Protocol: I4T-MC-JVDL(c)

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

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

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Protocol Electronically Signed and Approved by Lilly on 29 March 2016.
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Approval Date: 28-Mar-2018 GMT

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1. Synopsis

Protocol Title:

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

Summary of Study Design:

Study I4T-MC-JVDL is an open-label, multicenter Phase 1 study with an expansion cohort to evaluate the safety and preliminary efficacy of ramucirumab or necitumumab in combination with osimertinib. The dose-limiting toxicity (DLT) observation period and expansion cohort (safety and preliminary efficacy) will include patients with advanced T790M-positive epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer after progression on first-line *EGFR* tyrosine kinase inhibitor therapy.

Objectives and Endpoints:

	Objectives	**Endpoints**
Phase 1a: Dose-Finding Portion	**Primary:** To assess the safety and tolerability of ramucirumab or necitumumab in combination with osimertinib	Dose-limiting toxicities, observed during 2 cycles (28 days) for ramucirumab arm (Arm A) and 1 cycle (21 days) for necitumumab arm (Arm B) **Safety (including but not limited to):** TEAEs, SAEs, and deaths
	Secondary: To assess the PK of ramucirumab or necitumumab in combination with osimertinib	**PK:** C_{min} and approximate C_{max} of ramucirumab and necitumumab in serum
Phase 1b: Dose-Expansion Portion	**Primary:** To assess the safety and tolerability of ramucirumab in combination with osimertinib	**Safety (including but not limited to):** TEAEs, SAEs, and deaths
	Secondary: To assess the preliminary efficacy of ramucirumab in combination with osimertinib* To assess the PK of ramucirumab in combination with osimertinib	**Efficacy:** ORR (RECIST 1.1), DCR, DOR, PFS, and OS* **PK:** C_{min} and approximate C_{max} of ramucirumab in serum

Abbreviations: C_{max} = maximum concentration; C_{min} = minimum concentration; DCR = disease control rate; DOR= duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST 1.1= Response Evaluation Criteria In Solid Tumors Version 1.1; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

***Note:** Patients in the Dose-Finding Portion will be included in the overall preliminary efficacy analyses.

Treatment Arms and Duration:

Phase 1a: Dose-Finding Portion (3 + 3 dose de-escalation design)

Length of Study Portion

The duration of the Dose-Finding Portion from first patient enrolled to the last patient completing the DLT observation period is estimated to be approximately 6 months.

- **Arm A:** 28 days (2 cycles) for ramucirumab in combination with osimertinib for DLT observation
- **Arm B:** 21 days (1 cycle) for necitumumab in combination with osimertinib for DLT observation

All patients will be treated until confirmed progressive disease, unacceptable toxicity, or discontinuation for any other reason.

Dosing Schedules

- **Arm A:**

  Dose Level 0: ramucirumab 10 mg/kg on Day 1 every 2 weeks (Q2W) and osimertinib 80 mg daily, in 3 patients

  Dose Level -1: ramucirumab 8 mg/kg on Day 1 Q2W and osimertinib 80 mg daily, in 3 patients

- **Arm B:**

  Dose Level 0: necitumumab 800 mg on Days 1 and 8 every 3 weeks (Q3W) and osimertinib 80 mg daily, in 3 patients

  Dose Level -1: necitumumab 600 mg on Days 1 and 8 Q3W and osimertinib 80 mg daily, in 3 patients

Number of patients: up to 24 DLT-evaluable patients (up to 12 enrolled in each arm)

Phase 1b: Dose-Expansion Portion

Length of Study Portion

The duration of the Dose-Expansion Portion (excluding the Continued Access Period) from first patient enrolled to the completion of the study is approximately 2 years after last patient enrolled, or when adequate number of events are observed for survival outcome estimation, whichever comes first.

Treatment Cohort

- **Cohort A:** ramucirumab at recommended dose + osimertinib 80 mg daily (22 patients)

Number of patients: 22 evaluable patients

Statistical Analysis:

For Dose-Finding Portion, a 3+3 dose de-escalation design will be used to assess the safety of ramucirumab or necitumumab in combination with osimertinib. Additional patients will be enrolled to achieve the minimum of 3 evaluable patients at each dose level for each arm, if dropouts or dose interruptions or reductions occur that result in a patient being non-evaluable for DLTs. Data will be reviewed by dose schedule group (3 patients) for each arm.

For Dose-Expansion Portion, the primary data analysis will be conducted approximately 6 months after last patient receives initial dose, and the final analysis will occur upon the completion of the study. All patients enrolled in the Dose-Finding Portion (Arm A) and the Dose-Expansion Portion (Cohort A) will be included for all planned analyses. Patients enrolled in Arm B of the Dose-Finding Portion will be analyzed separately.

Descriptive statistics will be derived where appropriate. The rate of DLTs will be summarized by arm; dose exposure for each study drug will be calculated.

2. Schedule of Activities

Table JVDL.1. Baseline Schedule of Activities

Days before C1D1	≤28	≤14	≤7	Instructions
Procedure				
Informed consent	X			ICF must be signed before any protocol-specific procedures are performed; if the ICF is revised during the course of the study, re-consenting of patients may be required if deemed necessary by Lilly or the IRB/ERB.
Inclusion/exclusion criteria			X	
Physical examination			X	Including height, weight, and vital signs (temperature, blood pressure, pulse rate, and respiration rate)
ECOG performance status			X	
Medical history		X		Including assessment of preexisting conditions, historical illnesses, and habits (such as tobacco and alcohol use)
Prior and current medication		X		
AE collection	X			CTCAE Version 4.0
Radiologic imaging and measurement of palpable or visible lesions	X			RECIST 1.1
Brain scan	X			Baseline brain scan by contrast CT or MRI
ECG		X		Triplicate, see Exclusion Criterion [40] in Section 6.2.
ECHO or MUGA		X		
Hematology			X	
Coagulation			X	
Clinical chemistry			X	
T3, free T4, TSH			X	
Urinalysis			X	
Tumor tissue		X		It is required to provide a tumor tissue specimen from a biopsy taken after disease progression on the most recent *EGFR* TKI treatment.
Pregnancy test			X	Applies only to women of childbearing potential. See Appendix 3.
Sample collection				See Appendix 4.
Pharmacokinetics		X		
Immunogenicity		X		
Pharmacogenetics (whole blood)		X		
Biomarkers		X		

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); ICF = informed consent form; IRB/ERB = institutional review board / ethical review board; MUGA = multiple-gated acquisition; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1 (Eisenhauer et al. 2009); TSH = thyroid-stimulating hormone.

Note: Baseline Period begins when the ICF (study entry) is signed and ends at the first dose of study treatment (or at discontinuation, if no treatment is given).

Table JVDL.2. On-Study-Treatment Schedule of Activities

Treatment Period Schedule for Ramucirumab Arm and Cohort

	Study Period	Treatment Period									Comments
	Cycle (14-day cycle ± 3 days)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9-X**	Visits will be changed to once every 6 weeks if a patient permanently discontinues from ramucirumab but still on treatment with osimertinib.
	Relative Day within Dosing Cycle	1	1	1	1	1	1	1	1	1	
Procedure Category	**Procedure**										
Physical Examination	Physical exam (including weight)	X	X	X	X	X	X	X	X	X	Patients should be weighed at the beginning of each cycle. Height measurements to be performed at baseline only.
	ECOG performance status	X	X	X	X	X	X	X	X	X	Complete prior to treatment infusion.
	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, immediately prior to and at the completion of each infusion. If there is a postinfusion observation period, then vital signs measurements should also be obtained at the end of the observation period. In the event of an IRR, the respiration rate will be collected. Refer to Section 7.7.1.1 for details.
Lab/Diagnostic Tests	Hematology	X	X	X	X	X	X	X	X	X	Performed within 3 days prior to treatment on Day 1 of each cycle. If results of the laboratory tests obtained at planned Day 1 of the next cycle require a delay in the start of the subsequent cycle, any repeat laboratory tests should be obtained, as clinically indicated.
	Serum chemistry	X	X	X	X	X	X	X	X	X	Performed within 3 days prior to treatment on Day 1 of each cycle. For dosing decisions, bilirubin and AST/ALT are required to be collected. If enrollment serum chemistry profile is collected within 4 days of C1D1, the profile does not need to be repeated.
	Coagulation profile	X			X				X	X	Performed within 3 days prior to treatment on C1D1. Beginning at Cycle 4, within 3 days prior to treatment on Day 1 of the cycles, coagulation profile performed every 4 cycles or more frequently, as clinically indicated if patient is on oral anticoagulation therapy. Coagulation parameters to be tested include INR or PT, and PTT/aPTT.
	Urinalysis	X	X	X	X	X	X	X	X	X	While a patient is being treated with ramucirumab collect every cycle, dipstick or routine analysis measurements should be done within 3 days prior to treatment. If enrollment urinalysis is collected within 4 days of C1D1, the profile does not need to be repeated at C1D1. Results should be available at the time of the next dosing decision.
	Pregnancy test		X		X		X		X	X	Pregnancy test (see Appendix 3, minimum sensitivity 25 IU/L or equivalent units of β-hCG). Within 3 days prior to treatment on Day 1 of every 2 cycles, (or per institutional guidelines, whichever is more frequent) pregnancy testing for women of childbearing potential will be performed.
	ECG	X	X	X	X	X	X	X	X	X	Twelve-lead ECG within 3 days prior to treatment on Day 1 of each cycle (and if clinically indicated) for first 6 months then every other cycle, at the discontinuation of any study drugs, and at the short-term follow-up.
	ECHO or MUGA						X				Every 12 weeks from C1D1 and if clinically indicated

