Statistical Analysis Plan: I4T-MC-JVDL (Version 2)

An Open-Label, Multicenter, Phase 1 Study with Expansion Cohorts of Ramucirumab or Necitumumab in Combination with Osimertinib in Patients with Advanced T790M-Positive EGFR-Mutant Non-Small Cell Lung Cancer after Progression on First-Line EGFR TKI Therapy

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Ramucirumab (LY3009806), Necitumumab (LY3012211), and Osimertinib (AZD9291)

Phase 1 Study with Expansion Cohort of Ramucirumab plus Osimertinib or Necitumumab plus Osimertinib in Patients with Advanced T790M-Positive EGFR-Mutant Non-Small Cell Lung Cancer, after Progression on First-Line EGFR TKI Therapy.

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Protocol I4T-MC-JVDL
Phase 1

Statistical Analysis Plan electronically signed and approved by Lilly:
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Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

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2. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit.

The overall changes and rationale for the changes incorporated in Version 2 are as follows:

The following changes were made to Version 2 of the SAP to reflect changes made in protocol amendments (a) and (b):

- Section 3.2. Secondary Objectives – removed "necitumumab" from the 2 secondary objectives. Added "Arm A" to the phase 1a dose-finding portion of the study.
- Section 4.1. Sample Size Determination – removed "necitumumab" from the dose-expansion portion of the study.
- Section 4.1.2. Phase 1b –
    - Phase 1b Dose-Expansion Portion – changed number of patients for Cohort A from 50 patients to 22 patients and removed reference to Cohort B.
    - Dose-Expansion Portion – changed number of patients from 25 patients per cohort to 22 patients in Cohort A and removed reference to Cohort B.
- Section 4.2. Derived Endpoint Definition – removed "electrocardiogram (ECG) parameters" from the list of safety measures.
- Section 4.2.1.1. Dose-Limiting Toxicity – changed "cohorts" to "study arms" when referring to subjects.
- Section 4.5.1. General Considerations – moved the note stating "Data may be summarized by the same indication and dose schedule in combination with the Phase 1b part." to Section 4.5.1.1. Phase 1a Dose-Finding Portion.
- Section 4.5.3.1. Demographics and Baseline Characteristics – removed alcohol consumption habits from the list of patient demographics and baseline characteristics to be summarized and listed.
- Section 4.5.6. Exposure –
    - Added "phase" to the exposure related variables.
    - Changed "infusion(s)" to "cycle(s)" and removed "number of patients with dose modification: dose reduction, dose delay, and dose omission".
    - Removed reference to exposure-related variables to be reported using summary statistics by phase and cohort, along with cumulative dose, overall weekly dose intensity, and overall relative dose intensity as variables.
- Section 4.5.7.1. Treatment-Emergent Adverse Events –
    - Removed "Grade 3-4" from list of categories for TEAEs to be summarized.
    - Removed sentence, "A listing of TEAEs will be produced".
- Section 4.5.7.2. Deaths, Serious Adverse Events, and Other Significant Adverse Events –
    - Reasons for deaths to be summarized were changed for reason 2 from "deaths up to 30 days after the last infusion of study treatment" to "deaths on therapy", and

for reason 3 from "deaths after 30 days of last infusion of study drug" to "deaths within 30 days of treatment discontinuation".
    - The following additional analyses were removed from the list
        - Maximum NCI CTCAE v 4.0 Grad 3-5 AEs by NCI CTCAE term
        - AEs leading to study treatment dose modification by PT
        - Listing of AESIs
- Section 4.5.8 Clinical Laboratory Evaluation – the word "abnormal" was removed from the sentence describing the listing of all laboratory data to be provided with a flag for values outside of normal.
- Section 4.5.9. Efficacy Analyses –
    - "All planned efficacy analyses will include all patients enrolled in the Dose-Finding Portion (Arm A) and the Dose-Expansion Portion (Cohort A). No efficacy analysis is pre-planned for Arm B" was added.
    - The words "for each chohort" were removed from the ORR analyses.
    - The words "for each treatment arm" were removed from the DCR analyses.
    - The sentence, "Efficacy analyses will be based on the evaluable patients" was removed from PFS and DOR analyses.
    - The sentence, "For example, brain metastases status as baseline" was added to subgroup analyses of interest to be further explored.
- Section 4.5.13. Interim Analysis –
    - Removed "PK" data from the dose-finding portion of the study to be reviewed.
    - The following was removed from the dose-expansion portion of the study: "…however, a separate interim safety and futility analysis will be conducted approximately 3 months after the 12th patient receives initial treatment in each cohort, respectively. The sponsor will review safety data at the interim to determine whether there are sufficient safety concerns to justify dose modification or the termination of study treatment and/or enrollment. Futility for the interim analysis will be determined in terms of ORR. As guidance, the trial may be stopped for futility if 5 or fewer responses out of 12 patients for each cohort were observed so that the probability of futility is at least 10% if the true ORR is 60% or less (based on the beta-binomial posterior distribution using a non-informative Beta Bayesian prior). The stopping guidance should be viewed as only guidance, not an absolute rule. The interim analysis may be combined with the ongoing trial-level safety review or annual safety review for annual safety update reporting."

