Protocol I4T-MC-JVCY(f)

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

NCT02411448

Approval Date: 23-Apr-2018

1. Protocol I4T-MC-JVCY(f)

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)

Study I4T-MC-JVCY is a multicenter, randomized, double-blind, Phase 3 study that will compare the efficacy and safety of treatment with erlotinib (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 erlotinib.

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Protocol Electronically Signed and Approved by Lilly on: 11 December 2014
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Approval Date: 23-Apr-2018 GMT

2. Synopsis

Study Rationale

Inhibition of angiogenesis is considered a promising approach to the treatment of cancer and vascular endothelial growth factor (VEGF) family members are important regulators of angiogenesis. Ramucirumab (LY3009806) is a recombinant human monoclonal antibody that specifically binds to the extracellular domain of VEGF Receptor 2 (VEGFR-2) with high affinity. REVEL (Study I4T-MC-JVBA), a Phase 3 study of ramucirumab plus docetaxel in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression after platinum-based chemotherapy, demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS), and statistically significant treatment effects were observed across efficacy endpoints of progression-free survival (PFS) and objective response rate (ORR). Improvement in disease control rate (DCR) was also observed, and the favorable effect of ramucirumab-docetaxel combination on OS and PFS was demonstrated for all major prognostic subgroups.

Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs; for example, erlotinib, gefitinib, and afatinib) significantly prolong progression-free survival in patients with *EGFR* mutation-positive advanced NSCLC when compared with platinum-based chemotherapy doublets; hence, these *EGFR* TKIs have become the standard of care in countries where approved. The rationale for such treatment is supported by the results of studies such as BR.21, EURTAC, OPTIMAL, IPASS, and LUX-Lung 3.

Recently, ATLAS, BeTa, and JO25567 trials reported that the combination of the antiangiogenic agent bevacizumab in combination with the *EGFR* TKI erlotinib provided additional PFS and OS benefit in the subgroup of patients with *EGFR* mutations. The ATLAS study results (bevacizumab plus erlotinib vs. bevacizumab plus placebo after chemotherapy with bevacizumab) demonstrated that the subgroup of patients with *EGFR* mutations (n = 52) had improved/longer duration of PFS and OS in the bevacizumab plus erlotinib arm as compared to the bevacizumab plus placebo arm (hazard ratio [HR] = 0.44 and 0.46, respectively). The BeTa trial (erlotinib plus bevacizumab vs. erlotinib plus placebo) showed that OS favored erlotinib plus bevacizumab in the subgroup of patients with *EGFR* mutations (n = 30). The median OS was not reached (95% confidence interval [CI]: 22.6, not reached) in the erlotinib plus bevacizumab arm (n = 12) and 20.2 months (95% CI: 16.4, 31.1), in the erlotinib arm, with HR = 0.44 (95% CI: 0.11, 1.67); however, the results should be interpreted with caution based on the small number of patients and the wide 95% CI for the HR. A randomized Phase 2 study (JO25567) in 154 first-line patients with *EGFR* mutation-positive NSCLC randomized 1:1 to receive erlotinib with or without bevacizumab showed a statistically significant PFS improvement in the erlotinib plus bevacizumab arm (16.0 months) as compared to the erlotinib monotherapy arm (9.7 months) (HR = 0.54). The DCR was 99% in the bevacizumab plus erlotinib arm versus 88% in the erlotinib arm. The treatment effect was observed across both *EGFR* mutation types (exon 19 deletion [median PFS 18.0 vs. 10.3 months; HR = 0.41,

p=0.0011] and L858R mutation [numerically longer but not significant median PFS 13.9 vs. 7.1 months; HR = 0.67, p=0.1653]).

This JVCY study is being conducted globally to determine whether an *EGFR*-TKI (erlotinib) in combination with ramucirumab as compared to *EGFR*-TKI (erlotinib) in combination with placebo would improve efficacy outcomes in previously untreated patients with *EGFR* mutation-positive NSCLC.

Clinical Protocol Synopsis: Study I4T-MC-JVCY

Name of Investigational Product: Ramucirumab (LY3009806)	
Title of Study: 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	
Number of Planned Patients: Part A (Phase 1b) Entered: 20 Enrolled: at least 12 Part B (Phase 3) Entered: 550 Enrolled/Randomized: 450	**Phase of Development:** 3
Length of Study (Part A and Part B, excluding the Continued Access Period): Approximately 61 months Planned first patient visit: APR 2015 Planned last patient visit: MAY 2020 (Part B) Planned analyses: Analysis 1 (Part A, dose-limiting toxicity [DLT] evaluation): After 6 patients enrolled from Japan and 6 patients enrolled from North America and/or Europe have completed 2 treatment cycles Endpoint: DLTs Analysis 2 (Part B, Interim Safety): After approximately 50 randomized patients have completed at least 3 cycles of treatment or discontinued from all study therapies due to any reason prior to 3 cycles Endpoint: Safety Analysis 3 (Part B, Interim Futility): Approximately 107 PFS events Endpoint: PFS and safety Analysis 4 (Part B Primary PFS Analysis): Approximately 270 PFS events Endpoint: PFS (Primary) and other secondary and exploratory objectives Analysis 5 (Part B, Final Overall Survival): Approximately 300 OS events Endpoint: OS (Secondary) 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.	

Objectives

Part A Objective:

The primary 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 *EGFR* mutation-positive metastatic NSCLC.

Part B:

Primary Objectives:

The primary objective of Part B is to compare PFS of ramucirumab administered in combination with erlotinib versus placebo in combination with erlotinib as therapy in previously untreated patients with *EGFR* mutation-positive metastatic NSCLC.

Secondary Objectives:

The secondary objectives of Part B of the study are:

- 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 (using Lung Cancer Symptom Scale [LCSS] and EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L])

Exploratory Objectives:

The exploratory objectives of Part B of the study are as follows:

- Assessment of the association between biomarkers and clinical outcome
- Comparison of progression-free survival 2 (PFS2) between treatment arms

The exploratory objectives in only the gefitinib/osimertinib cohort in Addendum 9, conducted in the East-Asian region including Japan, are as follows:

- 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
- to evaluate the efficacy and safety of ramucirumab when administered in combination with osimertinib in patients with T790M-positive metastatic NSCLC whose disease has progressed on ramucirumab plus gefitinib in this study, in the East-Asian region including Japan
- to assess PK and immunogenicity of ramucirumab
- to assess patient-reported outcomes (using LCSS and EQ-5D-5L)

Study Design: This is a Phase 1b/3 study of previously untreated patients with metastatic *EGFR* mutation-positive NSCLC. The Phase 1b single-arm and open-label part (Part A) will assess the safety and tolerability of the recommended dose for the Phase 3 part (Part B) where ramucirumab (10 mg/kg every 2 weeks) will be administered in combination with erlotinib (150 mg daily). The target enrollment is 12 patients in Part A. Patients will be enrolled in 1 of 2 cohorts (Cohort 1 will include 6 patients from Japan and Cohort 2 will include 6 patients from North America and/or Europe). Part A patients may be enrolled concurrently into selected cohorts. The Phase 3 dose will be selected based on the Phase 1b outcome. Note: On 16 December 2015, the Assessment Committee reviewed the safety data for the Phase 1b portion (Part A) and recommended to initiate the randomized Phase 3 portion of the study (Part B) with ramucirumab at 10 mg/kg every 2 weeks. Part B randomization will proceed after the completion of Part A DLT assessment. The decision on the final dose for Part B (Phase 3) will be communicated to the investigative sites after the completion of DLT assessment. The Phase 3, randomized, double-blinded portion of the trial will compare the efficacy and safety of ramucirumab in combination with erlotinib versus placebo in combination with erlotinib. Approximately 450 patients will be randomized evenly between the 2 treatment arms using the following stratification factors:

- *EGFR* mutation (exon 19 deletion vs. exon 21 [L858R] substitution mutation)
- Gender (male vs. female)
- Region (East Asia vs. other)
- *EGFR* testing method (*Therascreen*® [Qiagen] and *Cobas*® [Roche] vs. other PCR and sequencing-based methods)

Treatment in Parts A (ramucirumab plus erlotinib) and B (ramucirumab/placebo plus erlotinib) will continue until disease progression, unacceptable toxicity, or another permitted reason for study discontinuation. The study treatment in this protocol is considered ramucirumab or placebo in combination with erlotinib, or any component of the combination.

Diagnosis and Main Criteria for Inclusion and Exclusions: The study will enroll male or female patients, 18 years of age or older (20 years of age or older in Japan and Taiwan). Main inclusion criteria include: metastatic NSCLC patients who are eligible for first-line treatment with erlotinib based on previously documented evidence of tumors that have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, ECOG PS ≤1. Key exclusion criteria include: patients with known T790M mutation; metastatic CNS lesions; ophthalmologic abnormalities; active interstitial lung disease; and any prior systemic chemotherapy for advanced or metastatic NSCLC, including prior TKI therapy for any stage.

Test Product, Dosage, and Mode of Administration:

Ramucirumab: injection for intravenous (IV) use, supplied in sterile, preservative-free single-use vials containing 500 mg of ramucirumab, at a final concentration of 10 mg/mL in a histidine based formulation (10mM histidine, 75mM sodium chloride, 133mM glycine, and 0.01% polysorbate 80 at a pH of 6.0), administered as an IV infusion at a dose of 10 mg/kg every 2 weeks. The infusion should be delivered over approximately 60 minutes on Day 1 of each cycle. The infusion rate should not exceed 25 mg/min.

Placebo: injection for IV use, supplied in single-use 50-mL vials containing histidine buffer only. Since investigators and ancillary medical personnel will be blinded to the assignment of ramucirumab or placebo, the volume of placebo to be administered will be calculated as if it were ramucirumab formulated at 10 mg/mL and will be administered as an intravenous infusion at a dose of 10 mg/kg every 2 weeks.

Reference Therapy, Dose, and Mode of Administration:

Erlotinib: 150 mg taken orally once daily.

Planned Duration of Treatment:

A treatment cycle will be defined as 2 weeks. Patients will be treated until there is radiographic or symptomatic progressive disease (PD) (symptomatic PD should be objectively confirmed radiographically), toxicity requiring cessation, withdrawal of consent from further study treatment or study participation, or until other discontinuation criteria are met.

Criteria for Evaluation:

Efficacy:

Part A: Efficacy data will not be collected during the conduct of Part A; however, the same baseline tumor assessments, including gadolinium-enhanced MRI of the CNS, required for Part B will also apply for Part A, and will be performed prior to study enrollment. Investigators are required to follow institutional guidelines for regular follow-up for the disease under treatment to assess the disease response to the study treatment.

Part B: Efficacy assessments will be performed only for patients enrolled in Part B.

Tumor measurements: Investigators will read and perform tumor assessments for response according to Response Evaluation Criteria In Solid Tumors Version 1.1 guidelines. Despite any treatment delays, imaging must be performed every 6 weeks (±7 days) following first dose of study therapy, and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days) until documented objective PD. If a patient discontinues treatment due to objective disease progression, one additional tumor scan will be collected at the 30-day short-term follow-up visit unless the patient has received additional anticancer therapy prior to this visit. Thereafter, radiologic tests are no longer required. Imaging requirements include computed tomography (CT) scan or magnetic resonance imaging (MRI) of chest and abdomen including both adrenal glands, with pelvic imaging performed if clinically indicated. It is recommended that CT imaging of the abdomen/pelvis be performed with intravenous contrast. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then gadolinium-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, contrast-enhanced MRI of the chest/abdomen/pelvis is encouraged. A gadolinium-enhanced MRI of the CNS will be performed at baseline prior to randomization for all patients (per exclusion criterion regarding CNS metastases). While on study, a gadolinium-enhanced MRI of the CNS should be performed if clinically indicated to assess disease progression.

- **PFS** is defined as the time from the date of randomization to the date of radiographically documented PD based on investigator assessment, or the date of death due to any cause, whichever is first.
- **OS** is defined as the time from the date of randomization to the date of death from any cause.
- **ORR** is defined as the proportion of randomized patients achieving a best overall response of PR or CR.
- **DCR** is defined as the proportion of randomized patients achieving a best overall response of PR, CR, or SD.
- **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 last evaluable tumor assessment.

Safety:

Part A:

Safety will be evaluated based on reported adverse events (AEs), clinical laboratory assessments, vital signs, and physical examinations. 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

DLTs will be assessed during the first 2 cycles of treatment (DLT Assessment Period). Safety data throughout the Part A will be evaluated based on reported AEs, clinical laboratory assessments, vital signs, and physical examinations as outlined in the body of the protocol.

Part B:

Safety will be evaluated based on reported AEs, clinical laboratory assessments, vital signs, and physical examinations. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) and graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events, Version 4.0 (NCI-CTCAE v4.0). Clinical laboratory toxicity will also be graded using NCI-CTCAE criteria v4.0.

Health Outcomes:

All Part B patients will undergo assessment for symptoms, quality of life, and health status using the LCSS, a self-administered, lung cancer-specific questionnaire instrument, and the EuroQol EQ-5D-5L. Patients will complete the instruments at baseline, at Cycle 2, thereafter at every other cycle, and at the 30-day short-term follow-up visit.

Immunogenicity:

Serum samples will be analyzed for antibodies to ramucirumab on all Part B patients at baseline, at specified time points during treatment (Cycle 1 Day 1 and Cycle 4 Day 1), and at the 30-day short-term follow-up visit. In the event of an infusion-related reaction (IRR), blood samples will be collected for both PK and immunogenicity analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

Pharmacokinetics:

Ramucirumab

Minimum ramucirumab concentration (C_{min}) and concentration at 1-hour post end of ramucirumab infusion (approximately maximum concentration [C_{max}]) in serum will be assessed on all Part B patients at specified time points during treatment. Additional blood samples will be collected at the 30-day follow-up visit and in the event of an IRR (as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event) to assess ramucirumab concentration in serum.

Exploratory:

Translational Research

CCI [redacted]

PFS2 (Part B)

PFS2 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.

Statistical Methods:

Part A:

Two cohorts of patients will be enrolled initially to assess the tolerability of 'ramucirumab 10 mg/kg every 2 weeks (q2w) + erlotinib 150 mg daily'. One cohort will include 6 patients enrolled from Japan and the other cohort will include 6 patients enrolled from North America and/or Europe. The Assessment Committee (AC, internal to Lilly and independent of JVCY study team), will be established for reviewing the DLT analysis and providing recommendation to the study team with regards to the starting dose of Part B.

- If DLT < 33% (0 or 1 DLT) from each of the cohorts during the first 2 cycles, move to Part B (Phase 3) using 'ramucirumab 10 mg/kg q2w + erlotinib 150 mg daily'.
- If DLT ≥ 33% (2 or more DLTs) in any of the 2 cohorts during the first 2 cycles, the ramucirumab starting dose in part B will depend on AC recommendation.

Part B:

Approximately 450 patients will be randomized through an interactive web response system (IWRS). At randomization, patients will be stratified as stated above in the study design.

An interim futility analysis (Analysis 3 above) was conducted at 114 investigator-assessed PFS events (data cutoff date 16 October 2017) and the IDMC recommended to continue the trial without modification. A nominal alpha <0.00001 was spent in order to maintain type-I error. Assuming an HR of 0.71, this design yields at 80% statistical power to detect superiority of the ramucirumab plus erlotinib arm over placebo plus erlotinib arm with the use of a 1-sided log-rank test and a type I error rate of 0.02499.

Efficacy:

The primary efficacy analysis will be performed in the intent-to-treat population, consisting of all randomized Phase 3 patients grouped according to treatment assigned at randomization. The primary analysis will compare the investigator-assessed PFS between the 2 treatment groups (erlotinib with vs. without ramucirumab) using the p-value from a stratified log-rank test based on the stratification factors. Additional analyses will be performed using the Kaplan-Meier method to estimate the PFS curves and rates, and the stratified Cox proportional hazards model will be used to estimate the PFS HRs and corresponding 95% CI.

Safety:

Part A (Phase 1b): Safety for the patients enrolled in Part A will be reviewed at the end of DLT period to assess the tolerability and safety of ramucirumab in combination with erlotinib. The number of patients who experience any DLT will be presented based on all DLT-evaluable patients (DLT population). DLT population is defined as all enrolled patients in Part A who either completed Cycle 2 or discontinued study treatment or study participation

before completing 2 cycles due to a DLT. The recommended dose of ramucirumab plus erlotinib for Phase 3 (Part B) will be decided based on the rules established in advance. Patients may continue study treatment after the DLT period until disease progression, development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision.

Part B (Phase 3): All safety summaries and analyses will be based on the Safety Population, defined as all randomized patients receiving any quantity of study treatment in Part B. Patients will be grouped according to treatment received in Cycle 1.

Interim safety analyses will be conducted by the IDMC several times during the course of the study. It will occur after approximately 50 treated patients have completed 3 cycles of treatment or discontinued from all study therapies due to any reasons prior to 3 cycles, thereafter at the other interim analyses, including, if not limited to, approximately twice a year.

Safety analyses will include the incidence and percentage of patients with at least 1 occurrence of a preferred term, by maximum CTCAE grade (v4.0) during the study treatment period or within 30 days after the decision is made to discontinue study treatment. Additionally, the following safety-related outcomes will be summarized:

- study treatment discontinuations due to AEs
- deaths during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- adverse events (AEs), treatment emergent AEs (TEAEs), serious adverse events (SAEs) during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- hospitalizations and transfusions during the study treatment period or within 30 days after the decision is made to discontinue study treatment

Health Outcomes:

For all Part B patients in the ITT population (censoring patients with no baseline data), time to deterioration (TtD) for each LCSS item is defined as the time from the date of randomization to the date of the first 15-mm increase from baseline (or censored at date of last assessment). TtD will be analyzed using the Kaplan-Meier method and treatments will be compared using a Cox regression model to generate an HR. LCSS data will also be analyzed with repeated measures. EQ-5D-5L data will be summarized descriptively for each assessment period.

Pharmacokinetics/Immunogenicity:

Pharmacokinetics

Ramucirumab: C_{min} and concentrations at 1 hour post end of infusion (approximately C_{max}) will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate.

Immunogenicity

Incidence of anti-ramucirumab antibodies will be tabulated. Correlation to ramucirumab drug level, activity, and safety will be assessed, as appropriate.

Exploratory Outcomes:

Translational Research

Translational research will be performed to analyze relevant biomarkers and to correlate them to clinical outcome.

PFS2

The time to PFS2 event will be analyzed with the Kaplan-Meier method by treatment groups, along with a summary of associated statistics (for example, median survival time and survival rates, including the corresponding two-sided 95% CIs).

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
AC	Assessment Committee
AE	adverse event Any new untoward medical occurrence or worsening of preexisting medical condition in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBI	Average Symptom Burden Index
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BIRC	Blinded Independent Radiological Review Committee
BP	blood pressure
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
collection database	A computer database where clinical trial data are entered and validated.

compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CR	complete response
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	Clinical Research Scientist
CT	computed tomography
cycle	A cycle in this trial is considered to be 2 weeks (14 days ± 3 days).
DCR	disease control rate
DCSI	Development Core Safety Information
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
***EGFR* mutation-positive**	*EGFR* mutation-positive includes exon 19 deletions or exon 21 (L858R) substitution mutations.
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been deemed eligible and have been assigned to a treatment. Part A (Phase 1b): Enroll Part B (Phase 3): Enroll/Randomize

enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FFPE	formalin-fixed paraffin embedded
FSH	follicle-stimulating hormone
GCP	good clinical practice
G-CSFs	granulocyte-colony stimulating factors
GI	Gastrointestinal
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ILD	interstitial lung disease
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

IRR	infusion-related reaction
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine contraceptive device
I.V.	intravenous(ly)
IWRS	interactive web-response system
LCSS	Lung Cancer Symptom Scale
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LIRC	Lilly Internal Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
MRI	magnetic resonance imaging
NCI-CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (v4.0 includes all of the minor versions [4.0x] generally typographical changes)
NSAIDs	non-steroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
patient	a study participant who has the disease or condition for which the study drugs are targeted
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2

PK	Pharmacokinetics
PR	partial response
PRO/ePRO	patient-reported outcome/electronic patient-reported outcome
PS	performance status
PT	Preferred Term
PTT	partial thromboplastin time
QoL	quality of life
randomize/ randomization	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria In Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SMD	Senior Management Designee
SpO_2	peripheral capillary oxygen saturation
study completion	This study will be considered complete after final analysis of overall survival is performed.
study drug, study treatment, or study therapy	ramucirumab/placebo and erlotinib, or any component of the combination
SUSARs	suspected unexpected serious adverse reactions

TEAE	treatment-emergent adverse event 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.
TPO	third-party organization
TtD	time to deterioration
TTP	time to progression
UA	Urinalysis
ULN	upper limits of normal
US	United States
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

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5. Introduction

5.1. Ramucirumab Background

One promising approach to the treatment of cancer is inhibition of angiogenesis. Investigators have identified a number of growth factors as positive regulators of angiogenesis, including members of the vascular endothelial growth factor (VEGF) family. VEGF-A is one of several related cytokines and is distinct in that it acts as an endothelial cell-specific mitogen and is the growth factor most extensively studied and most consistently up-regulated in conditions associated with angiogenesis. VEGF-A binds with high affinity to 2 structurally similar tyrosine kinase receptors, VEGF Receptor 1 and VEGF Receptor 2, which are both expressed on tumor vasculature. Inhibition of the VEGF Receptor 2 signaling pathway has been investigated via a number of approaches, including anti-VEGF antibodies, anti-VEGF Receptor 2 antibodies, and small molecule tyrosine kinase inhibitors (TKIs) targeting the receptor; these approaches have been shown to inhibit new blood vessel formation and tumor growth in a variety of animal models. Therapeutic agents that interfere with the function of VEGF and its receptors represent efficacious approaches to antiangiogenic and antitumor therapy.

Significant tumor growth inhibition has been observed with DC101, a rat monoclonal antibody (mAb) targeting murine VEGF Receptor 2, in multiple in vivo models across a broad range of doses (Skobe et al. 1997; Prewett et al. 1999; Bruns et al. 2000). CCI

The affinity of DC101 for murine VEGF Receptor 2 is approximately 6- to 9-fold lower than the affinity of ramucirumab for the human VEGF Receptor 2 (Zhu et al. 2003; data on file, notebook BE01241-012); however, clinical inhibition of cancer growth has frequently proven more difficult than inhibition of human tumor growth in many murine models.

Clinical activity was seen early in the development of ramucirumab. In Phase 1 studies, ramucirumab has been generally well tolerated and exhibited preliminary evidence of antitumor activity in patients with solid tumors. The maximum tolerated dose (MTD) of ramucirumab was identified as 13 mg/kg when given once weekly in the Phase 1 dose-escalation study, Study I4T-IE-JVBM (JVBM). Preliminary activity was observed across a range of doses, including the 2-mg/kg dose. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study, I4T-IE-JVBN (JVBN). No MTD was identified for every-2-week or every-3-week dosing; all dose regimens were well tolerated, and preliminary evidence of clinical efficacy was observed across a range of dose/schedule cohorts.

Ramucirumab (IMC-1121B, LY3009806, CYRAMZA™) is a human receptor-targeted mAb that specifically binds to VEGF Receptor 2. Phase 1 studies and initial Phase 2 studies investigating ramucirumab drug product (DP; hereafter referred to as ramucirumab) have provided information regarding safety and tolerability at clinically relevant doses, with preliminary evidence of clinical efficacy in a variety of human cancers.

Recently, a Phase 3 study (Study I4T-IE-JVBD; REGARD) indicated ramucirumab monotherapy following disease progression on initial therapy could improve overall survival (OS; median 5.2 months vs. 3.8 months, hazard ratio [HR] = 0.776, 95% confidence interval [CI]: 0.603, 0.998, p=0.0473) and progression-free survival (PFS; median 2.1 months vs. 1.3 months, HR = 0.483, 95% CI: 0.376, 0.620, p<0.0001) as compared with placebo and best supportive care (BSC) in patients with advanced gastric cancer. Consequently, in April 2014, ramucirumab (trade name CYRAMZA™) was approved by the US Food and Drug Administration (FDA) for use as a single-agent treatment in patients with advanced gastric cancer in the second-line setting.

RAINBOW (Study I4T-IE-JVBE) was a global, randomized, double-blind, placebo-controlled Phase 3 study that compared the use of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of patients with advanced (metastatic or locally advanced, unresectable disease) gastric or gastroesophageal adenocarcinoma following first-line platinum- and fluoropyrimidine-containing therapy with or without an anthracycline (epirubicin or doxorubicin). RAINBOW met its primary endpoint of OS and demonstrated a statistically significant and clinically meaningful improvement in OS and PFS in patients treated with ramucirumab plus paclitaxel compared with those treated with placebo plus paclitaxel. Additionally, consistent significant improvements were observed across all other efficacy endpoints: time to progression (TTP), objective response rate (ORR), and disease control rate (DCR).

REVEL (Study I4T-MC-JVBA) was a global, randomized, placebo-controlled, double-blind Phase 3 study that compared the use of ramucirumab plus docetaxel versus placebo plus docetaxel in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression after platinum-based chemotherapy. REVEL was the first study to demonstrate a statistically significant and clinically meaningful improvement in OS for a novel agent in combination with a standard chemotherapy in advanced NSCLC patients with progression after platinum-based chemotherapy.

ROSE (Study I4T-IE-JVBC) was a multicenter, global, randomized, double-blind study of ramucirumab with docetaxel v/s placebo and docetaxel in patients with previously untreated human epidermal growth factor receptor 2-negative, unresectable, locally recurrent or metastatic breast cancer. The PFS endpoint was not met. While the direction of the HR favored the ramucirumab arm, the p-value did not meet the prespecified two-sided 0.05 statistical significance level.

REACH (Study I4T-IE-JVBF) was a global, randomized, double-blind Phase 3 study of ramucirumab plus best supportive care compared to placebo and BSC as a second-line treatment in patients with hepatocellular carcinoma who have been previously treated with sorafenib in the

first-line setting. REACH did not meet its primary endpoint of OS; although the OS results favored the ramucirumab arm, they were not statistically significant. Encouraging single-agent ramucirumab activity was observed, with meaningful improvements in key secondary endpoints of PFS, ORR, and TTP.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ramucirumab may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the ramucirumab may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.2. Use of Tyrosine Kinase Inhibitors in NSCLC

Epidermal growth factor receptor (*EGFR*) TKIs (for example, erlotinib and gefitinib) significantly prolong PFS in patients with advanced *EGFR* mutation-positive NSCLC when compared with placebo or platinum-based chemotherapy doublets; hence, these *EGFR* TKIs have become the standard of care in countries where approved. The rationale for such treatment is supported by the results of studies such as BR.21 (Shepherd et al. 2005) and IPASS (Mok et al. 2009).

Despite currently available options in NSCLC, there continues to be a need for new first-line treatment options with improved efficacy, without adding significant toxicity for those patients with *EGFR* mutation-positive NSCLC. BR.21 and IPASS studies demonstrated a higher benefit with *EGFR* TKI in patients with *EGFR* mutation-positive NSCLC subgroup of study population (Shepherd et al. 2005; Mok et al. 2009). LUX-Lung3 study demonstrated prolongation of PFS with afatinib when compared with standard doublet chemotherapy in patients with *EGFR* mutations positive advanced lung adenocarcinoma (Sequist et al 2013). EURTAC study, a randomized, multicenter, open-label trial, compared erlotinib (n=86) to platinum-based doublet chemotherapy (n=87) in patients with *EGFR* mutation-positive metastatic NSCLC. The median PFS was 9.7 months (95% CI: 8.4, 12.3) in the erlotinib group, compared with 5.2 months (95% CI: 4.5, 5.8) in the standard chemotherapy group (HR = 0.37, 95% CI: 0.25, 0.54; p<0.0001) (Rosell et al. 2012). OPTIMAL study, a multicenter, open-label, randomized, Phase 3 study, compared erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive NSCLC. Median PFS was significantly longer in erlotinib-treated patients than in those on chemotherapy (13.1 months [95% CI: 10.58, 16.53] vs. 4.6 months [95% CI: 4.21, 5.42] months; HR = 0.16, 95% CI: 0.10, 0.26; p<0·0001) (Zhou et al. 2011).

Several preclinical studies have shown that the VEGF and *EGFR* pathways are known to be interrelated. For example, cells with an *EGFR* mutation express higher levels of VEGF and VEGF is down regulated by *EGFR* inhibition (Byers and Heymach 2007). In xenograft models, acquired resistance to cetuximab, a mAb targeting *EGFR*, was associated with increased VEGF levels and increased tumor angiogenesis in vivo (Viloria-Petit et al. 2001). These studies suggest that dual blockade of the VEGF and *EGFR* pathways would be more effective than either

approach alone and may also have activity in tumors with acquired resistance to *EGFR* inhibitors. However, it is unknown whether this finding extends to resistance to *EGFR* TKIs. In an experiment done in different cell lines, it was shown that dual inhibition of the *EGFR* and VEGF pathways did not only dramatically reduced endothelial cell proliferation but also abrogated primary and secondary resistance to *EGFR* TKIs (Naumov et al. 2009).

