Protocol Addendum I4T-MC-JVCY (9)

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: 15-Aug-2017

1. Protocol Addendum I4T-MC-JVCY(9) 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)

This addendum is to be performed in addition to all procedures required by Protocol I4T-MC-JVCY or any subsequent amendments to that protocol.

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Protocol Addendum (9) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 15-Aug-2017 GMT

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Protocol Addendum I4T-MC-JVCY(9) A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination with Ramucirumab or Placebo in Previously Untreated Patients with EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

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3. Rationale for Addendum

This addendum adds a cohort of patients (Part C) to the main protocol (I4T-MC-JVCY [JVCY]), and will only be applicable to sites in Japan.

Part C is an open-label, 2-period, single-arm, exploratory study. The purpose of this addendum is to provide the evaluation of the efficacy and safety of ramucirumab when administered in combination with gefitinib in previously untreated Japanese patients with epidermal growth factor receptor *(EGFR)* mutation-positive metastatic non-small cell lung cancer (NSCLC) (Period 1), and of ramucirumab when administered in combination with osimertinib in Japanese patients with T790M-positive metastatic NSCLC and who were previously treated with ramucirumab plus gefitinib in this study (Period 2).

4. Protocol Additions

The following sections describe the additions to Protocol JVCY that are applicable to this addendum.

All sections of Protocol JVCY apply to this addendum, except as described in this addendum. All protocol references to randomization, the independent data monitoring committee, or treatment with erlotinib and placebo do not apply to this addendum.

5.2. Use of Tyrosine Kinase Inhibitors in NSCLC

Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) (for example, erlotinib and gefitinib) significantly prolong progression-free survival (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).

Data from 2 recent Japanese Phase 3 trials (NEJ002 and WJTOG3405) have shown that first-line treatment with gefitinib resulted in significantly improved PFS times in patients with advanced or recurrent NSCLC with *EGFR* mutations compared with platinum-based doublet chemotherapy (Mitsudomi et al. 2010; Inoue et al. 2013). In the NEJ002 study, median PFS values on gefitinib therapy versus carboplatin-paclitaxel chemotherapy were: 10.8 versus 5.4 months (hazard ratio [HR] = 0.322, 95% confidence interval [CI]: 0.236, 0.438; $p<0.001$). In the WJTOG3405 study, the gefitinib group had significantly longer median PFS compared with the cisplatin-docetaxel group (9.2 months [95% CI: 8.0, 13.9] vs. 6.3 months [95% CI: 5.8, 7.8]; HR = 0.489, 95% CI: 0.336, 0.710; log-rank $p<0.0001$). Similar results have been observed in subgroup analyses of the IPASS study in which gefitinib monotherapy resulted in significantly longer PFS than platinum-based doublet chemotherapy in chemonaïve, East Asian patients with advanced non-squamous NSCLC and *EGFR* mutations (9.5 vs. 6.3 months, HR = 0.48; 95% CI: 0.36, 0.64; $p<0.001$ [Mok et al. 2009; Govindan 2010]). Concurrently with the PFS advantage provided by gefitinib in patients with an *EGFR* mutation, the IPASS trial showed significantly shorter PFS (HR = 2.85, 95% CI: 2.05, 3.98; $p<0.001$) in gefitinib-treated patients with wild-type *EGFR*. This result indicates that patients in whom an *EGFR* mutation has been identified will benefit most from first-line therapy with gefitinib. The recent real-world clinical practice data in Japan showed 56.1% of patients with advanced/recurrent NSCLC and EGFR mutation were treated with gefitinib as the first-line treatment (Inoue et al. 2016).

Osimertinib (AZD9291) is a novel, third-generation, and irreversible *EGFR* TKI with selectivity against mutant versus wild-type forms of *EGFR*. Osimertinib is a mono-anilino-pyrimidine compound that is structurally and pharmacologically distinct from all other TKIs, including another third-generation compound, rociletinib (CO-1686) (Cross et al. 2014).

Osimertinib (TAGRISSO®, PI) 80 mg once-daily tablet has been recently approved in the United States and European Union for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC, who have progressed on or after *EGFR* TKI therapy.

Osimertinib potently inhibits *EGFR* phosphorylation in activating mutations and resistance cell lines in vitro, with much less activity against wild-type *EGFR* lines.

Preclinical data comparing efficacy of afatinib+cetuximab (A+C) and osimertinib showed that both A+C and osimertinib inhibited proliferation of T790M-positive cells in long-term (10-day) growth inhibition assays, but osimertinib induced more growth inhibition than A+C (Meador et al. 2015). Moreover, xenograft-derived A+C-resistant cell lines displayed in vitro and in vivo sensitivity to osimertinib, but osimertinib-resistant cell lines demonstrated cross-resistance to A+C. Interestingly, addition of cetuximab to osimertinib did not confer additive benefit in any preclinical disease setting.

Available data from a Phase 1 clinical trial with osimertinib reveal high response rates in patients with *EGFR* TKI resistance whose tumors harbored *EGFR*-T790M (objective response rate [ORR] 61%; 95% CI: 52, 70), and lower response rates in patients whose tumors lacked *EGFR*-T790M (ORR 21%; 95% CI: 12, 34). The median PFS was 9.6 months (95% CI: 8.3, not reached) in *EGFR* T790M-positive patients and 2.8 months (95% CI: 2.1, 4.3) in *EGFR* T790M-negative patients. The most common adverse events (AEs) were diarrhea (47%), rash (40%), nausea (22%), and decreased appetite (21%) (Jänne et al. 2015).

Due to its margin of potency between T790M mutant *EGFR* and wild-type *EGFR*, the incidence and severity of wild-type *EGFR* AEs (for example, rash and diarrhea) appear to be lower than those observed with first- and second-generation *EGFR* TKIs.

The combination of an *EGFR* TKI and an antiangiogenic agent has shown promising efficacy improvement without significant additional toxicity. Recently, ATLAS (Johnson et al. 2013) and BeTa (Herbst et al. 2011) trials reported that the combination of bevacizumab with erlotinib provided additional PFS and overall survival (OS) benefit in the subgroup of patients with *EGFR* mutations. In addition, the JO25567 study showed statistically significant improvement in PFS (erlotinib plus bevacizumab vs erlotinib alone, HR = 0.54 [95% CI: 0.36, 0.79]; log-rank test p=0.0015) (Seto et al. 2014). Similarly, BELIEF, which is a single-arm Phase 2 study of first-line erlotinib plus bevacizumab in patients with *EGFR*-mutant NSCLC, showed that for all 109 patients, the 1-year PFS is 55.6% (95% CI: 44.7, 66.6), with a median of 13.6 months, while for patients with T790M-positive NSCLC determined pretreatment by a sensitive method, 1-year PFS is 60.2% (95% CI: 45.6, 74.8) with a median of 15.4 months (Stahel et al. 2015).