Treatment Period Schedule for Ramucirumab Arm and Cohort

Study Period	Treatment Period									Comments
Cycle (14-day cycle ± 3 days)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9-X**	Visits will be changed to once every 6 weeks if a patient permanently discontinues from ramucirumab but still on treatment with osimertinib.
Relative Day within Dosing Cycle	1	1	1	1	1	1	1	1	1	

Procedure Category	Procedure									
	Sample collection for pharmacokinetics, immunogenicity, and biomarkers	See Appendix 4.								Immunogenicity blood work to be collected BEFORE the first infusion of ramucirumab on C1D1 of treatment. If a patient experiences an IRR on 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.
	Tumor tissue	X								Patients may be asked to undergo optional collection of an additional biopsy specimen after treatment with study drug(s) has been initiated. See Section 9.8.2 for additional details.
Adverse Events Collection/CTCAE Grading	Toxicity assessment	X								All AEs/SAEs will be collected for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Efficacy Assessment	Imaging/Tumor Assessments (every 6 wk ± 7 d)			X			X			X	Disease assessment will be every 6 weeks (±7 days) as calculated from the first dose of study therapy. After 24 weeks, tumor assessment will be conducted 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.
Concomitant Therapy	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	Premedication	X	X	X	X	X	X	X	X	X	
Treatment Administration	Ramucirumab (I.V.)	X	X	X	X	X	X	X	X	X	Osimertinib (80 mg) will be self-administered *per os* (by mouth) once daily with administer diary.
	Osimertinib (orally)	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: β-hCG = beta human chorionic gonadotropin; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; *EGFR* = epidermal growth factor receptor; INR = International Normalized Ratio; IRR = infusion-related reaction; I.V. = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PT = prothrombin time; PTT/aPTT = partial thromboplastin time / activated partial thromboplastin time; SAE = serious adverse event; TKI = tyrosine kinase inhibitor; wk = week.

Treatment Period Schedule for Necitumumab Arm

				Comments
		Repeat every 3 weeks		
	Cycle (3-week cycle)	1-X		
	Relative day within a cycle	1	8	Except for the C1D1 visit, allowable cycle windows are ±3 days, unless indicated otherwise. Visits will be changed to once every 6 weeks if a patient permanently discontinues from necitumumab but still on treatment with osimertinib.
Procedure Category	**Procedure**			
Physical Examination	Physical exam (including weight)	X		Patients should be weighed at the beginning of each cycle. Height measurements to be performed at baseline only.
	ECOG performance status	X		Complete prior to treatment infusion.
	Vital signs	X	X	Includes blood pressure, pulse, respiratory rate, and temperature. To be obtained at every treatment visit, immediately prior to and at the completion of each infusion. If there is a postinfusion observation period, then vital signs measurements should also be obtained at the end of the observation period. In the event of an IRR, the respiration rate will be collected. Refer to Section 7.7.1.1 for details.
Laboratory/ Diagnostic Tests	Hematology	X	X	Additional tests can be used for on-study dosing decisions. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8). Hepatic monitoring tests to be done in the event of a treatment-emergent hepatic abnormality. In case of neutropenia or thrombocytopenia Grade 4 during Cycle 1 (dose finding part only), repeat every 2 days until recovery.
	Chemistry	X	X	Additional tests can be used for on-study dosing decisions. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8). Hepatic monitoring tests to be done in the event of a treatment-emergent hepatic abnormality. In case of Grade 3 elevation of transaminases, bilirubin, or change of electrolytes (see DLT criteria), repeat every 2 days until recovery.
	Coagulation	X*		* To be performed within 3 days prior to treatment on Day 1 of the cycle for every second cycle starting from Cycle 2
	T3, free T4, TSH	X*		* To be performed within 3 days prior to treatment on Day 1 of the cycle for every second cycle starting from Cycle 2
	Urinalysis	X*		* To be performed within 3 days prior to treatment on Day 1 of the cycle for every second cycle starting from Cycle 2
	Pregnancy test	X		Pregnancy test (see Appendix 3, minimum sensitivity 25 IU/L or equivalent units of β-hCG). Within 3 days prior to treatment on Day 1 of every 2 cycles (or per institutional guidelines, whichever is more frequent), pregnancy testing for women of childbearing potential will be performed.
	ECG	X*		* To be performed within 3 days prior to treatment on Day 1 of every cycle for first 6 months, then every other cycle
	ECHO or MUGA	X*		* Every 12 weeks from C1D1 and if clinically indicated.
	Sample collection for pharmacokinetics, immunogenicity, and biomarkers	See Appendix 4.		Immunogenicity blood work to be collected BEFORE the first infusion of necitumumab on C1D1 of treatment. If a patient experiences an IRR on necitumumab, 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.
	Tumor tissue	X		Patients may be asked to undergo optional collection of an additional biopsy specimen after treatment with study drug(s) has been initiated. See Section 9.8.2 for additional details.

					Comments
			Repeat every 3 weeks		
		Cycle (3-week cycle)	1-X		
		Relative day within a cycle	1	8	Except for the C1D1 visit, allowable cycle windows are ±3 days, unless indicated otherwise. Visits will be changed to once every 6 weeks if a patient permanently discontinues from necitumumab but still on treatment with osimertinib.
Procedure Category	**Procedure**				
Adverse Events Collection/CTCAE Grading	Toxicity assessment		X	X	All AEs/SAEs will be collected for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.
Efficacy Assessment	Imaging/Tumor Assessments (every 6 wk ± 7 d)		X		Disease assessment per RECIST version 1.1 will be performed every 6 weeks (±7 days) as calculated from the first dose of study therapy. After 24 weeks, tumor assessment will be conducted 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.
Concomitant Therapy	Concomitant medications		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.
Treatment Administration	Necitumumab (I.V.)		X	X	Osimertinib (80 mg) will be self-administered *per os* (by mouth) once daily with administer diary.
	Osimertinib (orally)		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: β-hCG = beta human chorionic gonadotropin; AE = adverse event; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; *EGFR* = epidermal growth factor receptor; DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; IRR = infusion-related reaction; I.V. = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PK = pharmacokinetic; SAEs = serious adverse events; TKI = tyrosine kinase inhibitor; TSH = thyroid-stimulating hormone; wk = week.