3. Study Objectives

3.1. Primary Objective

The primary objective of Phase 1a Dose-Finding Portion and Phase 1b Dose-Expansion Portion is to assess the safety and tolerability of ramucirumab or necitumumab in combination with osimertinib.

3.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the pharmacokinetics (PK) of ramucirumab in combination with osimertinib (Phase 1a Dose-Finding Portion, Phase 1b Dose-Expansion Portion)
- To assess the preliminary efficacy of ramucirumab in combination with osimertinib (Phase 1b Dose-Expansion Portion)*

*Note: Patients in Phase 1a Dose-Finding Portion Arm A will be included in the overall preliminary efficacy analyses.

3.3. Exploratory Objectives

The exploratory objective of Phase 1b Dose-Expansion Portion is to explore the association between biomarkers and clinical outcomes.

4. A Priori Statistical Methods

4.1. Sample Size Determination

The primary objective for the Dose-Finding Portion and the Dose-Expansion Portion is to evaluate safety and tolerability. The sample size of the Dose-Expansion Portion is selected to allow adequate assessment of safety at the recommended doses for ramucirumab in combination with osimertinib.

4.1.1. Phase 1a

Phase 1a Dose-Finding Portion: up to 12 Dose-Limiting Toxicity (DLT)-evaluable patients each for Arms A and B.

4.1.2. Phase 1b

Phase 1b Dose-Expansion Portion: 22 patients each for Cohort A.

During the Dose-Expansion Portion, 22 patients in Cohort A will be treated, to provide a preliminary assessment of tumor response and an assessment of safety. The null hypothesis is based on the assumption that the objective response rate (ORR) is no greater than 60% and the target treatment effect (alternative response rate) of the combination treatment on ORR is greater than 70% and 75%, respectively. Based on these assumptions, a sample size of n=22 provides statistical power of approximately 58% and 78%, respectively, with a 1-sided 0.20 significance level.

4.2. Derived Endpoint Definition

Safety measures that will be used in the study include adverse events (AEs), DLT in Phase 1a, clinical laboratory test results, and vital signs. All AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Adverse event terms will also be derived from verbatim text using the Medical Dictionary for Regulatory Activities (MedDRA™) dictionary.

4.2.1. Safety Endpoint

4.2.1.1. Dose-Limiting Toxicity

A DLT is defined as one of the following AEs reported during the DLT observation period, if considered to be definitely, probably, or possibly related to ramucirumab, necitumumab, and/or osimertinib by the investigator; and fulfills any 1 of the following criteria using NCI CTCAE Version 4.0:

1. Any nonhematologic toxicity Grade ≥3 will be considered as DLT with the following exceptions:
    a) Liver function abnormality: Grade ≥3 elevation in aminotransferase (AST) or alanine amino transferase (ALT) that persists for less than 7 days. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, either one of the level ≥10x upper limit of normal (ULN) lasting for ≥7 days will be considered a DLT.

b) Renal function abnormality: Grade ≥3 renal function test elevation that persists for less than 7 days
c) Skin rash: Grade 3 rash that resolves to Grade ≤2 within 14 days with appropriate supportive therapy
d) The following are not considered a DLT if they are transient (<7 days) and after treatment, decrease to Grade 2 or lower:
   - Grade ≥3 hypersensitivity and injection site reactions
   - Grade ≥3 myalgia, fatigue, and constipation, with full supportive therapy
   - Grade ≥3 electrolyte imbalance, nausea, vomiting, and diarrhea

2. Hematologic toxicity will be considered a DLT as the following:
   a) Grade 4 toxicity lasting ≥7 days, or
   b) Grade 3 or 4 thrombocytopenia if associated with bleeding or requires platelet transfusion, or
   c) Febrile neutropenia
3. Grade 5 toxicity (that is, death) if considered related to study treatment
4. Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting, for example:
   a) Any toxicity (such as confirmed interstitial lung disease/pneumonitis) that is possibly related to study treatment that requires the withdrawal of the patient from the study during observation period, or
   b) A delay of >14 days due to persistent Grade ≥2 treatment-related toxicities in the initial 2 cycles, or
   c) If a total of at least 75% of the planned dose for either agent cannot be administered in the first 2 cycles due to toxicity.

