selected prognostic factor happens to be also a stratification factor, that factor will be used in stratification, instead of as a covariate in the model.
- An analysis of the primary investigator-assessed PFS stratified using the eCRF values instead of IWRS values.
- An analysis of investigator-assessed PFS using an unstratified log-rank test and unstratified Cox model
- An analysis of investigator assessed PFS based on the PP population
- An analysis of investigator assessed PFS without censoring for new anticancer therapy
- An analysis of investigator assessed PFS without censoring for missing 2 or more tumor assessments prior to PD/death
- An analysis of investigator assessed PFS counting clinical progression and radiographic PD as progression
- An analysis of primary investigator assessed PFS without censoring for missing 2 or more tumor assessments prior to PD/death and without censoring for new anticancer therapy.
- An analysis of investigator assessed PFS treating lost to follow up as progression
- An analysis of primary OS based on the PP population
- An analysis of the primary OS analysis stratified by the eCRF values
- An analysis of primary OS using an unstratified log-rank test and an unstratified Cox model
- An analysis of final OS censoring at the start of new anticancer therapy
- Similarly to PFS, an analysis of OS using a multivariate Cox PH model to be constructed by selecting variables among all the variables listed in Section 5.6 using stepwise selection method (for age, only include 65 as cut-off).
- A sensitivity analysis of ORR/DCR/DOR based on independent assessment will be conducted.

Additional post-hoc sensitivity analyses of PFS or OS may be performed as deemed necessary.

5.12. Postdiscontinuation Therapies

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, and by type of therapy (surgery, radiotherapy, or systemic therapy, for the Part B ITT population and for the Part C ITT population. Surgery and radiotherapy will be further characterized by intent. Systemic therapy will be further categorized by WHO drug terms.

The analyses above might be repeated for 1st, 2nd, ⋯, subsequent therapies.

5.13. Patient-Reported Outcome Analyses

There is no PRO analysis planned for Part A. Descriptive analyses with each PRO instrument will be performed for Parts B and C.

For each instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study and alive). Percentage compliance will be summarized by treatment arm and overall. Reasons for noncompliance will be described.

5.13.1. Lung Cancer Symptom Scale

The LCSS assessments will be used primarily to calculate TtD for each of the 9 items, ASBI, and LCSS total score as defined in Section 5.3.3.

- The Kaplan-Meier method will be used to estimate parameters for time-to-event analyses on each treatment arm. Kaplan-Meier curves by treatment arm will be produced.
- HRs for treatment effect and their 2-tailed 95% CIs will be estimated using the Cox PH model stratified identically to the stratified log-rank tests. A Forest plot of the estimated HRs and their 95% CIs will be generated.
- The LCSS data will be summarized descriptively by baseline and cycle for actual measurement and change from baseline by treatment arm. For the LCSS (each item, ASBI and Total LCSS), maximum improvement over baseline is defined as the largest magnitude decrease from baseline. The analysis of maximum improvement will be conducted to compare the study treatment arms for each score using analysis of covariance (using only baseline score as a covariate) and the Mann-Whitney-Wilcoxon test. Percentage of patients who improved, remained stable, or worsened will be reported. Additionally, mean change from baseline will be estimated using Mixed effect Model Repeat Measurement (MMRM) regression and will include independent variables treatment, visit, treatment*visit, and baseline. A negative change will indicate improvement.

Additional exploratory analyses, including pattern mixture model as a sensitivity analysis to assess missingness, subgroup analysis, association with clinical outcomes, time to sustained deterioration, and predictive modeling, may be performed as deemed appropriate.

5.13.2. EuroQol EQ-5D-5L: Health State Utilities

Summary statistics for the index and VAS will be calculated for each assessment period by treatment arm. The EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages by treatment arm. Mean change from baseline will be estimated for the EQ-5D-5L index value and the EQ VAS self-rated health score using longitudinal MMRM regression models and will include independent variables treatment, visit, treatment*visit, and baseline. A negative change from baseline will indicate improvement.

5.14. Pharmacokinetics and Immunogenicity

There is no PK analysis or immunogenicity analysis planned for Part A.

5.14.1. Pharmacokinetics

In Part B, serum concentrations of ramucirumab prior to infusion (minimum or trough concentration [C_{min}]) and at 1 hour post-end of ramucirumab infusion (approximately maximum or peak concentration [C_{max}]) will be summarized using descriptive statistics. Additional analysis utilizing a population PK (PopPK) approach based on an established PopPK model may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored. Detailed exposure-response analysis plan is described separately.