Table JVDL.3. Post-Treatment Follow-Up Schedule of Activities

Procedure	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	Instructions
Physical examination	X		Including weight and vital signs (temperature, blood pressure, pulse rate, and respiration rate)
Concomitant medication	X		
AE collection	X		CTCAE Version 4.0
ECOG performance status	X		
Radiologic imaging and measurement of palpable or visible lesions	X	X	Perform every 6 weeks (±7 days) according to RECIST 1.1, by the same method used at baseline and throughout the study. After 24 weeks, tumor assessment will be conducted every 12 weeks (± 7 days), until: • the patient has objective disease progression, or • the study's final analysis of overall survival. After the patient has objective disease progression, radiologic tests are no longer required.
Collection of survival information	X	X	Perform every 2 months (±7 days). If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
Collection of post-study-treatment anticancer therapy information	X	X	Perform every 2 months (±7 days) for the first 2 years after discontinuation from study treatment and every 6 months (±14 days) thereafter until death or study completion.
Hematology	X		
Coagulation	X		
Clinical chemistry	X		
T3, free T4, TSH	X		
Urinalysis	X		
Sample collection	For all sample collection, see Appendix 4.		
Pharmacokinetics			
Biomarkers			

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); MUGA = multiple-gated acquisition; q = every; RECIST 1.1 = Response Criteria In Solid Tumors Version 1.1 (Eisenhauer et al. 2009); TSH = thyroid-stimulating hormone.

a Short-term (Safety) follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment, and lasts approximately 30 days (±7 days). No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent. ECHO or MUGA may be performed during short-term follow-up if clinically indicated.

b Long-term (Survival) follow-up begins the day after short-term follow-up is completed, and lasts until disease progression on or after the study regimen, all patients will be assessed every 2 months (±7 days) to obtain information about survival status and detailed information on any subsequent systemic anticancer therapy and disease progression (for patients not having a radiographic progression) for as long as the patient is alive, or until study completion.

Table JVDL.4. Continued Access Schedule of Activities

Procedure[b]	Study Treatment	Follow-Up[a]	
AE collection	X	X	CTCAE Version 4.0
Pharmacokinetics and Immunogenicity			If a patient experiences an IRR, collect blood samples for pharmacokinetics and immunogenicity analysis 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.
Administer study drug	X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction.

[a] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

3. Introduction

3.1. Study Rationale

Lung cancer is the most common cancer worldwide and the leading cause of cancer-related mortality, with an estimated 1.6 million new cases and an estimated 1.4 million cancer-related deaths per year (Bray et al. 2012; Bunn 2012). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. The incidence of epidermal growth factor receptor (*EGFR*) mutations in the Caucasian population is about 10% but can be as high as 40% in East Asian populations (Bell et al. 2005; Shigematsu et al. 2005; Jänne et al. 2015).

Molecularly targeted therapies have been proven to be superior to chemotherapy for NSCLC patients whose tumors have activating mutations in *EGFR* (Mok et al. 2009; Zhou et al. 2011; Rosell et al. 2012; Sequist et al. 2013). *EGFR* tyrosine kinase inhibitors (TKIs; for example, erlotinib, gefitinib, and afatinib) significantly prolong progression-free survival (PFS) in patients with metastatic NSCLC whose tumors had *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations when compared with platinum-based chemotherapy doublets and have become the standard of care in countries where approved. The rationale for such treatment is supported by the results of studies such as BR.21 (Shepherd et al. 2005) and IPASS (Mok et al. 2009).

Despite excellent tumor response to initial targeted therapy, *EGFR* mutation-positive patients eventually develop disease progression after 9 to 12 months of treatment. One important mechanism of acquired resistance is the T790M gatekeeper *EGFR* mutation in exon 20, which is found in about 50% to 60% of patients upon disease progression from first-line *EGFR* TKI therapy. This mutation increases the affinity of the kinase for ATP, and thus reduces the inhibitor efficacy (Peters et al. 2014). Prior to the availability of third-generation *EGFR* TKI targeting T790M, these patients are candidates for systemic chemotherapy (NCCN Guideline v.4 2016) unless oligoprogressive disease is diagnosed. Of note, existing data for cytotoxic chemotherapy in patients with acquired resistance to *EGFR* inhibitors suggest that benefits are also of relatively short duration, with studies showing median PFS (mPFS) of 4.0 to 5.5 months (Goldberg et al. 2013; Mok et al. 2014).

Osimertinib, a third-generation *EGFR* TKI targeting activating *EGFR* mutations including T790M but sparing wild-type *EGFR*, is an oral, irreversible, selective inhibitor. Osimertinib (TAGRISSO®, package insert [PI] and Summary of Product Characteristics [SmPC]) 80-mg once-daily tablet has been recently approved in the United States (US) and European Union (EU) for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC, who have progressed on or after *EGFR* TKI therapy. Ongoing Phase 1/2 trials showed an overall objective response rate (ORR) of 61% in patients with *EGFR* T790M-positive NSCLC after prior *EGFR* TKI therapy, including an ORR of 70% at the 80-mg dose level. ORR was 21% in patients with *EGFR*-mutant NSCLC but negative for T790M (Jänne et al. 2015). Based on these data, several Phase 3 registration studies are currently ongoing.

Separately, necitumumab (PORTRAZZA®, PI), an *EGFR*-directed monoclonal antibody (mAb), has obtained marketing authorization in the US and EU, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC. Although another *EGFR* mAb cetuximab has been proven to be ineffective with respect to ORR when given as single agent to patients with progressive disease (PD) to erlotinib or gefitinib (Hanna et al. 2006; Neal et al. 2010), the combination of cetuximab with afatinib has demonstrated promising results. Among 126 patients with acquired resistance to erlotinib or gefitinib, ORR was 29% and comparable in T790M-positive and T790M-negative tumors (32% vs. 25%; p=0.341). Median PFS was 4.7 months (95% confidence interval [CI]: 4.3-6.4), and the median duration of confirmed objective response (OR) was 5.7 months (range: 1.8-24.4). Patients with T790M-positive and T790M-negative tumors had median durations of confirmed OR of 5.6 months (range: 1.8-24.4) and 9.5 months (range: 2.9-14.8), respectively. Median PFS was similar for T790M-negative and T790M-positive patients (4.6 vs. 4.8 months; p=0.643) (Janjigian et al. 2014).

On the basis of the clinical data that suggested modest benefit from continued *EGFR* TKI therapy despite acquired resistance (Goldberg et al. 2013; Yoshimura et al. 2013), synergistic effect of combining *EGFR* mAb and *EGFR* TKI, and preclinical data that support the use of necitumumab together with *EGFR* TKI (Lilly unpublished data S180914, S089213), we hypothesize that simultaneous inhibition of the *EGFR* signaling pathway using both osimertinib and necitumumab would improve efficacy of osimertinib in patients that progress on prior *EGFR* TKI and have T790M-positive NSCLC. A separate study of necitumumab in combination with osimertinib is being conducted in NSCLC *EGFR*-mutant patients that progressed on first-generation *EGFR* TKI and are negative for T790M (NCT02496663).

In addition, inhibition of angiogenesis is considered a promising approach to the treatment of cancer. Ramucirumab (Cyramza®), a human immunoglobulin G, subclass 1 (IgG1) anti-vascular endothelial growth factor (VEGF) Receptor 2 (VEGFR2) mAb, has obtained marketing authorization in the US, EU, and Japan for the treatment of advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma as monotherapy (REGARD) or in combination with paclitaxel (RAINBOW); in the US and EU for the treatment of advanced NSCLC in combination with docetaxel (REVEL); and in the US and EU for the treatment of metastatic colorectal cancer (mCRC) in combination with FOLFIRI (irinotecan, 5-fluorouracil, and folinic acid; RAISE). Recently, ATLAS (Johnson et al. 2013) and BeTa (Herbst et al. 2011) trials reported that the combination of the antiangiogenic agent bevacizumab with erlotinib provided additional PFS and overall survival (OS) benefit in the subgroup of patients with *EGFR* mutations. Additionally, the JO25567 study, which is a randomized Phase 2 study of erlotinib with or without bevacizumab as first-line therapy for patients with *EGFR*-mutant NSCLC, showed that mPFS was 16.0 months (95% CI: 13.9-18.1) with erlotinib plus bevacizumab and 9.7 months (95% CI: 5.7-11.1) with erlotinib alone (hazard ratio [HR]: 0.54 [95% CI: 0.36-0.79]; log-rank test p = 0.0015). A greater proportion of patients achieved disease control with erlotinib plus bevacizumab (99% vs. 88%; p=0.0177) (Seto et al. 2014). RELAY, a Phase 3 randomized study of erlotinib with or without ramucirumab as first-line therapy for patients with *EGFR*-mutant NSCLC, is ongoing (NCT02411448).