6.3. Exploratory Objectives

The exploratory objectives of Part C of study 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
- 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 ramucirumab plus gefitinib in this study
- to assess pharmacokinetics (PK) and immunogenicity of ramucirumab

- to assess patient-reported outcomes (using Lung Cancer Symptom Scale and EuroQol 5 dimension, 5-level questionnaire)

7.1. Inclusion Criteria

All inclusion criteria included in the main protocol are applicable to patients participating in Part C Period 1, except where noted below.

[4] Criterion is applicable only for patients enrolled in Part A and Part B.

[5] Criterion is applicable only for patients enrolled in Part B. An archived formalin-fixed paraffin embedded Stage IV NSCLC tissue sample collection is optional for patients enrolled in Part C.

The following additional inclusion criterion applies to patients participating in Part C Period 1:

[40] The patient must be eligible for first-line treatment with gefitinib for Period 1 of Part C based on previously documented evidence of tumor that has *EGFR* exon 19 deletion or exon 21 (L858R) substitution mutation.

7.3.2. Discontinuation of Study Treatment

7.3.2.1. Ramucirumab

- Any event that would warrant ramucirumab to be held for >2 consecutive cycles (missing 2 consecutive doses), except in the transition between Periods 1 and 2 of Part C. 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 may be considered and must be discussed with the Sponsor Physician or designee.

Patients who are permanently discontinued from ramucirumab due to AEs should be excluded from Period 2 of Part C.

7.3.2.4. Gefitinib

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

- The patient requests to be withdrawn from gefitinib ("Patient Decision to Discontinue" or "Patient Withdraws" per electronic case report form [eCRF]).
- The investigator decides that the patient should be discontinued from gefitinib, according to the local practice and approved product information.
- If the investigator decides to discontinue gefitinib therapy, due to the patient having had a 3-week delay in this therapy because of an gefitinib-related toxicity.
- 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 gefitinib.

- If interstitial lung disease is confirmed, the patient should be treated appropriately.
- If liver function tests demonstrate severe abnormal laboratory results. (Table JVCY(9).3)
- If the patient experiences gastrointestinal (GI) perforation; severe bullous, blistering, or exfoliation skin conditions; corneal perforation or severe ulceration.
- Patient compliance with gefitinib will be assessed at each visit (refer to Section 7.6). 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 gefitinib will continue to be in the study and may be further treated with ***ramucirumab***. Conditions that might cause gefitinib discontinuation should be treated appropriately per standard of care. In addition, discontinuation of gefitinib in the setting of AEs and guidelines for treatment management are detailed in Section 9.4.2.3.

7.3.2.5. Osimertinib

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

- The patient requests to be withdrawn from osimertinib ("Patient Decision to Discontinue" or "Patient Withdraws" per eCRF).
- The investigator decides that the patient should be discontinued from osimertinib, according to the local practice and approved product information.
- If the investigator decides to discontinue osimertinib therapy, due to the patient having had a 3-week delay in this therapy because of an osimertinib-related toxicity.
- 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 osimertinib.
- If interstitial lung disease is confirmed, the patient should be treated appropriately.
- If electrocardiogram (ECG) tests demonstrate severe corrected QT interval (QTc) prolongation results (Table JVCY(9).4).
- If the patient experiences GI perforation; severe bullous, blistering, or exfoliation skin conditions; corneal perforation or severe ulceration.
- Patient compliance with osimertinib will be assessed at each visit (refer to Section 7.6). 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 discontinue osimertinib may continue treatment with ***ramucirumab***. Conditions that might cause osimertinib discontinuation should be treated appropriately per standard of care. In addition, discontinuation of osimertinib in the setting of AEs and guidelines for treatment management are detailed in Section 9.4.2.4.

7.3.2.6. All Study Treatment for Part C

The investigator will withdraw a patient from ***all study treatment*** (ramucirumab plus gefitinib and ramucirumab plus osimertinib) 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's 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's 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's 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.
- Radiographic progressive disease (PD) or symptomatic PD. If patient experiences symptomatic deterioration and progression is suspected, every attempt should be made to confirm PD radiographically as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria prior to/soon after the patient's discontinuation from the study treatment.
  Gefitinib: For patients whose disease has progressed in Part C Period 1, gefitinib may be continued at the discretion of the investigator, provided that the patient can still benefit from the treatment. Patients who continue on gefitinib after disease progression cannot continue onto Period 2.
  Ramucirumab: For patients whose disease has progressed in Part C Period 1, treatment with ramucirumab will continue into Period 2. For patients who are not eligible to continue onto Period 2, ramucirumab should be discontinued.
- If a patient deteriorates to an Eastern Cooperative Oncology Group performance status (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 the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (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 serious adverse event (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.

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 (Part C Attachment 1). 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 Part C Attachment 1. 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 8.1.5.4.

8.1. Summary of Study Design

Part C of Study JVCY is an open-label, 2-period, single-arm, multicenter, exploratory study. Period 1 will evaluate the efficacy and safety of treatment with gefitinib (250 mg daily) plus

ramucirumab (10 mg/kg every 2 weeks) in previously untreated Japanese patients with *EGFR* mutation-positive metastatic NSCLC. Period 2 will evaluate the efficacy and safety of treatment with osimertinib (80 mg daily) plus ramucirumab (10 mg/kg every 2 weeks) in Japanese patients with T790M- positive metastatic NSCLC and who were previously treated with ramucirumab plus gefitinib in this study.

Part C will enroll approximately 100 patients.