In Part C, for Ramucirumab, C_{min} and concentrations at 1 hour post end of infusion (approximately maximum concentration [C_{max}]) will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety may be explored.

5.14.1.1. Drug-Drug Interaction Substudy

In the DDI substudy, PK parameters of erlotinib will be calculated by non-compartmental analysis and will be summarized using descriptive statistics. The effect of concomitant ramucirumab on PK of erlotinib will be assessed using erlotinib PK data from the ramucirumab plus erlotinib arm compared with erlotinib PK data from the placebo plus erlotinib arm. All patients with valid PK parameters (AUC and C_{max}) will be included in the analysis. A two-sample t-test will be used to analyze the log-transformed PK parameters of AUC and C_{max}. Means and 90% CIs for the differences of AUC and C_{max} between the 2 treatment arms in log scale were estimated, then transformed back to the original scale to estimate the ratio of geometric means and 90% CIs for the comparison (ramucirumab + erlotinib arm versus erlotinib arm).

5.14.2. Immunogenicity

For immunogenicity analyses, the number and percentage of patients with positive ramucirumab antibody response will be summarized per part. Additional efficacy or safety analyses may be performed in the subgroup of patients who are identified as treatment-emergent anti-drug antibodies (ADA) positive. The antibody response and any alteration in ramucirumab PK may

also be explored, as well as any relationship with experiencing an infusion reaction. Further exploratory analyses may be performed as appropriate.

5.15. Safety Evaluation

5.15.1. Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be evaluated for Part A only.

DLT definitions include:

- Grade ≥4 anemia
- Grade ≥3 thrombocytopenia
- Grade ≥3 febrile neutropenia
- Grade 4 neutropenia lasting >7 days
- Elevated urine protein of ≥3 g/24 hour
- Grade 4 or refractory hypertension
- Grade ≥3 nonhematologic toxicity excluding electrolyte abnormality or Grade 3 skin rash

An Assessment Committee (AC) will be established as a Lilly internal review committee independent from the study team and will follow an approved AC Charter. The AC will evaluate the DLT analysis and provide consultation and recommendation to the study team with regards to the starting dose of Part B (refer to Section 9.4.1 of the protocol).

The recommended dose of ramucirumab in the Part B population will be decided based on the following rules:

- If the proportion of patients experiencing DLT is < 33% (0 or 1 patient with any DLT) for DLT-eligible patients from each of the cohorts during the first 2 cycles, the ramucirumab starting dose in Part B will be 10 mg/kg every 2 weeks.
- If the proportion of patients experiencing DLTs is ≥33% (2 or more patients with any DLTs) for DLT-eligible patients from any of the cohorts during the first 2 cycles, the ramucirumab starting dose in Part B will depend on AC recommendation.

The study team could request an earlier AC review of the data generated before the planned database lock. For example, in case each cohort enrolled 5 DLT-evaluable patients but DLT is not observed during the DLT assessment period in these patients, an earlier data review by AC could be initiated by the study team to proceed accordingly.

Upon review of safety data, AC may recommend one of the following:

- To start enrollment in Part B with the starting dose of 10 mg/kg every 2 weeks
- To enroll 3 additional patients at 10 mg/kg every 2 weeks and reassess the dose tolerability once the additional 3 patients complete the DLT Assessment Period
- To start enrollment in Part B with the starting dose of 8 mg/kg every 2 weeks
- To stop the study

Summary of reasons for DLT non-evaluable patients will be reported. A patient listing of all DLTs will be provided.

5.15.2. Exposure

The following exposure-related variables will be reported for each part as specified:

- Exposure:
  - For both ramucirumab and erlotinib duration of treatment; number of patients with dose adjustments, i.e., dose reduction, dose delay (ramucirumab only), and dose omission (Parts A and B separately)
  - For both ramucirumab and gefitinib duration of treatment; number of patients with dose adjustments, i.e., dose reduction, dose delay (ramucirumab only), and dose omission (for Part C Period 1 only)
  - For both ramucirumab and osimertinib duration of treatment; number of patients with dose adjustments, i.e., dose reduction, dose delay (ramucirumab only), and dose omission (for Part C Period 2 only)
  - For erlotinib: number of patients received < one week of treatment, ≥ one week of treatment, ≥ two weeks of treatment, ⋯, x weeks of treatment, and mean, standard deviation
  - Note: Patient is considered to have received a week of therapy after receiving at least seven doses of study drug ERLOTINIB either partial or complete.
  - For ramucirumab only: number of infusions received; number of patients completing < one infusion, ≥ one infusion, ≥ two infusions, ⋯, x infusions, and mean, standard deviation
  - For gefitinib: number of patients received < one week of treatment, ≥ one week of treatment, ≥ two weeks of treatment, ⋯, x weeks of treatment, and mean, standard deviation
  - For osimertinib: number of patients received < one week of treatment, ≥ one week of treatment, ≥ two weeks of treatment, ⋯, x weeks of treatment, and mean, standard deviation
- Reasons for dose adjustments and dose delays for ramucirumab, dose reductions and dose omissions (scheduling conflict, AE summarized by PT) for each