Considering the improvement in PFS and disease control rate (DCR) with the combination of erlotinib and bevacizumab in *EGFR*-mutant NSCLC, as well as promising ORR in *EGFR*-mutant lung cancer patients treated with combination of afatinib and cetuximab after progression on first-generation *EGFR* TKI, we would like to examine whether the combination of osimertinib and ramucirumab or necitumumab in *EGFR*-mutant NSCLC after progression on first-line *EGFR* TKI would also lead to improvement in efficacy in patients with acquired T790M. This study allows for an efficient and streamlined approach for identifying combinations that may have the best success in future randomized controlled trials.

3.2. Background

3.2.1. Ramucirumab

Ramucirumab (Cyramza®), a human IgG1 anti-VEGFR2 mAb, has obtained marketing authorization in the US, EU, and Japan for the treatment of advanced gastric or GEJ (gastric-GEJ) adenocarcinoma as monotherapy (REGARD) or in combination with paclitaxel (RAINBOW), with disease progression on or after prior fluoropyrimidine- and/or platinum-containing chemotherapy. Ramucirumab is also approved in the US and EU for the treatment of advanced NSCLC in combination with docetaxel (REVEL), with disease progression on or after prior platinum-based chemotherapy. Patients with *EGFR* or anaplastic lymphoma kinase genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving ramucirumab. Ramucirumab is also approved in the US and EU for the treatment of mCRC in combination with FOLFIRI (RAISE) with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

In addition, the toxicity profile of ramucirumab has been manageable given as a monotherapy or in combination. In REGARD, a single-agent, placebo-controlled, Phase 3 gastric cancer study, 25 patients (10.5%) receiving ramucirumab discontinued study treatment due to adverse events (AEs). The most common adverse drug reactions reported in ≥10% of ramucirumab-treated patients were abdominal pain, diarrhea, and hypertension. Clinically relevant reactions (including Grade ≥3) associated with antiangiogenic therapy observed in ramucirumab-treated patients across clinical trials were proteinuria, infusion-related reactions, and gastrointestinal (GI) perforations.

3.2.2. Necitumumab

Necitumumab (LY3012211) is a recombinant human mAb of the IgG_1 class, which targets *EGFR*. Necitumumab demonstrates a high affinity to its target and blocks ligand-induced receptor phosphorylation and downstream signaling. In vitro studies further demonstrate that necitumumab inhibits *EGFR*-dependent tumor cell proliferation, and can exert cytotoxic effect in tumor cells through antibody-dependent cell cytotoxicity. Necitumumab (PORTRAZZA®, PI) in combination with gemcitabine and cisplatin, has been approved for first-line treatment of patients with metastatic squamous NSCLC in the US and EU.

The pivotal, randomized Phase 3 trial SQUIRE (I4X-IE-JFCC) compared gemcitabine/cisplatin plus necitumumab (GC+N) versus gemcitabine/cisplatin (GC) as first-line therapy in 1093

patients with Stage IV squamous NSCLC (Thatcher et al. 2015). The study met its primary objective, demonstrating a statistically significant improvement in OS in the GC+N Arm compared with the GC Arm (HR = 0.84; p = 0.012). This was supported by a statistically significant improvement in PFS (HR = 0.85; p = 0.02). Several prespecified subgroup analyses for OS and PFS showed a consistent treatment effect in favor of GC+N. Post-progression anticancer therapy was similar (47% vs. 45%). The safety data obtained in SQUIRE overall were consistent with the safety profile expected for an anti-*EGFR* mAb, with skin reactions (any grade: 79% vs. 12%, including Grade ≥3: 8.2% vs. 0.6%) and hypomagnesemia (any grade: 31% vs. 16%, including Grade ≥3: 9.3% vs. 1.1%) being the most frequently reported events (pooled terms) occurring at higher rates for patients receiving necitumumab. The Grade ≥3 treatment-emergent adverse events (TEAEs) with highest incidence for which incidence was higher in the necitumumab arm than in the control arm were hypomagnesemia (8.7% vs. 1.1%), rash (3.7% vs. 0.2%), pulmonary embolism (3.5% vs. 1.8%), hypokalemia (3.0% vs. 1.5%), and vomiting (2.8% vs. 0.9%).

In another randomized Phase 3 trial, INSPIRE (I4X-IE-JFCB [JFCB]), 947 patients were planned to be randomly assigned to necitumumab plus pemetrexed-cisplatin (PC+N) versus pemetrexed-cisplatin (PC) as first-line therapy for Stage IV nonsquamous NSCLC (Paz-Ares et al. 2015). Enrollment was halted, following an independent data monitoring committee (IDMC) recommendation, after 633 patients because of safety concerns related to thromboembolism as well as the overall number of deaths from all causes that were unbalanced against the experimental group; the trial continued for patients that had been enrolled. Based on the final analysis, PC+N did not improve the efficacy outcome over PC alone in advanced nonsquamous NSCLC (OS HR = 1.01, p=0.96; PFS HR = 0.96, p=0.66). The addition of necitumumab resulted in a higher frequency of Grade ≥3 TEAEs. Grade ≥3 TEAEs occurring more frequently in the necitumumab arm included skin or subcutaneous disorders (14.1 vs. 0.3%), thromboembolic events (9.5 vs. 6.4%), hypomagnesaemia (7.6 vs. 2.2%), asthenia (6.9 vs. 1.9%), vomiting (6.6 vs. 3.2%), dyspnea (5.3 vs. 2.6%), and diarrhea (4.3 vs. 2.2%).

The randomized Phase 2 trial, I4X-MC-JFCL, compared paclitaxel-carboplatin plus necitumumab versus paclitaxel-carboplatin in the first-line treatment of patients with Stage IV squamous NSCLC. The overall efficacy and safety results were generally consistent with those of SQUIRE. Several other Phase 1 and 2 trials of necitumumab are ongoing to evaluate the efficacy and safety of necitumumab in combination with chemotherapy or other targeted therapies in patients with NSCLC.

For more details regarding the necitumumab development program, reference is made to the Investigator's Brochure (IB).

3.2.3. Osimertinib

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 and SmPC) 80-mg once-daily tablet has been recently approved in the US and EU 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 reveals high response rates in patients with *EGFR* TKI resistance whose tumors harbored *EGFR*-T790M (ORR 61%; 95% CI: 52%-70%) and lower response rates in patients whose tumors lacked *EGFR*-T790M (ORR 21%; 95% CI: 12%-34%). The mPFS was 9.6 months (95% CI: 8.3 to not reached) in *EGFR* T790M-positive patients and 2.8 months (95% CI: 2.1 to 4.3) in *EGFR* T790M-negative patients. The most common 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.

3.3. Benefit/Risk Assessment

Osimertinib inhibits *EGFR* tyrosine kinase activity by irreversibly competing with ATP for binding in the kinase domain. Necitumumab binds to the extracellular domain of *EGFR* and prevents ligand activation of the receptor. In *EGFR*-dependent human xenograft models of lung cancer, necitumumab led to significant and durable tumor regression. CCI [redacted] By binding the extracellular domain of *EGFR*, necitumumab may provide additional antitumor effect via activation of antibody-dependent cellular cytotoxicity and inhibition of the autocrine loop of cancer cell signaling (Riemenschneider et al. 2005; Patel et al. 2011).

Phase 1 studies have shown that various combinations of *EGFR* TKIs and *EGFR*-directed mAb can be administered to patients with NSCLC, although efficacy and/or safety profile of such combination has not been encouraging (Ramalingam et al. 2008; Janjigian et al. 2011; Wheler et al. 2013; Janjigian et al. 2014). However, combined *EGFR* inhibition with third-generation

EGFR TKI and *EGFR*-directed mAb has not been prospectively studied in patients with acquired resistance to first-generation *EGFR* TKIs (Janjigian et al. 2011).

On the basis of preclinical data of necitumumab in lung adenocarcinoma harboring a drug sensitive L858R and drug resistant T790M mutation, we hypothesize that simultaneous inhibition of the *EGFR* signaling pathway using both osimertinib and necitumumab would improve efficacy of osimertinib in tumors that progress on prior first-generation *EGFR* TKI in patients with T790M-positive NSCLC. Both necitumumab and osimertinib may cause skin rash, hence some overlap is expected; however, the rate of rash with third-generation *EGFR* TKIs is believed to be less than that of the first- and second-generation.