Unless determined at the DLT review meeting to initiate Dose Levels -1, no intrasubject dose escalation or reduction is allowed during the DLT observation period. For the purpose of subject management, DLTs will lead to dose interruption during the DLT observation period. Depending on the AE profile, dose modifications of study drugs will be permitted after the initial DLT observation period.

Additional patients will be enrolled in a study arm to achieve the minimum of 3 evaluable patients. Noncompliant patients or patients who withdraw from the study during the DLT observation period for reasons other than a DLT may be replaced within the same dose level. For the purpose of making decisions from a safety perspective, subjects will be considered evaluable if they have completed 4 weeks for Arm A or 3 weeks for Arm B of observation and have received at least 75% of the arm-specified dose of study treatment. In addition, patients with dosing delays in Cycle 1 of ≥2 weeks for non-DLT events will be considered not evaluable for making decisions and should be replaced.

After each of the 3 patients in a dose schedule completes the observation period, a safety analysis will occur; the data will be reviewed by study investigators and the Lilly clinical research physician/clinical research scientist (CRP/CRS), and the findings documented, indicating

whether each dose schedule is or is not well tolerated. The results will inform the decision whether or not to move onto the Dose-Expansion portion.

4.2.1.2. Exposure-related Variables

- **Cumulative dose**
  - For ramucirumab and necitumumab, 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 osimertinib, cumulative dose (mg) is calculated as sum of all dose levels.
- **Duration of treatment (week)**
  - Duration of treatment (week) of ramucirumab is calculated as (date of first dose in last cycle – date of first dose + 14)/7.
    Note. Fourteen days is added because ramucirumab is planned to be administrated every 1 cycle (14 days). Last dose stands for planned dose, regardless of whether the actual dose received is 0 or not.
  - Duration of treatment (week) of necitumumab is calculated as (date of first dose in last cycle – date of first dose + 21)/7.
    Note. Fourteen days is added because ramucirumab is planned to be administrated every 1 cycle (14 days). Last dose stands for planned dose, regardless of whether the actual dose received is 0 or not.
  - 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 electronic case report form (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 ≤28 days 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 + 28)/7, if patient discontinues >28 days after the date of the last time when erlotinib is distributed.
      *Twenty-eight days is added because erlotinib is planned to be dispensed every 2 cycles (28 days).
- **Dose intensity** (mg/kg/week for ramucirumab and necitumumab or mg/day for osimertinib) is calculated as cumulative dose / component-specific duration of treatment.
- **Relative dose intensity** (%) is calculated as dose intensity / planned dose intensity * 100, where for Dose Level 0, ramucirumab planned dose intensity = 5 mg/kg/week and it is 4 mg/kg/week for Dose Level -1. For Dose Level 0, necitumumab planned dose intensity = 267 mg/week and it is 200 mg/week for Dose Level -1. The planned dose intensity = 80 mg/day for osimertinib (or according to the planned dose recorded in the eCRF).

4.2.1.3. Adverse Event-related Variables

- **Dose-limiting toxicity (DLT):** Please refer to Section 4.2.1.1 for the definition of DLT.

- **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 compound level. Each AESI is defined by a set of MedDRA preferred terms (PTs). For compound level AESIs, the lists of associated PTs were developed by the lead physician and the safety physician for the compound. For study-specific AESIs, the PT lists were developed by the study physician. For the rest of the AESIs, the PTs were identified through medical review of all unique PTs collected in all ramucirumab studies for compound-level AESIs. Categories of AESI may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be reported in the clinical study report (CSR).
- **Consolidated AEs** include abdominal pain, anemia, leukopenia, myocardial infarction, neuropathy, neutropenia, rash, renal failure, thrombocytopenia, and urticarial.
  Note. Consolidated AEs are composite AE terms consisting of synonymous PTs to allow meaningful interpretation of the AE data. Additional consolidated AE categories may be added as needed. The final list of consolidated AE categories will be reported in the CSR.
- **Serious adverse event (SAE)** is any AE that results in 1 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 an event that first occurred or worsened in severity between first dose of study treatment and 30 days after the last dose of study treatment and related SAEs reported beyond 30 days after the last dose of study treatment, where last dose stands for actual dose, that is, 0 dose is not counted as last dose.

4.2.2. Efficacy Endpoint

Definition of efficacy analysis variables are listed alphabetically.