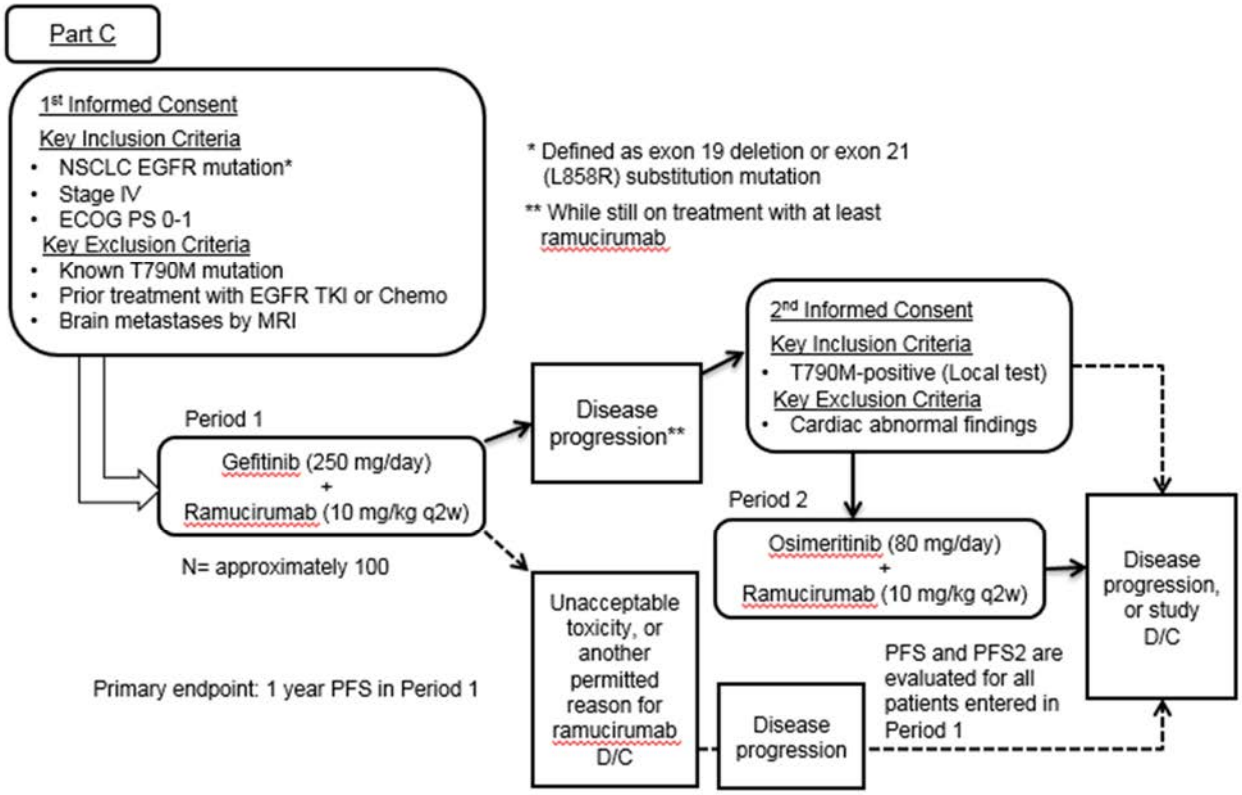
The study treatment in Part C is considered to be ramucirumab in combination with gefitinib (Period 1) and ramucirumab in combination with osimertinib (Period 2) or any component of the combination.

Patients in Part C will receive ramucirumab 10 mg/kg every 2 weeks, in combination with gefitinib (Period 1; Figure JVCY(9).1). Ramucirumab and gefitinib treatment will continue until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met. For patients whose disease has progressed in Part C Period 1, gefitinib may be continued at the discretion of the investigator, provided that the patient can still benefit from treatment. Patients continuing on gefitinib following disease progression cannot continue onto Period 2. For patients whose disease has progressed in Part C Period 1, treatment with ramucirumab will continue into Period 2. For patients who are not eligible to continue onto Period 2, ramucirumab should be discontinued.

Screening period for Period 2 begins 1 day after that the patient signs his or her informed consent to participate in Period 2. Patients who meet continuation criteria for Period 2 will receive ramucirumab 10 mg/kg every 2 weeks in combination with osimertinib (Period 2; Figure JVCY(9).1). Patients who do not meet continuation criteria of Period 2 (see Section 8.1.5.2.1) within 12 weeks from decision of study treatment discontinuation of Period 1 should be discontinued from study.

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(9).1 for Part C illustrate the study design.



Abbreviations: D/C = discontinuation; ECOG PS = Eastern Cooperative Oncology Group performance status; *EGFR* = epidermal growth factor receptor; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PFS = progression-free survival; q2w = every 2 weeks; TKI = tyrosine kinase inhibitor.

Figure JVCY(9).1. Illustration of study design for Clinical Protocol I4T-MC-JVCY in Part C.

8.1.5. Part C (Exploratory study)

8.1.5.1. Baseline and Study Treatment Period Assessments

Baseline radiographic assessment of disease will be performed within 28 days in both Periods 1 and 2 prior to enrollment. For Period 1, first dose of any study treatment will be administered within 7 days of enrollment assigning a patient to the treatment. Imaging requirements include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the 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 (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 reaction(s) to CT contrast material, a contrast-enhanced MRI of the chest/abdomen/pelvis is encouraged. A contrast-enhanced MRI of the central nervous system (CNS) will be performed at baseline prior to first dose of any study treatment for all patients in Part C (per Exclusion Criterion [15]

regarding CNS metastases). Scans performed prior to the date of consent may be used provided they are within 28 days of first dose of any study treatment. 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) in both Periods 1 and 2, and include the period of treatment with gefitinib in Period 1 or osimertinib in Period 2 given on Day 1 in combination with ramucirumab. 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 will receive:

- Ramucirumab on Day 1 of every 2-week cycle as an IV infusion over approximately 60 minutes, followed by a 1-hour observation period. If there is no evidence of an infusion-related reaction (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).
- Gefitinib tablets in Period 1 or osimertinib tablets in Period 2 orally every day. On Day 1 of each cycle, patients will receive gefitinib or osimertinib after completion of the ramucirumab infusion (after the observation period post ramucirumab infusion).

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

The criteria for starting the next cycle are defined in Section 9.4.2.1.1. Dose reductions for ramucirumab 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 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 in Period 1 and does not continue onto Period 2, 1 additional tumor scan will be collected at the short-term follow-up visit unless the patient has received additional anticancer therapy or study treatment prior to this visit. Thereafter, radiologic tests are no longer required (Part C Attachment 1).

For Period 1, patients 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 whose disease has progressed in Part C Period 1, gefitinib may be continued at the discretion of the investigator, provided that the patient can still benefit from the treatment. Patients on gefitinib cannot continue onto Period 2. For patients whose disease has progressed in Part C Period 1, treatment with ramucirumab will continue into

Period 2. For patients who are not eligible to continue onto Period 2, ramucirumab should be discontinued. 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, death, start of Period 2. Long-term 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 8.1.5.4.

During the screening period for Period 2, radiographic assessment should be completed as part of the baseline assessment of Period 2 within 28 days prior to enrollment of Period 2.

For Period 2, radiographic assessments are to be performed every 6 weeks (±7 days) following enrollment of Period 2 for the 72 weeks, and every 12 weeks (±7 days) thereafter, even if treatment is delayed, until there is radiographic documentation of PD. Further radiographic assessments after treatment discontinuation will not be required for patients who discontinue for reasons other than radiographically documented PD to commence alternative treatment.