Recently reported results from several NSCLC clinical trials that include antiangiogenics in combination with TKIs have demonstrated that there is a significantly longer PFS and OS in the subgroup of patients with *EGFR* mutations, as compare to all-comers.

ATLAS was a second-line Phase 3 trial that randomized 1145 advanced NSCLC patients to receive bevacizumab plus placebo or bevacizumab plus erlotinib. The median PFS was 3.7 months in the placebo arm versus 4.8 months in the erlotinib arm (HR = 0.708; $p < 0.001$). The median OS was 13.3 versus 14.4 months, respectively, and was found to not be significant (HR = 0.917, $p = 0.5341$). In the overall NSCLC patient population, the addition of erlotinib to bevacizumab improved PFS but not OS. However, subgroup analyses demonstrated that patients with *EGFR* mutations (n=52) had a longer duration of PFS (HR = 0.44) in the erlotinib arm (n=27) versus the placebo arm (n=25) and OS results also showed a similar difference (HR = 0.46) (Johnson et al. 2013).

In the second-line Phase 3 BeTa trial, 636 patients with advanced NSCLC were randomized to receive erlotinib plus bevacizumab or erlotinib plus placebo. The primary endpoint of OS was not found to be significant (9.3 months in the bevacizumab arm vs. 9.2 months in the placebo arm; HR=0.97). Subgroup analysis of patients with *EGFR* mutation-positive status (n=30) suggested that OS favored bevacizumab (n=12; median OS Not Reached [22.6 - Not Reached]) in patients with *EGFR* mutations as compared to the control arm (n=18; 20.2 months [95% CI: 16.4 - 31.1]) (HR = 0.44 [95% CI: 0.11 - 1.67]); however, the results should be interpreted with caution because of the small number of patients and the 95% CI for the HR were wide and overlapping (Herbst et al. 2011).

In the first-line Phase 2 JO25567 study, 154 Japanese patients with *EGFR* mutation-positive NSCLC were randomized 1:1 to receive erlotinib with or without bevacizumab. Median PFS was 16.0 months in the erlotinib in combination with bevacizumab arm and 9.7 months in the erlotinib arm (HR, 0.54; 95% CI: 0.36, 0.79; log-rank $p = 0.0015$). In the *EGFR* exon 19 deletion subgroup, the median PFS in the erlotinib plus bevacizumab arm was 18.0 months and in the erlotinib arm was 10.3 months. In the L858R subgroup, median PFS was 13.9 months for the combination and 7.1 months for erlotinib alone. The DCR was 99% in the bevacizumab plus erlotinib arm versus 88% in the erlotinib arm (Kato et al. 2014; Seto et al. 2014).

In these 3 clinical trials, the combination of bevacizumab and erlotinib in patients with advanced NSCLC demonstrated that this regimen (antiangiogenic agent + *EGFR* TKI) was well tolerated and the safety profile was acceptable.

5.3. Rationale for Selection of Ramucirumab Dose Regimen (10 mg/kg on Day 1 Every 2 Weeks)

Ramucirumab administered at 10 mg/kg on Day 1 on an every-2-week schedule will be examined in both portions of this study. This dose regimen of ramucirumab is different compared to the REVEL study. In REVEL, conducted in a second-line NSCLC setting, ramucirumab was administered at a dose of 10 mg/kg every 3 weeks. Exposure-response (efficacy/safety) findings from Phase 3 ramucirumab trials, REGARD, RAINBOW, and REVEL, and pharmacokinetic (PK) simulations were used to guide the dose selection in this JVCY study.

Efficacy

Exposure-efficacy response analyses performed on data obtained from REGARD, RAINBOW, and REVEL demonstrated that an increase in exposure is associated with improvement in efficacy in terms of both OS and PFS.

The following 4 exposure measures were tested, and the findings were consistent for all of them:

- minimum concentration after first dose administration,
- minimum concentration at steady state ($C_{min,ss}$),
- maximum concentration at steady state, and
- average concentration at steady state.

In REGARD (n=72 [number of patients with evaluable PK data]), patients with greater-than-median ramucirumab exposure demonstrated longer OS and PFS and significantly better treatment effects (smaller HR) as compared to patients with less than median ramucirumab exposure.

In RAINBOW (n=321 [number of patients with evaluable PK data]), patients with ramucirumab exposure greater-than-median (in the 3rd and 4th quartile groups) were associated with longer OS and PFS and significantly better treatment effects (smaller HR) as compared to patients with ramucirumab exposure lower than median (in the 1st and 2nd quartile groups).

In REVEL (n=376 [number of patients with evaluable PK data]), significantly longer OS and PFS favoring ramucirumab were generally observed in the highest exposure quartile group (the 4th group), while marginal increases on OS and PFS were observed in other exposure quartile groups.

Safety

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in Phase 1 Study JVBM. An MTD for weekly dosing was identified as 13 mg/kg every week. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study JVBN). All dose regimens in Study JVBN were well tolerated and no MTD was identified in this study.

The same ramucirumab dose regimen (8 mg/kg every 2 weeks) was used in REGARD and RAINBOW. REGARD demonstrated a well-tolerated safety profile in the gastric cancer

monotherapy setting. Due to the low incidence of hypertension and neutropenia, no safety-exposure relationship was identified. In RAINBOW, ramucirumab in combination with paclitaxel was also well tolerated in patients with gastric cancer, with manageable AEs. An increasing ramucirumab exposure was correlated with increased incidence of Grade ≥3 hypertension, neutropenia, and leukopenia. Of note, there were no Grade 4 or 5 hypertension events in RAINBOW. Hypertension was managed primarily by the use of standard antihypertensive medication. Neutropenia and leukopenia are known risks with paclitaxel treatment. Overall, the safety profile of ramucirumab plus paclitaxel was largely consistent with the safety profiles of the individual treatment components and the combination revealed no unexpected safety findings.

The safety profile observed in REVEL was consistent with the safety profile for ramucirumab established in gastric cancer (REGARD and RAINBOW), as well as the established safety profile for docetaxel, and was manageable in the NSCLC population. An increasing ramucirumab exposure was correlated with increased incidence of Grade ≥3 hypertension and febrile neutropenia. Of note, there were no Grade 4 or 5 hypertension events in REVEL. Hypertension was managed primarily by the use of standard antihypertensive medication. In addition, incidence of febrile neutropenia appeared to reach plateau at the third exposure quartile.

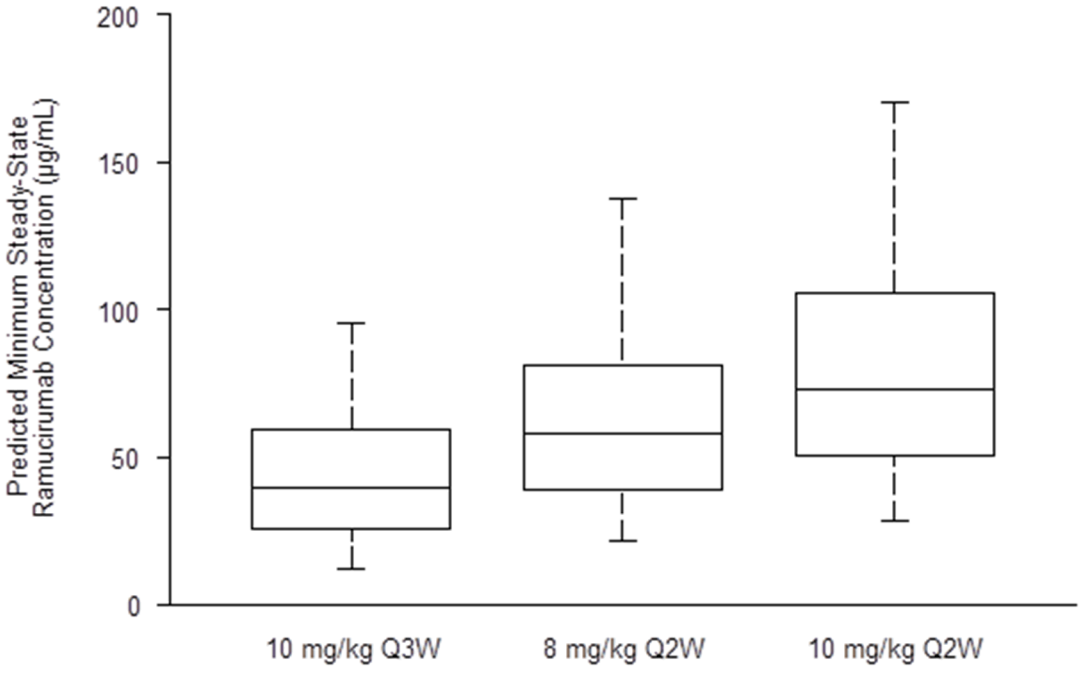
These exposure-efficacy and exposure-safety data indicate that there is an opportunity to further enhance efficacy of ramucirumab while maintaining an acceptable safety profile. Based on PK simulation, a dose regimen of 10 mg/kg on Day 1 every 2 weeks was selected for Study JVCY for the following reasons:

- This dose regimen may produce $C_{min,ss}$ that is higher than the 4th $C_{min,ss}$ quartile obtained from 10 mg/kg every-3-week regimen in REVEL, in at least 70% of the patient population (Figure JVCY.1) and is therefore expected to produce better clinical efficacy outcomes relative to the 10-mg/kg every-3-week regimen.
- It is expected that ramucirumab-related AEs in the NSCLC indication may not be significantly increased using the selected ramucirumab dose of 10 mg/kg every 2 weeks, since the selected dose for Study JVCY is still approximately 60% lower than the maximum tolerated weekly dose identified in the Phase 1 dose-escalation study, Study JVBM (13 mg/kg weekly).
- The ramucirumab exposure distribution of the 10-mg/kg every-2-week regimen significantly overlaps with that of the 8-mg/kg every-2-week regimen studied in REGARD and RAINBOW.
- In addition, an early safety lead-in portion of the study (Part A described in Section 8.1.1) will be performed to mitigate any potential risk, since the selected ramucirumab dosing schedule and combination therapy for Study JVCY are different from what was studied in REVEL.

Part A (Phase 1b) is being conducted to assess the safety and tolerability of ramucirumab administered at 10 mg/kg every 2 weeks in combination with erlotinib administered daily at 150 mg. In the event that dose-limiting toxicities (DLTs) are reported to occur in this patient population at the prescribed ramucirumab dose, the Phase 3 starting dose could be determined to

be 8 mg/kg every 2 weeks, depending on the nature of the DLTs and the recommendations from the Assessment Committee (AC). If that is the case, the recommendation for the dosing level may be modified for the Phase 3 part of the trial.

This early safety assessment will ensure the higher ramucirumab dose regimen of 10 mg/kg every 2 weeks can still maintain an acceptable safety profile in combination with erlotinib in NSCLC patients. Based upon the review of the early safety analysis, study modifications may be warranted.



Box plots depict the 5th, 25th, 50th, 75th, and 95th percentiles.

Abbreviations: $C_{min,ss}$ = minimum concentration at steady state; Q = every; W = week. Box plots depict the 5th, 25th, 50th, 75th, and 95th percentiles calculated from 1000 simulation iterations.

Figure JVCY.1. Predicted $C_{min,ss}$ following different dose regimens.

In summary, the dosing regimen of ramucirumab 10 mg/kg on Day 1 every 2 weeks in combination with erlotinib is anticipated to produce a favorable benefit-risk profile in patients with *EGFR* mutation-positive metastatic NSCLC.

The Assessment Committee reviewed the safety data for the Phase 1b portion (Part A) and recommended to initiate the randomized Phase 3 portion of the study (Part B) with ramucirumab at 10 mg/kg every 2 weeks.

6. Objectives

6.1. Primary Objective

The study is divided into 2 parts. Part A is the Phase 1b portion of the trial and Part B is the Phase 3 portion of the trial. Once the Assessment Committee (AC) has completed the DLT assessment for Part A, the outcome of those results will confirm the Part B dose and Part B enrollment will proceed. 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 *EGFR* mutation-positive metastatic NSCLC.

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

6.2. Secondary Objectives

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 (using Lung Cancer Symptom Scale [LCSS] and EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L])

6.3. Exploratory Objectives

The exploratory objectives of Part B of the study are as follows:

- to assess the association between biomarkers and clinical outcome.
- to compare progression-free survival 2 (PFS2) between treatment arms.

The exploratory objectives in only the gefitinib/osimertinib cohort in Addendum 9, conducted in the East-Asian region including Japan, are as follows:

- 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
- to evaluate the efficacy and safety of ramucirumab when administered in combination with osimertinib in patients with T790M-positive metastatic NSCLC whose disease has progressed on ramucirumab plus gefitinib in this study, in the East-Asian region including Japan
- to assess PK and immunogenicity of ramucirumab
- to assess patient-reported outcomes (using LCSS and EQ-5D-5L)

There are no secondary or exploratory objectives planned for Part A in this study.

7. Study Population

The study will enroll male or female patients, 18 years of age or older (20 years of age or older in Japan and Taiwan), who are diagnosed with *EGFR* mutation-positive (exon 19 deletions or exon 21 [L858R] substitution mutations) metastatic NSCLC who will be treated for their disease for the first time. Patients with known T790M mutation will be excluded from study participation.

All patients meeting the eligibility requirements will be considered for enrollment regardless of race, religion, or gender. The investigator or the Sponsor will not grant exceptions to eligibility criteria.

Patients who do not meet the criteria for participation within the 21-day screening period (screen failure) may be rescreened. Note that repeating laboratory tests during the 21-day screening period does not constitute rescreening. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the 21-day screening period. If a repeat screening laboratory value meets eligibility, it is recommended that the test is rechecked to confirm stability.

Patients may be considered for rescreening after discussion with the Medical Monitor or designee. Individuals may be rescreened up to 3 times. Each time rescreening is performed, the patient must sign a new informed consent form (ICF) and will be assigned a new identification number. In addition, laboratory criteria eligibility must be confirmed with new labs for each new re-screening period. The maximum duration of time between re-screenings should be 28 days.

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

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria prior to enrollment:

[1] The patient has given their written informed consent to participate in the study and is amenable to compliance with protocol schedules and testing.

[2] Males or females: aged ≥18 years, ≥20 years in Japan and Taiwan at the time of study entry.

[3] The patient has cytologically or histologically confirmed diagnosis of Stage IV NSCLC as defined by the American Joint Committee on Cancer Staging Criteria for Lung Cancer (AJCC 7th edition 2009) (Edge et al. 2009).

- Patients with recurrent metastatic disease are permitted to enter the study as long as the adjuvant or neo-adjuvant therapy was completed at least 12 months prior to the development of metastatic disease. However, prior adjuvant or neo-adjuvant therapy is not required.

[4] The patient must be eligible for first-line treatment with erlotinib based on previously documented evidence of tumor that has *EGFR* exon 19 deletion or exon 21 (L858R) substitution mutation.

[5] The patient consents to submit an archived formalin-fixed paraffin embedded (FFPE) Stage IV NSCLC tissue sample for assessment of biomarkers unless restricted per local regulations. Archived NSCLC tissue samples derived from other than Stage IV disease may be acceptable, based on approval by Lilly CRP; For patients who do not submit Stage IV disease tissue samples, a plasma sample for disease characterization is required unless restricted by local regulations. Once consented, availability of an adequate tumor tissue sample or any necessary plasma sample is required for study eligibility.

Note: This tissue sample collection is not mandatory for patients enrolled in Part A.

[6] The patient has at least one or more measurable lesion attributed to NSCLC at the time of study entry, documented by computed tomography (CT) scan or magnetic resonance imaging (MRI), as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Attachment 7).

[7] The patient is able to swallow tablets.

[8] The patient has Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at study entry (Attachment 5).

[9] Prior radiation therapy is allowed:

- For local palliation or prevention of symptoms (such as pain, bleeding, or obstruction) where at least 7 days have elapsed from last radiation treatment prior to enrollment (and provided that 25% or less of total bone marrow had been irradiated).
- If the patient has completed palliative thoracic radiotherapy 28 days before enrollment.

[10] The patient has adequate hematologic and organ function, defined as:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, hemoglobin ≥9.0 g/dL, and platelets $\geq 100 \times 10^9$/L
- Total bilirubin less than or equal to the upper limit of normal value (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN, or ≤5 x ULN if the transferase elevation is due to liver metastases
- The patient has a calculated creatinine clearance (CrCl) ≥50 mL/min per the Cockcroft-Gault formula (see Attachment 6). If the value is below this parameter, then a 24-hour urine collection should be done to rectify or ratify the estimated creatinine clearance.
- The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 or prothrombin time (PT) ≤1.5 x ULN, and partial thromboplastin time (PTT/aPTT) ≤1.5 x ULN. Patients who are on low molecular

weight heparin (LMWH) are eligible; whereas, patients receiving warfarin should be switched to LMWH as per institutional guidelines, and should have achieved stable coagulation profile prior to enrollment. Note that a patient with a venous thrombosis is permitted to enroll provided that the patient is clinically stable, asymptomatic, and adequately treated with anticoagulants at the discretion of the investigator.

- The patient's urinary protein is ≤1+ on dipstick or routine urinalysis (UA). If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <1000 mg (< 1 g) of protein in 24 hours to allow participation in the study.

[11] Eligible patients of reproductive potential (both sexes) must agree to use adequate contraceptive methods (hormonal or barrier methods) during the study period and for at least 12 weeks after the last dose of study therapy. Eligible female patients of childbearing potential must have a negative serum pregnancy test within 7 days before enrollment.

- A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.
- Men who are sterile (including vasectomy confirmed by post-vasectomy semen analysis) or who agree to use a reliable method of birth control and to not donate sperm during the study and for at least 12 weeks following the last dose of ramucirumab or country requirements, whichever is longer.
- Women who agree to use a reliable method of birth control, or are not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or due to menopause, are eligible. A "menopausal woman" is a woman meeting either of the following criteria:
  - Spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy).
  - Spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level >40 mIU/mL.

[12] The patient has resolution to Grade ≤1 (except alopecia), by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4.0, of all clinically significant toxic effects of prior locoregional therapy, surgery, or other anticancer therapy.

[13] The patient has a life expectancy of at least 3 months and, in the judgment of the investigator, will be able to complete at least 2 cycles of treatment.

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria prior to enrollment:

[14] The patient has known T790M EGFR mutation.

[15] The patient has known leptomeningeal carcinomatosis, uncontrolled/unstable spinal cord compression, or brain metastases.

[16] The patient has undergone major surgery within 28 days or subcutaneous venous access device placement within 7 days prior to enrollment. Furthermore, any patient with postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months will be excluded.

[17] The patient has pleural effusion, pericardial fluid, or ascites requiring drainage every other week or more frequently.

[18] The patient has superior vena cava syndrome.

[19] The patient has clinically relevant congestive heart failure (New York Heart Association [NYHA] II-IV; see Attachment 6) or symptomatic or poorly controlled cardiac arrhythmia.

[20] The patient has a serious illness or medical condition that would compromise their safety or impair their ability to comply with the protocol's requirements, including, but not limited to, the following:

- Severely immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive
- Hepatic Impairment:
  - Severe liver cirrhosis Child-Pugh Class B (or worse)
  - Cirrhosis with a history of hepatic encephalopathy
  - Clinically meaningful ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.
  - Patients with a history of hepatorenal syndrome should also be excluded.
- Previous or concurrent malignancy except for basal or squamous cell skin cancer (non-melanoma) and/or pre-invasive carcinoma of the cervix, mucosal gastrointestinal (GI) or uterine carcinoma, or other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to enrollment.
- Known allergy or hypersensitivity reaction to any of the treatment components.
- The patient has a known history of active drug abuse.

- History of uncontrolled heredity or acquired thrombotic disorder.
- The patient has had a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to enrollment.
- Uncontrolled metabolic disorders or other nonmalignant organ or systemic diseases or secondary effects of cancer that induce a high medical risk and/or make assessment of survival uncertain.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient ineligible for entry into this study.

[21] The patient has uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg despite standard medical management.

[22] The patient is being treated with CYP3A4 inducers or strong inhibitors (see Attachment 9 for the list).

[23] The patient is receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs; for example, indomethacin, ibuprofen, naproxen, or similar agents) or other antiplatelet agents (for example, clopidogrel, ticlopidine, dipyridamole, or anagrelide) within 7 days prior to first dose of study treatment. Aspirin use at doses up to 325 mg/day is permitted.

[24] The patient has a history of gross hemoptysis (defined as the presence of ≥ 1/2 teaspoon of gross blood) within 2 months prior to enrollment.

[25] The patient has significant bleeding disorders, vasculitis, or experienced Grade 3/4 GI bleeding within 3 months prior to enrollment.

[26] The patient has radiologically documented evidence of major blood vessel invasion or encasement by cancer.

[27] The patient has radiographic evidence of intratumor cavitation, regardless of tumor histology.

[28] The patient has a history of GI perforation, peptic ulceration, diverticular disease, and/or fistulae within 6 months prior to enrollment.

[29] The patient has a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (for example, hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

[30] The patient has experienced any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment.

[31] The patient has any known significant ophthalmologic abnormalities of the surface of the eye. The use of contact lenses is not recommended during the study.

[32] The patient requires daily use of prescription or over-the-counter proton pump inhibitors (such as Nexium® [esomeprazole magnesium] or Prilosec® [omeprazole]).

[33] The patient is currently enrolled in a clinical trial involving an investigational product (IP) or non-approved use of a drug or device (other than the study drugs used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Patients participating in surveys or observational studies are eligible to participate in this study.

[34] The patient received his/her last dose of nonapproved use of a drug or device in a clinical trial within 30 days before the date of enrollment.

[35] The patient had any prior anticancer therapy for Stage IIIB/IV NSCLC (for example, chest radiotherapy, systemic chemotherapy [including TKIs], immunotherapy, or biological therapy).

- Patients who received adjuvant therapy are permitted to enter the study as long as the adjuvant therapy was completed at least 12 months prior to the development of recurrent metastatic disease. However, prior adjuvant therapy is not required.

[36] The patient has any evidence of clinically active interstitial lung disease. Asymptomatic patients with chronic, stable, radiographic changes are eligible.

[37] The patient has preexisting idiopathic pulmonary fibrosis as evidenced by CT scan/X-ray at baseline; have or had any disease of acute lung injury, idiopathic pulmonary fibrosis, or pneumoconiosis evident on an X-ray; have or had any disease of radiation pneumonia or drug-induced pneumonia.

[38] The patient has $SpO_2 < 94$ (room air).

[39] The patient is pregnant or breastfeeding.

7.2.1. Rationale for Exclusion of Certain Study Candidates

The exclusion criteria have been carefully selected by the Sponsor to ensure their ethical and scientific acceptability, and to help establish specificity of the patient population for both efficacy and safety analyses.

Exclusion Criteria [16], [20], [21], [23], [24], [25], [26], [27], [28], [29], and [30] are written for patient safety based on what is known about the side effect profile of an antiangiogenic agent such as ramucirumab. Exclusion Criteria [31] and [36] are written for patient safety based on what is known about the side effect profile of TKI such as erlotinib. Exclusion Criteria [17], [18], and [19] are written in the interest of patient's overall safety. Exclusion Criteria [14], [15], [35], [37], and [38] are written to maintain the specificity of the patient population intended for

enrollment and analyses. Exclusion Criteria [22], [32], [33], and [34] are written to ensure that both erlotinib and ramucirumab are novel treatments, so that treatment safety and efficacy are not confounded by prior exposure and known treatment failure. Exclusion Criterion [39] is based on the lack of experience with use of ramucirumab among women who are either pregnant or lactating.

7.3. Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients. All patients who discontinue, regardless of whether or not they received study treatment, will have procedures performed as shown in the Study Schedule (Attachment 1 or Attachment 2).

Patients who are discontinued from the study treatment will have follow-up procedures performed as shown in the Study Schedule (Attachment 1 or Attachment 2).

If a patient withdraws informed consent from continuing in the study participation, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal, consistent with the original authorization.

7.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the Sponsor must be notified. If the Sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without study treatment. Inadvertently enrolled patients may be maintained in the study and on study drugs when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study treatment if the Lilly CRP does not agree with the investigator's determination. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

The patient may continue to receive study treatment if all of the following conditions are met:

- The Lilly CRP or clinical research scientist (CRS) determines that no effective alternative therapy exists
- The Lilly CRP or CRS and the investigator agree there is no safety concern meriting discontinuance of study drugs, and
- In the opinion of the investigator, the patient is receiving benefit.

7.3.2. Discontinuation of Study Treatment

Patients who discontinue study treatment will continue to be followed for survival until study completion.

7.3.2.1. Ramucirumab/Placebo

The investigator will discontinue a patient from ***ramucirumab/placebo*** for any of the following reasons:

- The patient requests to be withdrawn from ramucirumab/placebo ('Patient Decision to Discontinue' or 'Patient Withdraws' per electronic case report form [eCRF]).
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient) considered by the investigator to be attributed to ramucirumab/placebo.
- Any Grade 4 nonhematologic toxicity considered by the investigator to be attributed to ramucirumab/placebo (Section 9.4.2.1.2).
- A Grade 3 or 4 infusion-related reaction (IRR) that in the opinion of the investigator is considered to be attributed to ramucirumab/placebo (see Section 9.4.2.1.2.1).
- Grade 4 hypertension or persistent/recurrent hypertension that is refractory (see Section 9.4.2.1.2.2).
- A Grade 3 or 4 arterial thromboembolic event (ATE; see Section 9.4.2.1.2.3.1).
- A Grade 3 or 4 venous thromboembolic event (VTE) that is considered by the investigator to be life-threatening, or symptomatic and cannot be adequately treated by anticoagulation therapy (see Section 9.4.2.1.2.3.2).
- Any pulmonary embolism/deep vein thrombosis that intensifies during anticoagulant therapy
- A Grade 3 or 4 bleeding or hemorrhagic event (see Section 9.4.2.1.2.4)
- Hemoptysis that exceeds the severity grade present at baseline (see Section 9.4.2.1.2.4)
- Event of a GI perforation (see Section 9.4.2.1.2.5)
- A confirmed occurrence of a gastrointestinal or non-GI fistula (see Section 9.4.2.1.2.6)
- Proteinuria level is >3 g/24 hours, or there is a third occurrence of proteinuria ≥2 g/24 hours, or the proteinuria level does not return to <2 g/24 hours within 2 weeks of dose delay (see Section 9.4.2.1.2.7 and proteinuria algorithm in Attachment 10)
- Any Grade 3-4 events consistent with congestive heart failure (CHF; see Section 9.4.2.1.2.8)
- A persistence of impaired wound healing (for example, wounds could generate significant morbidity to the patient) greater than 28 days after suspension of ramucirumab/placebo therapy (see Section 9.4.2.1.2.9)

- A new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis (see Section 9.4.2.1.2.10)
- The diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS) is confirmed (see Section 9.4.2.1.2.11).
- Any event that would warrant the dose of ramucirumab/placebo to be modified for a higher number of times then permitted in the protocol (see Section 9.4.2.1.2).
- Any event that would warrant ramucirumab/placebo to be held for >2 consecutive cycles (missing 2 consecutive doses). In situations where >2 consecutive doses have been missed, events related to the missed doses have resolved, and there is evidence of ongoing disease control, continuation of ramucirumab/placebo may be considered and must be discussed with the Sponsor Physician or designee.

Patients who are discontinued from ramucirumab/placebo will continue to be in the study, and may be further treated with ***erlotinib***.

7.3.2.2. Erlotinib

The investigator will discontinue a patient from ***erlotinib*** for any of the following reasons:

- The patient requests to be withdrawn from erlotinib ('Patient Decision to Discontinue' or 'Patient Withdraws' per eCRF).
- The investigator decides that the patient should be discontinued from erlotinib, according to the local practice and approved product information.
- If the patient does not tolerate at least the 50-mg daily erlotinib dose.
- If the investigator decides to discontinue erlotinib therapy, due to the patient having had a 2-week delay in this therapy because of an erlotinib-related toxicity (an additional 1-week delay may be permitted per Section 9.4.2.2.1).
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient) that in the opinion of the investigator is considered to be attributed to erlotinib.
- If interstitial lung disease is confirmed. The patient should be treated appropriately.
- If liver function tests demonstrate severe abnormal laboratory results (Table JVCY.6).
- If the patient experiences GI perforation; severe bullous, blistering, or exfoliation skin conditions; corneal perforation or sever ulceration.
- Patient compliance with erlotinib will be assessed at each visit (refer to Section 9.7). Patients who are consistently out of the compliance range may be discontinued. A Lilly representative should be contacted upon the second instance of treatment noncompliance.

Patients who are discontinued from erlotinib will continue to be in the study and may be further treated with ***ramucirumab/placebo***. Conditions that might cause erlotinib discontinuation should be treated appropriately per standard of care. In addition, discontinuation of erlotinib in the setting of AEs and guidelines for treatment management are detailed in Section 9.4.2.2.