The following exposure-related variables will be reported using summary statistics (number of patients, mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum) by treatment arm:

- Dose intensity: cumulative dose; weekly dose intensity; relative dose intensity, overall weekly dose intensity, overall relative dose intensity.

Details of study drug administration will be included in patient listings.

5.15.3. Adverse Events

All AEs will be summarized by MedDRA System Organ Class (SOC) and PT. The incidence and percentage of patients with at least one occurrence of a preferred term will be included, according to the most severe National Cancer Institute - Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0) grade.

Unless otherwise specified, when summarized by PT, AEs will be presented in decreasing frequency of PT across treatment arms; when summarized by SOC and PT, AEs will be presented in decreasing frequency of PT within SOC across treatment arms. If more than one AE is recorded for a patient within any SOC or PT term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

A summary of AEs will be presented for Parts A, B and C separately.

5.15.3.1. Overall Summary of Adverse Events

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages:

- patients with at least one TEAE, SAE, or NCI-CTCAE Grade ≥3 TEAE
- patients with AEs that led to death (on study treatment, within 30 days of discontinuation from study treatment)
- patients with AEs that led to discontinuation
- patients with SAEs that led to discontinuation

The summary will be provided for regardless of study drug causality, and repeated for events deemed by the investigator to be possibly related to study treatment.

A patient listing of all AEs will be provided.

5.15.3.2. Treatment-Emergent Adverse Events

The following summaries of TEAEs will be provided, with treatment comparison using Fisher's exact test ([*]repeat for events deemed by the investigator to be possibly related to study medication, [†]include consolidated summary):

- by SOC and/or by PT[*†]
- by maximum NCI-CTCAE grade and by SOC and/or by PT[*†]

5.15.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Reasons for deaths (study disease, AE [any study drug-related, procedural related]) will be summarized separately for 1) all deaths, 2) deaths on therapy, 3) deaths within 30 days of treatment discontinuation, and 4) deaths on therapy or within 30 days of treatment discontinuation, 5) deaths after 30 days of treatment discontinuation.

Serious adverse events will be summarized by PT and repeated for events deemed by the investigator to be possibly related to study medication, with consolidated summary performed if needed. A listing of SAEs will be produced.

In addition, the following analyses will be performed ([*]repeated for events deemed by the investigator to be possibly related to study medication, [†]include consolidated summary):

- AEs leading to death by PT[†]
- AEs leading to study treatment discontinuation by PT[†]
- AEs leading to study treatment dose adjustments by PT[†]
- AESIs by PT[*]
- Listing of AESIs
- Listing of deaths
- Summary of TEAEs by Narrow-Scope SMQs and Preferred Term

5.15.5. Clinical Laboratory Evaluation

The severity of laboratory results will be graded according to NCI-CTCAE Version 4.0, when applicable. Grading will be purely based on the numeric results and no investigator assessment will be considered. Laboratory values will be converted to standard (SI) units, as referenced in the NCI-CTCAE v 4.0. Laboratory results not corresponding to a NCI-CTCAE v 4.0 terms will not be graded.

For graded laboratory parameters, shift tables in NCI-CTCAE toxicity grading from baseline to worst grade postbaseline (first dose up to 30 days after the last dose of study treatment) will be produced. A patient listing of all laboratory data will be provided with a flag for values outside of the laboratory normal range as well as investigator site, patient identifier, age, gender, race, weight, and visit.

5.15.6. Hospitalizations and Transfusions for Parts B and C

The frequency and percentage of patients with any hospitalizations experienced during the study treatment period or within 30 days of treatment discontinuation will be summarized by treatment arm. Hospitalization incidence rates will be compared between the treatment arms using Fisher's exact test. In addition, total number of days in hospital and admissions will be summarized and compared using the Wilcoxon rank sum test. These will be further characterized by reason.

Note. Discharge date will be imputed with last contact date for hospitalizations that are still ongoing at time of analysis.

The frequency and percentage of patients with any blood transfusions experienced during the study treatment period or within 30 days of treatment discontinuation follow-up period will be summarized by treatment arm. Transfusions will be further characterized by transfused blood product (for example, packed red blood cells, platelets, fresh frozen plasma, or whole blood).