Separately, 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 OS benefit in the subgroup of patients with *EGFR* mutations. In addition, the JO25567 study, which is a randomized Phase 2 study of erlotinib with or without bevacizumab as first-line therapy for patients with *EGFR*-mutant NSCLC, showed that mPFS was 16.0 months (95% CI: 13.9-18.1) with erlotinib plus bevacizumab and 9.7 months (5.7-11.1) with erlotinib alone (HR: 0.54 [95% CI: 0.36–0.79]; log-rank test p=0.0015). A greater proportion of patients achieved disease control with erlotinib plus bevacizumab (99% vs. 88%; p=0.0177) (Seto et al. 2014). No significant toxicity was observed with the addition of bevacizumab to erlotinib. 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). RELAY, a Phase 3 randomized study of erlotinib with or without ramucirumab as first-line therapy for patients with *EGFR*-mutant NSCLC, is ongoing (NCT02411448).

Considering the improvement in PFS and DCR with the combination of erlotinib and bevacizumab in *EGFR*-mutant NSCLC, as well as no significant worsening toxicity observed with the addition of bevacizumab to erlotinib, we anticipate a similarly favorable benefit/risk ratio would apply to the same class of agents with similar mechanisms of action. Therefore, we would like to examine whether the combination of osimertinib and ramucirumab in *EGFR*-mutant T790M-positive NSCLC after progression on first-line *EGFR* TKI would also lead to improvement in efficacy with tolerable toxicity.

This study will provide benefit-risk data on the coadministration of osimertinib with ramucirumab or necitumumab. More information about the known benefits, risks, serious adverse events (SAEs) and anticipated AEs of ramucirumab, necitumumab, and osimertinib are to be found in the IB of each agent.

4. Objectives and Endpoints

Table JVDL.5 shows the objectives and endpoints of the study.

Table JVDL.5. Objectives and Endpoints

	Objectives	Endpoints
Phase 1a: **Dose-Finding Portion**	**Primary:** To assess the safety and tolerability of ramucirumab or necitumumab in combination with osimertinib	Dose-limiting toxicities, observed during 2 cycles (28 days) for ramucirumab arm (Arm A) and 1 cycle (21 days) for necitumumab arm (Arm B) **Safety (including but not limited to):** TEAEs, SAEs, and deaths
	Secondary: To assess the PK of ramucirumab or necitumumab in combination with osimertinib	**PK:** C_{min} and approximate C_{max} of ramucirumab and necitumumab in serum
Phase 1b: **Dose-Expansion Portion**	**Primary:** To assess the safety and tolerability of ramucirumab in combination with osimertinib	**Safety (including but not limited to):** TEAEs, SAEs, and deaths
	Secondary: To assess the preliminary efficacy of ramucirumab in combination with osimertinib* To assess the PK of ramucirumab in combination with osimertinib	**Efficacy:** ORR (RECIST 1.1), DCR, DOR, PFS, and OS* **PK:** C_{min} and approximate C_{max} of ramucirumab in serum
	Tertiary/Exploratory: To explore the association between biomarkers and clinical outcomes	**Biomarkers:** Genetic and other molecular markers (e.g. assessments of DNA, RNA, and protein) from tissue and blood samples

Abbreviations: C_{max} = maximum concentration; C_{min} = minimum concentration; DCR = disease control rate; DNA = deoxyribonucleic acid; DOR= duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; RNA = ribonucleic acid; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

*Note: Patients in the Dose-Finding Portion will be included in the overall preliminary efficacy analyses.

5. Study Design

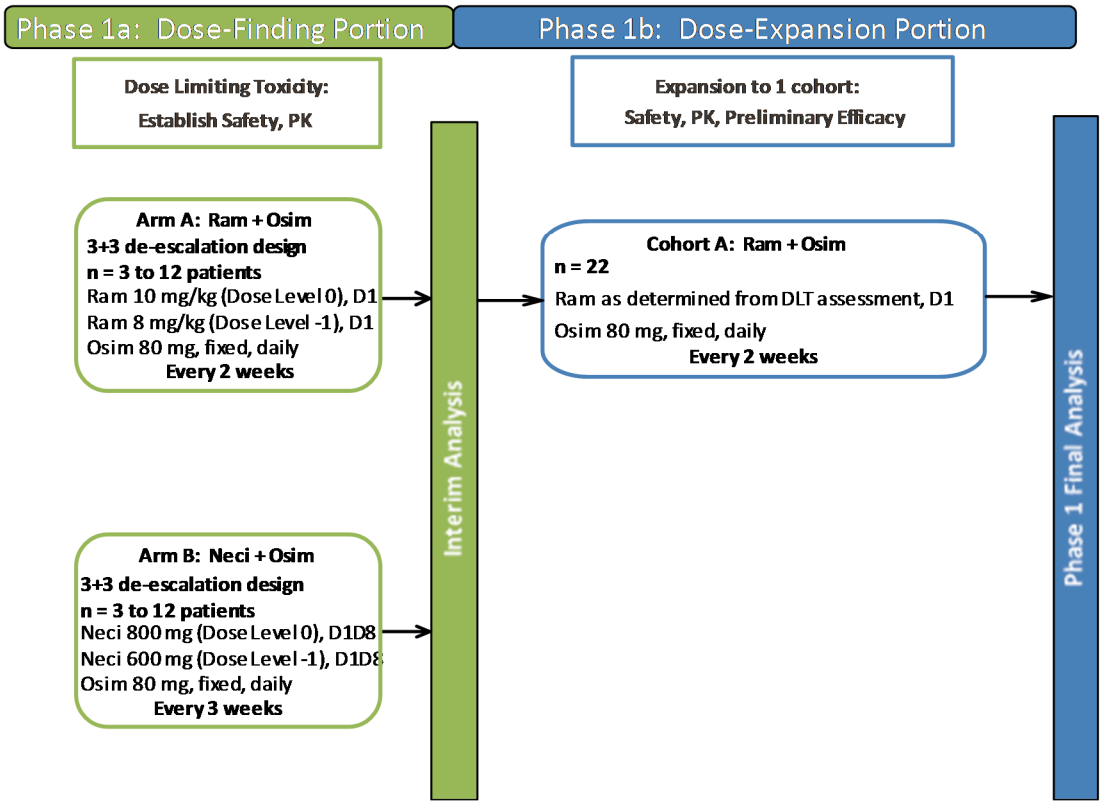
5.1. Overall Design

Study I4T-MC-JVDL (JVDL) is an open-label, multicenter Phase 1 study with an expansion cohort to evaluate the safety and preliminary efficacy of ramucirumab or necitumumab in combination with osimertinib in patients with advanced T790M-positive *EGFR*-mutant NSCLC who have relapsed after first-line *EGFR* TKI therapy.

The study consists of the Dose-Finding Portion (dose-limiting toxicity [DLT] observation) and the Dose-Expansion Portion (expansion cohort).

- Phase 1a: Dose-Finding Portion consists of 2 arms. Arm A is the combination of ramucirumab and osimertinib and Arm B is the combination of necitumumab and osimertinib.
- Phase 1b: Dose-Expansion Portion consists of 1 cohort. Cohort A is the combination of ramucirumab and osimertinib.

Figure JVDL.1 illustrates the study design.



Abbreviations: D1 = Day 1; D8 = Day 8; DLT = dose-limiting toxicity; n = number of patients; Neci = Necitumumab; Osim = Osimertinib; PK = pharmacokinetics; Ram = ramucirumab.

Note: The results of the interim analysis will confirm the dosing regimen to be used in the expansion cohort. Dose reductions, delays, and discontinuations may occur per the guidelines in Section 7.4.

Figure JVDL.1. Illustration of study design.

5.1.1. Dose-Finding Portion: Dose-Limiting Toxicity Observation

The Dose-Finding Portion will employ a 3+3 dose de-escalation design with a fixed dose of osimertinib at 80 mg once daily (QD). The DLT observation period is 2 cycles (4 weeks) for Arm A and 1 cycle (3 weeks) for Arm B, as shown in Figure JVDL.1.

DLTs will be determined based on the incidence, intensity, and duration of AEs that occur up to 4 weeks for Arm A and 3 weeks for Arm B following the first dose of both study drugs (see Section 7.2.1.1 for selection and timing of doses). Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

The definition for DLTs and the criteria used to determine progress of the study are provided in Section 7.2.1.1.