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

8.1.5.2. Screening Period for Period 2

The screening period for Period 2 begins one day after the patient signs his or her informed consent to participate in Period 2. Patients who meet continuation criteria of Period 2 can start administration of study treatment of Period 2 (see Section 8.1.5.2.1). Patients who do not meet continuation criteria of Period 2 within 12 weeks from a first PD after study treatment of Period 1 should be discontinued from the study. Patients who will start next treatment other than Period 2 treatment or decide not to move to Period 2 must be followed for 30 days (±7 days) after the decision is made that the patient will be discontinued from the study.

8.1.5.2.1. Continuation criteria for Part C Period 2: Transition from Period 1 (Ramucirumab/Gefitinib) to Period 2 (Ramucirumab/Osimertinib)

Patients who meet continuation criteria of Period 2 can continue into Period 2.

Patient who hascontinued ramucirumab after disease progression should maintain the same schedule as Period 1.

Patients who do not meet the continuation criteria of Period 2 within 12 weeks from a first PD after study treatment of Period 1 should be discontinued from the study.

If ramucirumab was permanently discontinued in Period 1 (i.e. toxicities/AEs), this patient cannot be included in Period 2.

Ramucirumab can be administered once the patient has recovered from the prior toxicities/AEs. Osimertinib can be administered after continuation criteria are met.

Those patients who do not meet discontinuation criteria (see Section 7.3) are eligible to be included in Period 2 only if they meet the following continuation criteria prior to study treatment in Period 2:

- The patient has given their written informed consent to participate in Period 2 of the study and is amenable to compliance with protocol schedules and testing.
- The patient has confirmed T790M-positive status using a test validated and performed locally after disease progression on gefitinib treatment received in Period 1 of the study.
- The patient has serum albumin that is ≥25 g/L at the time of screening period for Period 2.
- The patient has resolution to Grade ≤1 (except alopecia, hypertension), by the NCI-CTCAE, v4.0, of all clinically significant toxic effects in Period 1 of the study.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.
- The patient did not permanently discontinue ramucirumab treatment prior to Period 2 for a reason other than PD (that is, AE or toxicity).
- The patient does not have superior vena cava syndrome.
- The patient does not have any evidence of clinically active interstitial lung disease. Asymptomatic patients with chronic, stable, radiographic changes are eligible.
- The patient does not have 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.
- The patient does not have SpO_2 <94 (room air).
- The patient does not have any of the following cardiac abnormal findings:
    - Mean resting QTc >470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value
    - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG; for example, complete left bundle branch block, third-degree heart block, or second-degree heart block
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives, or any concomitant medication known to prolong the QT interval

- Have a history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest

8.1.5.3. Postdiscontinuation Follow-Up Period Assessments

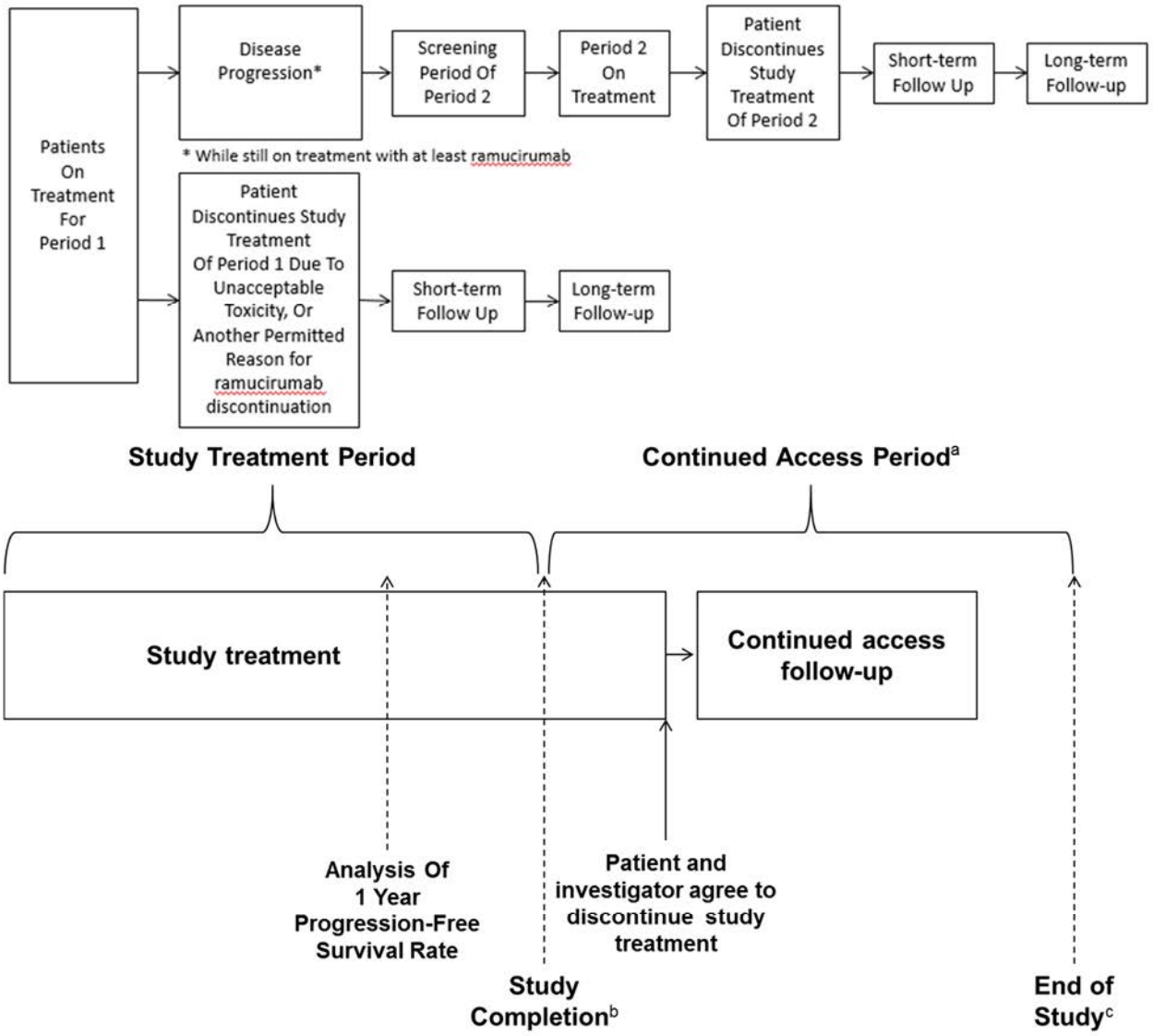
If a patient discontinues treatment due to objective disease progression in Period 1 and does not continue onto Period 2, 1 additional tumor scan will be collected at the short-term follow-up visit unless the patient has received additional anticancer therapy or study treatment prior to this visit. Thereafter, radiologic tests are no longer required (Part C Attachment 1).