- **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.
- **Time-to-response (TTR)** is the time from the date of first study treatment until the first evidence of a confirmed CR or PR.

- **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.
- **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.
- **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 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).
- **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) based on investigator assessment or the date of death due to any cause, whichever is earlier. Table JVDL.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 progressive disease (PD) or death has been observed for the patient; otherwise,
    - If a patient is not known to have died or have investigator-assessed 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 1 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 / censor - Date of randomization + 1.

Table JVDL.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

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

4.3. 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.

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 (both components).
- 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 Section 4.2.2 for details.

4.4. Analysis Population

Patients **entered** into the trial are those who sign the informed consent document.

Patients **enrolled** in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.

Safety Population: All enrolled (randomized) patients that received at least 1 dose of any study treatment. Patients will be grouped according to treatment received in Cycle 1. Safety population will be used for all dosing/exposure, AEs, and resource utilization analyses.

DLT-Evaluable Population (Phase 1a Dose-Finding Portion):

- Arm A: 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.

- Arm B: patients who either completed the first cycle of treatment (approximately 21 days + 3 days) or discontinued from study treatment or study participation before completing the first cycle due to a DLT would be considered DLT-evaluable.

Intention-to-Treat (ITT) Population: All patients who will be randomized (enrolled) to study treatment. Patients will be grouped according to randomized treatment. This population will be used for all baseline and efficacy analyses.

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

4.5. Description of Analysis

4.5.1. General Considerations

This document describes the statistical analyses planned prior to first visit. 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. 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 CSR, 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 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 number of patients with an observation (n), mean, standard deviation, median, minimum, and maximum for continuous variables; and population size (N), the number of events, the number of subjects with events (n) and the proportion of subjects with events (p=n/N) for categorical variables
- Study period
    - **Dose-limiting toxicity assessment period for Phase 1a:** 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 in Arm A.

      Note. Two cycles are considered completed on the 14th day from the second dose of ramucirumab.

- completed 1 cycle of treatment or discontinued from study treatment or study participation before completing 1 cycle due to a DLT in Arm B.

Note: One cycle is considered completed on the 21th day from the first dose of necitumumab.

- **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 eCRF as the Date of Discontinuation from all study treatment.
- **Short-term (Safety) follow-up period** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days).
- **Long-term (Survival) follow-up period** begins the day after short-term follow-up is completed, and last until disease progression on or after the study regimen, all patients will be assessed every 2 months (±7 days) to obtain information about survival status and detailed information on any subsequent systemic anticancer therapy and disease progression (for patients not having a radiographic progression) for as long as the patient is alive, or until study completion.

Data will be summarized by assigned dose levels and schedules for preliminary analysis unless stated otherwise.

4.5.1.1. Phase 1a Dose-Finding Portion

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

Note. Data may be summarized by the same indication and dose schedule in combination with the Phase 1b part.

4.5.1.2. Phase 1b Dose-Expansion Portion

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

4.5.2. Patient Disposition

All patient discontinuation data collected on the eCRF will be listed, including the extent of the patient participation in the study. If known, a reason for their discontinuation from treatment and from study will be listed and summarized. All patients entered in the study will be included in the summary and listing.

All significant protocol violations will be listed by pre-determined categories (eg, inclusion/exclusion criteria, errors/missing data in the informed consent/assent process, noncompliance with protocol procedures, errors and missing data in drug dosage/intervention, errors in recording of DLTs, use of excluded treatments, patients continuing after meeting withdrawal criteria, or other violations as recorded on eCRFs or monitoring reports).

4.5.3. Demographics and Baseline Characteristics

4.5.3.1. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized and listed for all enrolled patients. At a minimum, sex, age, race, basis for initial diagnosis, initial pathological diagnosis, stage at initial diagnosis, baseline Eastern Cooperative Oncology Group performance status, height, weight, and tobacco consumption habits will be summarized. For some subsets of patients, intermediate and study entry pathological diagnosis data will also be listed.

4.5.3.2. Historical Illnesses and Prior Therapies

Historical illnesses are events in the past that ended before the date informed consent is signed. Historical illnesses (coded according to the MedDRA dictionary) will be listed for all enrolled patients.

Prior therapies, including systemic therapy, radiotherapy and surgeries will be listed for all enrolled patients. Prior radiotherapy and systemic therapy will be summarized by the number of patients with at least 1 of each type of treatment, as well by reason for regimen (eg, palliative, curative, etc.). Additionally, the number of regimens of prior systemic therapy, and (where available) the reason for prior regimens will be summarized.

4.5.4. Concomitant Therapy

Concomitant medications will be summarized and listed for the safety population.