5.1.2. Dose-Expansion Portion: Expansion Cohort

Based on the safety profile observed during the Dose-Finding Portion, the sponsor may determine the dosing regimen to be investigated in the Dose-Expansion Portion of the study and expand to further evaluation of the combination therapy in this patient population.

The patients in the Dose-Expansion Portion will meet the same eligibility criteria as for Dose-Finding Portion of the study. The Dose-Expansion Portion consists of 1 cohort for patients with acquired *EGFR* T790M-positive NSCLC. Only patients with T790M-positive tumors using a test validated and performed locally will be assigned to ramucirumab + osimertinib (Cohort A). All patients will be treated until PD, intolerable toxicity despite dose reduction, or patient/investigator decision to terminate the study participation. Dose reductions, delays, and discontinuations may occur per the guidelines in Section 7.4.

The purpose of the Dose-Expansion Portion is to gather additional safety, tolerability, pharmacokinetics (PK), and preliminary efficacy information regarding ramucirumab in combination with osimertinib.

Note: For both study portions, tests for T790M that are currently recommended for the use of osimertinib in the US and in the EU, respectively, include the following:

- In the US, as approved by the Food and Drug Administration, the cobas® *EGFR* Mutation Test Version 2 is a real-time polymerase chain reaction test for the qualitative detection of defined mutations of the *EGFR* gene in DNA derived from formalin-fixed paraffin-embedded tumor tissue from NSCLC patients. The test is intended to aid in identifying patients with NSCLC whose tumors have defined *EGFR* mutations and for whom safety and efficacy of a drug have been established as follows:
    - Tarceva® (erlotinib) - Exon 19 deletions and L858R
    - Tagrisso® (osimertinib) - T790M
- In the EU, according to the currently approved SmPC for osimertinib as a treatment for locally advanced or metastatic NSCLC, a validated test is recommended to determine *EGFR* T790M mutation status. As indicated in the SmPC, the mutation status should be tested using either tumor DNA derived from a tissue sample or circulating tumor DNA (ctDNA) obtained from a plasma sample. Only robust, reliable, and sensitive tests with demonstrated utility for the determination of T790M mutation status of tumor-derived DNA (from a tissue or a plasma sample) should be used. Positive determination of T790M mutation status using either a tissue-based or plasma-based test indicates eligibility for treatment with osimertinib. If a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

5.2. Number of Patients

Approximately 90 patients will be screened and up to 46 patients enrolled. For the Dose-Finding Portion, up to 24 DLT-evaluable patients will be enrolled (12 in each arm). For the Dose-Expansion Portion, 22 evaluable patients will be enrolled into Cohort A.

5.3. Study Completion and End of Trial Definition

There will be a database lock to report the primary data analyses approximately 6 months after last patient receives initial dose in the Dose-Expansion Portion of the study.

The completion of the study (Study Completion) is defined as approximately 2 years after last patient enrolled, or when adequate number of events are observed for survival outcome estimation, whichever comes first.

Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient, including patients participating in the continued access period (see Section 7.8.1), if applicable. Section 7.1 describes the maximum duration of study treatment.

5.4. Scientific Rationale for Study Design

This is a Phase 1, open-label study that will evaluate safety and preliminary efficacy of ramucirumab or necitumumab in combination with osimertinib. This Phase 1 study includes a 3+3, dose de-escalating design for the Dose-Finding Portion followed by the Dose-Expansion Portion with 1 cohort. As detailed in Section 3.1, Study Rationale, and Section 3.3, Benefit/Risk Assessment, this study enrolls patients with *EGFR*-mutant NSCLC who recently developed disease progression on first-line *EGFR* TKI therapy. Although the combination of osimertinib and ramucirumab or necitumumab may work in patients with either T790M-positive or T790M-negative NSCLC, the response rates and other efficacy measures are expected to be different, and this study only enrolls patients with T790M-positive NSCLC to reduce heterogeneity of patients in a study with relatively small sample size.

5.5. Justification for Dose

5.5.1. Dose Selection for Ramucirumab

Ramucirumab administered at 10 mg/kg on Day 1 on an every-2-week (Q2W) schedule will be examined in this study. This dose regimen of ramucirumab is different compared to the REVEL study. In REVEL, conducted in a second-line NSCLC setting, ramucirumab was administered at a dose of 10 mg/kg every 3 weeks (Q3W). Exposure-response (efficacy/safety) findings from Phase 3 ramucirumab trials, REGARD, RAINBOW, and REVEL and PK simulations were used to guide the dose selection in this study. A recent safety review of the DLT Assessment Period data from Phase 1b of the study RELAY concluded that ramucirumab at 10 mg/kg Q2W is safe and tolerable for *EGFR* mutation-positive NSCLC patients.

Efficacy

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

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

- minimum concentration after first dose administration,

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

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

In RAINBOW (n=321 [number of patients with evaluable PK data]), patients with ramucirumab exposure greater-than-median (in the third and fourth quartile groups) were associated with longer OS and PFS and significantly better treatment effects (smaller HR) as compared to patients with ramucirumab exposure lower-than-median (in the first and second quartile groups).

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

Safety

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in Phase 1 Study I4T-MC-JVBM (JVBM). A maximal tolerated dose (MTD) for weekly dosing was identified as 13 mg/kg every week. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study I4T-MC-JVBN [JVBN]). All dose regimens in Study JVBN were well tolerated and no MTD was identified in this study.

The same ramucirumab dose regimen (8 mg/kg every 2 weeks) was used in REGARD and RAINBOW. REGARD demonstrated a well-tolerated safety profile in the gastric cancer monotherapy setting. Due to the low incidence of hypertension and neutropenia, no safety-exposure relationship was identified. In RAINBOW, ramucirumab in combination with paclitaxel was also well tolerated in patients with gastric cancer, with manageable AEs. An increasing ramucirumab exposure was correlated with increased incidence of Grade ≥3 hypertension, neutropenia, and leukopenia. Of note, there were no Grade 4 or 5 hypertension events in RAINBOW. Hypertension was managed primarily by the use of standard antihypertensive medication. Neutropenia and leukopenia are known risks with paclitaxel treatment. Overall, the safety profile of ramucirumab plus paclitaxel was largely consistent with the safety profiles of the individual treatment components and the combination revealed no unexpected safety findings.

The safety profile observed in REVEL was consistent with the safety profile for ramucirumab established in gastric cancer (REGARD and RAINBOW), as well as the established safety profile for docetaxel, and was manageable in the NSCLC population. An increasing ramucirumab exposure was correlated with increased incidence of Grade ≥3 hypertension and febrile neutropenia. Of note, there were no Grade 4 or 5 hypertension events in REVEL.

Hypertension was managed primarily by the use of standard antihypertensive medication. In addition, incidence of febrile neutropenia appeared to reach plateau at the third exposure quartile.

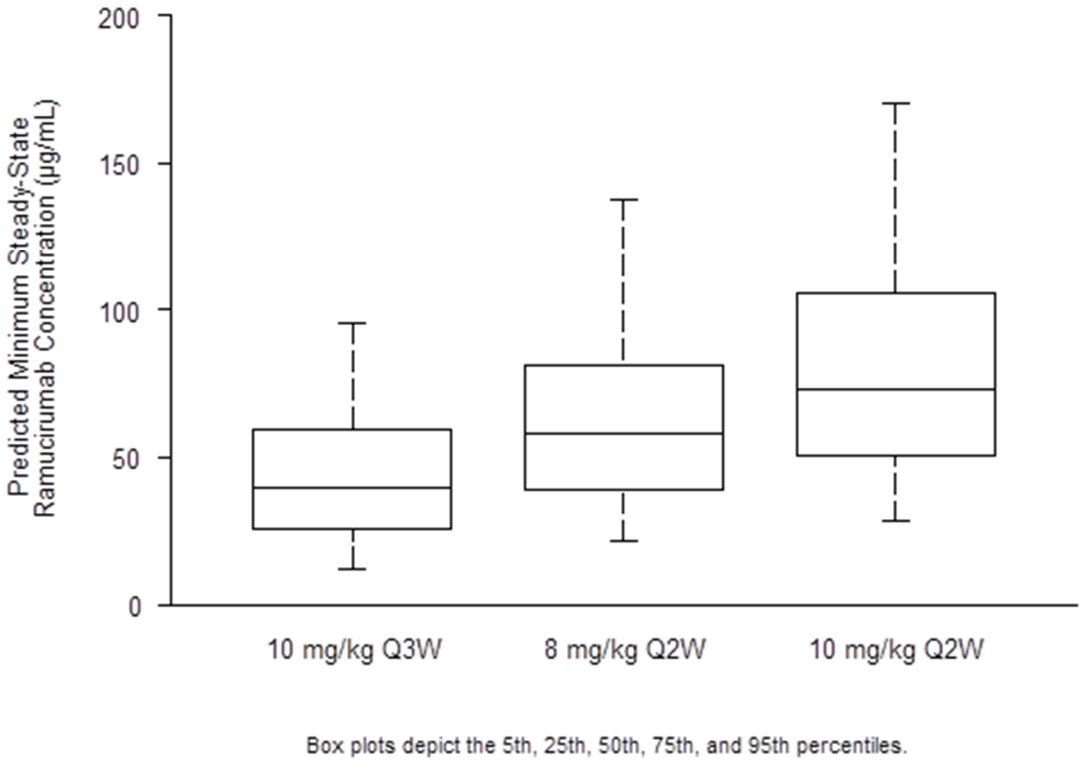
These exposure-efficacy and exposure-safety data indicate that there is an opportunity to further enhance efficacy of ramucirumab while maintaining an acceptable safety profile. Based on PK simulation, a dose regimen of 10 mg/kg on Day 1 every 2 weeks was selected for Study JVDL for the following reasons:

- This dose regimen may produce $C_{min,ss}$ that is higher than the fourth $C_{min,ss}$ quartile obtained from 10-mg/kg every-3-week regimen in REVEL, in at least 70% of the patient population (Figure JVDL.2) and is therefore expected to produce better clinical efficacy outcomes relative to the 10-mg/kg every-3-week regimen.
- It is expected that ramucirumab-related AEs in the NSCLC indication may not be significantly increased using the selected ramucirumab dose of 10 mg/kg every 2 weeks, since the selected dose for Study JVDL is still approximately 60% lower than the maximum tolerated weekly dose identified in the Phase 1 dose-escalation study, Study JVBM (13 mg/kg weekly).
- The ramucirumab exposure distribution of the 10-mg/kg every-2-week regimen significantly overlaps with that of the 8-mg/kg every-2-week regimen studied in REGARD and RAINBOW.

DLT observation is being conducted to assess the safety and tolerability of ramucirumab administered at 10 mg/kg every 2 weeks in combination with osimertinib administered daily at 80 mg.

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

Out of 12 DLT evaluable patients, only 1 patient had DLT. No SAE or Grade 4 or 5 TEAEs were observed for the combination of ramucirumab 10 mg/kg Q2W plus erlotinib 150 mg/day; no unexpected safety signals were identified.



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

Figure JVDL.2. Predicted $C_{min,ss}$ following different dose regimens.

In summary, the dosing regimens of ramucirumab 10 or 8 mg/kg on Day 1 every 2 weeks in combination with osimertinib are anticipated to produce a favorable benefit-risk profile in patients with *EGFR* mutation-positive metastatic NSCLC.

5.5.2. Dose Selection for Necitumumab

The recommended dose and treatment schedules for necitumumab are 800 mg QW, 800 mg Q2W, or 800 mg (Days 1 and 8 of a 21-day cycle), based on safety and PK data from 2 Phase 1 studies in heavily pretreated patients with advanced solid tumors (JFCA and JFCE). The necitumumab 800-mg dose administered intravenously (I.V.) on Days 1 and 8 of each 21-day cycle has also been used in the recent pivotal, randomized Phase 3 trial SQUIRE in combination with gemcitabine/cisplatin as first-line therapy in 1093 patients with Stage IV squamous NSCLC (Thatcher et al. 2015). The starting dose of necitumumab will be at Dose Level 0 at 800 mg on Days 1 and 8 Q3W.

Although the exposure-response analysis of SQUIRE data showed an association between drug exposure and efficacy, the vast majority of patients had sufficient exposure of necitumumab, as 99.6% of patients had exposures superseding half-maximal effective concentration (82 µg/mL)

for OS, with the median exposure resulting in close to maximum efficacy. Necitumumab disposition showed a less-than-proportional dependence on patient body weight. Simulations based on population PK (PopPK) and pharmacodynamic models show that weight- or body surface area-based dosing would not lead to a decreased PK variability or improvement of OS.

There was no correlation detected between necitumumab PK and hepatic or renal function markers, and there were no differences in disposition across age, sex, or race (White vs. Asian). No clear relationship was observed between drug exposure and safety events. In summary, PopPK/Pharmacodynamic analysis supports the administration of 800 mg necitumumab on Days 1 and 8 of a 21-day cycle as an appropriate dose in the target population.

5.5.3. Dose Selection for Osimertinib

Osimertinib was slowly absorbed following oral dosing with median time to reach maximum plasma concentration in patients and healthy volunteers ranging from 6 to 8 hours across doses. Osimertinib exhibited low to moderate apparent clearance and high volume of distribution in a low fluctuation of exposure (maximum/minimum plasma concentration [C_{max}:C_{min}] ratio of approximately 1.6) with steady-state achieved by 15 days of dosing. In NSCLC patients, the population estimated mean maximum steady-state concentration and the area under the plasma concentration-time curve at steady state (AUC_{ss}) at 80-mg dose is 501 nM and 11258 nM.h, respectively.

Based on PopPK analysis, dose adjustment is not required based on patient's age, gender, body weight, ethnicity or smoking status. Based on an exposure-response analysis of the pooled data from efficacy studies (AURA Phase 1 component, AURA extension and AURA2), there was no evidence of a relationship between plasma exposure (AUC_{ss}) of osimertinib and efficacy endpoints (probability of response or best percent change in tumor size or duration of response [DOR] for T790M mutation-positive patients with advanced NSCLC who have progressed on or after *EGFR* TKI therapy). Overall, the PK profile of osimertinib supports once a day continuous dosing.

The AURA studies in NSCLC patients with *EGFR* T790M mutation-positive tumors who had progressed following prior therapy with an *EGFR* TKI agent have demonstrated that osimertinib 80 mg QD offers benefits. ORR was 66.1% (95% CI: 61.2, 70.7) based on blinded independent central review (BICR), which is substantially higher than that reported with chemotherapy in second- or later-lines. The high ORR was regardless of line of therapy or other demographic or disease characteristics. DOR was 8.5 months (95% CI: 8.5, not calculable [NC]) based on investigator assessment. The preliminary estimate of mPFS was 9.7 months (95% CI: 8.3, NC) based on assessments of both BICR and investigator. An improvement in patient-reported outcome (PRO)-reported lung cancer symptoms was supportive of the Response Evaluation Criteria In Solid Tumors (RECIST) efficacy data.

Osimertinib 80 mg QD has an acceptable safety profile for the intended advanced NSCLC population.

The 20-mg starting dose was sufficient to inhibit *EGFR* T790M, whereas doses equivalent to 80 mg or more were expected to lead to more profound inhibition of tumor growth (Cross et al.

2014). The current ongoing Phase 2 (AURA2) and Phase 3 (AURA3) studies employ 80-mg QD regimen for advanced *EGFR* T790M-positive NSCLC patients.

In summary, PK analysis and preclinical and clinical data support 80-mg once daily regimen in advanced *EGFR* T790M-positive NSCLC patients.

6. Study Population

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

6.1. Inclusion Criteria

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

[1] Have a diagnosis of NSCLC with at least 1 measurable lesion assessable using standard techniques by the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1; Eisenhauer et al. 2009)

[2] Have locally advanced or metastatic NSCLC not amenable to curative therapy

[3] Have lung cancer with documented evidence of one of the 2 common *EGFR* mutations known to be associated with *EGFR* TKI sensitivity (Ex19del, L858R)

[4] Have disease progression immediately following first-line *EGFR* TKI treatment (with disease control as the best response to the first-line *EGFR* TKI treatment) regardless of prior chemotherapy

[5] Have T790M-positive status using a test validated and performed locally after disease progression on *EGFR* TKI treatment

[6] Tumor tissue from a biopsy taken after disease progression on the most recent *EGFR* TKI treatment is required. Patients for whom newly obtained samples cannot be obtained (for example, inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the Sponsor.