7.3.2.3. All Study Treatment

The investigator will withdraw a patient who continues in the study from ***all study treatment*** (ramucirumab/placebo plus erlotinib) for the following reasons:

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator decision:
    - The investigator decides that the patient should be discontinued from the study treatment.
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study treatment occurs prior to introduction of the new agent.
- Patient decision:
    - The patient requests to be withdrawn from the study treatment. If the patient withdraws consent to treatment, he or she may still enter short- and/or long-term follow-up if follow-up consent is not withdrawn. It should be clarified with the patient and documented in the patient's file whether follow-up information on tumor assessment, antitumor therapies, and survival can be still obtained, and if so, to what extent. Investigations scheduled for the post-discontinuation follow-up period should be carried out as much as possible.
- Sponsor decision:
    - Lilly stops the study or stops patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Radiographic progressive disease or symptomatic progressive disease (PD). If patient experiences symptomatic deterioration and progression is suspected, every attempt should be made to confirm PD radiographically as per RECIST criteria prior to/soon after the patient's discontinuation from the study treatment.
- If a patient deteriorates to an ECOG PS of ≥3, all study treatments are to be discontinued. In case of PS deterioration of <3, disease progression should be ruled out.
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient) or any study treatment-related event that is deemed life-threatening, regardless of NCI-CTCAE, v4.0 grade, and that in the opinion of the investigator cannot be attributed to a specific study agent. For example:
    - In case of an SAE or a clinically significant laboratory value, appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately in the event of an SAE (Section 10.3).

  - An intercurrent illness or changes in the patient's condition that render the patient unsuitable for further treatment.

- Occurrence of pregnancy during treatment.
- Patient's significant noncompliance with this study protocol. Patients who miss appointments shall be contacted by site personnel to determine the reason for the missed appointment and to try to reschedule the appointment. The date(s) the patient was contacted and the type of contact used should be recorded in the study documentation.
- The patient in Part A experiences a DLT in Cycle 1 or Cycle 2 (see Section 9.4.1).

After termination of study treatment, the patient will be treated as clinically indicated by the investigator or referring physician. All patients should be followed until resolution or stabilization of any SAE or study drug-related toxicities resolve, stabilize, return to baseline, or are deemed irreversible.

If a patient is discontinued from ***all study treatment***:

- The reason(s) for discontinuation should be documented in the patient's medical record and eCRF.
- A follow-up evaluation should be performed 30 days (±3 days) after the decision is made to discontinue study treatment, as described in the Study Schedule (Attachment 1 or Attachment 2). In addition, patients with unresolved study treatment-related toxicities will be followed at regularly scheduled intervals (as determined by the investigator) until these toxicities resolve, stabilize, return to baseline, or are deemed irreversible.
- For patients who discontinue for reasons other than PD, radiographic assessments should continue as scheduled (every 6 weeks [±7 days] following the first dose of study drug, and after 72 weeks while on study, imaging will be performed every 12 weeks [±7 days]) until objective radiographic evidence of PD.

Follow-up evaluations should be performed as described in Attachment 1 or Attachment 2. All patients will be followed for survival at regularly scheduled intervals (every 3 months ± 14 days), for as long as the patient remains alive, or until study completion, whichever comes first, as defined in Section 8.1.2.3.

7.3.3. Discontinuation from the Study Participation

Patients will be discontinued from the study in the following circumstances:

- The investigator decides that the patient should be discontinued from the study.
- The patient becomes pregnant during the study. See Section 10.3.1 regarding reporting requirements on fetal outcome and breastfeeding.
- The patient or the patient's designee (for example, parents or legal guardian) requests that the patient be withdrawn from the study.
- Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.4. Patients Who Are Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow. Each failed attempt to contact the patients should be documented in the source document.

Site personnel, or an independent third party, will attempt to collect the vital status (that is, alive or dead) for all enrolled patients who are lost to follow-up, including enrolled patients who do not receive study treatment, within legal and ethical boundaries. Site personnel, or an independent third party, may search public sources for vital status information. If the patient's vital status is determined, the vital status will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

7.3.5. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges discontinuation of study site participation necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.6. Discontinuation of the Study

The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study I4T-MC-JVCY (JVCY) is a Phase 1b/3 design to treat previously untreated patients with *EGFR* mutation-positive metastatic NSCLC.

The Phase 1b part (Part A) of Study JVCY is single-arm and open-label, where the objective is to assess the safety and tolerability of the recommended Phase 3 (Part B) dose of ramucirumab administered at 10 mg/kg every 2 weeks in combination with daily oral dose of erlotinib at 150 mg/day. In Part A, the target enrollment is 12 patients, where patients will be enrolled into 1 of 2 cohorts: Cohort 1 will include 6 patients from Japan and Cohort 2 will include 6 patients from North America and/or Europe. Part A patients may be enrolled concurrently into selected cohorts.

Part B will proceed after the completion of the DLT assessment in Part A.

The Phase 3 part (Part B) of Study JVCY is a multicenter, randomized, double-blind study that will compare the efficacy and safety of treatment with erlotinib (150 mg daily) plus ramucirumab (10 mg/kg every 2 weeks) (**Arm A**) versus erlotinib (150 mg daily) plus placebo (10 mg/kg every 2 weeks) (**Arm B**) in previously untreated patients with *EGFR* mutation-positive metastatic NSCLC.

The ramucirumab/placebo starting dose for Part B will be 10 mg/kg every 2 weeks unless, during Part A, the combination therapy (ramucirumab 10 mg/kg every 2 weeks + erlotinib 150 mg every day) is not tolerated. Following DLT review in Part A, the AC may recommend adopting 8 mg/kg every 2 weeks as starting dose for ramucirumab in Part B. After the AC recommendations are made, a notification letter will be sent to investigative sites to inform the starting dose for ramucirumab for Part B. Refer to Section 9.2.2 for preparation of first and subsequent dosing details.

Approximately 450 patients will be randomized evenly between the 2 treatment arms using the following stratification factors:

- *EGFR* mutation (exon 19 deletion vs. exon 21 [L858R] substitution mutation)
- Gender (male vs. female)
- Region (East Asia vs. other)
- *EGFR* testing method (*Therascreen*® [Qiagen] and *Cobas*® [Roche] vs. other PCR and sequencing-based methods)

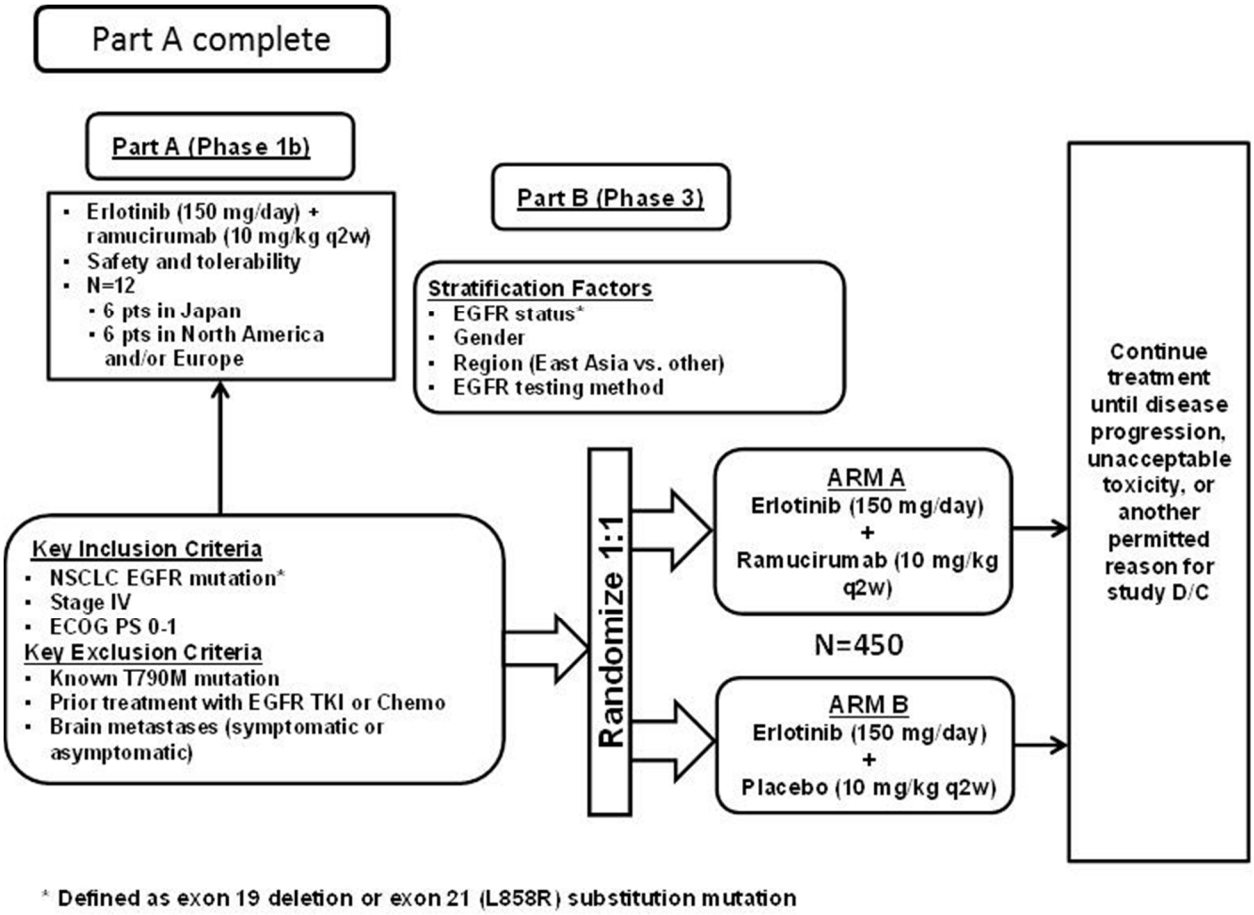
The chosen stratification factors have been identified as variables with the potential influence on the primary objective of PFS. The patients with *EGFR* mutations benefit from targeted therapy whether it is exon 19 deletion or exon 21 substitution mutation; however, the degree of benefit may differ based on the type of mutation (Seto et al. 2014). Gender is linked with prognosis; therefore, this is included as a stratification factor (Ou et al. 2009; Siddiqui et al. 2010). The other stratification factor included in the study is region due to the potential regional heterogeneity of standards of care. *EGFR* testing methods are considered as one of the key

stratification factors given that the existing heterogeneity in testing methods may increase the enrollment of patients with false positive *EGFR* mutations.

Treatment in Parts A and B will continue until disease progression, unacceptable toxicity, or another permitted reason for study discontinuation. The study treatment in this protocol is considered ramucirumab in combination with erlotinib, or any component of the combination.

The duration of a cycle in this study is defined as 2 weeks (14 days ±3 days). The windows during the treatment cycles and at other times defined in this protocol allow for the accommodation of scheduling conflicts, such as holidays, weekends, bad weather, or other unforeseen circumstances, and will not be considered a protocol deviation.

Figure JVCY.2 illustrates the study design.



Abbreviations: D/C = discontinuation; ECOG PS = Eastern Cancer Oncology Group performance status; *EGFR* = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; q2w = every 2 weeks.
Note: If, in Part A, the combination therapy is not tolerated and the dose for ramucirumab is determined to be 8 mg/kg every 2 weeks based on the Assessment Committee recommendation, then the ramucirumab/placebo dose level for Part B will start at 8 mg/kg every 2 weeks. Patients in Part A will continue to receive study treatment until disease progression, unacceptable toxicity, or other reasons for discontinuation; however, efficacy or survival data will not be collected.
Note: On 16 December 2015, the Assessment Committee reviewed the safety data for the Phase 1b portion (Part A) and recommended to initiate the randomized Phase 3 portion of the study (Part B) with ramucirumab at 10 mg/kg every 2 weeks.

Figure JVCY.2. Illustration of study design for Clinical Protocol I4T-MC-JVCY.

Terms used to describe the periods during the study are defined below:

- **Baseline Period:** begins when the ICF (study entry) is signed and ends at the first dose of study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first dose of study treatment and ends at study completion. The study period does not include the continued access period.

- **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.
  - ***DLT Assessment Period for Part A:*** begins at the first dose of study treatment and ends at the end of the second cycle.
- **Post-discontinuation Follow-Up Period**: begins the day after the patient and the investigator agree that the patient will no longer continue any study treatment.
  - ***Short-term follow-up*** 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). The short-term follow-up visit occurs at or near the end of the follow-up period (±3 days).
  - ***Long-term follow-up*** (Part B only) begins the day after short-term follow-up is completed, and imaging continues to be collected every 6 weeks (± 7 days); after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days) until PD. For patients who discontinue study treatment for reasons other than radiographically documented PD, tumor response will continue to be evaluated according to the protocol schedule, except when not feasible in the opinion of the investigator due to patient's clinical status. Once radiographic assessments are no longer performed, the patient will be followed every 3 months (±14 days) until death, study completion, or withdrawal from study participation. The long-term follow-up consists of follow-up for survival and/or PFS2. During the long-term follow-up period, only SAEs that are related to protocol procedures or any component of study treatment will be collected. In addition to the collection of SAEs during long-term follow-up, the investigator should report any SAEs they learn of after the long-term follow-up (see Section 10.3.1.1), if investigator considers it related to study treatment or protocol procedure.

- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up. Refer to Section 8.1.3 for more details.
  - **Continued access follow-up:** begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days (± 3 days). The continued access follow-up visit occurs at or near the end of the continued access follow-up period (±3 days).

8.1.1. Part A (Phase 1b)

The Phase 1b part is single arm to determine the recommended dose for Phase 3 part. Two cohorts of patients will be enrolled to assess the safety and tolerability of **'ramucirumab 10 mg/kg q2w + erlotinib 150 mg daily'**. It is estimated that up to 20 patients will be entered into Part A to achieve at least 12 evaluable patients (6 patients in Cohort 1 enrolled from Japan and 6 patients in Cohort 2 enrolled from North America and/or Europe).

8.1.1.1. Baseline and Study Treatment Period Assessments

Baseline radiographic assessment of disease will be performed within 28 days prior to enrollment; first treatment will be administered within 7 days following enrollment. Imaging requirements include CT scan or MRI of chest and abdomen including both adrenal glands, with pelvic imaging performed if clinically indicated. It is recommended that CT imaging of the abdomen/pelvis be performed with intravenous (I.V.) contrast. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then contrast-enhanced MRI is preferred. For patients with known serious allergic reaction(s) to CT contrast material, a contrast-enhanced MRI of the chest/abdomen/pelvis is encouraged. A gadolinium-enhanced MRI of the CNS will be performed at baseline prior to enrollment for all patients (per Exclusion Criterion [15] regarding CNS metastases). While on study, a gadolinium-enhanced MRI of the CNS should be performed if clinically indicated to assess disease progression. Patients will receive any necessary premedication (see Section 9.1.1) prior to the infusion of study therapy at each treatment cycle. A treatment cycle will be defined as 2 weeks (14 days ± 3 days) and includes the period of treatment with erlotinib given on Day 1 in combination with ramucirumab. The start of treatment will be considered Cycle 1 Day 1 (C1D1) or the day that the first dose of any study treatment is administered.

Following administration of premedication (see Section 9.1.1), the patients in Part A will receive the following:

- Ramucirumab on Day 1 of every 2-week cycle, administered as an I.V. infusion over approximately 60 minutes followed by a 1-hour observation period. If there is no evidence of an IRR after the initial and second infusions of ramucirumab, no observation period is required for subsequent treatment cycles (in the event an IRR occurs thereafter, then the 1-hour observation should be reinstituted).
- Erlotinib tablets orally every day. On Day 1 of each cycle, patients will receive erlotinib after completion of ramucirumab infusion (after the observation period post ramucirumab infusion).

Administration of study treatment will occur as described in Section 9.1.

Criteria for starting the next cycle are defined in Section 9.4.2.1.1.

At least 6 patients from each of the 2 cohorts will be treated with ramucirumab and erlotinib. The DLT Assessment Period will be through 2 treatment cycles, Cycles 1 and 2 (totaling approximately 4 weeks). Delays of study treatment administration (within 3 days) are permitted in the DLT Assessment Period of Part A due to any reasons.

A DLT-evaluable patient is considered to be one who either completed 2 cycles of treatment or discontinued from study treatment or study participation before completing 2 cycles due to a DLT.

A DLT-non-evaluable patient is considered one who experienced disease progression, was noncompliance, or discontinued for reasons other than AEs within the first 2 cycles of treatment. Any patient who discontinued from the study before completing safety monitoring for the DLT Assessment Period for any other reason than DLT will be considered non-evaluable for DLT assessment. Additional patients may be enrolled as replacements for non-evaluable patients.

The DLT definitions and rules are listed in Section 9.4.1.

Efficacy data will not be collected during the conduct of Part A. Investigators are required to follow institutional guidelines for regular follow-up for the disease under treatment to assess the disease response to the study treatment.

8.1.1.2. Postdiscontinuation Follow-up Period Assessment

Patients may continue on study treatment after the DLT Assessment Period until one of the following is reached: disease progression, development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision. Adverse event (AE) information will be collected until at least 30 days after the decision is made to discontinue study treatment. After the 30-day short-term follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.

8.1.1.3. Study Completion and End of Trial

The objective of Part A is to assess the safety and tolerability of ramucirumab when administered in combination with erlotinib. Part A completion is considered when the DLT assessment has been completed. Patients may continue to receive study treatment per investigators discretion. The end of trial occurs after study completion and after the last patient has discontinued all study treatment and completed any applicable continued access follow-up.

8.1.1.4. Study Duration

The duration of the Phase 1b portion of the study from study entry to the completion of the DLT Assessment Period is estimated to be approximately 6 months.

8.1.2. Part B (Phase 3)

Part B will start once the Part A DLT Assessment Period for all evaluable patients has concluded and the dose recommendations have been made. After the AC recommendations are made, a notification letter will be sent to investigative sites to inform the starting dose for ramucirumab for Part B.

8.1.2.1. Baseline and Study Treatment Period Assessments

Baseline radiographic assessment of disease will be performed within 28 days prior to randomization; first treatment will be administered within 7 days of enrollment (also within 3 days of randomization). Imaging requirements include CT scan or MRI of chest and abdomen including both adrenal glands, with pelvic imaging performed if clinically indicated. It is

recommended that CT imaging of the abdomen/pelvis be performed with I.V. contrast. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then contrast-enhanced MRI is preferred. For patients with known serious allergic reaction(s) to CT contrast material, a contrast-enhanced MRI of the chest/abdomen/pelvis is encouraged. A contrast-enhanced MRI of the CNS will be performed at baseline prior to randomization for all patients in Part B. Scans performed prior to the date of consent may be used provided they are within 28 days of randomization. While on study, a gadolinium-enhanced MRI of the CNS should be performed if clinically indicated to assess disease progression. Patients in both arms will receive any necessary premedication (see Section 9.1.1) prior to the infusion of study therapy at each treatment cycle.

A treatment cycle will be defined as 2 weeks (14 days ± 3 days) in each arm and include the period of treatment with erlotinib given on Day 1 in combination with either ramucirumab or ramucirumab placebo. The start of treatment will be considered C1D1 or the day that the first dose of any study treatment is administered.

Following administration of premedication (see Section 9.1.1) patients in **Arm A** will receive:

- Ramucirumab on Day 1 of every 2-week cycle as an I.V. infusion over approximately 60 minutes, followed by a 1-hour observation period. If there is no evidence of an IRR after the initial and second infusions of ramucirumab, no observation period is required for subsequent treatment cycles (in the event an IRR occurs thereafter, then the 1-hour observation should be reinstituted).
- Erlotinib tablets orally every day. On Day 1 of each cycle, patients will receive erlotinib after completion of ramucirumab infusion (after the observation period post ramucirumab infusion).

Following administration of premedication (see Section 9.1.1) patients in **Arm B** will receive:

- Placebo on Day 1 of every 2-week cycle as an I.V. infusion over approximately 60 minutes, followed by a 1-hour observation period. If there is no evidence of an IRR after the initial and second infusions of ramucirumab placebo, no observation period is required for subsequent treatment cycles (in the event an IRR occurs thereafter, then the 1-hour observation should be reinstituted).
- Erlotinib tablets orally every day. On Day 1 of each cycle, patients will receive erlotinib after completion of placebo infusion (after the observation period post ramucirumab/placebo infusion).

Administration and dosing of all therapeutic products will occur as described in Section 9.1.

Criteria for starting the next cycle are defined in Section 9.4.2.1.1. Dose reductions for ramucirumab/placebo will be made in the event of specific treatment-related AEs, as described in Section 9.4.2.1.2. Supportive care guidelines are detailed in Section 9.6.1. No dose escalations or re-escalations for ramucirumab/placebo are permitted.

Patients will undergo radiographic assessment of disease status (CT or MRI) according to RECIST v. 1.1, every 6 weeks (± 7 days), as calculated from the first dose of study therapy

regardless of treatment delay or omissions, and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days) until there is radiographic documentation of PD. If a patient discontinues treatment due to objective disease progression, one additional tumor scan will be collected at the 30-day short-term follow-up visit unless the patient has received additional anticancer therapy prior to this visit. Thereafter, radiologic tests are no longer required (Attachment 2).

Patients in both arms will be treated until there is radiographic or symptomatic PD (symptomatic PD should be objectively confirmed radiographically), toxicity requiring cessation of treatment, withdrawal of consent from further study treatment or study participation, or until other discontinuation criteria are met. For patients who discontinue treatment for any reason other than radiographically documented PD (for example, symptomatic deterioration), radiographic assessments should continue as scheduled every 6 weeks (± 7 days) following the first dose of study therapy, and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days) until objective radiographic evidence of PD. Follow-up will continue as long as the patient is alive, the patient requests not to be followed for survival, or until study completion as defined in Section 8.1.2.3.

Following all study treatment discontinuation, follow-up information regarding further anticancer treatment and survival status will be collected every 3 months (± 14 days).

8.1.2.2. Postdiscontinuation Follow-Up Period Assessments

If a patient discontinues treatment due to objective disease progression, one additional tumor scan will be collected at the 30-day short-term follow-up visit unless the patient has received additional anticancer therapy prior to this visit. Thereafter, radiologic tests are no longer required (Attachment 2).

Adverse event (AE) information will be collected until at least 30 days after the decision is made to discontinue from all study treatment. After the 30-day short-term follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.

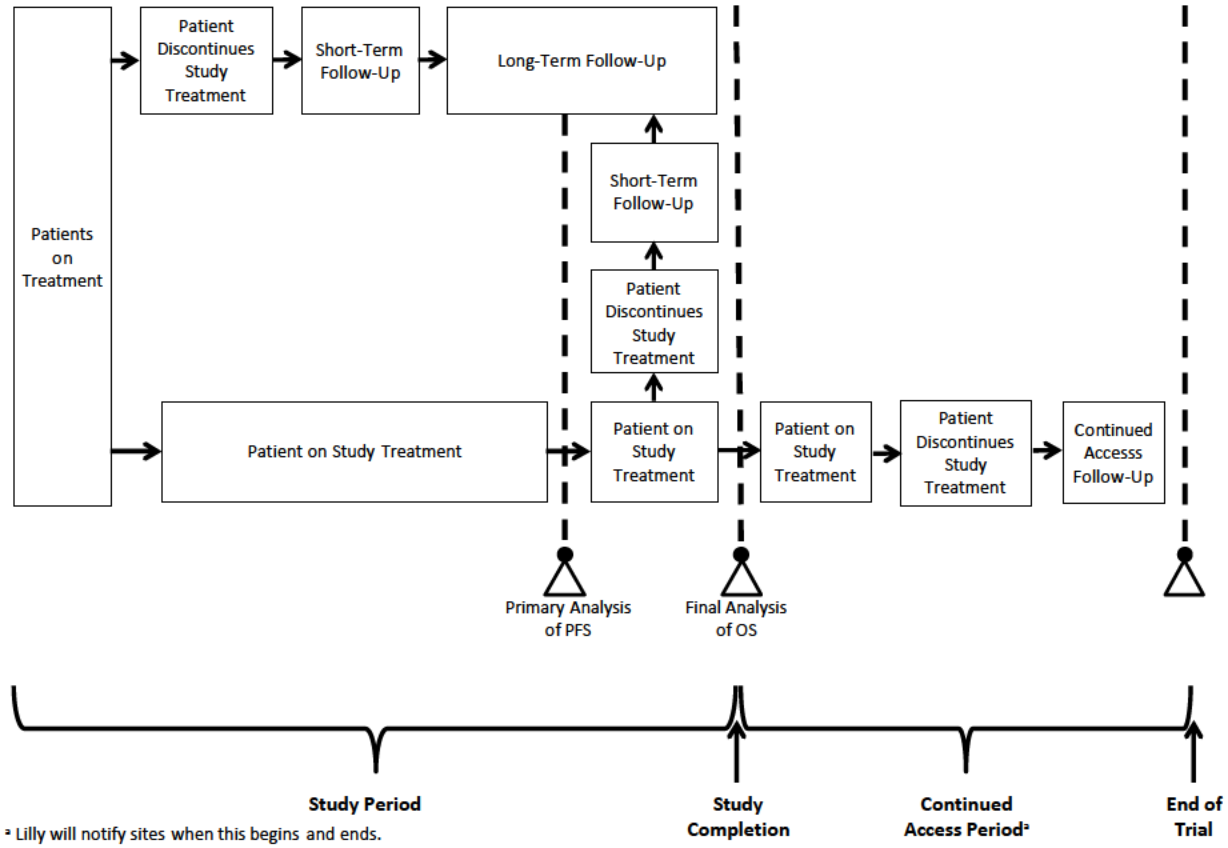
8.1.2.3. Study Completion and End of Trial

The primary objective is investigator-assessed PFS. When approximately 270 PFS events have occurred among the study population, there will be a database lock to report the primary objective of the study.

Figure JVCY.3 is a diagram of the study period and continued access period. This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis of OS, as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient, including patients participating in the continued access period, if applicable.

Upon study completion, investigators and patients may be unblinded to study treatment assignment.

The end of trial occurs after study completion and after the last patient has discontinued all study treatment and completed any applicable continued access follow-up.



Abbreviations: OS=overall survival; PFS= progression-free survival.

Figure JVCY.3. Study period and continued access period diagram.

8.1.2.4. Study Duration

The planned length of study (Part A and Part B, excluding the Continued Access Period) is approximately 61 months.

The planned study duration of Part A is approximately 6 months.

The duration in Part B from first patient randomized until last patient visit (LPV) for OS (secondary endpoint) is approximately 55 months.

8.1.3. Continued Access Period

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs.

After study completion, all patients who are on study treatment and who are eligible for continued access will be unblinded. Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the continued access period until one of the criteria for discontinuation is met (see Section 7.3). During the continued access period, placebo will no longer be administered, therefore patients in erlotinib plus placebo arm may continue on erlotinib as monotherapy, and crossover will not be permitted. Lilly will notify investigators when the continued access period begins. Refer to Section 8.1 for continued access design.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and study treatment exposure will be reported on the eCRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE. Blood samples for PK and immunogenicity analysis will be collected only in the event of an IRR.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

Once patients have entered the continued access period, the sponsor may allow patients to enroll in a ramucirumab "rollover" protocol to provide long-term continued access for patients enrolled in this study.

8.1.4. Committees

The following committees will be established to evaluate or patients' safety or efficacy of the study treatment. There will be charters for these committees to follow.

Assessment Committee (AC)

The Assessment Committee (AC) will be established as a Lilly internal safety review committee independent from the study team for Part A (Phase 1b) of the study and will follow an approved AC Charter. The AC will evaluate DLT analysis and communicate back to the study team about dosing decisions.

Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) will be established to conduct interim analyses as specified in Section 12.2.16.2 and will follow an approved IDMC charter. The IDMC will communicate back to Lilly Senior Management Designee (SMD) about their assessment.

Lilly Internal Review Committee (LIRC)

The Lilly Internal Review Committee (LIRC) will propose actions back to the study team based upon the IDMC's recommendation and LIRC assessment, if necessary.

Blinded Independent Radiological Review Committee (BIRC)

The Blinded Independent Radiographic Review Committee (BIRC) will review the CT scans and MRI scans for tumor assessments from all patients. Details will be described in the statistical analysis plan (SAP).

8.2. Discussion of Design and Control

Part A (Phase 1b) is single-arm and open-label; there is no randomization and no control arm.

Part B is a randomized, double-blind, placebo-controlled, Phase 3 portion of this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

Investigational treatment administration in this study is double-blind; that is, patients, investigational sites, and the Sponsor study team do not have immediate access to treatment assignments for any patients. This design feature minimizes potential bias due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in Part A (Phase 1b) of the study:

- Ramucirumab (10 mg/kg) will be administered as an I.V. infusion over approximately 1 hour on Day 1 of each cycle (14 days [±3 days]); erlotinib (150 mg) will be taken orally once daily.

The following treatments will be administered in Part B (Phase 3) of the study:

- Experimental **Arm A**: ramucirumab (10 mg/kg) will be administered as an I.V. infusion over approximately 1 hour on Day 1 of each cycle (14 days [±3 days]); erlotinib (150 mg) will be taken orally once daily.
- Control (Placebo) **Arm B**: placebo (10 mg/kg) will be administered as an I.V. infusion over approximately 1 hour on Day 1 of each cycle (14 days [±3 days]); erlotinib (150 mg) will be taken orally once daily.