The proportions of patients having blood transfusions will be compared between the treatment arms using Fisher's exact test.

Details of hospitalizations and transfusions will be included in patient listings.

5.15.7. Vital Signs, Physical Examinations, and Other Observations Related to Safety

A summary of ECOG PS at each scheduled time point will be provided. Actual value and change from baseline for vital sign measurements will be summarized at each assessment time point using summary statistics. Echocardiogram or Multiple Gated Acquisition Scan (MUGA) measurements will be summarized at each assessment time point using summary statistics. Electrocardiogram (ECG) counts and frequencies will also be summarized.

Listings of ECOG PS, vital signs, ECG, and echocardiogram or MUGA data will be provided.

5.15.8. Subgroup Analyses for Safety Evaluation

There is no subgroup analysis planned for Parts A or C.

Selected disposition and safety analyses will be performed for the following safety subgroups in Part B only:

- age (<65 years versus ≥65 years)
- gender (females versus males)
- race (Asian vs other)
- age (<70 years versus ≥70 years)
- region (East Asia versus other)
- mutation type (exon 19 versus 21)

Below is the list of the selected disposition and safety analyses for subgroup analyses for Part B and Part C:

Demographic and Other Baseline Characteristics

- Patient demographics
- Potential baseline prognostic factors for NSCLC (see Section 5.6)

Patient Disposition

- Patient disposition by investigator site and country and overall
- Reasons for treatment discontinuation

Exposure

- Summary statistics for exposure-related variables
- Dose intensity of study drugs

- Reasons for any drug adjustments

Adverse Events

- Overview of AEs
- TEAEs summarized by PT*
- CTCAE v 4.0 Grade 3 and 4 AEs*
- SAEs summarized by PT*
- AESIs by PT*
- Reasons for deaths
- AEs leading to all study treatment discontinuations summarized by PT
- AEs leading to all study drug adjustment summarized by PT

*Repeat for events deemed by the investigator to be possibly related to study medication.

5.16. Interim Analyses

There is no interim analysis planned for Part A.

An external Independent Data Monitoring Committee (IDMC) will be established prior to the inclusion of the first patient in Part B to conduct interim analyses for Part B as specified in Section 12.2.15.2 of the protocol and will follow an approved DMC charter. The IDMC will communicate back to Lilly Senior Management Designee (SMD) about their assessment.

Only the IDMC are authorized to evaluate unblinded interim efficacy and safety analyses; however, unblinding of groups of cases is required to make a determination that the group of cases represents a suspected adverse reaction for the purpose of expedited reporting in some countries or situations. Such unblinding is performed by Lilly Global Patient Safety (GPS) personnel external to the study to ensure the blinding integrity of the study. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

The Independent Data Monitoring Committee (IDMC) for Part B will also review the safety data for Part C. The IDMC safety review will be performed approximately every 6 months for both Parts B and C.

There will be no prespecified rules for stopping the trial due to safety concerns. The IDMC members will review safety data to determine whether there are sufficient safety concerns to recommend protocol modification, termination, or additional safety review at specified time points proposed by the IDMC.

There are 2 planned interim analyses for Part B. These interim analyses will be performed by an independent statistician outside of Lilly. Patient enrollment will continue during the conduct of interim analyses.

- A safety interim analysis will be performed after the first 50 treated patients completed 3 cycles or discontinued from all study therapies due to any reason prior to 3 cycles. The safety data will be reviewed by IDMC. There will be no prespecified rules for stopping the trial due to safety concerns. The IDMC members will review unblinded safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.
- A futility and safety interim analysis will be performed after approximately 107 investigator-assessed PFS events were observed. Futility for the interim analysis will be determined in terms of PFS. The futility rule will be based on stratified log-rank test. As guidance, an IDMC may recommend stopping the trial for futility if the p-value of the stratified log-rank test for PFS is >0.39 (this corresponds to approximately a HR >0.95 under a Cox PH model). The testing boundary will be adjusted based on actual number of events at the futility interim analysis, according to the alpha-spending functions. The stopping guidance should be viewed as only guidance, not the absolute rules. The IDMC will be instructed to engage the Lilly SMD, who may subsequently convene a Lilly Internal Review Committee to propose actions based upon the IDMC's recommendation.

Additional safety reviews will be conducted approximately twice a year after the first interim safety analysis until primary PFS analysis. The frequency of safety reviews could be reduced to once a year after the primary PFS analysis or earlier based on IDMC recommendation.