Adverse event information will be collected until at least 30 days after the decision is made to discontinue from all study treatments of Period 1 and those of Period 2. After the short-term follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.

8.1.5.4. Study Completion and End of Trial

Figure JVCY(9).2 is a diagram of the study period and continued access period. Study period of Part C will be considered complete (that is, the scientific evaluation will be complete [study completion]) when study completion of Part B has occurred, or when OS events have occurred in half of the patients entered into Period 1, whichever comes later. "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.

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.



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Study period of Part C will be considered complete when study completion of Part B has occurred, or when OS events have occurred in half of the patients entered into Period 1, whichever comes later. Lilly will notify sites when study completion occurs.
[c] End of study occurs at the last visit or last scheduled procedure for the last patient.

Abbreviation: OS = overall survival.

Figure JVCY(9).2. Study period and continued access period diagram for Part C.

8.1.5.5. Study Duration

The duration in Part C from first patient treatment until last patient visit for PFS2 is approximately 55 months.

9.1. Treatments Administered

Table JVCY(9).1 shows the treatment regimens in Period 1 of Part C.

Table JVCY(9).1. Treatment Regimens/Dosing Schedule in Period 1 of Part C

Study Drug	Dose	Route	Timing
Ramucirumab[a]	10 mg/kg	IV	Over 60 minutes infusion on Day 1 of each 2-week cycle
1-hour observation period[b] followed by			
Gefitinib[c]	250 mg	PO	Daily

Abbreviations: IV = intravenous; PO = orally.

a Premedication is required prior to infusion of ramucirumab. Recommended premedication agents include histamine H_1 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 Grades 1 to 2 infusion-related reaction, as detailed in Section 9.4.2.1.2.1. All premedications 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 if an infusion-related reaction occurs thereafter, then the 1-hour observation period should be reinstituted.

c Gefitinib will be taken after the observation period (if reinstituted), 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 gefitinib.

Table JVCY(9).2 shows the treatment regimens in Period 2 of Part C.

Table JVCY(9).2. Treatment Regimens/Dosing Schedule in Period 2 of Part C

Study Drug	Dose	Route	Timing
Ramucirumab[a]	10 mg/kg[b]	IV	Over 60 minutes infusion on Day 1 of each 2-week cycle
1-hour observation period[c] followed by			
Osimertinib[d]	80 mg	PO	Daily

Abbreviations: IRR = infusion-related reaction; IV = intravenous; PO = orally.

a Premedication is required prior to infusion of ramucirumab. Recommended premedication agents include histamine H_1 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 Grades 1 to 2 IRR, as detailed in Section 9.4.2.1.2.1. All premedications administered must be adequately documented in the electronic case report form.

b Dose escalations are NOT allowed after dose reductions in Period 1.

c 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 IRR during the initial 2 infusions of ramucirumab, then no observation period is required for subsequent treatment cycles. In the event if an IRR occurs thereafter, then the 1-hour observation period should be reinstituted. Refer to Section 9.4.2.1.2.1 for further instructions in detail.

d Refer to Section 9.4 for further instructions on taking osimertinib.

9.1.1. Premedication

9.1.1.3. Premedication Prior to Gefitinib

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

9.1.1.4. Premedication Prior to Osimertinib

Investigators should consult the manufacturer's instructions for osimertinib for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of osimertinib. 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 will be supplied to sites by Lilly. Gefitinib and osimertinib may be supplied by the sites where commercially available or supplied to the sites by Lilly Japan.

9.2.1. Study Drugs

9.2.1.4. Gefitinib

Gefitinib is a commercially available product. Investigators should consult the manufacturer's instructions for gefitinib for complete prescribing information and follow institutional procedures for the administration of gefitinib, 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.

9.1.2.1.5. Osimertinib

Osimertinib is a commercially available product. Investigators should consult the manufacturer`s instructions for osimertinib for complete prescribing information and follow institutional procedures for the administration of osimertinib, including testing for T790M mutation status. The specific mutation(s) identified and the name of the test method used to document evidence of T790M mutation positivity will be documented in the eCRF.

9.2.2. Storage and Preparation

9.2.2.3. Gefitinib Storage and Preparation

Refer to the most recent version of the gefitinib (IRESSA®) package insert for storage guidance.

9.2.2.4. Osimertinib Storage and Preparation

Refer to the most recent version of the osimertinib (TAGRISSO®) package insert 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 in Part C.

9.4. Selection and Timing of Doses

For Part C, ramucirumab will be administered over a 1-hour IV infusion on Day 1 of each cycle (every 2 weeks) at a dose of 10 mg/kg.

Gefitinib will be administered orally as a once-daily dose of 250 mg. Refer to the most recent version of the gefitinib (IRESSA®) package insert for administration, and prohibited and restricted concomitant therapy.

Osimertinib will be administered orally as a once-daily dose of 80 mg. Refer to the most recent version of the osimertinib (TAGRISSO®) package insert for administration, and prohibited and restricted concomitant therapy.

9.4.2. Dose Delays or Dose Modifications

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

Part C:

If the criteria listed above are not met, the next ramucirumab dosing should be delayed for up to 2 weeks to allow for recovery. The gefitinib and osimertinib treatment should be continued during the delay of ramucirumab if the patient does not meet the criteria of delay and/or discontinuation for gefitinib and osimertinib dosing per package insert (refer to Sections 9.4.2.3.1 and 9.4.2.4.1, respectively). 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, except in the transition between Periods 1 and 2 in Part C regardless occurrence of AE. The gefitinib and osimertinib treatment should be continued, with the patient remaining in the study, if clinically indicated. For patients whose disease has progressed in Part C Period 1, treatment with ramucirumab will continue into Period 2. For patients who are not eligible to continue onto Period 2, ramucirumab should be discontinued.

9.4.2.3. Gefitinib

9.4.2.3.1. Dose Delays and Dose Modifications for Gefitinib

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

Patients should be treated following the recommendations, warnings, and precautions given for gefitinib in the package insert or the user guidance of gefitinib. Patients also may refer to the following dose modification guidance in Table JVCY(9).3.