The ramucirumab/placebo starting dose for Part B will be 10 mg/kg every 2 weeks unless, during Part A, the combination therapy (ramucirumab 10 mg/kg every 2 weeks + erlotinib 150 mg every day) is not tolerated. Following DLT review in Part A, the AC may recommend adopting 8 mg/kg every 2 weeks as starting dose for ramucirumab in Part B. After the AC recommendations are made, a notification letter will be sent to investigative sites to inform the starting dose for ramucirumab for Part B. Refer to Section 9.2.2 for preparation of first and subsequent dosing details.

The first administration of study treatment will be performed no more than 7 days after enrollment (and also within 3 days of randomization in Part B). On Day 1 of each cycle, patients must receive ramucirumab or placebo before they take erlotinib. Erlotinib will be taken after the observation period (whenever instituted) and once a day thereafter. Scheduled clinic visits will be approximately every 14 days and will occur on the days that the patients receive ramucirumab/placebo.

Patients will receive ramucirumab or placebo every 14 days (±3 days) until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision.

Table JVCY.1 and Table JVCY.2 show the treatment regimens for Part A and Part B, respectively, of this study.

Table JVCY.1. Part A Treatment Regimen/Dosing Schedule

Study Drug	Dose	Route	Timing
Ramucirumab[a]	10 mg/kg	I.V.	approximately 1 hour infusion Day 1 of each cycle
1-hour observation period[b] followed by			
Erlotinib[c]	150 mg	PO	Daily

Abbreviations: I.V. = intravenous; PO = orally.

a Premedication is required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 9.4.2.1.2.1. All premedication administered must be adequately documented in the electronic case report form.

b A 1-hour observation period is required after the administration of the first and second doses of ramucirumab. If there is no evidence of an infusion-related reaction during the initial 2 cycles of ramucirumab, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted.

c Erlotinib will be taken after the observation period (if instituted), subsequent to the completion of the ramucirumab infusion on Day 1 and once a day thereafter. Refer to Section 9.4 for further instructions on taking erlotinib.

Table JVCY.2. Part B Treatment Regimen/Dosing Schedule

	Study Drug	Dose	Route	Timing
ARM A	Ramucirumab[a]	10 mg/kg	I.V.	approximately 1 hour infusion Day 1 of each cycle
	1-hour observation period[b] followed by			
	Erlotinib[c]	150 mg	PO	daily
	OR			
ARM B	Placebo[a]	10 mg/kg	I.V.	approximately 1 hour infusion Day 1 of each cycle
	1-hour observation period[b] followed by			
	Erlotinib[c]	150 mg	PO	daily

Abbreviations: I.V. = intravenous; PO = orally.

a Premedication is required prior to infusion of ramucirumab or placebo. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 9.4.2.1.2.1. All premedication administered must be adequately documented in the electronic case report form.

b A 1-hour observation period is required after the administration of the first and second doses of ramucirumab/placebo. If there is no evidence of an infusion-related reaction during the initial 2 cycles of ramucirumab/placebo, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted.

c Erlotinib will be taken after the observation period (if instituted), subsequent to the completion of the ramucirumab/placebo infusion on Day 1 and once a day thereafter. Refer to Section 9.4 for further instructions on taking erlotinib.

Any measurements used to determine ramucirumab/placebo dose should be taken at each cycle, and dose should be recalculated if needed. Refer to Section 9.2.2 for ramucirumab/erlotinib dose preparation details.

Dose reductions of study drugs will be made in the event of specific treatment-related AEs, as described in Section 9.4.2.1.2. Supportive care guidelines are detailed in Section 9.6.1 and prohibited and restricted concomitant therapies are detailed in Section 9.6.2.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study treatment dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study treatment so that the situation can be assessed.

9.1.1. Premedication

9.1.1.1. Premedication Prior to Infusion of Ramucirumab or Placebo

Premedication with a histamine H1 antagonist (for example, 50 mg of intravenous diphenhydramine or equivalent, unless otherwise restricted by local requirements) is required 30 to 60 minutes prior to infusion of ramucirumab or placebo. Additional premedication may be provided at investigator discretion. Premedication must be provided in the setting of a prior Grade 1 or 2 IRRs, as detailed in Section 9.4.2.1.2.1. All premedication administered must be adequately documented in the eCRF.

9.1.1.2. Premedication Prior to Erlotinib

Investigators should consult the manufacturer's instructions for erlotinib for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of erlotinib. All premedications administered must be adequately documented in the eCRF.

9.2. Materials and Supplies

Clinical trial materials will be labeled according to the country's regulatory requirements. Ramucirumab and placebo will be supplied to sites by Lilly. Erlotinib may be purchased by the sites where commercially available or supplied to the sites by Lilly.

9.2.1. Study Drugs

9.2.1.1. Ramucirumab

CCI [redacted]

All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab excipients.

9.2.1.2. Placebo

CCI [redacted]

All excipients used for the manufacture of placebo are of pharmacopeial grade. No animal-derived components are used in the manufacture of placebo excipients.

9.2.1.3. Erlotinib

Erlotinib is a commercially available product. Investigators should consult the manufacturer`s instructions for erlotinib for complete prescribing information and follow institutional procedures for the administration of erlotinib, including testing for *EGFR* mutation status. The specific mutation(s) identified and the name of the test method used to document evidence of *EGFR* mutation positivity will be documented in the eCRF.

9.2.2. Storage and Preparation

9.2.2.1. Ramucirumab/Placebo Storage and Preparation

Refer to the IB or CYRAMZA package insert (or Summary of Product Characteristics [SPC]) for detailed information for ramucirumab storage and preparation. Ramucirumab placebo should be stored and prepared according to the same guidelines as used for ramucirumab.

Aseptic technique must be used when preparing and handling ramucirumab/placebo for infusion.

Patients will receive ramucirumab/placebo by I.V. infusion over approximately 1 hour at 10 mg/kg every 14 days (± 3 days) in the absence of disease progression or other discontinuation criteria. The first dose of ramucirumab/placebo is dependent upon the patient's baseline body weight in kilograms. Patients should be weighed at the beginning of each cycle. Subsequent doses of ramucirumab/placebo must be recalculated if there is a ≥10% change (increase or decrease) in body weight from the last dose calculation; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from the last dose calculation. For patients undergoing repeated palliative drainage procedures to remove pleural or peritoneal fluid, dry weight will be defined as weight obtained after the drainage procedure and before fluid reaccumulation. In such circumstances, dry weight will be used for dose calculation, if obtained within 30 days prior to dose. If no recent dry weight is available, actual weight will be used.

Ramucirumab is compatible with common infusion containers. The use of a low protein-binding 0.22-micron in–line filter is required, unless local requirements specify otherwise. Based on the calculated volume of ramucirumab, add (or remove from pre-filled [with 0.9% normal saline] I.V infusion container) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to make the total volume 250 mL. For dose volumes greater than 250 mL, the addition of sterile normal saline is not required. Do not use dextrose-containing solutions. The container should be gently inverted to ensure adequate mixing. The infusion should be delivered via infusion pump in approximately 60 minutes. The infusion rate should not exceed 25 mg/minute. Infusions of duration longer than 60 minutes are permitted in specific circumstances (that is, for

larger patients in order to maintain an infusion rate that does not exceed 25 mg/minute, or in the setting of prior ramucirumab IRR); the infusion duration must always be accurately recorded. The infusion set must be flushed post infusion with sterile 0.9% normal saline equal to or greater than infusion set hold-up volume to ensure delivery of the calculated dose.

CAUTION: Infusion-related reactions may occur during or following ramucirumab administration (see Section 9.4.2.1.2.1 for a definition of Grade 3 and 4 IRRs). During the administration of ramucirumab/placebo, patients should be in an area with resuscitation equipment and treatments necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (for example, epinephrine), oxygen, glucocorticoids, antihistamines, I.V. fluids, and so forth. A 1-hour observation period is required after the administration of the first and second doses of ramucirumab/placebo. If there is no evidence of an IRR during the initial 2 cycles of ramucirumab/placebo, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour observation period should be reinstituted.

9.2.2.2. Erlotinib Storage and Preparation

Refer to the most recent version of the erlotinib (TARCEVA®) package insert or SPC for storage guidance.

9.3. Method of Assignment to Treatment

Upon completion of all screening evaluations to confirm a patient's eligibility, the site will register the patient by the Interactive Web Response System (IWRS), which is web-based and accessible 24 hours a day. The IWRS registration consists of assigning the patient a unique study identification number for all patients (Parts A and B) and patients in Part B will be randomized into 1 of the 2 treatment arms on a 1:1 basis.

The IWRS will assign Part B patients to treatment arms according to a stratified method of randomization (that is, independent randomization within each of 16 strata, or cells), defined by all 16 combinations of the following 4 prognostic factors:

- *EGFR* mutation (exon 19 deletion vs. exon 21 [L858R] substitution mutation)
- Gender (male vs. female)
- Region (East Asia vs. other)
- *EGFR* testing method (*Therascreen*® [Qiagen] and *Cobas*® [Roche] vs. other PCR and sequencing-based methods)

Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

9.4. Selection and Timing of Doses

Patients in Part A will receive ramucirumab with erlotinib. Patients in Part B will be randomly assigned to receive either ramucirumab plus erlotinib *or* placebo plus erlotinib (see Section 8.1). Study drug will be administered as shown in Section 9.1.

Ramucirumab/placebo will be administered over a 1-hour I.V. infusion on Day 1 of each cycle at a dose of 10 mg/kg. The Phase 3 dose will be selected based on the Phase 1b outcome.

The ramucirumab/placebo starting dose for Part B will be 10 mg/kg every 2 weeks unless, during Part A, the combination therapy (ramucirumab 10 mg/kg every 2 weeks + erlotinib 150 mg every day) is not tolerated. Following DLT review in Part A, the AC may recommend adopting 8 mg/kg every 2 weeks as starting dose for ramucirumab in Part B. If this AC recommendation comes, a notification letter will be sent to the sites of this change prior to starting treatment in the Phase 3. Refer to Section 9.2.2 for preparation of first and subsequent dosing details. Erlotinib will be administered orally as a once daily dose of 150 mg. On the day of the I.V. infusion with either ramucirumab or placebo, erlotinib should be taken after the observation period (when instituted) or after the infusion. It is recommended that tablets should be taken on an empty stomach with up to 200 mL of water, either 1 hour before or 2 hours after food intake. Refer to Section 9.6.2 for details on prohibited and restricted therapies while on erlotinib that effect erlotinib plasma concentrations (such as CYP3A4 inducers and inhibitors, H_2-receptor antagonists and antacids, and proton pump inhibitors). Patient compliance with erlotinib self-administration will be assessed at the beginning of each cycle.

A patient may continue to receive study treatment every 14 days (±3 days) until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient from further study treatment, investigator decision, or until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3).

9.4.1. Dose-Limiting Toxicities in Part A

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 hours
- Grade 4 or refractory hypertension (refer to Section 9.4.2.1.2.2)
- Grade ≥ 3 nonhematologic toxicity excluding electrolyte abnormality or Grade 3 skin rash

A patient who either completed Cycle 2 or discontinued from study treatment or study participation before completing 2 cycles due to a DLT would be considered DLT-evaluable. 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 DLTs) 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.

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 these 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

The confirmed dose for Part B may be applied to Part A at investigator discretion.

9.4.2. Dose Delays or Dose Modifications

The timing of starting next cycle will be 14 days (± 3 days) from the last administration of ramucirumab/placebo.

If patients meet the discontinuation criteria for ramucirumab/placebo and continue on erlotinib only, the patients still follow the study schedule with a 14-day (± 3 days) cycle, based on the last dose of ramucirumab/placebo.

9.4.2.1. Ramucirumab or Placebo

9.4.2.1.1. Dose Delays (Delays for Subsequent Cycles) for Ramucirumab/Placebo

To start next ramucirumab/placebo dosing, the following criteria must be fulfilled:

- Total bilirubin ≤ ULN
- AST and ALT ≤2.5 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases
- ANC ≥1.5 × 10^3/μL (≥1.5 × 10^9/L), platelets ≥100 × 10^3/μL (≥100 × 10^9/L)
- Ramucirumab/placebo-related AEs that are NCI-CTCAE, v4.0 Grade <2 or equivalent severity to baseline (except for alopecia; for hypertension, see Section 9.4.2.1.2.2, and for proteinuria, see Section 9.4.2.1.2.7).

Patients not meeting the criterion for total bilirubin may be allowed to continue treatment with ramucirumab or placebo in specific cases (for example, Gilbert's syndrome) after the Lilly CRP and investigator agree that it is medically appropriate for these patients. The decisions and supporting rationale must be documented in writing.

For patient and study site convenience and safety, treatment decisions will be based upon results of tests performed locally. For dosing decisions, bilirubin, AST, and ALT will be required to be collected locally and centrally; ANC and platelets will be collected locally. The duplicate test results obtained locally will not be collected on the eCRF, unless it impacts treatment decision, in which case the critical finding should be documented in the appropriate eCRF as part of the rationale for dose modification. Discrepancies between the local and central laboratory that may have an impact on treatment decisions will not be considered protocol violations.

Part A:

During the DLT Assessment Period, if these criteria listed above are not met, the ramucirumab dose for Cycle 2 can be delayed for up to 3 days. Thereafter, a delay of up to 2 weeks is permitted to allow for recovery from these criteria. The erlotinib treatment should be continued during the delay of ramucirumab if the patient does not meet the criteria of delay and/or discontinuation for erlotinib dosing per package insert (refer to Section 9.4.2.2.1). If a delay of >2 cycles (missing 2 consecutive doses or >42 days have lapsed since last ramucirumab infusion) due to unresolved toxicity is necessary, ramucirumab should be discontinued. The erlotinib treatment should be continued, with the patient remaining in the study, if clinically indicated.

Part B:

If the criteria listed above are not met, the next ramucirumab/placebo dosing should be delayed for up to 2 weeks to allow for recovery. The erlotinib treatment should be continued during the delay of ramucirumab/placebo if the patient does not meet the criteria of delay and/or discontinuation for erlotinib dosing per package insert (refer to Section 9.4.2.2.1). If a delay of >2 cycles (missing 2 consecutive doses or >42 days have lapsed since last ramucirumab infusion) due to unresolved toxicity is necessary, ramucirumab/placebo should be discontinued. The erlotinib treatment should be continued, with the patient remaining in the study, if clinically indicated. Ramucirumab/placebo should be continued until PD, at the discretion of the investigator, in the event that erlotinib is discontinued.

9.4.2.1.2. Dose Modifications for Ramucirumab/Placebo

The starting dose in Part B will be based upon the results of Part A. Based on the starting dose outlined in Part B, one of the following 2 dose modification dosing schemas in Table JVCY.3 would be applicable:

Table JVCY.3. 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

Dose modifications (for those evaluable patients outside of the DLT Assessment Period in Part A and all patients in Part B) are permitted for ramucirumab/placebo in the setting of non-life-threatening and reversible Grade 3 clinical AEs (for example, fever) considered to be at least possibly related to ramucirumab/placebo and that resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle (approximately 2 weeks).

If a Grade 4 AE occurs and is deemed at least possibly related to ramucirumab/placebo, then ramucirumab/placebo should be discontinued except in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities. If Grade 4 fever or laboratory abnormalities resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle (approximately 2 weeks), treatment with ramucirumab/placebo may be continued at the discretion of the investigator. In these

settings, ramucirumab/placebo may be re-administered at starting dose. If a second instance of such an event occurs, ramucirumab/placebo should be subsequently re-administered at a Dose Level -1. A second dose reduction to Dose Level -2 is permitted for this level of event (Grade 3 or 4 event). If the starting dose is 10 mg/kg, then a third dose reduction to Dose Level -3 is permitted in the event that additional postponement of ramucirumab/placebo is required. If the dose of ramucirumab/placebo is reduced because of potentially related AEs, subsequent dose increases are not permitted.

Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE, v4.0 Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator.

Note that this section of the protocol pertains only to general dose modifications for ramucirumab/placebo. Specific AEs requiring dose modifications are outlined below, and include:

- Infusion-Related Reactions
- Hypertension
- Proteinuria
- Thromboembolic Events
- Bleeding/hemorrhage Events
- GI Perforations
- RPLS
- CHF
- Fistula Formation
- Surgery and Impaired Wound Healing
- Liver Injury/Failure

Table JVCY.4 shows the dose-modification criteria and guidelines for management of common ramucirumab/placebo toxicities.

Table JVCY.4. Ramucirumab/Placebo Dose Modification Table

Event and Grade[a]	Specifics	Ramucirumab/Placebo Dose Modifications	Guidelines for Management
IRR Events			
Grades 1 or 2		Reduce the infusion rate by 50% for the duration of the infusion and all subsequent infusions	Grade 1: reduce rate and monitor for worsening of condition. Grade 2: stop infusion; treat with dexamethasone (or equivalent) and acetaminophen; resume at 50% infusion rate once resolved to Grade ≤1; and monitor for worsening of condition. Premedicate with dexamethasone (or equivalent) and acetaminophen prior to each subsequent ramucirumab/placebo infusion.
Grade 3 or 4		Discontinue	
Hypertension			
Grade 1-3	*Asymptomatic*	Maintain dose level	Manage with antihypertensive therapy as clinically indicated, per institutional guidelines
	Symptomatic	Hold until resolution	Manage with antihypertensive therapy as clinically indicated, per institutional guidelines
Grade 4 or refractory		Discontinue	
Proteinuria	*Urine Protein Level: Refer to Attachment 10 for Detailed Proteinuria Algorithm*		
Grades 2 or 3[b]	>3 g/24 hours or in the setting of nephrotic syndrome	Discontinue	
	2-3 g/24 hours	Hold dose Discontinue after second consecutive occurrence	Reassess at next cycle
	<2 g/24 hours	Maintain dose at first occurrence Reduce dose thereafter	

Abbreviation: IRR = infusion-related reaction.

a National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0 (NCI 2009).

b If urine protein remains elevated at ≥ 2 g/24 hour for 2 consecutive cycles, then discontinue ramucirumab/placebo.

9.4.2.1.2.1. Infusion-Related Reactions

Any treatment-related, infusion-related reactions (IRRs) are defined according to the NCI-CTCAE v4.0 definition (section "General disorders and administration site conditions"). Symptoms occurring during or following infusion of ramucirumab/placebo may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (NCI-CTCAE, v4.0 section "Immune system disorders"). In the setting of symptoms occurring

during or following infusion of ramucirumab/placebo, investigators are encouraged to use the AE term IRR and any additional terms (including those not listed here) that best describe the event. These reactions should be graded as shown in Attachment 10.

As with other monoclonal antibodies, IRRs were reported in clinical trials with ramucirumab, with the majority of events occurring during or following a first or second ramucirumab infusion. It is thus required that patients are premedicated prior to each administration of ramucirumab/placebo. Recommended agents include histamine H1 antagonists such as diphenhydramine hydrochloride. Monitor patients during the infusion for signs of hypersensitivity reactions with resuscitation equipment readily available. Symptoms included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension.

Reduce the infusion rate of ramucirumab/placebo by 50% for the duration of the infusion and all subsequent infusions (the infusion duration should not exceed approximately 2 hours) for Grade 1 IRRs; monitor the patient for worsening of condition. If a patient experiences a Grade 2 IRR: stop the infusion; treat with dexamethasone (or equivalent) and acetaminophen; resume the infusion at 50% of the prior rate once the IRR has resolved or decreased to Grade 1 (the infusion duration should not exceed approximately 2 hours; all subsequent infusions should be administered at 50% infusion rate); and monitor the patient for worsening of condition. For patients who have previously experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each ramucirumab/placebo infusion.

Immediately and permanently discontinue ramucirumab/placebo for Grade 3 or 4 IRRs.

9.4.2.1.2.2. Hypertension

An increased incidence of severe hypertension was reported in patients receiving ramucirumab as compared to placebo. In most cases, hypertension was controlled using standard antihypertensive treatment.

Pre-existing hypertension should be controlled before starting ramucirumab/placebo treatment. Monitoring of blood pressure (BP) is recommended during therapy.

Temporarily suspend ramucirumab/placebo for severe hypertension until controlled with medical management. Permanently discontinue ramucirumab/placebo if medically significant hypertension cannot be controlled with antihypertensive therapy.

Patients whose hypertension is poorly controlled for > 4 weeks (>160 mm Hg systolic or >100 mm Hg diastolic) despite appropriate oral medication (>2 oral agents at maximum tolerated dose) is considered refractory. The patient will be discontinued from ramucirumab/placebo. Treatment with erlotinib may be continued, if appropriate in the opinion of the investigator.

9.4.2.1.2.3. Thromboembolic Events

9.4.2.1.2.3.1. Arterial Thromboembolic Events

Serious, sometimes fatal arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials. Permanently discontinue ramucirumab/placebo in patients who experience a severe (Grade 3 or 4) ATE.

9.4.2.1.2.3.2. Venous Thromboembolic Events

Venous thromboembolic events (VTEs) are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. VTEs have been reported from clinical studies investigating ramucirumab, particularly in the context of metastatic disease or in regions adjacent to implanted venous access devices.

Most VTEs lack early warning signs; therefore, awareness and prompt treatment is important, especially in those patients with risk factors and/or previous history of VTEs (Chen and Cleck 2009; Suter and Ewer 2013).

Ramucirumab/placebo therapy should be discontinued in the event of any Grade 3/4 VTE that is considered by the investigator to be life threatening, or symptomatic and not adequately treated by anticoagulation therapy. At the investigator's discretion, ramucirumab/placebo therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab/placebo should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

9.4.2.1.2.4. Bleeding (Hemorrhagic) Events

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Severe GI hemorrhages, including fatal events, have been reported in patients with gastric cancer treated with ramucirumab in combination with paclitaxel.

Permanently discontinue ramucirumab/placebo in patients who experience Grade 3 or 4 bleeding.

9.4.2.1.2.5. Gastrointestinal Perforation

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of GI perforations. Permanently discontinue ramucirumab/placebo in patients who experience GI perforations.

9.4.2.1.2.6. Fistula

Gastrointestinal and non-GI fistula formation have been associated with other antiangiogenic agents, including bevacizumab and sunitinib (Kamba et al. 2007). Some fistulas can be resolved

with surgical procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009).

Patients may be at increased risk for the development of fistula when treated with ramucirumab. Ramucirumab/placebo treatment should be discontinued in patients who develop fistula.

9.4.2.1.2.7. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGF Receptor 2 pathway. Proteinuria has been associated with ramucirumab in clinical studies. The majority of events were Grade 1-2.

Refer to Attachment 10 for a detailed schema of the dosing algorithm for proteinuria.

Monitoring for the development or worsening of proteinuria during ramucirumab/placebo therapy is advised. Delay ramucirumab/placebo therapy if the urine protein level is 2 to 3 g/24 hours. Reinitiate ramucirumab/placebo at a reduced dose of Dose Level -1 once the urine protein returns to <2 g/24 hours. If the protein level 2-3 g/24 hours reoccurs, interrupt ramucirumab/placebo and reduce the dose to Dose Level -2 once the urine protein level returns to <2 g/24 hours. A third dose reduction to Dose Level -3 (if applicable) is permitted in the event that urine protein level elevates to ≥2 g/24 hours after the second dose reduction, and then returns again to <2 g/24 hours after a temporary discontinuation. In the event that the urine protein continues to be elevated at the lowest dose, then the ramucirumab/placebo will be permanently discontinued. Permanently discontinue ramucirumab/placebo for urine protein level of ≥2 g/24 hours is sustained for 2 consecutive cycles or for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome.

9.4.2.1.2.8. Congestive Heart Failure in Patients Who Received Ramucirumab Drug Product in Combination with Mitoxantrone or Following Prior Anthracycline Therapy

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies.

While the mechanism of action is currently unknown, based on the safety data received to date it is likely that treatment with ramucirumab enhances the cardiotoxicity associated with mitoxantrone and has the potential to enhance cardiotoxicity of other agents within the anthracycline/anthracenedione class of chemotherapy medications.

Patients with risk factors should be closely monitored for signs and symptoms of CHF.

Caution should be exercised when treating patients with clinically significant cardiovascular disease, such as pre-existing coronary artery disease or CHF. Patients with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be

enrolled in clinical trials with ramucirumab. Ramucirumab/placebo should be discontinued in the event of any Grade 3-4 events consistent with CHF.

9.4.2.1.2.9. Surgery and Impaired Wound Healing

The impact of ramucirumab has not been evaluated in patients with serious or non-healing wounds. In a study conducted in animals, ramucirumab did not impair wound healing. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld for at least 4 weeks prior to scheduled surgery. Note: Central venous line replacement, such as a Hickman line, should not be consider a significant surgery and would not require discontinuation of ramucirumab.

If a patient develops wound healing complications during therapy, delay ramucirumab/placebo until the wound is fully healed. Should the wound persist beyond 2 cycles (28 days*), permanently discontinue ramucirumab/placebo.

* This 28-day time period is approximate and begins on the day that the next cycle of ramucirumab/placebo should have been administered but was withheld specifically for toxicity.

9.4.2.1.2.10. Liver Failure, Other Significant Liver Injury in Patients with Child-Pugh Class B Cirrhosis, or Cirrhosis (Any Degree) and a History of Hepatic Encephalopathy or Clinically Meaningful Ascites

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with the following conditions should not be enrolled in clinical trials with ramucirumab: 1) cirrhosis at a level of Child-Pugh Class B (or worse) *or* 2) cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

Ramucirumab/placebo should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

9.4.2.1.2.11. Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical and radiologic syndrome typically consisting of reversible cortical neurological dysfunction and brain-imaging findings of subcortical edema involving the posterior circulation, particularly the occipital lobes (Hinchey et al. 1996). The symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits (Hinchey et al. 1996; Garg 2001; Lee et al. 2008). Magnetic resonance imaging (MRI) represents the most reliable method for the diagnosis (Lee et al. 2008). Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported (Hinchey et al. 1996; Tajima et al. 1999; Garg 2001; Lee et al. 2008).

Based on the Ramucirumab IB (Version 11.0), across the clinical program, 2 blinded cases of RPLS have been reported. Both cases occurred in the ongoing double-blind, randomized, placebo-controlled Phase 3 Study I4T-MC-JVBB (IMCL CP12-0920) evaluating FOLFIRI in combination with ramucirumab versus FOLFIRI in combination with placebo for patients with metastatic colorectal cancer.

Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of BP, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures (Stott et al. 2005).

If the diagnosis of RPLS is confirmed, ramucirumab/placebo should be permanently discontinued.

9.4.2.2. Erlotinib

Refer to the most recent version of the erlotinib (TARCEVA®) package insert or SPC.

9.4.2.2.1. Dose Delays and Dose Modifications for Erlotinib

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 (Table JVCY.5). 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.

Table JVCY.5. Erlotinib Dose Reduction Schedule

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

Table JVCY.6 shows the dose modification criteria and guidelines for management of common erlotinib toxicities.

Table JVCY.6. Erlotinib Dose Modification Table

Event and Grade[a]	Erlotinib Dose Modifications	Guidelines for Management
Pulmonary Events		
All grades (acute onset of new or progressive pulmonary symptoms such as dyspnea, cough, or fever)	Interrupt, pending the diagnostic evaluation; if ILD is diagnosed, discontinue study treatment and institute appropriate treatment. If ILD is ruled out, resume erlotinib at same dose.	
Diarrhea		
Grade 1	None	Consider loperamide: 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours
Grade 2	Reduce if diarrhea persists over 48 to 72 hours despite optimal medical management	Manage as for Grade 1
Grade 3 or any grade unresponsive to loperamide, or diarrhea that causes dehydration	Interrupt until resolution to Grade ≤1 and restart at next reduced dose; do not re-escalate	Manage as for Grade 1
Grade 4	Discontinue erlotinib treatment	Manage as for Grade 1
Rash		
Tolerable rash (Grade 2 or 3)	None	Any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)
Intolerable rash	Consider interruption or dose reduction if unresponsive to symptomatic management.	Manage as for Grade 1
Grade 4	Discontinue erlotinib treatment	Manage as for Grade 1
Severe Hepatitis, Liver Failure, Liver Dysfunction	Hold erlotinib administration. If event does not improve significantly or resolve within 3 weeks, then discontinue erlotinib.	Supportive care as appropriate
Abnormal Liver Function Test (hepatitis without liver failure)		
Grade 1 (>ULN - 3.0xULN)	Erlotinib administration can continue at same dose.	Supportive care as appropriate
Grade 2 (>3.0xULN - 5.0xULN)	Hold erlotinib up to 3 weeks. If event resolves to Grade ≤ 1 during this period, then resume erlotinib at the same dose.	Supportive care as appropriate
Grade 3 (>5.0xULN - 20.0xULN)	Hold erlotinib up to 3 weeks. If event resolves to Grade ≤ 1, then resume erlotinib at a dose reduced by 50 mg.	Supportive care as appropriate
Grade 4 (>20.0xULN)	Discontinue erlotinib.	Supportive care as appropriate

Abbreviations: ILD = interstitial lung disease; ULN = upper limit of normal.

[a] National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0 (NCI 2009).

In addition to the common erlotinib toxicities in Table JVCY.6, if a patient experiences other Grade 3 or 4 events that are considered at least possibly related to erlotinib, erlotinib administration may be omitted for up to 2 weeks. If patient could not restart erlotinib at that point, a discussion between the investigator and Lilly CRP must occur to assess if erlotinib dose delay can be extended for another week.