4.5.5. Post-discontinuation Therapy

The numbers and percentages of patients reporting post-discontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

4.5.6. Exposure

The following exposure-related variables will be reported using summary by phase and treatment group:

- Exposure: duration of treatment; number of cycles received; number of patients completing ≥1 cycle, ≥2 cycles, …, x cycles, and mean, standard deviation;
- Reasons for dose modification (delays, omissions, and reductions) (scheduling conflict, AE summarized by PT).
- Dose intensity: weekly dose intensity, relative dose intensity,

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

4.5.7. Safety Analyses

All patients who receive at least 1 dose of study therapy will be summarized for safety and toxicity.

Dose-Limiting Toxicity will be listed for Phase 1a only by ramucirumab or necitumumab dose schedules.

The most current version of MedDRA at time of analysis will be used when reporting AEs by MedDRA terms. The NCI-CTCAE version 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. Unless otherwise specified, when summarized by PT, AEs will be presented in decreasing frequency of PT across treatment arms; when summarized by system organ class (SOC) and PT, AEs will be presented in decreasing frequency of PT within SOC across treatment arms. If more than 1 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 patient listing of all AE will be provided.

4.5.7.1. Treatment-Emergent Adverse Events

Treatment-emergent adverse events will be summarized by decreasing frequency of SOC by PT and by CTCAE grade regardless of causality and related to any study drug separately.

Note: "by CTCAE grade" refers to the categories of all grades and Grade 3-5. The consolidated TEAEs will also be summarized.

A listing of TEAEs will be produced.

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

Reasons for deaths will be summarized separately for 1) all deaths, 2) deaths on therapy, and 3) deaths within 30 days of treatment discontinuation. Reasons of deaths will also be listed.

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):

- AEs leading to death by PT
- AEs leading to study treatment discontinuation by PT
- AESIs by PT*

4.5.8. Clinical Laboratory Evaluation

A patient listing of all laboratory data will be provided with a flag for values outside of the laboratory normal. Abnormal results will be listed separately for all enrolled patients.

In addition to the investigator-reported AEs, all relevant hematology and chemistry laboratory values will be graded according to CTCAE version 4.0. These derived values will be included on the listings of laboratory data.

4.5.9. Efficacy Analyses

All planned efficacy analyses will include all patients enrolled in the Dose-Finding Portion (Arm A) and the Dose-Expansion Portion (Cohort A). No efficacy analysis is pre-planned for Arm B.

Best overall response will be summarized for all patients evaluable for efficacy whose disease is assessable by RECIST 1.1.

If appropriate, the following analyses will be performed.

- ORR will be estimated and reported with exact 90% confidence interval (CI) for each arm.
- DCR will be summarized and exact 90% CIs for each arm will be provided.
- PFS and DOR will be estimated using a Kaplan-Meier method (Kaplan and Meier 1958) by median and exact 90% CI. Additional exploratory analyses using proportional hazards models to control for other factors may be performed.
- OS will be summarized using the Kaplan-Meier method.
- TTR will be summarized.
- If deemed appropriate, subgroup analysis of interest will be further explored. For example, brain metastases status at baseline.

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

All vital signs including temperature, blood pressure, heart rate, and respiratory rate will be listed for all enrolled patients.

4.5.11. Pharmacokinetic/Pharmacodynamic Analyses

All PK/pharmacodynamics analysis and creation of table, figures, and listings will be the responsibility of Lilly Global PK/pharmacodynamic and Pharmacometrics group based on applicable Global PK/ pharmacodynamic and Pharmacometrics Standard Operating Procedures and software approved by Global PK/pharmacodynamic and Pharmacometrics group's management. Detailed exposure-response analysis plan is described separately.

4.5.12. Biomarker Analysis

Plans for the exploratory biomarker analyses will be described separately.

4.5.13. Interim Analysis

For the Dose-Finding Portion, safety data will be reviewed on an arm-by-arm basis during the study. The purpose of these data reviews is to evaluate the safety and tolerability for each dose schedule and determine if a DLT has been observed. The investigators and the Lilly study team will evaluate the totality of data to determine whether or not to move into the Dose-Expansion Portion.

For the Dose-Expansion Portion, the primary analysis will occur at 6 months after the last patient enrolled and the final analysis will occur upon the completion of the study

4.5.14. 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

group will be performed. The summary will be provided as a dataset in XML format to be consistent with www.ClinicalTrials.gov requirements.

5. References

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.02, DCTD, NCI, NIH, DHHS. 2009. Publish date: 15 Sep 2009.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J. Am Stat Assoc.* 1958;53:457-481.

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