Table JVCY(9).3. Gefitinib Dose Modification

Event and Grade[a]	Gefitinib 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 ruled out, resume gefitinib treatment • If ILD is diagnosed, permanently discontinue study treatment and institute appropriate treatment	
Gastrointestinal perforation		
All grades	Interrupt, pending the diagnostic evaluation: • If gastrointestinal perforation is ruled out, resume gefitinib treatment • If gastrointestinal perforation is diagnosed, permanently discontinue study treatment and institute appropriate treatment	
Diarrhea		
Grade 1 or 2	None	Consider loperamide: 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours
Grade 3 or any grade unresponsive to loperamide, or diarrhea that causes dehydration	Interrupt until resolution to Grade ≤1 (up to 3 weeks) or baseline, and resume gefitinib treatment	Manage as for Grade 1; supportive care as appropriate (refer to Section 9.6.1.1)
Grade 4	Discontinue gefitinib treatment	Manage as for Grade 1; supportive care as appropriate (refer to Section 9.6.1.1)
Skin reaction		
Tolerated rash (Grade 2 or 3)	None	Any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)
Intolerated rash	Interrupt dosing, up to 3 weeks until be successfully managed followed by resuming of gefitinib treatment	Manage as for Grade 1
Grade 4	Discontinue gefitinib treatment	Manage as for Grade 1
Severe hepatitis, liver failure, liver dysfunction	Interrupt dosing, up to 3 weeks until be successfully managed followed by restart of gefitinib treatment	Supportive care as appropriate

Event and Grade[a]	Gefitinib Dose Modifications	Guidelines for Management
Abnormal liver function test (hepatitis without liver failure)		
Grade 1 (>ULN - 3.0×ULN)	Gefitinib treatment can be continued	Supportive care as appropriate
Grade 2 (>3.0×ULN - 5.0×ULN) or Grade 3 (>5.0×ULN - 20.0×ULN)	Interrupt until resolution to Grade ≤1 (up to 3 weeks) or baseline and restart gefitinib treatment	Supportive care as appropriate
Grade 4 (>20.0×ULN)	Discontinue gefitinib treatment	Supportive care as appropriate
Eye symptoms (such as pain)		
Signs and symptoms of severe or worsening ocular disorders including keratitis	Interrupt gefitinib therapy, after symptoms and eye changes have resolved, the decision should be made concerning resume of gefitinib treatment	Removal of an aberrant eyelash if present
Persistent ulcerative keratitis	Discontinue gefitinib treatment	

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 gefitinib toxicities in Table JVCY(9).3, if a patient experiences other Grade 3 or 4 events that are considered at least possibly related to gefitinib, gefitinib administration may be delayed for up to 3 weeks until resolution.

If the event resolves to ≤Grade 1 or baseline, the patient may restart gefitinib treatment.

9.4.2.4. Osimertinib

9.4.2.4.1. Osimertinib Dose Adjustments, Delays, and Discontinuation

Patients should be treated following the recommendations, warnings, and precautions given for osimertinib in the package insert or the user guidance of osimertinib. Patients may also refer to the following dose modification guidance in Table JVCY(9).4.

Table JVCY(9).4. Osimertinib Dose Modifications

Target Organ	Adverse Reaction[a]	Osimertinib Dose Modification
Pulmonary	Interstitial lung disease (ILD)/pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at a 40-mg dose
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue osimertinib
	Asymptomatic, absolute decrease in LVEF of 10% from baseline and below 50%	Withhold osimertinib for up to 3 weeks • If improved to baseline LVEF, resume • If not improved to baseline, permanently discontinue
	Symptomatic congestive heart failure	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks
	If improvement to Grades 0-2 within 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	If no improvement within 3 weeks	Permanently discontinue osimertinib

Abbreviations: ECGs = electrocardiograms; LVEF = left ventricular ejection fraction; QTc = QT interval corrected for heart rate.

[a] Adverse reactions graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).

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 IV 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 IRESSA and TAGRISSO package insert and Sections 9.4.2.3.1 and 9.4.2.4.1 for gefitinib and osimertinib dose delays and modifications for guidance.

9.6.2. Prohibited and Restricted Concomitant Therapy

For Part C, refer to the IRESSA and TAGRISSO package insert for gefitinib and osimertinib prohibited and restricted concomitant therapy for guidance.

9.7. Treatment Compliance

Patient compliance with gefitinib and osimertinib 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.

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

For Part C, the method of tumor assessment used at baseline must be used consistently throughout the study. Patients must be enrolled with at least 1 measurable disease based on RECIST, version 1.1. Disease assessment will be undertaken at baseline (within 28 days prior to enrollment) for each of Period 1 and Period 2 (if applicable), and then every 6 weeks (±7 days) as calculated from the first dose of study therapy for each of Period 1 and Period 2 (if applicable), 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).

10.4.2. Samples for Translational Research

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

- plasma samples from the whole blood (mandatory for Part C; see Sections 10.4.2.1 and 10.4.2.3)
- whole blood sample for DNA collection (mandatory for Part C; see Section 10.4.2.2)
- archived tumor tissue (optional for Part C; see Section 10.4.2.3)

CCI [redacted]

10.4.2.1. Blood Sample for Plasma Collection

CCI [redacted] Sampling timepoints are shown in the Study Schedule (Part C Attachment 1 and Part C Attachment 2).

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 (Part C Attachment 1). Variable response to ramucirumab and gefitinib/osimertinib 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 gefitinib/osimertinib. 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. Tumor Tissue Samples

Submission of archived tumor tissue is highly encouraged for Part C but is not mandatory. Pathology notes accompanying archival tissue may also be requested (de-identified and translated).

CCI [redacted] The paraffin-embedded blocks will be sectioned and sent back to the site. Slides will not be returned.

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 on C1D1). For patients in

Part C, additional blood samples for immunogenicity testing will be collected BEFORE the infusion of ramucirumab on C4D1, and at the 30-day short-term follow-up visit (as noted in Part C Attachment 2).

10.4.4. Samples for Ramucirumab Drug Concentration Measurements Pharmacokinetics

Whole blood samples will be collected for all patients in Part C and processed as serum, as specified in the Part C Schedule for Ramucirumab Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule (Part C Attachment 2).

In either Part C, 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.

12.1. Determination of Sample Size

Part C:

Approximately, 100 previously untreated Japanese patients with EGFR mutation-positive metastatic NSCLC will be enrolled and treated with ramucirumab plus gefitinib.

A 1-year PFS rate for bevacizumab plus gefitinib in patients with EGFR mutation-positive metastatic NSCLC reported 56.7% (95% CI: 39.9, 70.5) (Ichihara et al. 2015). Given an expected 1-year PFS rate of 55% for ramucirumab plus gefitinib, 96 patients are required to generate 1-year PFS rate estimate whose 95% confidence half-width is <10%.