- If the event resolves to ≤ Grade 1 or baseline, the patient may restart erlotinib treatment at a reduced dose (see Table JVCY.5).
- If the event has not resolved to ≤ Grade 1 or baseline within 2 weeks, or another AE occurs during therapy at the reduced dose, a second dose reduction is permitted at the investigator's discretion.
- If the patient does not tolerate at least the 50-mg daily erlotinib dose, erlotinib must be discontinued.

9.5. Blinding

Part B is a double-blind study.

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.

Upon overall study completion (see Section 8.1.2.3), investigators may unblind patients to study treatment assignment.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from study treatment. In cases where there are ethical reasons to have the patient remain on study treatment, the investigator must obtain specific approval from a Sponsor physician or designee for the patient to continue on study treatment.

Patient-level unblinded data will not be shared with 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 that unblinded aggregate efficacy and safety results are not available until the time of final data analysis.

For this study, the following roles will be permitted to access unblinded data for interim analyses of safety and/or futility: IDMC members, select group of programmers/statistician performing interim analyses, and GPS. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly/TPO'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 Independent Data Monitoring Committee. See Section 12.2.16 for further details.

9.5.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. The occurrence of an SAE should not routinely precipitate the immediate unblinding of a study therapy or study treatment label. Study treatment is not to be unblinded for progressive disease. All unblinding events are recorded and reported by the IWRS.

9.5.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect in the oncolytic setting because the potential for individual unblinding exists due to treatment-related signs and symptoms. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications and its indication must be captured at each visit in the eCRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors, bisphosphonate usage. Details of interventions (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, steroids, or erythroid-stimulating agents), procedures (for example, paracentesis

or thoracentesis), or blood products (for example, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded in the eCRFs. Appropriate management of hypersensitivity reactions is described in Section 9.4.2.1.2.1. Guidelines regarding the use of other specific supportive care agents are presented below.

Prohibited and restricted concomitant therapies are listed in Section 9.6.2 may include CYP3A4 inducers or strong/moderate inhibitors, H_2-receptor antagonists and antacids, and proton pump inhibitors. Section 9.6.3 lists other study conditions during the study treatment period.

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational agents may not be administered to patients on this study.

9.6.1. Supportive Care

9.6.1.1. Antidiarrheal Agents

In the event of Grade 3 or 4 diarrhea, supportive measures may include hydration, loperamide, octreotide, and other antidiarrheals. If diarrhea is severe (that is, requires I.V. hydration) and associated with fever or severe (Grade 3 or 4) neutropenia with nausea and vomiting, the patient should be considered for hospitalization for appropriate treatment. Refer to the TARCEVA package insert and Section 9.4.2.2.1 for erlotinib dose delays and modifications for guidance.

9.6.1.2. Antiemetic Agents

The use of antiemetic agents is permitted during this study and at the discretion of the investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer and American Society of Clinical Oncology (ASCO); dexamethasone may be sufficient, but 5-HT3 antagonists and NK1 antagonists may be used (Kris et al. 2006; Gralla et al. 2010).

9.6.1.3. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. Aspirin use at doses up to 325 mg/day is permitted.

The chronic use of NSAIDs is discouraged except at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient.

9.6.1.4. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator. Acceptable agents include, but are not limited to, megestrol acetate and dronabinol.

9.6.1.5. Granulocyte-Colony Stimulating Factors (G-CSF)

The use of G-CSF is permitted during this clinical trial at the discretion of the investigator. G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC $<1.0 \times 10^3/\mu L$ [$1.0 \times 10^9/L$] with a single temperature ≥38.3°C or a sustained temperature of ≥38.0°C for >1 hour).

9.6.1.6. Erythroid Growth Factors

The use of erythroid-stimulating factors (for example, erythropoietin) is permitted at the discretion of the investigator based on ASCO and FDA guidelines (Rizzo et al. 2008; FDA 2009).

9.6.1.7. Bisphosphonate Usage

Bisphosphonates are permitted for use by patients on this study. However, there is a known increased risk for osteonecrosis of the jaw with long-term use of these treatments, especially in the setting of invasive dental procedures. Thus, for any patients who are on bisphosphonate therapy whether on study or not, it is important that patients observe good oral hygiene, undergo regular dental examination, and avoid invasive dental procedures while on bisphosphonate therapy when possible.

9.6.2. Prohibited and Restricted Concomitant Therapy

Patients are not permitted to use any anticancer therapy (other than the study treatments) during the study period, from enrollment until completion of treatment period.

9.6.2.1. CYP3A4 Inducers or Strong Inhibitors

There are potential interactions between erlotinib and CYP3A4 inhibitors and CYP3A4 promoters. Drugs that induce CYP3A4, such as rifampicin or phenytoin, may reduce the effects of erlotinib through increased erlotinib metabolism and decreased plasma concentrations. Conversely, CYP3A4 inhibitors, such as itraconazole and ketoconazole, may increase the effects of erlotinib through decreased erlotinib metabolism and increased plasma concentrations. Therefore, use of alternative treatments without CYP3A4 inducing or strong inhibiting activity is required whenever possible (Attachment 9). If an alternative treatment is unavailable, the dose of erlotinib should be adjusted according to the package insert or SPC when CYP3A4 inducers or strong inhibitors must be used.

9.6.2.2. Anticoagulants

Further INR elevations and/or bleeding events have been reported in patients taking warfarin whilst on erlotinib therapy. If a patient requires anticoagulation therapy after randomization, the use of low molecular weight heparin is required.

9.6.2.3. H_2-Receptor Antagonists and Antacids

Drugs affecting gastric pH decrease erlotinib plasma concentrations.

As per the TARCEVA® package insert, if the use of an H2-receptor antagonist (such as Tagamet® [cimetidine] or Zantac® [ranitidine]) is required, erlotinib should be taken 10 hours after and 2 hours before the dosing of the H_2-receptor antagonist.

Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, if an antacid (such as Tums® [calcium carbonate]) is necessary, dosing with an antacid should be separated by at least 4 hours prior to or after dosing with erlotinib.

9.6.2.4. Proton Pump Inhibitors

Drugs affecting gastric pH decrease erlotinib plasma concentrations.

Concomitant use of erlotinib with proton pump inhibitors is prohibited.

9.6.3. Other Study Conditions: Surgery and Palliative Radiotherapy (or Equally Considered Procedure) During Study Treatment Phase

If any surgery should be required during the study (palliative surgery or medically indicated by the investigator), the patient should undergo radiologic evaluation before surgery for documentation of disease status. Elective, nonemergent surgery is strongly discouraged during study participation. The time of study treatment interruption before surgery should be at least 28 days following the last dose of ramucirumab/placebo. Patients may resume all study treatment no less than 28 days following surgery, provided there has been adequate recovery in the opinion of the investigator. Following surgery, radiological evaluation of disease is required prior to resumption of ramucirumab/placebo.

Patients undergoing surgery before PD should be followed up by imaging every 6 weeks (±7 days), and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days) until radiographically documented PD.

Palliative radiation therapy is permitted, after discussion with and agreement of the Lilly CRP/CRS or designee, for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics; such areas must not constitute PD or meet RECIST criteria for PD. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor therapy will be cause for discontinuation of study therapy.

9.7. Treatment Compliance

Ramucirumab/placebo will be administered intravenously only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

Patient compliance with erlotinib will be assessed at Day 1 of each cycle by direct questioning, review of diary, and counting returned tablets. Deviations from the prescribed dosage regimen should be recorded in the "Study treatment: modifications" form. For patients who are significantly noncompliant (<70% or >130% of expected study drug taken in a visit interval, or missed 7 consecutive dose in a visit interval), investigative sites must counsel patients on the importance of study drug compliance and drug accountability. A patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more/less than the prescribed amount of medication. Patients who are consistently out of the compliance range may be discontinued. A Lilly representative should be contacted upon the second instance of treatment noncompliance.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations. Study procedures and their timing (including tolerance limits for timing) are summarized in the study schedule (Attachment 1 and Attachment 2).

10.1. Efficacy Measures

The patient has at least one or more measurable lesion attributed to NSCLC at the time of study entry. Disease assessment will be undertaken at baseline (scans performed prior to the date of consent may be used provided they are within 28 days of enrollment) and then every 6 weeks (±7 business days) as calculated from the first dose of study therapy, and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days). The imaging method used at baseline must be used consistently for tumor assessment.

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Computed tomography (CT), including spiral CT, scans and MRI are the preferred methods of measurement. Imaging requirements include CT scan or MRI of chest and abdomen including both adrenal glands, with pelvic imaging performed if clinically indicated. A gadolinium-enhanced MRI of the CNS will be performed at baseline prior to randomization for all patients.

Efficacy data will not be collected during the conduct of Part A; however, the same baseline tumor assessments, including gadolinium-enhanced MRI of the CNS, required for Part B will also apply for Part A, and will be performed prior to study enrollment. Investigators are required to follow institutional guidelines for regular follow-up for the disease under treatment to assess the disease response to the study treatment.

For Part B, the method of tumor assessment used at baseline must be used consistently throughout the study. Patients must be enrolled with at least one measurable disease based on RECIST, version 1.1. Disease assessment will be undertaken at baseline (within 28 days prior to randomization and may be prior to consent) and then every 6 weeks (±7 days) as calculated from the first dose of study therapy, and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days). Patients will be evaluated for response according to RECIST, v 1.1 guidelines (Eisenhauer et al. 2009).

During the continued access period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care, and these data will not be collected or analyzed.

See further details for timing of imaging studies in Attachment 1, Attachment 2, Attachment 5, and Attachment 7.

10.1.2. Efficacy Assessments during the Study Period Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1 or Attachment 2).

For those patients who discontinue one or both study treatment(s) without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response every 6 weeks (±7 days) as calculated from the first dose of study therapy, and after 72 weeks while on study, imaging will be performed every 12 weeks (±7 days) by the same method used at baseline and throughout the study until the patient has objective disease progression, or until final analysis of overall survival. In the Part B phase of this randomized trial where progression is the primary endpoint, confirmation of response is not required. If a patient discontinues treatment due to objective disease progression, one additional tumor scan will be collected at the 30-day short-term follow-up visit unless the patient has received additional anticancer therapy prior to this visit. Thereafter, radiologic tests are no longer required. The patient will be followed up approximately every 3 months (±14 days) until the patient's death or overall study completion, whichever occurs first.

Patients who are responding to study treatment but discontinued due to criteria other than PD, should have scheduled tumor assessment before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response.

After final analysis of OS, during the Continued Access Period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

Lilly will continue to collect survival and PFS2 data through study completion but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin. Although it is not mandatory, PFS2 based on radiographic assessment is recommended.

10.1.3. Primary Efficacy Measure

The progression-free survival (PFS) time is measured from the date of randomization to 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. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment. The detailed censoring rules are described in the SAP.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. An independent review of imaging scans will be performed by BIRC, where an audit of the scans will be conducted to verify the investigator-assessed PFS.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JVCY.7) will be collected at the times shown in the Study Schedule (Attachment 1 or Attachment 2).

Table JVCY.7. Secondary Efficacy Endpoints

Endpoint	Definition
Overall Survival (OS)	OS is defined as the time from the date of randomization until the date of death from any cause. If the patient was alive at the end of the follow-up period (or was lost to follow-up), OS data will be censored for analysis on the last date the patient was known to be alive.
Objective Response Rate (ORR)	ORR is defined as the proportion of randomized patients achieving a best overall response of PR or CR.
Disease Control Rate (DCR)	DCR is defined as the proportion of randomized patients achieving a best overall response of PR or CR or SD.
Duration of Response (DOR)	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 last evaluable tumor assessment.

Abbreviations: CR = complete response; DCR = disease control rate; DOR = duration of response; OS = overall survival; PR = partial response; SD = stable disease.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

All patients for whom there is a validated translation in which the patient is fluent will undergo assessment for symptoms, quality of life (QoL), and health status using the patient-reported LCSS and the EuroQol EQ-5D-5L. It is recommended that the instruments be administered together and in sequential order, with the LCSS presented first, followed by presentation of the EQ-5D-5L. Patients will complete the instruments according to the Study Schedule (Attachment 1 or Attachment 2). Patients will complete the instruments at baseline, at Cycle 2, thereafter at every other cycle, and at the 30-day short-term follow-up visit. On days that the patient receives ramucirumab/placebo, assessments will be completed prior to treatment administration and before any extensive contact and consultation with the clinician/study investigator in regards to the disease assessments.

10.2.1.1. Lung Cancer Symptom Scale (LCSS)

Disease-related symptoms and QoL will be assessed with the self-administered LCSS (Hollen et al. 1994). The LCSS is a validated and reliable instrument to assess lung cancer-specific symptoms and their impact on QoL. The LCSS consists of 9 items: 6 questions focused on lung cancer symptoms (appetite loss, fatigue, cough, shortness of breath, blood in sputum, and pain) plus 3 global items (symptom distress, difficulties with daily activities, and quality of life). Each item is assessed on a 100-mm visual analogue scale (VAS), with 0 representing no symptoms or better QoL. From the 9 items on the LCSS, the Average Symptom Burden Index (ASBI; mean of 6 symptom-specific items) and LCSS total score (mean of all 9 items) will be calculated for each patient at each assessment. For a given assessment, if any of the contributing items have not been completed, the ASBI and the LCSS total score will not be calculated. For each patient and any particular scale, the minimal important difference (MID) from baseline is defined as 15 mm (de Marinis et al. 2008).

Each of the 9 scales and 2 summary scores at each assessment time point will be compared to its baseline value and be categorized using the MID as follows:

- Deterioration: defined as an increase of 15 mm or more.
- Improvement: defined as a decrease of 15 mm or more.
- Stable: defined as no change or increase/decrease < 15 mm

The best response across all time points will be obtained for each of the 11 scores by categorizing the best score as deterioration, improvement, or stable. The worst response will be similarly obtained by categorizing the worst score.

10.2.1.2. EQ-5D-5L

The EQ-5D-5L (Janssen et al. 2008; van Hout et al. 2012) is a standardized instrument for use across diseases as a measure of self-reported health status. Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with advanced lung cancer. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D-5L consists of 2 parts. In the first part, patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment. The responses to the 5 dimensions are combined into an index score where 0 represents death and 1 represents perfect health. The second part is a VAS that allows patients to rate their present health condition. Possible scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

10.2.2. Resource Utilization

Investigators will be asked to document the use of BSC measures, concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study through the 30-day short-term postdiscontinuation follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, stabilized, returned to baseline, deemed irreversible, or otherwise explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1 or Attachment 2). Table JVCY.8 presents a summary of AE and SAE reporting guidelines. Table JVCY.8 also shows which database or system is used to store AE and SAE data.

Table JVCY.8. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study treatment	x	x
Continued access period	All AEs	x	
	All SAEs	x	x
Continued access follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up)	All SAEs related to protocol procedures or study treatment that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits. Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect. All AEs related to protocol procedures are reported to Lilly or its designee via eCRF. In addition, all AEs occurring after the patient receives the first dose of study treatment must be reported to Lilly or its designee via eCRF. Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study treatment via eCRF. Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures that result in a diagnosis should be reported as adverse events to Lilly or its designee via eCRF.

Cases of pregnancy that occur during maternal or paternal exposures to or up to 12 weeks after the last dose of study treatment should be reported as an SAE. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

The NCI-CTCAE v4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Initial or prolonged inpatient hospitalization
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received study treatment. If a patient experiences an SAE after signing informed consent, but prior to receiving study treatment, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study treatment.

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol; however, if an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study treatment, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information (DCSI) in the IB and that the investigator identifies as related to the study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- Trends in safety data
- Laboratory analytes
- Adverse events including monitoring of adverse events of special interest
- If during treatment, a patient experiences either:
    - elevated ALT $\geq$5× ULN and elevated total bilirubin $\geq$2× ULN *or*
    - elevated ALT $\geq$8× ULN (regardless of bilirubin level),

  then clinical and laboratory monitoring should be initiated by the investigator.

- For patients entering the study with ALT >3× ULN, monitoring should be triggered at ALT ≥5× ULN.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 4.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.16) can conduct additional analyses of the safety data.

For the purpose of this study, in which survival is an important secondary efficacy endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to assure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or other clinical AE is deemed serious, unexpected, and related to study treatment, only Lilly Global Patient Safety representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

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 personnel external to the study to ensure the blinding integrity of the study.

10.3.3. Complaint Handling

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for Part A sample collections in this study and Attachment 2 lists the schedule for Part B.

Attachment 3 lists the specific tests that will be performed for this study and whether these will be performed at a central and/or local laboratory. For patient and study site convenience and safety, treatment decisions will be based upon results of tests performed locally. For dosing decisions, bilirubin, AST, and ALT will be required to be collected locally and centrally. The duplicate test results obtained locally will not be collected, unless it impacts treatment decision, in which case the critical finding should be documented in the appropriate eCRF as part of the rationale for dose modification. Discrepancies between the local and central laboratory that may have an impact on treatment decisions will not be considered protocol violations.

Attachment 4 lists tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

Attachment 8 provides a summary of the sampling time points for PK analyses during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Translational Research

Required samples for biomarker and pharmacogenetics research to be collected from all patients in this study, unless restricted per local regulations, are the following:

- plasma samples from whole blood (mandatory for Parts A and B; see Section 10.4.2.1 and Section 10.4.2.3.
- whole blood sample for DNA collection (mandatory for Parts A and B; see Section 10.4.2.2)
- archived tumor tissue (mandatory for Part B only; see Section 10.4.2.3);

CCI [redacted]

CCI [redacted]

Mandatory FFPE tissue provided should be from the Stage IV NSCLC diagnosis and, ideally, not from an earlier staging. However, for patients in Part B, archived NSCLC tissue samples derived from other than Stage IV disease may be acceptable, based on approval by Lilly CRP.

10.4.2.1. Blood Sample for Plasma Collection

CCI [redacted]

For patients who do not submit Stage IV disease tissue samples, a plasma sample for disease characterization is required for patients entering the study at baseline and, if not provided at baseline for patients ongoing at the time of amendment d, may be requested during the treatment period.

10.4.2.2. Whole Blood Sample for DNA Collection

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a blood sample will be collected for pharmacogenetic analysis. Sampling for such analysis will be a one-time collection, as noted in the Study Schedule (Attachment 1 or Attachment 2). Variable response to ramucirumab and erlotinib may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, the mechanism of action of the drug, the availability of receptors, the disease etiology and/or the disease subtype itself.

CCI [redacted]

In the event of an unexpected AE or the observation of an unusual response, the samples may be genotyped and analysis may be performed to evaluate genetic association with response to ramucirumab and/or erlotinib. These investigations may include focused candidate gene studies or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease, cancer-related conditions, and drug under study in the context of this clinical program.

They will not be used for broad exploratory unspecified disease or population genetic analysis. Pharmacogenetic data will not be provided back to the investigator or the patient except where required by local law.

10.4.2.3. Mandatory Tumor Tissue Samples

Once the patient consents, collection of archived tumor tissue is mandatory for entry on Part B of this study. Submission of archived tumor tissue is highly encouraged for Part A but is not mandatory. If the mandatory archived tumor tissue is not collected during the baseline period, at any time during the study, tumor tissue should be provided from patients who consent to provide tissue. Fresh tissue is not required. Previously archived Stage IV NSCLC tissue from the initial diagnosis may be used; for patients in Part B, archived NSCLC tissue samples derived from other than Stage IV disease may be acceptable, based on approval by Lilly CRP. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested (de-identified and translated). CCI [redacted]. The paraffin-embedded whole blocks will be sectioned and sent back to the site. Partial blocks and slides will not be returned.

10.4.2.4. Collection Procedures for Translational Research

Plasma samples for biomarker research, whole blood samples for DNA, and tumor tissue samples will be collected at the times specified in the Study Schedule (Attachment 1 or Attachment 2). Translational research samples will be stored at a facility chosen by the Sponsor or designee.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment. Patients will not receive results of these investigations except where required by local law. Samples will be destroyed according to a process consistent with local regulation. Stored samples will retain the patient identifier (for example, the trial patient number) and will not be stored indefinitely.

Supplies required for the collection and shipment of the patients' stored samples will be supplied by the central laboratory vendor. Sample handling and shipment to the central laboratory will occur per instructions provided to the study site.

10.4.3. Samples for Immunogenicity Research

Blood samples will be collected on all patients to determine antibody production against ramucirumab at baseline (BEFORE the first infusion of ramucirumab/placebo on C1D1). For patients in Part B, additional blood samples for immunogenicity testing will be collected BEFORE the infusion of ramucirumab/placebo on C4D1, and at the 30-day short-term follow-up visit (as noted in Attachment 8).

In the event of an IRR, blood samples will be collected for both immunogenicity and PK analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event. To interpret the results of immunogenicity, a sample to measure the concentration of ramucirumab in the blood is also collected at the same time point (as noted in Section 10.4.4).

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the ramucirumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ramucirumab.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ramucirumab. The duration allows the sponsor to respond to regulatory requests related to ramucirumab.

10.4.4. Samples for Ramucirumab Drug Concentration Measurements Pharmacokinetics

Whole blood samples will be collected for all patients in Part B and processed as serum, as specified in the Part B Schedule for Ramucirumab/Placebo Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule (Attachment 8).

In either Part A or Part B, in the event of an IRR, with the immunogenicity sample, blood samples will be collected to determine serum ramucirumab concentrations, as described in Section 10.4.3.

Serum concentrations of ramucirumab will be assayed using validated methods. These samples will be analyzed at laboratories designated by the sponsor.

The PK samples will be stored at a facility designated by the Sponsor. The remaining sample materials collected for PK may be pooled and used for exploratory metabolism and other exploratory PK/pharmacodynamic work as deemed appropriate.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical samples collected to measure ramucirumab concentration will be retained for a maximum of 1 year following last patient visit for the study.

10.5. Appropriateness of Measurements

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Part A:
At least 12 previously untreated patients with *EGFR* mutation-positive metastatic NSCLC will be enrolled and treated with ramucirumab plus erlotinib.

Part B:
The primary objective of this study is to compare ramucirumab plus erlotinib versus placebo plus erlotinib in terms of PFS in previously untreated patients with *EGFR* mutation-positive metastatic NSCLC. The study will enroll approximately 450 patients in 1:1 randomization. The primary analysis will be performed after approximately 270 PFS events have occurred (40% censoring rate).

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 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.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all CIs will be given at a 2-sided 95% level, unless otherwise stated.

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 the statistical analysis plan (SAP).

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.

12.2.1.1. Analysis Populations

The following populations will be defined for this study:

Intention-to-Treat 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 all baseline, efficacy, and PRO analyses.

- **Part A Safety Population**: all patients enrolled in Part A and received at least 1 dose of any study treatment
- **Part A DLT-evaluable Population**: patients that either completed 2 cycles of treatment or discontinued from study treatment or study participation before completing 2 cycles due to a DLT would be considered DLT-evaluable. See Section 9.4.1 for detailed DLT definition.
- **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 Part A and B will be conducted separately, unless otherwise stated. Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset ITT population in Part B from whom a valid assay result (according to laboratory guideline) has been obtained.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient characteristics will include a summary by treatment arm of the following:

- Patient demographics
- Baseline disease characteristics
- Preexisting conditions
- Baseline prognostic factors for NSCLC

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized by treatment arm for the safety population.

12.2.5. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name, for the Part B ITT population.

12.2.6. Treatment Compliance

The number of dose omissions, reductions, and delays, the number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

Treatment compliance information for erlotinib will be collected on the eCRF by direct questioning, review of diary, and/or counting returned tablets at each visit and the number of tablets taken relative to the number expected to be taken will be summarized.

12.2.7. Primary Outcome and Methodology

12.2.7.1. Part A

Primary objective of Part A is to assess the safety and tolerability of ramucirumab when administered in combination with erlotinib.

Safety and tolerability will be assessed based on the DLT-evaluable population. The number of patients who experienced any DLT will be presented based on DLT-evaluable population. All other safety analyses will be performed using the Part A Safety population.

12.2.7.2. Part B

The primary endpoint of Part B of this study is investigator-assessed PFS. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment. The detailed censoring rules are described in 9.

Table JVCY.9. 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 post baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline 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 post-baseline 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: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at every 3 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates. The comparison of the PFS curves between treatment groups will be conducted by a stratified log-rank test with following stratification variables as the primary analysis:

- *EGFR* mutation (exon 19 deletion vs. exon 21 [L858R] substitution mutation)
- Gender (male vs. female)
- Region (East Asia vs. other)

- *EGFR* testing method (*Therascreen*® [Qiagen] and *Cobas*® [Roche] vs. other PCR and sequencing-based methods)

The stratified Cox proportional hazard model (Cox 1972) with assigned treatment as the only covariate will be used to estimate the HR and corresponding 95% CI for the primary analysis. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

12.2.8. Secondary Outcome and Methodology

The secondary objectives of the study for Part B are listed in Section 6.2.

12.2.8.1. Overall Survival

The treatment regimens will be compared in terms of OS; however, multiple postprogression anticancer treatments are expected, which will dilute the treatment effect in OS. In addition, unequal treatment after progression is expected to obscure any effect of ramucirumab plus erlotinib relative to erlotinib plus placebo.

The primary analysis of PFS described in Section 12.2.7.2 will also be performed in an analogous fashion for OS.

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.

The interim OS analysis may be performed at the time of primary PFS analysis (approximately 270 PFS events) and the final 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).

If it is determined that an additional interim analysis would provide further scientifically meaningful characterization of OS, then an additional interim analysis could be performed prior to the final analysis.

12.2.8.2. Objective Response Rate and Disease Control Rate

The ORR and DCR of each treatment arm will be calculated as defined by RECIST v1.1. The ORR with 95% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

12.2.8.3. Duration of Response

The survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using Cox regression model and log-rank test. The analysis is for responders only.

12.2.9. Sensitivity Analyses

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis.

Sensitivity analyses will include analyses using unstratified log-rank test and Cox models, the per-protocol population, including both radiographic and clinical progressions as PFS events, and analyses applying alternative PFS censoring rules (for example, post-discontinuation systemic anticancer therapy, missing tumor assessment, missing 2 or more tumor assessments prior to PD/death or lost to follow up, etc.; more details will be specified in the SAP).

In addition, a PFS analysis based on BIRC review will be conducted. 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 patients.

Additional sensitivity analyses may be specified in the SAP.

12.2.10. Pharmacokinetic and Immunogenicity Analyses

Pharmacokinetics:

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 will be explored. Details will be described in the SAP.

Immunogenicity:

Incidence of anti-ramucirumab antibodies will be tabulated. Correlation to ramucirumab drug level, activity, and safety will be assessed, as appropriate.

In the event of an infusion-related reaction, the immunogenicity and ramucirumab serum concentrations will be tabulated.

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population pharmacokinetic/pharmacodynamic model development processes for interim or final 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.

12.2.11. Progression-Free Survival 2

PFS2 is defined as the time from randomization to second disease progression (defined as objective radiological or symptomatic progression after the start of additional systemic anticancer treatment), or death from any cause, whichever occurs first. If the patient is alive at the cutoff for analysis and a second disease progression has not been observed, PFS2 data will be censored on the last date the patient was known to be alive.

- The analysis of PFS2 will be based on stratified log-rank test, stratified by randomization strata (IWRS). PFS2 median with 95% CI and survival curves for each treatment group will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata (IWRS).

- An additional sensitivity analysis may be explored in which an event is defined as discontinuation of second-line treatment, second disease progression, or death from any cause, whichever occurs first. Other sensitivity analyses may be specified in the SAP.

12.2.12. Translational Research Analyses

Biomarker results for translational research will be summarized, and will be analyzed for correlations with clinical outcomes.

12.2.13. Health Outcome/Quality of Life Analyses

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). Percentage compliance will be summarized by treatment arm for each assessment period and overall. Reasons for noncompliance will be described.

12.2.13.1.LCSS

The LCSS assessments will be used primarily to calculate time to deterioration (TtD) for each of the 9 items, ASBI, and LCSS total score as defined in Section 10.2.1. TtD for each LCSS 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 LCSS assessment.

- The Kaplan-Meier method will be used to estimate parameters for time-to-event analyses on each treatment group. Kaplan-Meier curves by treatment arm may be produced.
- Hazard ratios will be estimated using stratified Cox proportional hazards models with assigned treatment as the only covariate, reported with 2-tailed 95% CIs. These Cox models should be stratified identically to the stratified log-rank tests.
- The LCSS data will be summarized descriptively by baseline and cycle. For each patient, the maximum change (improvement or deterioration) over baseline score will be calculated for each of the scores. Data on maximum change (improvement or deterioration separately) will be compared statistically between study treatment arms for each of the scores using analysis of covariance (using only baseline score as a covariate) and the Mann-Whitney-Wilcoxon test.

12.2.13.2.EQ-5D-5L: Health State Utilities

Descriptive statistics (Herdman et al. 2011) for the 5 dimensions, index, and VAS will be calculated for each assessment period.

12.2.13.3.Resource Utilization

Hospitalizations, transfusions, and concomitant medications during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.14. Safety Analyses

12.2.14.1.Part A

Safety analysis will be performed in DLT-evaluable patients (refer to Section 9.4.1) for the AEs reported during the DLT Assessment Period. The number of patients who experienced any DLT will be presented based on all DLT-evaluable patients (DLT population).