The sponsor may analyze the data from Part C for reporting preliminary results to the regulatory authority, when the primary analysis for Part B is performed.

Trial Level Safety Review by Lilly Clinical Research Physician will periodically perform the safety monitoring for Part C approximately twice a year after the first patient has been entered to treatment in Period 1.

5.17. Translational Research

Plans for translational research analyses will be described separately.

CCI [redacted] The following regions or countries defined by patient enrollment (for example, Korea means patient enrolled in Korea) will be used:

- Japan
- East Asia (excluding Japan; that is, Hong Kong, Korea, and Taiwan)
- East Asia (including Japan, Hong Kong, Korea and Taiwan)
- Non-East Asia (that is, all participating countries other than those in East Asia)

Both efficacy and safety analyses will be performed with the 3 geographic regions or country subgroups stated above. Unless otherwise specified, the same analysis methods for the overall analysis populations as listed in Section 5.7.1 will be used.

Additional analyses may be performed as deemed appropriate. For example, Box plot of laboratory measurements by cycle (Safety population) will be provided.

5.19. Clinical Trial Registry Analyses

For the purpose of fulfilling the Clinical Trial Registry requirements, summary of SAEs (whether treatment emergent or not) and other AEs (that is, non-serious TEAEs) by PT and treatment arm will be performed. For each PT, the number of patients at risk, patients who experienced the events, and events will be presented. In addition, the summary will be provided as a dataset in XML format.

6. Unblinding Plan

Parts A and C are an open-label studies and there is no unblinding plan.

Part B is a double-blind study. In order to protect the blinding of the patients, the ramucirumab and placebo treatments will be visually indistinguishable.

To preserve the blinding of the study, a minimum number of Sponsor or designee personnel will see the randomization table and treatment assignments before the study is complete. Individuals (IWRS, clinical trials materials management, and data management personnel) validating the database do not have access to aggregate summary reports or statistics.

Randomization will occur after completion of the screening procedures using an IWRS. Assignment to treatment arms will be determined by a computer-generated random sequence. It is acknowledged that, although a double-blind design feature minimizes bias, double-blinding in a placebo-controlled trial is imperfect due to the potential onset of treatment-related AEs. 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 analysis.

Patient-level unblinded information will not be shared between sites until the study is completed. Treatment assignment will be scrambled in the reporting database until the database lock for data analysis. This will ensure unblinded aggregate efficacy results are not available until the time of primary data analysis.

The purpose of this unblinding plan is to maintain the scientific integrity of the study. The following actions/procedures will be put in place prior to any unblinding of the study data:

6.1. Site Level Unblinding

Upon overall study completion, investigators may unblind patients to study treatment assignment.

The procedure for site personnel to unblind an individual patient's treatment assignment for emergency is described in the protocol.

The site monitor is responsible for verifying compliance with the blinding procedures at the investigator site and verifying that access to the patients' treatment assignments remains restricted from the investigator and site personnel in direct contact with patients. The investigator and site personnel are instructed to make every attempt to contact Lilly personnel when a patient's treatment assignment is unblinded at the site.

A final Study Unblinding Summary will be prepared at the end of the study (at the study closeout).

6.2. Sponsor/Trial Level Unblinding

Planned trial level unblinding will only occur at interim safety, futility, and efficacy analyses. For this study, the following roles will be permitted to access unblinded data for interim analyses of safety and/or efficacy: IDMC members, select group of programmers/statistician who are independent of the study team performing interim analyses, and GPS. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly/third-party organization's data and statistical warehouse. Any changes to this unblinding plan may be described in a protocol amendment, the SAP, and/or a separate unblinding plan document.

- Interim analyses for safety and futility will be conducted, using unblinded data, under the guidance of an IDMC. These interim analyses will be performed by an independent statistician (not an employee of Lilly). Study team members will remain blinded until database lock for the primary PFS analysis occurs. They will not review unblinded results from the interim analyses. The study statistician will conduct quality review of blinded output with the treatment code scrambled during the course of the trial. Study team members will review blinded results with the treatment code scrambled as described in the trial level safety review plan. More details will be provided in an IDMC charter.
- In addition, a limited number of pre-identified individuals may gain access to the limited unblinded data prior to the PFS database lock, in order to initiate the population pharmacokinetic/pharmacodynamic model development processes for primary PFS analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

The study statistician will be responsible for keeping a running log of individuals given access to any unblinded study data. This log will include the person's name, title, date of unblinding, level of unblinding (that is, group or patient), and purpose of unblinding. The documentation is filed in the study files.

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