12.2.1.1. Analysis Populations

- Part C ITT Population: All patients who will be enrolled to study treatment during Part C.
- Part C Safety Population: All enrolled patients who received at least 1 dose of any study treatment in Part C. The Part C safety population will be used for all dosing/exposure, AEs, and resource utilization analyses. The safety summaries may be provided by period.

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

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 gefitinib/osimertinib 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

12.2.7.3. Part C

The primary endpoint of the exploratory Part C of Study JVCY is the investigator-assessed 1-year PFS rate in Period 1. A 1-year PFS rate is defined as the cumulative proportion of patients who survived during the first year (that is, 1 year from enrollment) in the study without disease progression. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment. The detailed censoring rules are described in Table JVCY.9. Progression-free survival curves, the median with 95% CI, and survival rates at various time points including 1-year PFS rate will be estimated using Kaplan-Meier method (Kaplan and Meier 1958).

12.2.8. Secondary Outcome and Methodology

12.2.8.4. PFS2 in Periods 1 and 2 and PFS in Period 2

To define either of PFS2 in Periods 1 and 2 or PFS in Period 2, the second occurrence of PD should be judged. The baseline tumor measurement of the second occurrence of PD should be performed immediately before starting osimertinib treatment. Progression-free survival 2 in Periods 1 and 2 is defined as the duration from enrollment (assignment to treatment) to the second occurrence of PD. Progression-free survival in Period 2 is defined as the duration from a day with the baseline tumor measurement before osimertinib treatment to the second occurrence of PD. Progression-free survival curves, the median with 95% CI, and survival rates at various time points will be estimated using Kaplan-Meier method (Kaplan and Meier 1958).

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 may be explored. Details will be described in the Statistical Analysis Plan.

12.2.14. Safety Analyses

12.2.14.3. Part C

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

- Adverse events, treatment-emergent adverse event (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, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage CSF), 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 TEAE is defined as an event that first occurred or worsened in severity after baseline.

12.2.16. Interim Analyses

12.2.16.3. Part C

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

Trial Level Safety Review by Lilly Clinical Research Physician will periodically perform the safety monitoring for Part C every 6 months since first subject has been entered to treatment in Period 1.

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Part C Attachment 1. Protocol JVCY Part C Study Schedule

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Baseline Schedule (Period 1 in Part C)

		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 of Part C Period 1. The patient will be enrolled 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 C1D1 physical examination.
	Att. 5	ECOG PS		X	A time window of -7 days is permitted for the C1D1 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 (Period 1 in Part C)

		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**
Laboratory/ Diagnostic Tests	7.1 Att. 3	Hematology (local)		X	Hematology will be collected for local laboratory 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	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 C but is not mandatory.
	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
	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 (Period 1 in Part C)

		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**
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 enrollment 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: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; FFPE = formalin-fixed paraffin embedded; FSH = follicle-stimulating hormone; HgbA1c = glycated hemoglobin; IWRS = Interactive Web Response System; LCSS = Lung Cancer Symptom Scale; LMWH = low molecular weight heparin; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumors; TSH = thyroid-stimulating hormone.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Treatment Period Schedule (Period 1 in Part C)

		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 examination (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 examination.
	Att. 5	ECOG PS	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 minutes 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.
Laboratory/ 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 INR or PT, and 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 (Period 1 in Part C)

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 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 gefitinib, at the discontinuation of ramucirumab, and at the short-term follow-up.
	10.4.3 10.4.4 Part C Att. 2	Immunogenicity	Refer to Part C Attachment 2 for timepoints.									Immunogenicity blood work to be collected BEFORE the first infusion of ramucirumab on C1D1 of treatment. 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.
	10.4.4 Part C Att. 2	Pharmacokinetics	Refer to Part C Attachment 2 for timepoints.									
	10.4.2.2 Part C Att. 2	Whole blood sample	Refer to Part C Attachment 2 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 Period 1 in Part C.
	10.4.2.1 Part C Att. 2	Plasma sample	Refer to Part C Attachment 2 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 Period 1 in Part C.

Treatment Period Schedule (Period 1 in Part C)

		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 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 the 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 dose of any study treatment will be administered within 7 days of enrollment. Gefitinib (250 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 gefitinib	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: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta-human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; INR = international normalized ratio; IRR = infusion-related reaction; LCSS = Lung Cancer Symptom Scale; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; SAE = serious adverse event; SNP = single nucleotide polymorphism.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule (Period 1 in Part C)

			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 examination (including weight)	X		
	Att. 5	Vital signs	X		Includes blood pressure, pulse, respiratory rate, and temperature.
	Att. 5	ECOG PS	X		
Laboratory/ Diagnostic Tests	Att. 3	Hematology (local)	X		Hematology will be collected for local laboratory testing.
	Att. 3	Serum chemistry including thyroid tests and HgbA1c (central)	X		Chemistry will be collected for central laboratory testing.
	Att. 3	Coagulation profile (local)	X		Coagulation will be collected for local laboratory 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 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 Part C Att. 2	Immunogenicity	Refer to Part C Attachment 2 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.
	Part C Att. 2	Pharmacokinetics	Refer to Part C Attachment 2 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 Part C Att. 2	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 EQ-5D-5L. 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 (Period 1 in Part C)

			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 weeks [±7 days], 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 in Period 1 and does not continue onto Period 2, 1 additional tumor scan will be collected at the short-term follow-up visit unless the patient has received additional anticancer therapy or study treatment 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.
	10.2.1	Survival information and subsequent anticancer 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.

Abbreviations: AE = adverse event; β-HCG = beta-human chorionic gonadotropin; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; IRR = infusion-related reaction; LCSS = Lung Cancer Symptom Scale; MUGA = multigated acquisition; PD = progressive disease; PFS2 = progression-free survival 2; PK = pharmacokinetic; PRO = patient-reported outcome; QoL = quality of life; 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. For patient to be entered into Period 2, the long-term follow-up began after a short-term follow-up in Period 2 is completed.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Continued Access Period Schedule (Period 1 in Part C)

		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.
Laboratory/Diagnostic Tests	10.4.3 10.4.4 Part C Att. 2	Immunogenicity/PK	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. Gefitinib (250 mg) is self-administered *per os* (by mouth) once daily.
Study Treatment	9.1	Administer ramucirumab	X		
	9.1	Administer gefitinib (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.