All other safety analyses will be performed using the safety population. The safety data collected in Part A will not be combined with the safety data in Part B.

12.2.14.2.Part B

All patients enrolled in the study and treated with at least 1 dose of study treatment will be evaluated for safety. Safety analyses will include summaries of the incidence of AEs by maximum NCI-CTCAE v 4.0 grade that occur during the study treatment period or within approximately 30 days after the decision is made for discontinuation from study treatment. Additionally, the following safety-related outcomes will be summarized:

- Study treatment discontinuations due to AEs
- Deaths during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- AEs, TEAEs, and SAEs during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- Hospitalizations and transfusions during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- Select concomitant medications, including growth factors (erythroid growth factors, G-CSF, granulocyte-macrophage colony-stimulating factor), antiemetics, CYP3A4 inducers and inhibitors, and antibiotics, during the study treatment period or within 30 days after the decision is made to discontinue study treatment.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline.

12.2.15. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for each of following potential prognostic subgroup variables:

- all baseline stratification factors
- age (<65 years vs. ≥65 years)
- age (<70 years vs. ≥70 years)

- smoking history (ever vs. never smoker)
- performance status (0 vs. 1)
- initial stage at diagnosis (Stage IV vs. other)

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

If a category of subgroup variable consists of fewer than 5% of randomized patients, then analysis within that category may be omitted.

Analyses will be done within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment performed.

Other subgroup analyses may be performed as deemed appropriate. If any safety analyses described in Section 12.2.14 identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

CCI [redacted] Details of the analyses will be described in the SAP.

12.2.16. Interim Analyses

Two independent committees will be formed to review the interim data and provide guidance to the study team, as described in Section 8.1.4.

The AC, which is internal to Lilly and independent of the JVCY study team, is responsible for reviewing the DLT analysis of Part A and providing consultation recommendation to the study team with regards to the starting dose of Part B (refer to Section 9.4.1), if needed after the completion of Part A.

The IDMC is responsible for providing external oversight for Part B of JVCY study independently of Lilly.

In general, the planned analyses include the following:

- Analysis 1 (Part A; DLT evaluation): after the 6 patients enrolled from Japan and 6 patients enrolled from North America and/or Europe have completed 2 treatment cycles
  Endpoint: DLTs
- Analysis 2 (Part B, Interim Safety): after approximately 50 randomized patients have completed 3 cycles of treatment or discontinued from all study therapies due to any reason prior to 3 cycles
  Endpoint: Safety profile
- Analysis 3 (Part B, Interim Futility): approximately 107 PFS events
  Endpoint: PFS and safety profile
- Analysis 4 (Part B, Primary PFS): approximately 270 PFS events
  Endpoint: PFS (Primary) and other secondary and exploratory objectives

- Analysis 5 (Part B, Final Overall Survival): approximately 300 OS events
  Endpoint: OS (Secondary)

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.

12.2.16.1. Part A

The DLT evaluation will be performed once all DLT-evaluable patients have completed 2 cycles of treatment or discontinued from the study treatment or study participation due to a DLT during the first 2 cycles. The evaluation will be based on the safety data reported during the first 2 cycles of treatment in this population. The AC is responsible for reviewing the DLT analysis of Part A and providing recommendation to the study team when requested by the study team.

12.2.16.2. Part B

An IDMC review 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 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.

Only the IDMC are authorized to evaluate unblinded interim futility 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 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.

Unblinding details are specified in the blinding section of the protocol (Section 9.5). If changes to the unblinding plan occurred after protocol approval, they may be described in either a protocol amendment, the unblinding plan section of the SAP, or in a separate unblinding plan document.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or, where permitted by local law or regulation, by the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatment.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's ERBs should be provided with the following:

- The current IB or package labeling and updates during the course of the study
- The ICF
- Relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- ICH GCP Guideline (E6)
- Applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in treating patients with lung cancer will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator chosen by the Sponsor or designee will serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JVCY Part A Study Schedule

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Baseline Schedule (Part A)

Procedure Category	Protocol Section	Procedure	Baseline		Comments
Study Period			Baseline		
Cycle			BL		
Visit			0		
Duration			Up to 21 days (except where noted)		
Relative Day of Cycle 1 Day 1 (C1D1)			≤21	≤7	
Study Entry/ Enrollment	7 13.1	Informed Consent Form signed (prior to conducting any protocol-specific tests/procedures)	X		Obtain informed consent prior to any study-related procedures or evaluations. The investigator or the Sponsor will not grant exceptions to eligibility criteria.
	7.1, 7.2	Inclusion/Exclusion evaluation		X	
Medical History	10.3.1 Att. 5	Initial history (including smoking history)/preexisting conditions/disease characteristics	X		Any preexisting and pretreatment toxicity (treatment or disease related) should be documented and recorded as part of the pretreatment medical history, as well as smoking history. Disease characteristics at initial diagnosis and at study entry will be collected.
	Att. 5	Demography	X		Date of birth, sex, and race/ethnicity will be collected at baseline.
	Att. 5	Prior treatment therapy of underlying disease	X		Prior treatment includes any treatment for underlying disease, including maintenance therapy. Start and stop dates should be documented as well.
Physical Examination	Att. 5	Physical examination (including height and weight)		X	Height measurements to be performed at baseline only. A time window of -3 days is permitted for the Day 1 physical exam.
	Att. 5	ECOG performance status		X	A time window of -3 days is permitted for the Day 1 ECOG PS.
	Att. 5	Vital signs		X	Includes blood pressure, pulse, respiratory rate, temperature, and SpO_2. The results of the SpO_2 test will not be collected on the eCRF.
Concomitant Medications	9.6	Concomitant medications	X (within 30 days)		Concomitant medications will be recorded, including any taken within 30 days prior to start of study treatment.

Baseline Schedule (Part A)

Study Period	Baseline	
Cycle	BL	
Visit	0	
Duration	Up to 21 days (except where noted)	
Relative Day of Cycle 1 Day 1 (C1D1)	≤21	≤7

Procedure Category	Protocol Section	Procedure			Comments
Lab/ Diagnostic Tests	7.1 Att. 3	Hematology (local)		X	Hematology will be collected for local lab testing. If enrollment hematology profile is collected within 4 days of C1D1, the profile does not need to be repeated at C1D1.
	7.1 Att. 3	Serum chemistry including thyroid tests and HgbA1c (selected tests local/central)		X	If enrollment chemistry profile is collected within 4 days of C1D1, the profile does not need to be repeated at C1D1. Central chemistry laboratory results will be used to determine patient eligibility at baseline. For dosing decisions, bilirubin and AST/ALT are required to be analyzed locally and centrally. Thyroid tests (TSH and free T4) and HgbA1c will be collected for safety monitoring and will be performed at a central lab.
	7.1 Att. 3	Coagulation profile (local)		X	If enrollment coagulation bloodwork is collected within 4 days of C1D1, the profile does not need to be repeated. Patients receiving warfarin should be switched to LMWH as per institutional guidelines, and have achieved stable coagulation profile prior to enrollment.
	7.1 Att. 3 Att. 10	Urinalysis (local)		X	At baseline, dipstick measurements should be done within 72 hours prior to treatment. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.
	7.1 Att. 3 Att. 5	Pregnancy test (local)		X	At baseline, serum pregnancy testing for women of childbearing potential will be performed locally. The results of this test will not be collected on the eCRF.
	7.1	Follicle-stimulating hormone (FSH) (local)		X	A baseline FSH test for eligibility will only be performed on women who have had spontaneous amenorrhea for 6-12 months prior to study entry.
	10.4.2.3	Tumor tissue	X		This tissue collection is for the evaluation of potential biomarkers. Either archived tumor tissue or tissue from a recent biopsy may be submitted. FFPE tissue provided should be from the Stage IV NSCLC diagnosis and not an earlier staging; Submission of archived tumor tissue is highly encouraged for Part A but is not mandatory.
	7.1 Att. 5	Echocardiogram or MUGA	X		
	7.1 Att. 5	ECG (local)	X		A single ECG is to be obtained within 21 days prior to enrollment. In the event the ECG is abnormal at baseline, a repeat confirmation triplicate ECG will be requested.

Baseline Schedule (Part A)

		Study Period	**Baseline**		
		Cycle	BL		
		Visit	0		
		Duration	Up to 21 days (except where noted)		
		Relative Day of Cycle 1 Day 1 (C1D1)	≤21	≤7	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Efficacy Assessment	10.1.1 Att. 5 Att. 7	Imaging/Tumor Assessments (according to RECIST v1 1)	X (within 28 days)		Baseline radiological tumor assessment per RECIST version 1.1 should be done during screening. CT scan or MRI of chest and abdomen including both adrenal glands, with pelvic imaging performed if clinically indicated. **A gadolinium-enhanced MRI of the CNS will be performed at baseline prior to enrollment for all patients.** For screening, scans performed prior to the date of consent may be used provided they are within 28 days of enrollment.
Patient Disposition			X		At the time that the patient is discontinued from Study Participation, information regarding the patient status will be collected.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; C1D1 = Cycle 1 Day 1; CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FFPE = formalin-fixed paraffin embedded; FSH = follicle-stimulating hormone; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition (scan); NSCLC = non-small cell lung cancer; RECIST = Response Evaluation Criteria In Solid Tumors.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Treatment Period Schedule (Part A)

		Study Period	Treatment Period									
		Cycle (14-day cycle ± 3 days)	1	2	3	4	5	6	7	8	9-X	
		Visit	1	2	3	4	5	6	7	8	9-X	
		Relative Day within Dosing Cycle	1	1	1	1	1	1	1	1	1	
Procedure Category	**Protocol Section**	**Procedure**										**Comments**
DLT Assessment Period	9.4.1	Monitor for DLTs	X	X								
Physical Examination	Att. 5	Physical exam (including weight)	X	X	X	X	X	X	X	X	X	Patients should be weighed at the beginning of each cycle. Height measurements to be performed at baseline only. A time window of -3 days is permitted for the Day 1 physical exam.
	Att. 5	ECOG performance status	X	X	X	X	X	X	X	X	X	Complete prior to treatment infusion. A time window of -3 days is permitted for the Day 1 ECOG PS.
	Att. 5	Vital signs	X	X	X	X	X	X	X	X	X	Includes blood pressure, pulse, respiratory rate, and temperature. To be obtained at every treatment visit, within 30 min prior to and after the completion of each infusion of ramucirumab. If there is a post-infusion observation period, then vital signs measurements should also be obtained at the end of the observation period. In the event of an infusion-related reaction, the respiration rate will be collected.
Lab/ Diagnostic Tests	Att. 3	Hematology (local)	X	X	X	X	X	X	X	X	X	Performed locally within 4 days prior to treatment on Day 1 of each cycle. If results of the laboratory tests obtained at planned Day 1 of the next cycle require a delay in the start of the subsequent cycle, any repeat laboratory tests should be obtained, as clinically indicated.
	Att. 3	Serum chemistry (selected tests local/central)	X	X	X	X	X	X	X	X	X	Performed centrally within 4 days prior to treatment on Day 1 of each cycle. For dosing decisions, bilirubin and AST/ALT are required to be collected locally and centrally. If enrollment serum chemistry profile is collected within 4 days of C1D1, the profile does not need to be repeated.
	Att. 3	Coagulation profile (local)	X			X				X	X	Performed locally within 4 days prior to treatment on C1D1. Beginning at Cycle 4, coagulation profile performed every 4 cycles or more frequently, as clinically indicated. Coagulation parameters to be tested include International Normalized Ratio (INR) or prothrombin time (PT), and partial thromboplastin time (PTT/aPTT).

Treatment Period Schedule (Part A)

Procedure Category	Protocol Section	Procedure	Study Period: Treatment Period Cycle (14-day cycle ± 3 days): 1	2	3	4	5	6	7	8	9-X Visit: 1	2	3	4	5	6	7	8	9-X Relative Day within Dosing Cycle: 1	1	1	1	1	1	1	1	1	Comments
	Att. 3 Att. 10	Urinalysis (local)	X	X	X	X	X	X	X	X	X	While a patient is being treated with ramucirumab collect every cycle, dipstick or routine analysis measurements should be done within 3 days prior to treatment. If enrollment urinalysis is collected within 4 days of C1D1, the profile does not need to be repeated at C1D1. Results should be available at the time of the next dosing decision. For further information, see Section 9.4.2.1.2.7 and Attachment 10.
	Att. 3 Att. 5	Pregnancy test (local)		X		X		X		X	X	Serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin [β HCG]). Every 2 cycles, (or per institutional guidelines, whichever is more frequent) pregnancy testing for women of childbearing potential will be performed locally (not collected on the eCRF).
	Att. 5	ECG (local)			X		X		X		X	Twelve-lead ECG within 4 days prior to treatment on C3D1, C5D1, and every 2 cycles thereafter (and if clinically indicated), at the discontinuation of erlotinib, at the discontinuation of ramucirumab, and at the short-term follow-up.
	10.4.3 10.4.4	Immunogenicity	X	X	Immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
	10.4.2.2	Whole blood sample	X	Mandatory whole blood sample will be used for SNP and possible other translational research assays, as applicable. It is highly recommended to draw the whole blood sample prior to the first dose. However, it can be collected later during the study if necessary.
	10.4.2.1	Plasma sample	X	The mandatory plasma sample will be used for the analysis of circulating markers and will be collected prior to the infusion on C1D1, and on C4D1.
	10.4.2.3	Tumor tissue	X	If the archived tumor tissue is not collected during the baseline period, at any time during the study, tumor tissue should be provided from patients who have consented to provide tissue. Fresh tissue is not required. Previously archived Stage IV NSCLC tissue from the initial diagnosis may be used. Submission of archived tumor tissue is highly encouraged for Part A but is not mandatory.

Treatment Period Schedule (Part A)

		Study Period	Treatment Period									
		Cycle (14-day cycle ± 3 days)	1	2	3	4	5	6	7	8	9-X	
		Visit	1	2	3	4	5	6	7	8	9-X	
		Relative Day within Dosing Cycle	1	1	1	1	1	1	1	1	1	
Procedure Category	**Protocol Section**	**Procedure**										**Comments**
Adverse Events Collection/ CTCAE Grading	10.3	Toxicity assessment	X									All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Concomitant Therapy	9.6	Concomitant medications	X	X	X	X	X	X	X	X	X	Concomitant medications will be recorded throughout the treatment period, including those taken during the 30 days after the last dose of all study treatment.
Premedication	9.1.1	Administer premedication (list on eCRF)	X	X	X	X	X	X	X	X	X	Refer Section 7.3 for discontinuation guidance and Section 9.4 for selection and timing of dosing. First treatment will be administered within 7 days of specified evaluations as summarized in the baseline schedule of events. Erlotinib (150 mg) is self-administered *per os* (by mouth) once daily.
Study Treatment	9.1	Administer ramucirumab	X	X	X	X	X	X	X	X	X	
	9.1	Administer erlotinib	X	X	X	X	X	X	X	X	X	
Patient Disposition			X									At the time that the patient is discontinued from any component of the study treatment or Study Participation, information regarding the patient status will be collected.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CxD1 = Cycle x Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IRR = infusion-related reaction; PTT = partial thromboplastin time; RECIST = Response Evaluation Criteria In Solid Tumors.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule (Part A)

			Study Period	Post-discontinuation Follow-Up	
				Short-Term Follow-Up	
			Visit	801	
			Duration	30 ± 3 days	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Physical Examination	Att. 5	Physical exam (including weight)		X	
	Att. 5	Vital signs		X	Includes blood pressure, pulse, respiratory rate, and temperature.
	Att. 5	ECOG performance status		X	
Lab/ Diagnostic Tests	Att. 3	Hematology (local)		X	Hematology will be collected for local lab testing.
	Att. 3	Serum chemistry including thyroid tests and HgbA1c (central)		X	Chemistry will be collected for central lab testing.
	Att. 3	Coagulation profile (local)		X	Coagulation will be collected for local lab testing.
	Att. 3 Att. 10	Urinalysis (local)		X	If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.
	Att. 3 Att. 5	Pregnancy test (local)		X	Serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin [β HCG]).
	Att. 5	Echocardiogram or MUGA		X	
	Att. 5	ECG (local)		X	A single ECG will be performed. In the event the ECG is abnormal, a repeat confirmation triplicate ECG will be performed.
	10.4.2	Plasma sample		X	The mandatory plasma samples will be used for the analysis of circulating markers, to be collected at the short-term follow-up
Adverse Events Collection/ CTCAE Grading	10.3	Toxicity assessment		X	All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Concomitant Medication Notation	9.6	Concomitant medications		X	Concomitant medications will be recorded throughout the treatment period, including those taken during the 30 days after the last dose of all study treatment.
Patient Disposition				X	At the time that the patient is discontinued from Study Participation, information regarding the patient status will be collected.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LCSS = Lung Cancer Symptom Scale; MUGA = multiple-gated acquisition (scan); PD = progressive disease; PRO = patient-reported outcome; QoL = quality of life; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event.

Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts until the short-term follow-up visit is completed, approximately 30 days (±3 days) after the end of study treatment.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Continued Access Period Schedule (Part A)

		Study Period	Continued Access Treatment Period	Continued Access Follow-Up Period	
		Cycle	X-Y	Follow-Up	
		Visit	501-5XX	901	
		Duration	1	30 ± 3 days	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Adverse Events Collection/CTCAE Grading	10.3	Toxicity assessment	X	X	All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Lab/Diagnostic Tests	10.4.3 10.4.4	Immunogenicity/Pharmacokinetics	X		If a patient experiences an IRR to ramucirumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Premedication	9.1.1	Administer premedication (list on eCRF)	X		Refer Section 7.3 for discontinuation guidance and Section 9.4 for selection and timing of dosing. In the event of a medication error, investigative sites must inform Lilly within 24 hours of becoming aware of the error. Erlotinib (150 mg) is self-administered *per os* (by mouth) once daily.
Study Treatment	9.1	Administer ramucirumab	X		
	9.1	Administer erlotinib (daily)	X		
Patient Disposition			X	X	At the time that the patient is discontinued from any component of the study treatment or study participation, information regarding the patient status will be collected. Information regarding the patient status will also be collected at the Continued Access Follow-up visit. This follow-up might be a phone-call to the patient, her/his family, or local doctor.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; PK = pharmacokinetics; SAE = serious adverse event.

Continued access follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment in the continued access period, and lasts until the continued-access follow-up visit is completed, approximately 30 days (±3 days) later.

Attachment 2. Protocol JVCY Part B Study Schedule

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Baseline Schedule (Part B)

		Study Period	Baseline		
		Cycle	BL		
		Visit	0		
		Duration	Up to 21 days (except where noted)		
		Relative Day to Enrollment	≤21	≤14	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Study Entry/ Enrollment	7 13.1	Informed Consent Form signed (prior to conducting any protocol-specific tests/procedures)	X		Obtain informed consent prior to any study-related procedures or evaluations. The investigator or the Sponsor will not grant exceptions to eligibility criteria.
	7.1, 7.2	Inclusion/Exclusion evaluation	X		All inclusion/exclusion criteria must be met for a patient to be considered eligible for study entry. The patient will be randomized via IWRS after meeting inclusion/exclusion criteria.
Medical History	10.3.1 Att. 5	Initial history (including smoking history)/preexisting conditions/disease characteristics	X		Any preexisting and pretreatment toxicity (treatment or disease related) should be documented and recorded as part of the pretreatment medical history, as well as smoking history. Disease characteristics at initial diagnosis and at study entry will be collected.
	Att. 5	Demography	X		Date of birth, sex, and race/ethnicity will be collected at baseline.
	Att. 5	Prior treatment therapy of underlying disease	X		Prior treatment includes any treatment for underlying disease, including maintenance therapy. Start and stop dates should be documented as well.
Physical Examination	Att. 5	Physical examination (including height and weight)		X	Height measurements to be performed at baseline only. A time window of -7 days is permitted for the Cycle 1 Day 1 physical exam.
	Att. 5	ECOG performance status		X	A time window of -7 days is permitted for the Cycle 1 Day 1 ECOG PS.
	Att. 5	Vital signs		X	Includes blood pressure, pulse, respiratory rate, temperature, and SpO_2. The results of the SpO_2 test will not be collected on the eCRF.
Concomitant Medications	9.6	Concomitant medications	X (within 30 days)		Concomitant medications will be recorded, including any taken within 30 days prior to start of study treatment.

Baseline Schedule (Part B)

Study Period	Baseline	
Cycle	BL	
Visit	0	
Duration	Up to 21 days (except where noted)	
Relative Day to Enrollment	≤21	≤14

Procedure Category	Protocol Section	Procedure			Comments
Lab/ Diagnostic Tests	7.1 Att. 3	Hematology (local)		X	Hematology will be collected for local lab testing. If enrollment hematology profile is collected within 7 days of C1D1, the profile does not need to be repeated at C1D1.
	7.1 Att. 3	Serum chemistry including thyroid tests and HgbA1c (central)		X	If enrollment chemistry profile is collected within 7 days of Day 1, Cycle 1, the profile does not need to be repeated at C1D1. Central chemistry laboratory results will be used to determine patient eligibility at baseline. For dosing decisions, bilirubin and AST/ALT are required to be collected locally and centrally. Thyroid tests (TSH and free T4) and HgbA1c will be collected for safety monitoring and will be performed at a central lab.
	7.1 Att. 3	Coagulation profile (local)		X	If enrollment coagulation bloodwork is collected within 7 days of C1D1, the profile does not need to be repeated. Patients receiving warfarin should be switched to LMWH as per institutional guidelines, and have achieved stable coagulation profile prior to enrollment.
	7.1 Att. 3 Att. 10	Urinalysis (local)		X	At baseline, dipstick measurements should be done within 7 days prior to C1D1. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.
	7.1 Att. 3 Att. 5	Pregnancy test (local)		X	At baseline, serum pregnancy testing for women of childbearing potential will be performed locally. The results of this test will not be collected on the eCRF.
	7.1	Follicle-stimulating hormone (FSH) (local)		X	A baseline FSH test for eligibility will only be performed on women who have had spontaneous amenorrhea for 6-12 months prior to study entry.
	10.4.2.3	Mandatory tumor tissue	X		This tissue collection is for the evaluation of potential biomarkers. Unless restricted by local regulations, mandatory FFPE tissue provided should be from the Stage IV NSCLC diagnosis and, ideally, not from an earlier staging; however, archived NSCLC tissue samples derived from other than Stage IV disease may be acceptable, based on approval by Lilly CRP. Tissue collection is mandatory in Part B.
	10.4.2.3	Plasma sample (see comments)	X		Unless restricted by local regulations, the plasma sample for disease characterization is required ONLY for patients who do not submit Stage IV disease tissue samples. Optionally, patients who entered the study prior to amendment d may provide this plasma sample during the study treatment period (see Treatment Period Schedule for Part B, below).

Baseline Schedule (Part B)

		Study Period	**Baseline**		
		Cycle	BL		
		Visit	0		
		Duration	Up to 21 days (except where noted)		
		Relative Day to Enrollment	≤21	≤14	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
	7.1 Att. 5	Echocardiogram or MUGA	X		
	7.1 Att. 5	ECG (local)	X		A single ECG is to be obtained within 21 days prior to enrollment. In the event the ECG is abnormal at baseline, a repeat confirmation triplicate ECG will be requested.
Health Outcomes	10.2.1	PRO Assessments (LCSS, EQ-5D-5L)		X	The instruments should be completed before any extensive contact and consultation which may bias patient responses. It is recommended that the instruments be administered together, with the LCSS completed first, followed by the EQ-5D-5L.
Efficacy Assessment	10.1.1 Att. 5 Att. 7	Imaging/Tumor Assessments (according to RECIST v1.1)	X (within 28 days)		Baseline radiological tumor assessment per RECIST version 1.1 should be done during screening. CT scan or MRI of chest and abdomen including both adrenal glands, with pelvic imaging performed if clinically indicated. **A gadolinium-enhanced MRI of the CNS will be performed at baseline prior to randomization for all patients.** Bone scans and PET scans may be performed if clinically indicated (refer to Attachment 5 for further details). All baseline radiological reports will be collected and sent to the central imaging vendor, preferably prior to C1D1. For screening, scans performed prior to the date of consent may be used provided they are within 28 days of enrollment.
Patient Disposition			X		At the time that the patient is discontinued from study participation, information regarding the patient status will be collected.

Abbreviations: BL = baseline; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FFPE = formalin-fixed paraffin embedded; FSH = follicle-stimulating hormone; INR = international normalized ratio; LCSS = Lung Cancer Symptom Scale; MRI = magnetic resonance imaging; PET = positron emission tomography; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumors.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Treatment Period Schedule (Part B)

		Study Period	Treatment Period									
		Cycle (14-day cycle ± 3 days)	1	2	3	4	5	6	7	8	9-X	
		Visit	1	2	3	4	5	6	7	8	9-X	
		Relative Day within Dosing Cycle	1	1	1	1	1	1	1	1	1	
Procedure Category	**Protocol Section**	**Procedure**										**Comments**
Physical Examination	Att. 5	Physical exam (including weight)	X	X	X	X	X	X	X	X	X	Patients should be weighed at the beginning of each cycle. Height measurements to be performed at baseline only. After Cycle 1, a time window of -4 days is permitted for the Day 1 physical exam.
	Att. 5	ECOG performance status	X	X	X	X	X	X	X	X	X	Complete prior to treatment infusion. After Cycle 1, a time window of -4 days is permitted for the Day 1 ECOG PS.
	Att. 5	Vital signs	X	X	X	X	X	X	X	X	X	Includes blood pressure, pulse, respiratory rate, and temperature. To be obtained at every treatment visit, within 30 min prior to and after the completion of each infusion of ramucirumab. If there is a post-infusion observation period, then vital signs measurements should also be obtained at the end of the observation period. In the event of an infusion-related reaction, the respiration rate will be collected.
Lab/ Diagnostic Tests	Att. 3	Hematology (local)		X	X	X	X	X	X	X	X	Performed locally within 4 days prior to treatment on Day 1 of each cycle, after Cycle 1. If results of the laboratory tests obtained at planned Day 1 of the next cycle require a delay in the start of the subsequent cycle, repeat laboratory tests should be obtained, as clinically indicated.
	Att. 3	Serum chemistry (selected tests local/central)		X	X	X	X	X	X	X	X	Performed centrally within 4 days prior to treatment on Day 1 of each cycle after Cycle 1. For dosing decisions, bilirubin and AST/ALT are required to be collected locally and centrally. If enrollment serum chemistry profile is collected within 7 days of C1D1, the profile does not need to be repeated.
	Att. 3	Coagulation profile (local)				X				X	X	Performed locally within 4 days prior to treatment on Day 1 of the required cycle (after Cycle 1). Beginning at Cycle 4, coagulation profile performed every 4 cycles or more frequently, as clinically indicated. Coagulation parameters to be tested include International Normalized Ratio or prothrombin time (PT), and partial thromboplastin time (PTT/aPTT).
	Att. 3 Att. 10	Urinalysis (local)		X	X	X	X	X	X	X	X	While a patient is being treated with ramucirumab, dipstick or routine analysis measurements should be done within 4 days prior to treatment at every cycle, after Cycle 1. Results should be available at the time of the next dosing decision. For further information on events of proteinuria, see Section 9.4.2.1.2.7 and Attachment 10.

Treatment Period Schedule (Part B)

Procedure Category	Protocol Section	Procedure	Study Period: Treatment Period Cycle (14-day cycle ± 3 days): 1	2	3	4	5	6	7	8	9-X	Comments
			Visit: 1	2	3	4	5	6	7	8	9-X	
			Relative Day within Dosing Cycle: 1	1	1	1	1	1	1	1	1	
	Att. 3 Att. 5	Pregnancy test (local)		X		X		X		X	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin [β HCG]). Every 2 cycles, (or per institutional guidelines, whichever is more frequent) pregnancy testing for women of childbearing potential will be performed locally (not collected on the eCRF). If the urine pregnancy test is positive, confirm with a serum pregnancy test.
	Att. 5	ECG (local)			X		X		X		X	Twelve-lead ECG within 4 days prior to treatment on C3D1, C5D1, and every 2 cycles thereafter (and if clinically indicated), at the discontinuation of erlotinib, at the discontinuation of ramucirumab/placebo, and at the short-term follow-up.
	10.4.3 10.4.4 Att. 8	Immunogenicity	Refer to Attachment 8 for timepoints.									Immunogenicity blood work to be collected BEFORE the first infusion of ramucirumab/placebo on C1D1 and C4D1 of treatment. If a patient experiences an IRR to ramucirumab/placebo, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
	10.4.4 Att. 8	Pharmacokinetics	Refer to Attachment 8 for timepoints.									
	10.4.2.2 Att. 8	Whole blood sample	Refer to Attachment 8 for timepoints.									Sample will be used for SNP and possible other translational research assays, as applicable. It is highly recommended to draw the whole blood sample prior to the first dose. However, it can be collected later during the study if necessary. Mandatory for Part B.
	10.4.2.1 Att. 8	Plasma sample	Refer to Attachment 8 for timepoints.									Plasma samples will be used for the analysis of circulating factors and will be collected prior to the infusion on C1D1, and on C4D1. Mandatory for Part B.
	10.4.2.3 Att. 8	Mandatory archived tumor tissue (once patient consents)	X									If the mandatory archived tumor tissue is not collected during the baseline period, at any time during the study, tumor tissue should be provided from patients who have consented to provide tissue. Fresh tissue is not required. Previously archived Stage IV NSCLC tissue from the initial diagnosis may be used; however, archived NSCLC tissue samples derived from other than Stage IV disease may be acceptable, based on approval by Lilly CRP. For patients who do not submit Stage IV disease tissue samples, a plasma sample for disease characterization may be requested unless restricted by local regulations. Tissue collection is mandatory in Part B.

Treatment Period Schedule (Part B)

		Study Period	Treatment Period									
		Cycle (14-day cycle ± 3 days)	1	2	3	4	5	6	7	8	9-X	
		Visit	1	2	3	4	5	6	7	8	9-X	
		Relative Day within Dosing Cycle	1	1	1	1	1	1	1	1	1	
Procedure Category	**Protocol Section**	**Procedure**										**Comments**
Health Outcomes	10.2.1	PRO Assessments (LCSS, EQ-5D-5L)		X		X		X		X	X	The patient will undergo assessment for symptoms and QoL using the LCSS and the EuroQol EQ-5D-5L at Cycle 2, thereafter at every other cycle. The instruments should be completed before any extensive contact and consultation which may bias patient responses. It is recommended that the instruments be administered together, with the LCSS completed first, followed by the EQ-5D-5L.
Efficacy Assessment	10.1.1 Att. 5 Att. 7	Imaging/Tumor Assessments			X			X			X	Disease assessment will be every 6 weeks (±7 days) as calculated from the first dose of study therapy, and after 72 weeks while on study, imaging must be performed every 12 weeks (±7 days). The method used at baseline must be used consistently for tumor assessment. CT scan or MRI of chest and upper abdomen including both adrenal glands are required, with pelvic imaging performed if clinically indicated. Bone scans and PET scans may be performed if clinically indicated (refer to Attachment 5 for further details).
Adverse Events Collection/ CTCAE Grading	10.3	Toxicity assessment	X									All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Concomitant Therapy	9.6	Concomitant medications	X	X	X	X	X	X	X	X	X	Concomitant medications will be recorded throughout the treatment period, including those taken during the 30 days after the last dose of all study treatment.
Premedication	9.1.1	Administer premedication (list on eCRF)	X	X	X	X	X	X	X	X	X	Refer Section 7.3 for discontinuation guidance and Section 9.4 for selection and timing of dosing. First treatment will be administered within 7 days of enrollment (also within 3 days of randomization). Erlotinib (150 mg) is self-administered *per os* (by mouth) once daily.
Study Treatment	9.1	Administer ramucirumab or placebo	X	X	X	X	X	X	X	X	X	
	9.1	Administer erlotinib	X	X	X	X	X	X	X	X	X	
Patient Disposition			X									At the time that the patient is discontinued from any component of the study treatment or Study Participation, information regarding the patient status will be collected.

Abbreviations: BSA = body surface area; CxD1 = Cycle x Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; PET = positron emission tomography; PTT = partial thromboplastin time; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule (Part B)

			Study Period	Post-discontinuation Follow-Up		
				Short-Term Follow-Up	Long-Term Follow-Up	
			Visit	801	802-8XX	
			Duration	30 ± 3 days	See footnote for duration	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Physical Examination	Att. 5	Physical exam (including weight)	X			
	Att. 5	Vital signs	X			Includes blood pressure, pulse, respiratory rate, and temperature.
	Att. 5	ECOG performance status	X			
Lab/ Diagnostic Tests	Att. 3	Hematology (local)	X			Hematology will be collected for local lab testing.
	Att. 3	Serum chemistry including thyroid tests and HgbA1c (central)	X			Chemistry will be collected for central lab testing.
	Att. 3	Coagulation profile (local)	X			Coagulation will be collected for local lab testing.
	Att. 3 Att. 10	Urinalysis (local)	X			If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.
	Att. 3 Att. 5	Pregnancy test (local)	X			Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin [β HCG]). If the urine pregnancy test is positive, confirm with a serum pregnancy test (pregnancy test results are not recorded on the eCRF).
	Att. 5	Echocardiogram or MUGA	X			
	Att. 5	ECG (local)	X			A single ECG will be performed. In the event the ECG is abnormal, a repeat confirmation triplicate ECG will be performed.
	10.4.3 10.4.4 Att. 8	Immunogenicity	Refer to Attachment 8 for timepoints and additional notes.			Immunogenicity sample to be collected at the short-term follow-up. In the event of an IRR reaction, blood samples will be collected for both PK and immunogenicity analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.
	Att. 8	Pharmacokinetics	Refer to Attachment 8 for timepoints and additional notes.			PK sample to be collected at the short-term follow-up. In the event of an IRR reaction, blood samples will be collected for both PK and immunogenicity analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.
	10.4.2 Att. 8	Plasma sample	X			The plasma samples will be used for the analysis of circulating proteins, to be collected at the short-term follow-up
Health Outcomes	10.2.1	PRO Assessments (LCSS, EQ-5D-5L)	X			The patient will undergo assessment for symptoms and QoL using the LCSS and the EuroQol EQ-5D. The instruments should be completed before any extensive contact and consultation which may bias patient responses. It is recommended that the instruments be administered together, with the LCSS completed first, followed by the EQ-5D-5L.

Post-Treatment Discontinuation Schedule (Part B)

			Study Period	Post-discontinuation Follow-Up		
				Short-Term Follow-Up	Long-Term Follow-Up	
			Visit	801	802-8XX	
			Duration	30 ± 3 days	See footnote for duration	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Efficacy Assessments	Att. 5 Att. 7	Imaging/Tumor Assessments (every 6 wk ±7d, and after 72 weeks while on study, imaging must be performed every 12 weeks [±7 days])		X	X	For patients who discontinue study treatment without objectively measured PD, disease assessment will continue to be assessed every 6 weeks (±7 days) as calculated from the first dose of study therapy, and after 72 weeks while on study, imaging must be performed every 12 weeks (±7 days). The method used at baseline must be used consistently for tumor assessment. If a patient discontinues treatment due to objective disease progression, one additional tumor scan will be collected at the short-term follow-up unless the patient has received additional anticancer therapy prior to this visit. Thereafter, radiologic tests are no longer required. The long-term follow-up consists of follow-up for survival and/or PFS2.
	10.1.2	Survival Information and Subsequent Anti-Cancer Treatments			X	Patients will be followed for survival data and subsequent anticancer treatments will be collected after discontinuation of study drug at regularly scheduled intervals (every 3 months [± 14 days]) until death or study completion, whichever occurs first. This follow-up might be a phone-call to the patient, her/his family, or local doctor for the collection of survival data and subsequent antitumor therapies.
Adverse Events Collection/ CTCAE Grading	10.3	Toxicity assessment		X	X	All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Concomitant Medication Notation	9.6	Concomitant medications		X		Concomitant medications taken during the 30 days after the last dose of all study treatment will be recorded.
Patient Disposition				X	X	At the time that the patient is discontinued from Study Participation, information regarding the patient status will be collected. T790M status, only if available, will be collected at the short-term follow-up visit.

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; LCSS = Lung Cancer Symptom Scale; PD = progressive disease; PFS2 = progression-free survival 2; PRO = patient-reported outcome; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts until the short-term follow-up visit is completed, approximately 30 days (±3 days) after the end of study treatment.

Long-term follow-up begins the day after short-term follow-up is completed and continues every 6 weeks (±7 days), and after 72 weeks while on study, imaging must be performed every 12 weeks (±7 days) until PD, thereafter every 3 months (±14 days) until the patient's death or overall study completion. For patients who discontinue study treatment for reasons other than radiographically documented PD, tumor response will continue to be evaluated according to the protocol schedule, except when not feasible in the opinion of the investigator due to patient's clinical status. Once radiographic assessments are no longer performed, the patient will be followed every 3 months (±14 days) until death, study completion, or withdrawal from study participation. The long-term follow-up consists of follow-up for survival and/or PFS2. Although it is not mandatory, PFS2 based on radiographic assessment is recommended.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Continued Access Period Schedule (Part B)

		Study Period	Continued Access Treatment Period	Continued Access Follow-Up Period	
		Cycle	X-Y	Follow-Up	
		Visit	501-5XX	901	
		Duration	1	30 ± 3 days	
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Adverse Events Collection/CTCAE Grading	10.3	Toxicity assessment	X	X	All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Lab/Diagnostic Tests	10.4.3 10.4.4 Att. 8	Immunogenicity/Pharmacokinetics	Only if applicable		If a patient experiences an IRR to ramucirumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
Premedication	9.1.1	Administer premedication (list on eCRF)	X		Refer Section 7.3 for discontinuation guidance and Section 9.4 for selection and timing of dosing. In the event of a medication error, investigative sites must inform Lilly within 24 hours of becoming aware of the error. Erlotinib (150 mg) is self-administered *per os* (by mouth) once daily.
Study Treatment	9.1	Administer ramucirumab or placebo	X		
	9.1	Administer erlotinib (daily)	X		
Patient Disposition			X	X	At the time that the patient is discontinued from any component of the study treatment or study participation, information regarding the patient status will be collected. Information regarding the patient status will also be collected at the Continued Access Follow-up visit. This follow-up might be a phone-call to the patient, her/his family, or local doctor.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; PK = pharmacokinetics; SAE = serious adverse event.

Continued access follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment in the continued access period, and lasts until the continued-access follow-up visit is completed, approximately 30 days (±3 days) later.

Attachment 3. Protocol JVCY Clinical Laboratory Tests

Hematology[a]:
Whole Blood Concentrations of the following:
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Coagulation Test[a,b]:
Prothrombin time (PT or INR)
Partial thromboplastin time (PTT or aPTT)

Pregnancy Test (WOCBP only)[a]:
Serum (baseline only) or urine

Thyroid Tests[c]:
TSH and free T4 (to be collected at baseline and short-term follow-up)

Exploratory Biomarker Tests[c]:
Refer to Section 10.4.2

Other[c]
Anti-ramucirumab antibody
Ramucirumab concentrations in serum

Clinical Chemistry[c]:
Serum Concentrations of the following:
Sodium
Potassium
Total bilirubin[d]
Direct bilirubin[d]
Alkaline phosphatase
Alanine aminotransferase (ALT)[d]
Aspartate aminotransferase (AST)[d]
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Calcium
Glucose, random
Albumin
Chloride
Total protein
Lactate dehydrogenase
Magnesium
Phosphorus
HgbA1c (to be collected at baseline and short-term follow-up)

Urinalysis[a]:
Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+ at evaluations, a 24 hour urine collection (to assess protein) must be obtained.

Follicle Stimulating Hormone[a]:
FSH

Tissue test[a]:
EGFR mutation

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial prothrombin time; AST = aspartate aminotransferase; eCRF = electronic case report form; INR = international normalized ratio; PT = prothrombin time; PTT = partial prothrombin time; RBC = red blood cells; WBC = white blood cells; WOCBP = women of child-bearing potential.

a Assayed by local or investigator-designated laboratory. For hematology, if a manual differential is not able to be performed, then an automated differential will be acceptable. Serum pregnancy test in WOCBP will be done at baseline, thereafter serum or urine pregnancy test will be required (minimum sensitivity 25 IU/L or equivalent units of beta human chorionic gonadotropin [β HCG]). Pregnancy test results will not be collected on the eCRF. If the urine pregnancy test is positive, confirm with a serum pregnancy test. A baseline FSH test for eligibility will only be performed on women who have had spontaneous amenorrhea for 6-12 months prior to study entry. For the *EGFR* mutation status, sites will enter on the eCRF the specific mutation(s) identified and the name of the test method used to document evidence of *EGFR* mutation positivity.

b For both prothrombin time and partial thromboplastin, whichever lab for each is selected at baseline should be followed throughout the study.

c PGx and 'Other' samples will be assayed by a sponsored-designated laboratory. Serum chemistry and thyroid tests will be assayed centrally. Thyroid tests (TSH and free T4) and HgbA1c will be collected at baseline and at the short-term follow-up visit.

d For dosing decisions, bilirubin and AST/ALT are required to be collected locally and centrally.

Attachment 4. Protocol JVCY Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a, b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; IgG =immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 5. Protocol JVCY Study Procedures

Informed Consent

Written informed consent will be given by each patient prior to undergoing study-specific evaluations and prior to receiving treatment.

Demography

Date of birth, sex, and race/ethnicity. Demographic data are collected to demonstrate that a trial population is representative of the to-be-treated population considered for regulatory approval. The representativeness could be, to a large degree, determined by race.

Medical History

Past and current medical conditions and treatments, current medications, medications taken within 30 days prior to enrollment, date of diagnosis, histopathological or cytological confirmation of malignancy, prior cancer therapy (surgery, radiotherapy, chemotherapy regimen, and any targeted therapy agents, maintenance therapy) including reason for discontinuation of the previous anticancer therapy. Any preexisting toxicity (e.g., Grade 1 fatigue) should be documented and recorded at this time.

Physical Examination

Complete Physical Examination - height (pretreatment only) and weight.

ECOG Performance Status – according to the ECOG PS criteria given in the table below.

ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al. 1982.

Toxicity/AE - Assessment including NCI-CTCAE v4.0 grade

Vital Signs - Measurements include temperature, pulse rate, respiratory rate, and blood pressure.

Clinical Tests

Laboratory Parameters – see Attachment 3.

Pregnancy Test –Women of child bearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle-stimulating hormone [FSH] level ≥ 40 mIU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, who are practicing abstinence, or whose partner is sterile (for example, vasectomy), should be considered to be of childbearing potential.

Other Tests

Electrocardiogram (ECG) – to be obtained at screening/baseline (≤ 21 days prior to enrollment), within 72 hours prior to treatment on Day 1 of Cycle 3, Cycle 5, and every 2 cycles thereafter (and if clinically indicated), at the discontinuation of chemotherapy, at the discontinuation of ramucirumab/placebo, and at the short-term follow-up visit.

Echocardiogram or Multiple Gated Acquisition Scan (MUGA) - to be obtained at screening/baseline (≤ 21 days prior to enrollment) and at the short-term follow-up visit.

Efficacy Assessments

Imaging Studies:

Imaging methods will be employed consistently during the course of each patient's evaluation during the study (for example, patients who have abdominal MRI as a baseline exam should continue to have abdominal MRI assessments as a means of determining response/progression).

- CT scan or MRI of chest and upper abdomen including both adrenal glands are required, with pelvic imaging performed if clinically indicated. Disease should be captured and metastases identified at baseline (within 28 days prior to enrollment). Subsequently, imaging studies required to investigate known disease should be repeated every 6 weeks ±7 days (as calculated from the first dose of study therapy) following the first dose of study therapy and despite any treatment delays, after 72 weeks while on study, imaging must be performed every 12 weeks (±7 days). It is recommended that CT imaging of the abdomen/pelvis be performed with IV contrast. If this is not feasible/advisable secondary to hypersensitivity or other conditions, then contrast-enhanced MRI is preferred. For patients with known serious allergic reactions to CT contrast material, a contrast-enhanced MRI of the chest/abdomen/pelvis is encouraged.
    - A gadolinium-enhanced MRI of the CNS will be performed at pretreatment. While on study, a gadolinium-enhanced MRI of the CNS may be performed if clinically indicated.

- Bone scans and positron emission tomography (PET) scans may be performed if clinically indicated, but may not be used to measure target lesions. Abnormal findings on bone scans at baseline that are suggestive or compatible with metastatic disease to the bone require radiographic confirmation (with plain films, CT, or MRI).

Radiographic scans will be collected locally and stored centrally. An independent review of all scans may be considered following the completion of the study.

Health Outcome/Quality of Life Measures: see Section 10.2

Other Study Procedures (see Sections 10.4.2, 10.4.3, and 10.4.4)

Translational Research

Immunogenicity Research

Pharmacokinetic Assessment

Postdiscontinuation Follow-Up Period:

The postdiscontinuation follow-up period includes the 30-day short-term follow-up and long-term follow-up visits, and will continue until death or study completion.

Short-Term Follow-Up:

The short-term follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days (±3 days).

For patients who stop treatment for reasons other than PD, imaging studies with tumor measurements/disease response assessments should continue to be performed every 6 weeks (± 7 days), after 72 weeks while on study, imaging must be performed every 12 weeks (±7 days) until documentation of radiographic PD.

Adverse events occurring during this period will be documented and reported according to Section 10.3.1.

Long-Term Follow-Up:

After the 30-day follow-up, only new and ongoing serious adverse events (SAEs) deemed related to study treatment will be collected.

Patients will be contacted every 3 months (± 14 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). Follow-up will continue as long as the patient is alive, or until study completion as defined in Section 7.3.

Attachment 6. Protocol JVCY Creatinine Clearance Formula and NYHA Classification

Note: This formula is to be used for calculating creatinine clearance (CrCl).

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}$$

[a] age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

New York Heart Association (NYHA) Classification

Functional Capacity
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

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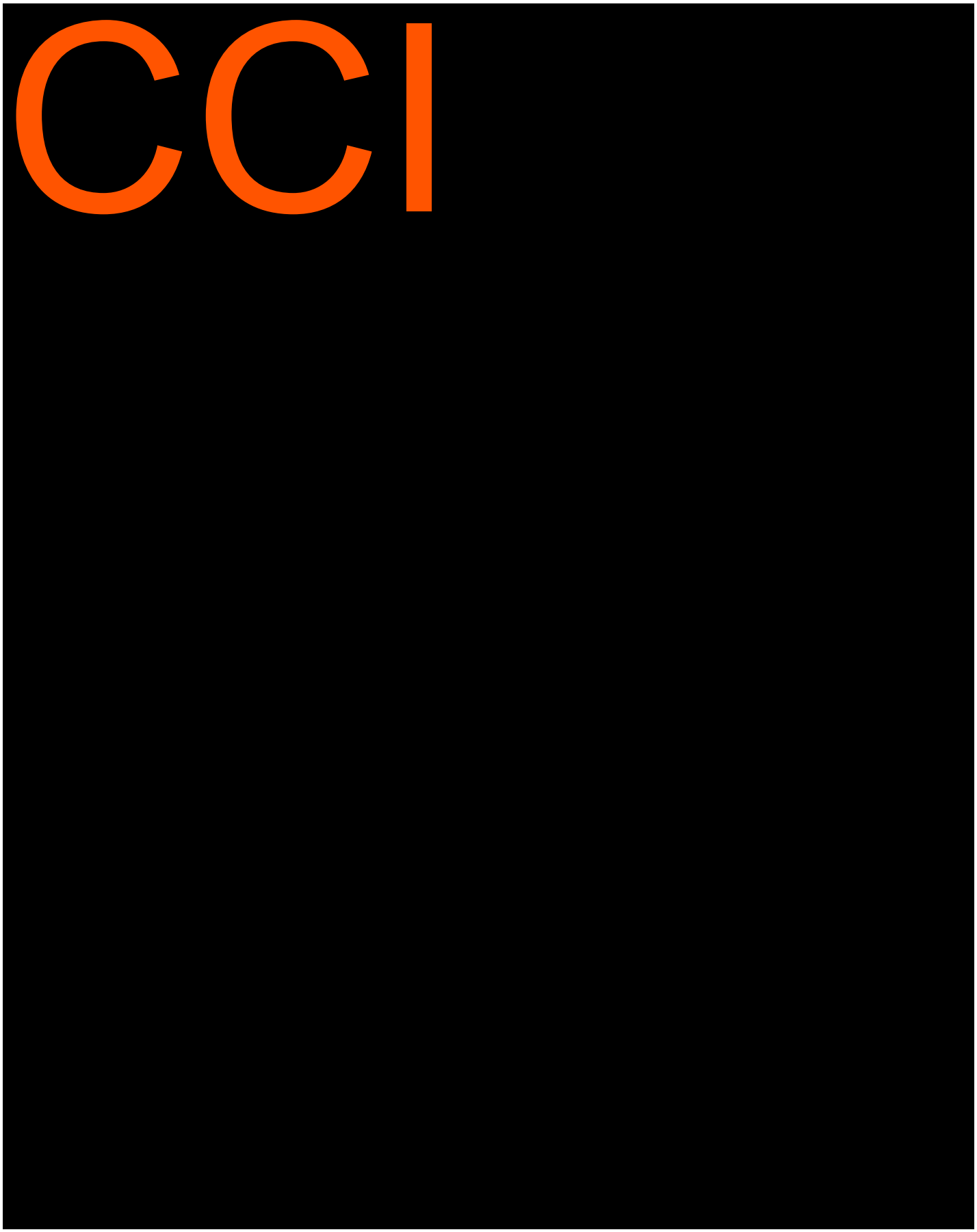
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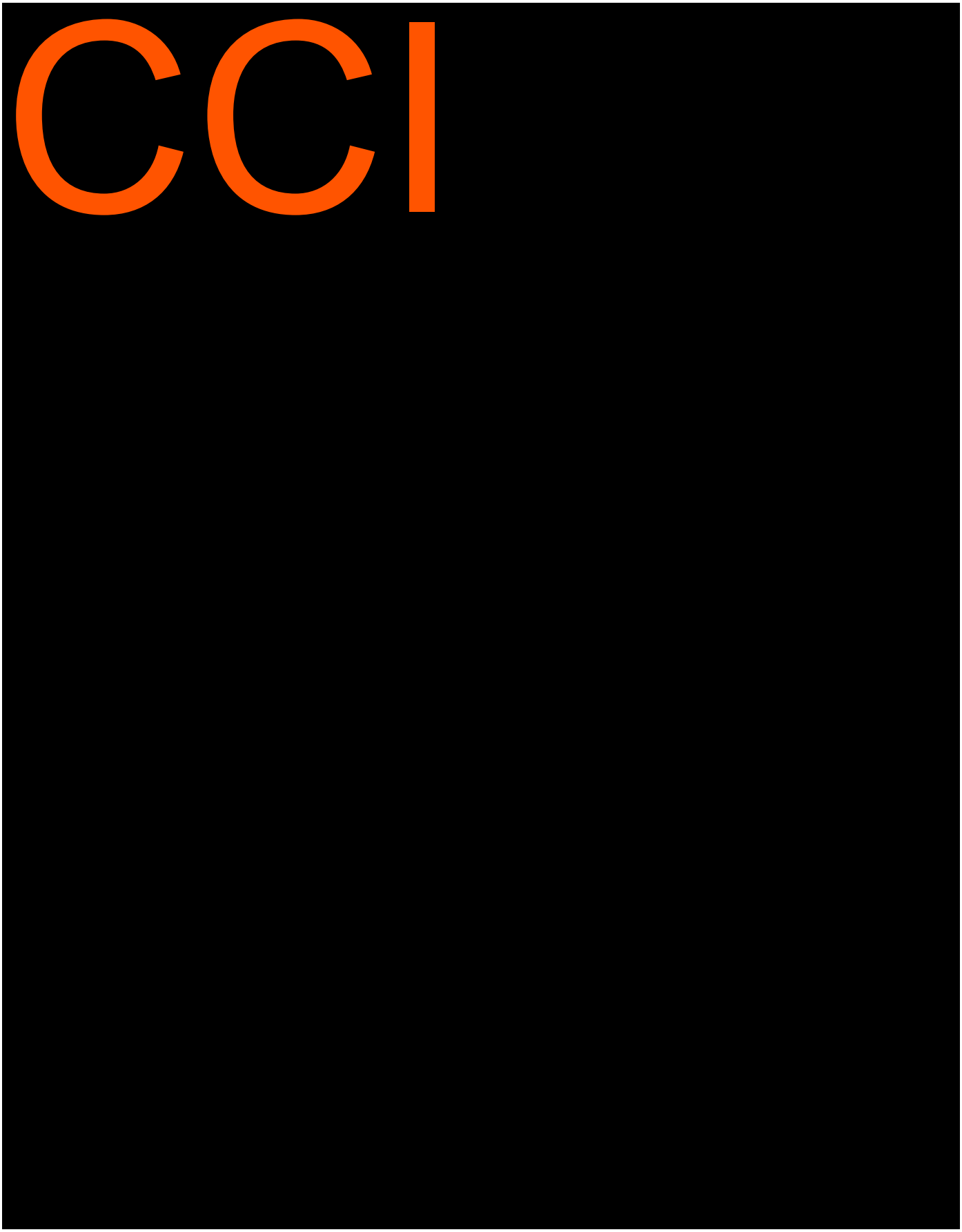
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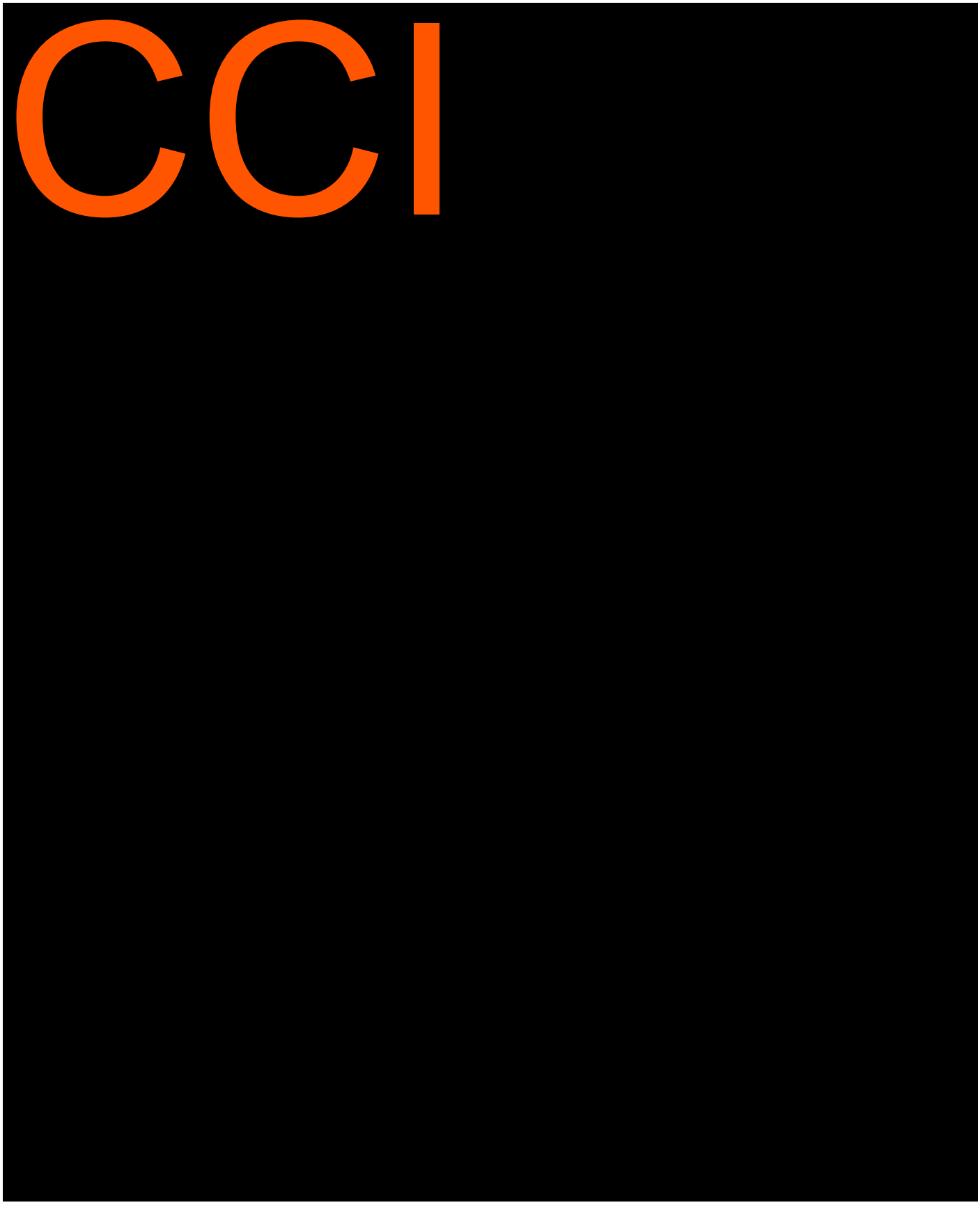
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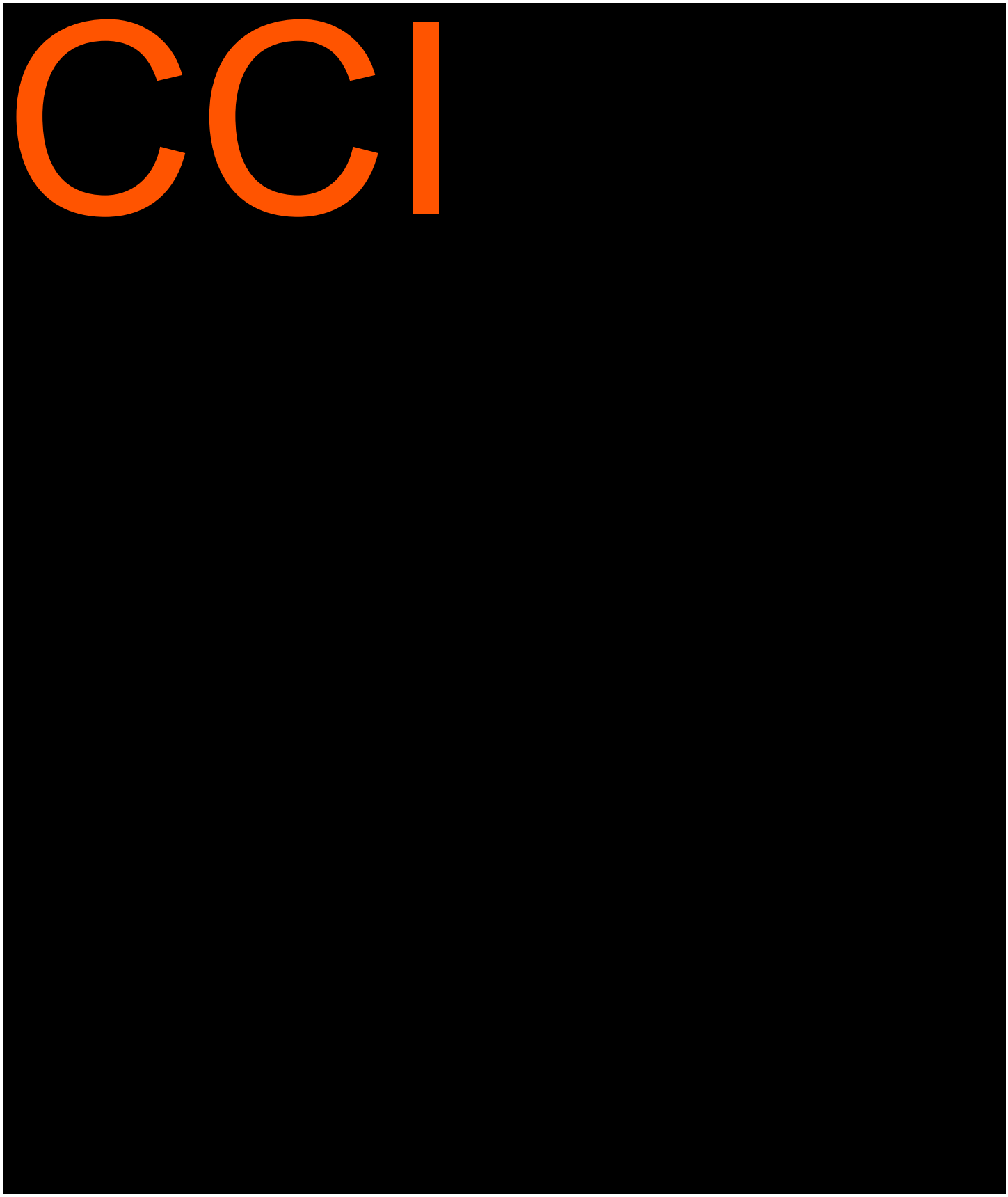
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Attachment 8. Protocol JVCY Part B Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule

It is essential that the exact infusion start and stop times (actual clock readings), as well as infusion parameters (such as, type of infusion pump, flow rate settings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the pharmacokinetic blood samples not be withdrawn from the same site as the drug infusion. Sample collection times may vary to within 1 to 1.5 hour after the end of ramucirumab/placebo infusion outlined in the PK sampling schedule.