Baseline Schedule (Period 2 in Part C)

			Study Period	Baseline		
			Cycle	BL		
			Visit	0		
			Duration	Up to 21 days (except where noted)[a]		
			Relative Day to Enrollment	≤21	≤14	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Study Entry/Enrollment	8.1.5.2.1 13.1	Informed Consent Form signed (prior to conducting any protocol-specific tests/procedures for Period 2)		X (allowable during 12 weeks after PD in Period 1)		Obtain informed consent prior to any study-related procedures or evaluations for entering Period 2. The investigator or the Sponsor will not grant exceptions to eligibility criteria.
	8.1.5.2.1	Continuation criteria evaluation		X		Patients who meet continuation criteria of Period 2 can continue into Part C Period 2
	8.1.5.2.1	T790M test (local)		X (allowable >21 days prior to starting treatment)		If the result of T790M has discrepancy between plasma and tissue, investigator use the result of tissue.
Physical Examination	Att. 5	Physical examination (including weight)			X	Height measurements to be performed at baseline only. A time window of -7 days is permitted for the C1D1 physical examination.
	Att. 5	ECOG PS			X	A time window of -7 days is permitted for the C1D1 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.
Laboratory/ Diagnostic Tests	Att. 3	Hematology (local)			X	Hematology will be collected for local laboratory testing. If enrollment hematology profile is collected within 7 days of C1D1, the profile does not need to be repeated at C1D1.
	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 laboratory.
	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.
	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.

Baseline Schedule (Period 2 in Part C)

Procedure Category	Protocol Section	Procedure	Study Period: Baseline Cycle: BL Visit: 0 Duration: Up to 21 days (except where noted)[a] Relative Day to Enrollment: ≤21	≤14	Comments
	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.
	10.4.2.3	Plasma sample	X		Required sample following gefitinib treatment prior to start of osimertinib treatment for all patients for disease characterization.
	Att. 5	Echocardiogram or MUGA	X		
	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 the 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.** 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: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; C1D1 = Cycle 1 Day 1; CNS = central nervous system; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; HgbA1c = glycated hemoglobin; LCSS = Lung Cancer Symptom Scale; LMWH = low molecular weight heparin; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumors; TSH = thyroid-stimulating hormone.

a If a procedure item is done in Period 1 within the allowance of the baseline, the item does not need to be repeated at the baseline of Period 2.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Treatment Period Schedule (Period 2 in Part C)

		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 examination (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 examination.
	Att. 5	ECOG PS	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 minutes 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.
Laboratory/ 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 INR or PT), and 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 (Period 2 in Part C)

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. 5	Pregnancy test (local)		X		X		X		X	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of 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 osimertinib, at the discontinuation of ramucirumab, and at the short-term follow-up.
		Echocardiogram or MUGA	X					X			X	Every 12 weeks from C1D1 or if clinically indicated.
	10.4.3 10.4.4 Part C Att. 2	Immunogenicity	Refer to Part C Attachment 2 for timepoints.									Immunogenicity blood work to be collected BEFORE the first infusion of ramucirumab on C1D1 of treatment. 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.
	10.4.4 Part C Att. 2	Pharmacokinetics	Refer to Part C Attachment 2 for timepoints.									
	10.4.2.2 Part C Att. 2	Whole blood sample	Refer to Part C Attachment 2 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 Period 2 in Part C.
	10.4.2.1 Part C Att. 2	Plasma sample	Refer to Part C Attachment 2 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 Period 2 in Part C.
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 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.

Treatment Period Schedule (Period 2 in Part C)

		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**
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 in Period 2, 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 dose of any study treatment will be administered within 7 days of enrollment. Osimertinib (80 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 osimertinib	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: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta-human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; IRR = infusion-related reaction; LCSS = Lung Cancer Symptom Scale; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; SAE = serious adverse event; SNP = single nucleotide polymorphism.

Study Schedule, Protocol I4T-MC-JVCY

Perform procedures as indicated.

Post-Treatment Discontinuation Schedule (Period 2 in Part C)

			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 examination (including weight)	X		
	Att. 5	Vital signs	X		Includes blood pressure, pulse, respiratory rate, and temperature.
	Att. 5	ECOG PS	X		
Laboratory/ Diagnostic Tests	Att. 3	Hematology (local)	X		Hematology will be collected for local laboratory testing.
	Att. 3	Serum chemistry including thyroid tests and HgbA1c (central)	X		Chemistry will be collected for central laboratory testing.
	Att. 3	Coagulation profile (local)	X		Coagulation will be collected for local laboratory 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 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 Part C Att. 2	Immunogenicity	Refer to Part C Attachment 2 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.
	Part C Att. 2	Pharmacokinetics	Refer to Part C Attachment 2 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 Part C Att. 2	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 EQ-5D-5L. 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 (Period 2 in Part C)

			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 weeks [±7 days], 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, 1 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 anticancer 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.

Abbreviations: AE = adverse event; β-HCG = beta-human chorionic gonadotropin; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; IRR = infusion-related reaction; LCSS = Lung Cancer Symptom Scale; MUGA = multigated acquisition; PD = progressive disease; PFS2 = progression-free survival 2; PK = pharmacokinetic; PRO = patient-reported outcome; QoL = quality of life; 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 (Period 2 in Part C)

			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.
Laboratory/Diagnostic Tests	10.4.3 10.4.4 Part C Att. 2	Immunogenicity/PK		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. Osimertinib (80 mg) is self-administered *per os* (by mouth) once daily.
Study Treatment	9.1	Administer ramucirumab		X		
	9.1	Administer osimertinib (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.

Part C Attachment 2. Protocol JVCY Part C 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 PK blood samples not be withdrawn from the same site as the drug infusion. Sample collection times may vary to within 1 to 1.5 hours after the end of ramucirumab infusion outlined in the PK sampling schedule.

Protocol I4T-MC-JVCY Schedule for Ramucirumab Pharmacokinetic, Immunogenicity, and Translational Research Sampling for Period 1 and Period 2 of Part C

Visit	Time	Serum Ramucirumab PK[a]		Immuno-genicity[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 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 Cycle 14	Predose[f]	X					
	1 hour after the end of ramucirumab 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 Optional. 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).

[d] 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 prior to Period 1., unless restricted by local regulations. For all patients continuing into Period 2 (regardless of whether a Stave IV disease tissue sample was provided), a plasma sample for updated disease characterization is required following gefitinib treatment prior to start of osimertinib treatment, 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 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 or ramucirumab and gefitinib/osimertinib, PK/IG serum and plasma samples will be collected 30 (±10) days thereafter. If a patient continues to take gefitinib/osimertinib after discontinuation of ramucirumab, additional PK/IG serum and plasma samples are NOT required after gefitinib/osimertinib discontinuation.

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