Protocol I4T-MC-JVCY Part B Schedule for Ramucirumab/Placebo Pharmacokinetic, Immunogenicity, and Translational Research Sampling

Visit	Time	Serum Ramucirumab PK[a]	Immunogenicity[a]	Tumor Tissue Collection[b]	Plasma	Whole Blood for DNA
Day 1 of Cycle 1	Predose[c]	X	X	X	X[d]	X[e]
	1 hour after the end of ramucirumab/ placebo infusion	X				
Day 1 of Cycle 2	Predose[f]	X				
Day 1 of Cycle 4	Predose[f]	X	X		X	
Day 1 of Cycle 7	Predose[f]	X				
Day 1 of Cycle14	Predose[f]	X				
	1 hour after the end of ramucirumab/ placebo infusion	X				
30 (±10) Days After Discontinuation of ramucirumab [g, h]	Anytime	X	X		X	

Note: It is essential that the draw dates and draw times are accurately recorded.

Abbreviations: C1D1 = Cycle 1, Day 1; IG = immunogenicity; PK = pharmacokinetic(s).

a In the event of an infusion-related reaction, blood samples will be collected for both PK and immunogenicity analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

b Refer to Section 10.4.2.3 for details on tumor tissue collection.

c Prior to the first infusion (baseline; may be obtained within 14 days prior to the initial infusion of ramucirumab/ placebo).

d For patients who do not submit Stage IV disease tissue samples, a plasma sample for disease characterization is required at baseline (for Part B), unless restricted by local regulations. If a plasma sample for disease characterization is not collected during the baseline period, the plasma sample may be requested during the treatment period.

e Prior to first infusion on C1D1 preferred, otherwise later during the trial is acceptable.

f Prior to ramucirumab/placebo infusion.

g The postdiscontinuation follow-up begins on the day after the patient and the investigator agree that the patient will no longer continue study treatment. The short-term 30-day follow-up visit occurs at or near the end of the short-term follow-up period.

h When a patient discontinues ramucirumab/placebo or ramucirumab/placebo and erlotinib, PK/IG serum and plasma samples will be collected 30 (±10) days thereafter. If a patient continues to take erlotinib after discontinuation of ramucirumab/placebo, additional PK/IG serum and plasma samples are NOT required after erlotinib discontinuation.

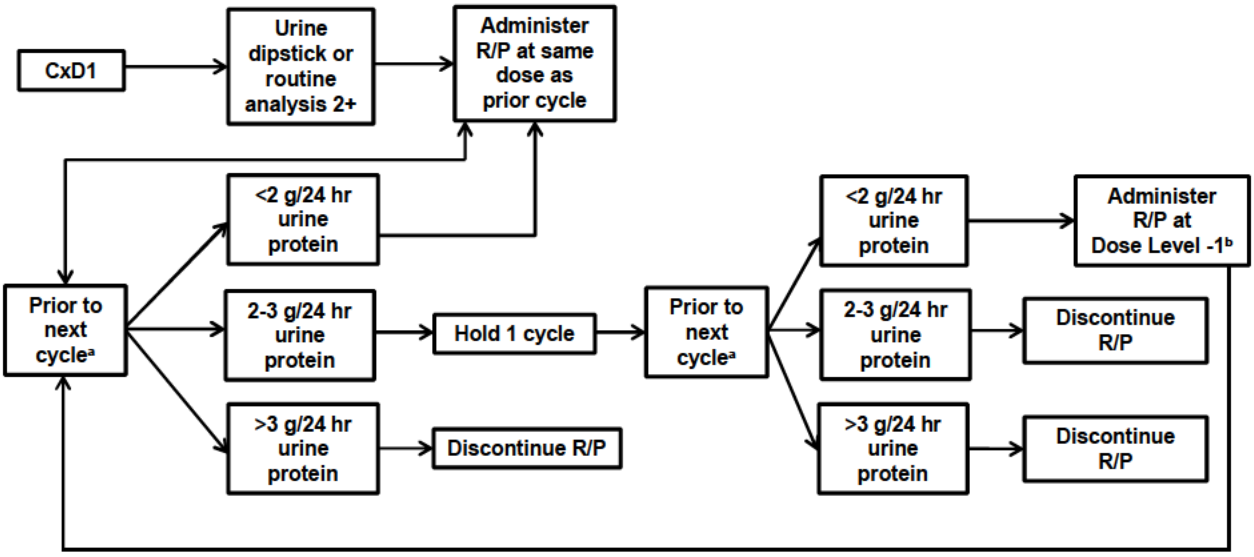
Attachment 9. Protocol JVCY CYP3A4 Modulators

CYP3A4 Inducers	Strong CYP3A4 Inhibitors
aminoglutethimide	clarithromycin
bosentan	chloramphenicol
carbamazepine	cobicistat
efavirenz (in liver only)	conivaptan
fosphenytoin	cremophor EL
nafcillin	cyclosporine
nevirapine	delavirdine
oxcarbazepine	diclofenac
pentobarbital	diltiazem
phenobarbital	elvitegravir and ritonavir
phenytoin	enoxacin
primidone	erythromycin
rifabutin	fosamprenavir
rifampin	grapefruit juice
rifapentine	indinavir
St. John's wort	indinavir and ritonavir
	itraconazole
	ketoconazole
	lopinavir and ritonavir
	mibefradil
	miconazole
	nefazodone
	nelfinavir
	nicardipine
	posaconazole
	quinidine
	ritonavir
	saquinavir
	telithromycin
	theophylline
	troleandomycin
	voriconazole

Attachment 10. Protocol JVCY NCI-CTCAE v4.0 Infusion-Related Reactions and Dosing Algorithm for Proteinuria

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤ 24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Dosing Algorithm for Proteinuria



Abbreviations: R/P= ramucirumab/placebo

a 4 days prior to the next cycle, collect 24-hour urine protein

b Dose level of R/P should be reduced 1 level down from prior dose level each time after 14-day hold (± 3 days), until 5 mg/kg is reached. If proteinuria persists after 5 mg/kg dose, then R/P should be discontinued.

Attachment 11. Protocol JVCY Amendment (f) Summary 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

Overview

Protocol I4T-MC-JVCY(e), 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, has been amended. The new protocol is indicated by amendment (f) and will be used to conduct the study in place of any preceding version of the protocol.

This amendment reflects revised statistical assumptions for both the control and the experimental arms. Accordingly, the number of PFS events required to perform the primary analysis has been updated from approximately 320 events to approximately 270 events. The following provides the rationale for the revised assumptions:

The performance of the control arm has been reassessed based on data from recent first-line erlotinib trials in patients with EGFR mutation-positive NSCLC (Soria et al. 2018), meta-analysis (Lee et al. 2017) and real-world evidence (Okamoto et al. 2018). These data show that the erlotinib control arm may perform better than the initially-assumed median PFS of 9.5 months. As a result, the median PFS assumption for the control arm was increased to 11 months. Additionally, recent positive data from the Phase 1b part (Part A) of this study have shown a median PFS of 17.1 months (Reck et al. 2017). Consequently, the median PFS assumption for the experimental arm was increased from approximately 13 months to 15.5 months. Under the assumption of exponential PFS, this translates to an HR of 0.71, and therefore the HR has been reduced to reflect the revised statistical assumptions from 0.72 to 0.71.

Additionally, this amendment removes the interim PFS efficacy analysis that was to occur at approximately 224 PFS events because the FDA recommended not to perform this interim analysis as it may not provide an accurate or reproducible estimate of treatment benefit.

The combined impact of (i) reducing the target HR to 0.71, (ii) having previously passed the futility analysis, and (iii) having removed the planned efficacy interim analysis resulted in the reduction in the number of PFS events needed for primary analysis from approximately 320 to approximately 270.

This amendment also aligns the Part C exploratory objectives in Section 6.3 with Addendum 9. Furthermore, an additional PFS censoring rule (starting new anticancer treatment and no tumor progression or death) was added to Table JVCY.9 to align with other ramucirumab Phase 3 studies. As the censoring rule for new anticancer therapy was added to Table JVCY.9, the PFS

sensitivity analyses 1 and 3 in Section 12.2.9 no longer apply. The current text was simplified and additional PFS sensitivity analyses were added to further evaluate the robustness of the primary analysis. The PFS analysis based on BIRC review will be conducted on all patients instead of a subset of patients. Other clarifications or corrections were made for consistency.

The following section shows all changes included in this protocol amendment.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore. Where existing language is underlined, additions have been identified by the use of double underscore.

Synopsis

Length of Study (Part A and Part B, excluding the Continued Access Period): Approximately 61 months
Planned first patient visit: APR 2015
Planned last patient visit: MAY 2020 (Part B)
Planned analyses:

Analysis 1 (Part A, dose-limiting toxicity [DLT] evaluation): After 6 patients enrolled from Japan and 6 patients enrolled from North America and/or Europe have completed 2 treatment cycles
Endpoint: DLTs

Analysis 2 (Part B, Interim Safety): After approximately 50 randomized patients have completed at least 3 cycles of treatment or discontinued from all study therapies due to any reason prior to 3 cycles
Endpoint: Safety

Analysis 3 (Part B, Interim Futility): Approximately 107 PFS events
Endpoint: PFS and safety

~~Analysis 4 (Part B, Interim Efficacy): Approximately 224 PFS events~~
~~Endpoint: PFS, OS, and safety~~

Analysis ~~5~~ 4 (Part B Primary PFS Analysis): ~~At least 320~~ Approximately 270 PFS events
Endpoint: PFS (Primary) and other secondary and exploratory objectives

Analysis ~~6~~ 5 (Part B, Final Overall Survival): Approximately 300 OS events
Endpoint: OS (Secondary)

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.

Exploratory Objectives:
The exploratory objectives of Part B of the study are as follows:

- Assessment of the association between biomarkers and clinical outcome
- Comparison of progression-free survival 2 (PFS2) between treatment arms

The exploratory objectives in only the gefitinib/osimertinib cohort in ~~Japan (~~Addendum 9~~)~~, conducted in the East-Asian region including Japan, are as follows:

- to evaluate the efficacy (for example, 1-year PFS rate) and safety of ramucirumab when administered in combination with gefitinib in previously untreated ~~Japanese~~ patients with *EGFR* mutation-positive metastatic NSCLC, in the East-Asian region including Japan
- to evaluate the efficacy and safety of ramucirumab when administered in combination with osimertinib in ~~Japanese~~ patients with T790M-positive metastatic NSCLC ~~and who were previously treated with~~ whose disease has progressed on ramucirumab plus gefitinib in this study, in the East-Asian region including Japan
- to assess PK and immunogenicity of ramucirumab
- to assess patient-reported outcomes (using LCSS and EQ-5D-5L)

Statistical Methods:
Part B:
Approximately 450 patients will be randomized through an interactive web response system (IWRS). At

randomization, patients will be stratified as stated above in the study design.

~~A 3-look group sequential design on the primary endpoint of PFS will be conducted, with 1 interim futility analysis, 1 interim efficacy analysis, and primary PFS analysis occurring at approximately 107 PFS events, approximately 224 PFS events, and approximately 320 PFS events, respectively. A Gamma family with parameter 0.5 was used to calculate the futility bound (non-binding approach). A spending function in rho family with parameter 16 was used to derive the efficacy bound to maintain the cumulative one-sided type I error 0.025.~~ An interim futility analysis (Analysis 3 above) was conducted at 114 investigator-assessed PFS events (data cutoff date 16 October 2017) and the IDMC recommended to continue the trial without modification. A nominal alpha <0.00001 was spent in order to maintain type-I error. Assuming an HR of ~~0.72~~ 0.71, this design yields at 80% statistical power to detect superiority of the ramucirumab plus erlotinib arm over placebo plus erlotinib arm with the use of a 1-sided log-rank test and a type I error rate of ~~0.025~~ 0.02499.

4. Abbreviations and Definitions

study completion This study will be considered complete after final ~~evaluation~~ analysis of overall survival is performed.

6.3. Exploratory Objectives

The exploratory objectives in only the gefitinib/osimertinib cohort in ~~Japan (~~Addendum 9~~)~~, conducted in the East-Asian region including Japan, are as follows:

- to evaluate the efficacy (for example, 1-year PFS rate) and safety of ramucirumab when administered in combination with gefitinib in previously untreated ~~Japanese~~ patients with *EGFR* mutation-positive metastatic NSCLC, in the East-Asian region including Japan
- to evaluate the efficacy and safety of ramucirumab when administered in combination with osimertinib in ~~Japanese~~ patients with T790M-positive metastatic NSCLC ~~and who were previously treated with~~ whose disease has progressed on ramucirumab plus gefitinib in this study, in the East-Asian region including Japan
- to assess PK and immunogenicity of ramucirumab
- to assess patient-reported outcomes (using LCSS and EQ-5D-5L)

8.1.2.3. Study Completion and End of Trial

The primary objective is investigator-assessed PFS., ~~and when there are at~~ When approximately ~~320~~ 270 PFS events have occurred among the study population, there will be a database lock to report the primary objective of the study.

Figure JVCY.3 is a diagram of the study period and continued access period. This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final ~~evaluation~~ analysis of OS, as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient, including patients participating in the continued access period, if applicable.

Upon study completion, investigators and patients ~~will~~ may be unblinded to study treatment assignment.

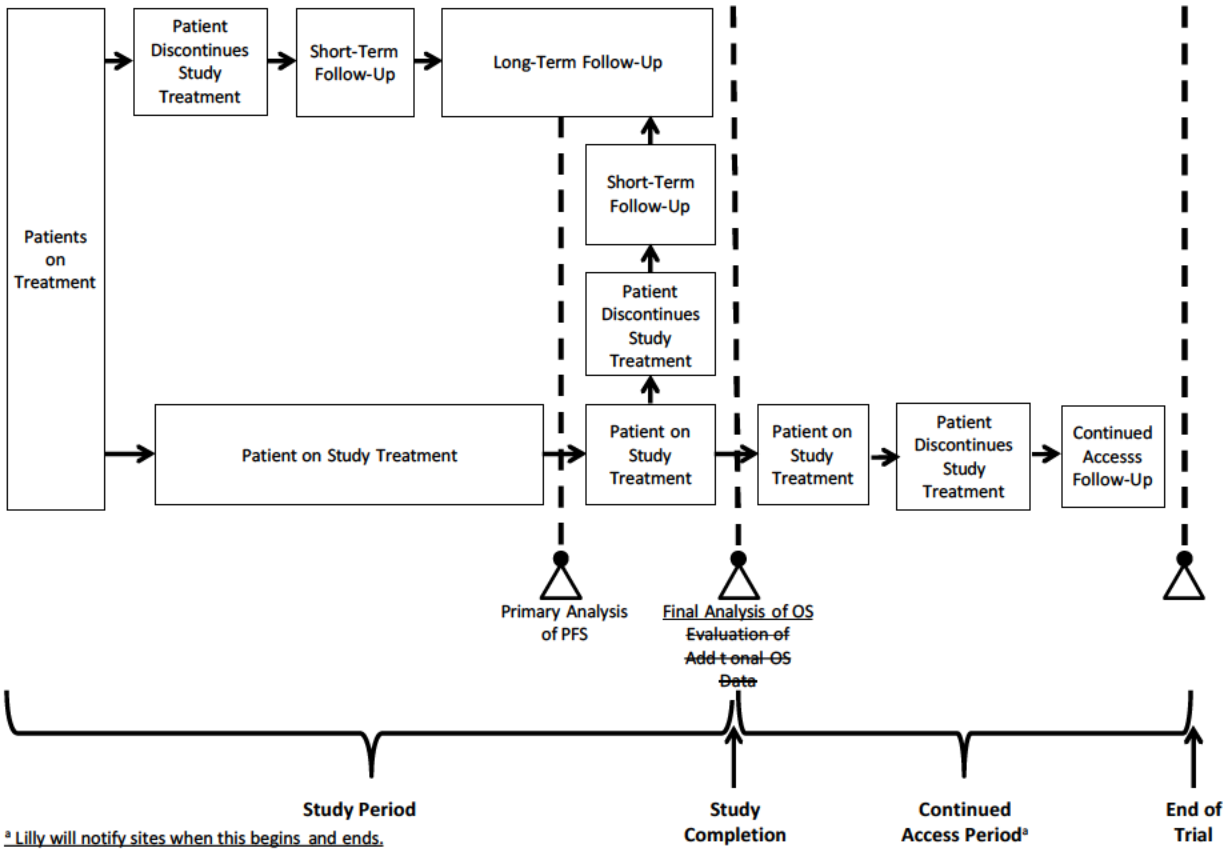


Figure JVCY.3. Study period and continued access period diagram.

9.5. Blinding

~~Efficacy information~~ Patient-level unblinded data will not be shared with 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 that unblinded aggregate efficacy and safety results are not available until the time of final data analysis.

For this study, the following roles will be permitted to access unblinded data for interim analyses of safety and/or ~~efficacy~~ futility: IDMC members, select group of programmers/statistician performing interim analyses, and GPS. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly/TPO'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 Independent Data Monitoring Committee. See Section 12.2.16 for further details.

12.1. Determination of Sample Size

Part B:
The primary objective of this study is to compare ramucirumab plus erlotinib versus placebo plus erlotinib in terms of PFS in previously untreated patients with *EGFR* mutation-positive metastatic NSCLC. The study will enroll approximately 450 patients in 1:1 randomization. The primary analysis will be performed after approximately ~~320~~ 270 PFS events have occurred (~~approximately 30%~~ 40% censoring rate). ~~An interim futility analysis will be conducted after approximately 107 PFS events and an interim efficacy analysis will be conducted after approximately 224 PFS 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 alpha <0.00001 was spent in order to maintain type-I error. Assuming an HR of ~~0.72~~ 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 ~~0.025~~ 0.02499. If the true median PFS for the placebo plus erlotinib arm is ~~9.5~~ 11 months, then the HR of ~~0.72~~ 0.71 amounts to an approximate ~~3.5~~ 4.5-month improvement in median PFS for the ramucirumab plus erlotinib arm under an additional assumption of exponential survival distribution.

12.2.7.2. Part B

Table JVCY.9. 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 post baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline 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 post-baseline 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: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

~~A group sequential design on the primary endpoint of PFS will be conducted, with 1 interim futility analysis, 1 interim efficacy analysis, and primary PFS analysis occurring at approximately 107 PFS events, approximately 224 PFS events, and approximately 320 PFS events, respectively (Table JVCY.10).~~

~~An interim futility analysis will be conducted after approximately 107 investigator-assessed PFS events (approximately 33%). A non-binding approach with gamma family of beta spending function (gamma=0.5) will be used to calculate the futility bound. A nominal alpha <0.00001 will be spent in order to maintain type-I error.~~

~~An interim efficacy analysis will be conducted after approximately 224 investigator-assessed PFS events. A spending function in rho family with parameter 16 was used to derive the efficacy bound to maintain the cumulative one-sided type I error 0.025.~~

~~All the testing boundaries will be adjusted based on actual number of events at each analysis, according to the alpha-spending functions.~~

~~If statistical significance is not declared at the interim PFS analysis, the primary PFS analysis will be performed after approximately 320 investigator-assessed PFS events have been observed based on investigator assessment.~~

~~Table JVCY.10. Property of the Design for PFS~~

~~Information Fraction~~	~~Cumulative PFS Events~~	~~Cumulative Alpha Spent~~	~~Cumulative Beta Spent~~	~~Boundary Reject of H_0~~	~~Boundary Futility~~
~~33%~~	~~107~~	~~<0.00001~~	~~0.078~~	~~NA~~	~~>0.39 (~ HR >0.95)~~
~~70%~~	~~224~~	~~0.00008~~	~~0.078~~	~~<0.00008 (~ HR <0.6)~~	~~NA~~
~~100%~~	~~320~~	~~0.025~~	~~0.199~~	~~<0.025~~	~~NA~~

~~Abbreviations: HR = hazard ratio; NA = not applicable; PFS = progression-free survival.~~

The stratified Cox proportional hazard model (Cox 1972) with assigned treatment as the only covariate will be used to estimate the HR and corresponding 95% CI for the primary analysis. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. ~~Additionally, the un-stratified Cox regression model will be employed.~~

12.2.8.1. Overall Survival

~~Up to a total of 2~~ One interim analyse~~i~~s 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.

The ~~first~~ interim OS analysis ~~will be performed at the time of the PFS interim efficacy analysis (approximately 224 PFS events). A second analysis will~~ may be performed at the time of primary PFS analysis (approximately ~~320~~ 270 PFS events) and the ~~last~~ final analysis ~~will~~ may be conducted ~~somewhat~~ later with the aim of providing as much information as possible on OS. This ~~last evaluation of the additional~~ final analysis of OS ~~data collected after the primary PFS analysis~~ 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 ~~3-look~~ Haybittle Peto type spending function (p-value bound 0.0001 at the interim analyse~~i~~s).

If it is determined that an ~~updated~~ additional interim analysis would provide ~~additional~~ further scientifically meaningful characterization of OS, then an ~~updated~~ additional interim analysis ~~will~~ could be performed ~~at an additional time point~~ prior to the final analysis.

12.2.9. Sensitivity Analysis~~i~~es

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis.

~~The following sensitivity analyses will be performed for PFS:~~

~~**Progression-Free Survival Sensitivity Analysis 1** (censoring for receiving subsequent systemic anticancer therapy): if a patient is initiated on another anticancer therapy prior to objective progression, including any postdiscontinuation treatment systemic therapy, radiotherapy, or surgical intervention, PFS will be censored at the date of the last complete objective progression-free disease assessment before initiation of the new therapy, regardless of whether or not this patient subsequently had objective progression or died.~~

~~**Progression-Free Survival Sensitivity Analysis 2** (censoring for missing two consecutive scheduled assessments): if a patient misses at least 2 consecutive scheduled disease assessments prior to objective progression, then the PFS time will be censored at the last objective progression-free disease assessment prior to the missed assessments, regardless of whether or not this patient subsequently had objective progression or died.~~

~~**Progression-Free Survival Sensitivity Analysis 3** (censoring for any of above 2 sensitivity analyses): if a patient has any of the scenarios outlined for sensitivity analyses 1 through 2 prior to objective progression, then the PFS time will be censored at the last objective progression-free disease assessment date prior to the earliest occurrence of any of these scenarios, regardless of whether or not this patient subsequently had objective progression or died.~~

Sensitivity analyses will include analyses using unstratified log-rank test and Cox models, the per-protocol population, including both radiographic and clinical progressions as PFS events, and analyses applying alternative PFS censoring rules (for example, post-discontinuation systemic anticancer therapy, missing tumor assessment, missing 2 or more tumor assessments prior to PD/death or lost to follow up, etc.; more details will be specified in the SAP).

In addition, a PFS analysis based on BIRC review will be conducted. 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 ~~a randomly selected subset of patients to evaluate the presence of investigator bias with the intention of evaluating the reliability of the treatment effect based on investigator assessment. Details concerning the size of the subset of patients and decision rules for conducting a central review of all patients will be described in a separate SAP~~all patients.

Additional sensitivity analyses may be specified in the SAP.

12.2.16. Interim Analyses

In general, the planned analyses include the following:

- Analysis 1 (Part A; DLT evaluation): after the 6 patients enrolled from Japan and 6 patients enrolled from North America and/or Europe have completed 2 treatment cycles
  Endpoint: DLTs
- Analysis 2 (Part B, Interim Safety): after approximately 50 randomized patients have completed 3 cycles of treatment or discontinued from all study therapies due to any reason prior to 3 cycles
  Endpoint: Safety profile
- Analysis 3 (Part B, Interim Futility): approximately 107 PFS events
  Endpoint: PFS and safety profile
- ~~Analysis 4 (Part B, Interim Efficacy): approximately 224 PFS events~~
  ~~Endpoint: PFS, OS, and safety profile~~
- Analysis ~~5~~ 4 (Part B, Primary PFS): ~~at least 320~~ approximately 270 PFS events
  Endpoint: PFS (Primary) and other secondary and exploratory objectives
- Analysis ~~6~~ 5 (Part B, Final Overall Survival): approximately 300 OS events
  Endpoint: OS (Secondary)

12.2.16.2. Part B

~~An efficacy interim analysis will be performed after approximately 224 investigator-assessed PFS events were observed. Interim efficacy analysis will be conducted for PFS. The stopping rule will be based on stratified log-rank test. As guidance, an IDMC may recommend stopping the trial for efficacy if the p-value of the stratified log-rank test for PFS is <0.00008 (this corresponds to approximately an HR <0.6 under a Cox PH model). The stopping guidance should be viewed as only guidance, not the absolute rules. The interim efficacy analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies.~~ 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.

Only the IDMC are authorized to evaluate unblinded interim ~~efficacy~~ futility 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 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.

14. References

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Attachment 2. Protocol JCVY Part B Study Schedule

Post-Treatment Discontinuation Schedule (Part B)

			Study Period	Post-discontinuation Follow-Up	
				Short-Term Follow-Up	Long-Term Follow-Up
			Visit	801	802-8XX
			Duration	30 ± 3 days	See footnote for duration
Procedure Category	Protocol Section	Procedure			Comments
Patient Disposition			X	X	At the time that the patient is discontinued from Study Participation, information regarding the patient status will be collected. T790M status, only if available, will be collected at the short-term follow-up visit.

Attachment 5. Protocol JVCY Study Procedures

Medical History

Past and current medical conditions and treatments, current medications, medications taken within ~~21~~ 30 days prior to enrollment, date of diagnosis, histopathological or cytological confirmation of malignancy, prior cancer therapy (surgery, radiotherapy, chemotherapy regimen, and any targeted therapy agents, maintenance therapy) including reason for discontinuation of

the previous anticancer therapy. Any preexisting toxicity (e.g., Grade 1 fatigue) should be documented and recorded at this time.

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Approval Date & Time: 23-Apr-2018 20:10:22 GMT
Signature meaning: Approved

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Approval Date & Time: 23-Apr-2018 20:10:22 GMT
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