[7] Have Eastern Cooperative Oncology Group Performance Status of 0 or 1 at the time of enrollment (Oken et al. 1982)

[8] Have provided signed informed consent and are amenable to compliance with protocol schedules and testing

[9] Have serum albumin that is ≥25 g/L at the time of enrollment

[10] Have urinary protein that is <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <2 g of protein in 24 hours to allow participation in the study.

[11] Have adequate organ function, as defined below, with all screening labs performed within 7 days of treatment initiation:

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (packed red blood cell transfusions are not allowed within 1 week prior to baseline hematology profile)
Renal	
Creatinine **OR** Measured or calculated creatinine clearance[a] (see Appendix 6)	≤1.5 x ULN **OR** ≥50 mL/min
Hepatic	
Total bilirubin	≤1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases
Coagulation[b]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	INR ≤1.5 x ULN or PT ≤ 5 seconds above ULN unless patient is receiving anticoagulant therapy as long as INR or PT is within therapeutic range of intended use of anticoagulants
Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (aPTT)	PTT or aPTT ≤ 5 seconds above ULN unless patient is receiving anticoagulant therapy as long as PTT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

[a] Creatinine clearance should be calculated per institutional standard.

[b] Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have an INR ≤3.0 x ULN and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study treatment) or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).

[12] Be at least 18 years old at the time of signing informed consent

[13] Have a life expectancy of ≥3 months

[14] Have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade ≤1 by NCI CTCAE Version 4.0

[15] For male patients, are sterile (including vasectomy confirmed by postvasectomy semen analysis) or agree to use a *highly effective method of contraception* (2 methods preferred), and to not donate sperm starting with the first dose of study therapy, during the study, and for at least 6 months following the last dose of study therapy or country requirements, whichever is longer. Refer to Appendix 1 for definition of *highly effective method of contraception*.

[16] For female patients, are surgically sterile, postmenopausal (see Section 6.3.2 in detail), or agree to use a *highly effective method of contraception* (2 methods preferred) during the study, and for 6 months following the last dose of study treatment or country requirements, whichever is longer. Refer to Appendix 1 for definition of *highly effective method of contraception.*

[17] For female patients and of child-bearing potential, must have a negative serum or urine pregnancy test within 7 days prior to enrollment, and should not be breast feeding

Note: Non-childbearing potential (by other than medical reasons) is defined in Section 6.3.2.

6.2. Exclusion Criteria

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

[18] Previous treatment with an *EGFR* mAb (except for past treatment for squamous cell carcinoma of head and neck or mCRC)

[19] Previous treatment with an *EGFR* TKI (for example, erlotinib or gefitinib) within 8 days or approximately 5x half-life, whichever is longer, of the first dose of study treatment (If sufficient wash-out time has not occurred due to schedule or PK properties, an alternative appropriate wash-out time based on known duration and time to reversibility of drug-related AEs could be agreed upon by the Sponsor and the investigator.)

[20] Previous treatment with osimertinib or other third-generation *EGFR* TKIs

[21] Patients with symptomatic or growing brain metastases less than 4 weeks prior to enrollment. Patients with asymptomatic and stable brain metastases, such as those who have completed radiotherapy for brain metastases at least 4 weeks prior to receiving treatment and requiring no steroids or anticonvulsants for at least 2 weeks prior to receiving treatment, are eligible.

[22] Have a serious concomitant illness or medical condition(s) including, but not limited to, the following:

- Active infection including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection. Screening for chronic conditions is not required.
- Active or uncontrolled clinically serious infection
- Active substance abuse disorders
- History of drug-induced interstitial lung disease (ILD), ILD, or radiation pneumonitis requiring treatment with steroid prior to study enrollment, or any evidence of clinically active ILD
- Known allergy or hypersensitivity reaction to any of the treatment components

[23] Have history of another malignancy in 3 years, EXCEPT:

- adequately treated nonmelanomatous skin cancer,
- curatively treated cervical carcinoma in situ,
- other noninvasive carcinoma or in situ neoplasm, or
- prostate cancer that is not expected to impact patient survival

[24] Have a significant bleeding disorder or vasculitis or had a Grade ≥3 bleeding episode within 12 weeks prior to enrollment. Patients with a history of gross hemoptysis (defined as bright red blood of ≥1/2 teaspoon) within 2 month prior to enrollment are excluded.

[25] Have experienced any arterial thrombotic event or arterial thromboembolic event, including myocardial infarction, unstable angina (history or evidence of current clinically relevant coronary artery disease of current ≥Class III as defined by Canadian Cardiovascular Society Angina Grading Scale [Campeau 1976] or congestive heart failure of current ≥Class III as defined by the New York Heart Association), cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment

[26] Have a history of deep vein thrombosis, pulmonary embolism, or any other significant venous thromboembolism (venous catheter thrombosis or superficial venous thrombosis not considered "significant") during the 3 months prior to study enrollment. Patients with venous thromboembolism occurring 3 to 6 months prior to study enrollment are allowed, if being treated with low molecular weight heparin.

[27] Have a history of GI perforation and/or fistula within 6 months prior to enrollment

[28] Have a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea

[29] Have uncontrolled hypertension, as defined in CTCAE Version 4.0, prior to initiating study treatment, despite antihypertensive intervention. CTCAE Version 4.0 defines uncontrolled hypertension as Grade >2 hypertension; clinically, the patient continues to experience elevated blood pressure (systolic >160 mmHg and/or diastolic >100 mmHg) despite medications.

[30] Are receiving chronic therapy with any of the following medications within 7 days prior to enrollment:

a. nonsteroidal anti-inflammatory agents (NSAIDs; such as indomethacin, ibuprofen, naproxen, or similar agents)

b. other antiplatelet agents (such as clopidogrel, ticlopidine, dipyridamole, or anagrelide)

Aspirin use at doses up to 325 mg/day is permitted.

[31] Have had a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to enrollment

[32] Have an elective or a planned major surgery during the course of the trial

[33] Have undergone major surgery within 28 days prior to enrollment, or minor surgical procedure such as central venous access device placement within 7 days prior to enrollment

[34] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study (except in the setting of *EGFR* TKI as detailed above). Patients participating in surveys or observational studies are eligible to participate in this study.

[35] Are pregnant, or breastfeeding

[36] Have radiologically documented evidence of major blood vessel invasion or encasement by cancer

[37] Have radiographic evidence of pulmonary intratumor cavitation, regardless of tumor histology

[38] Are receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, chemoembolization, or targeted therapy or radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks prior to enrollment (except in the setting of *EGFR* TKI as detailed above).

[39] Are currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inducers of CYP3A4 (refer to Appendix 7).

[40] Have any of the following cardiac abnormal findings:

- Mean resting corrected QT interval (QTc) >470 msec obtained from 3 electrocardiograms (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

[41] Have undergone chest irradiation within 2 weeks prior to study drug administration, have not recovered from all radiation-related toxicities, or requires corticosteroids. A 2-week washout is permitted for focal palliative radiation to non-central nervous system disease.

[42] Have refractory nausea and vomiting, inability to swallow the formulated product, or previous significant bowel resection that would preclude absorption

[43] Have any other serious uncontrolled medical disorders or psychological conditions that would, in the opinion of the investigator, limit the patient's ability to complete the study or sign an informed consent document

[44] Have liver cirrhosis at a level of Child-Pugh B (or worse) or liver cirrhosis (any degree) and a history of hepatic encephalopathy or clinical meaningful ascites resulting from cirrhosis

6.3. Lifestyle Restrictions

6.3.1. Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.3.2. Contraception

Based on ramucirumab's mechanism of action, it is likely that ramucirumab will inhibit angiogenesis and may potentially result in adverse effects during pregnancy and postnatal development.

Therefore, 1) non-pregnant, non-breast-feeding women may only be enrolled if they are willing to use a highly effective method of contraception or are considered to be of non-childbearing potential and 2) only men may be enrolled who use an effective method of contraception, or who are sterile (including confirmed vasectomy) and do not donate sperm (Section 6.1).

For female patients, non-childbearing potential (by other than medical reasons) is defined as any one of the following:

- ≥45 years of age and has not had menses for greater than 2 years
- Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation (FSH level >40 mIU/mL)
- At least 6 weeks following surgical bilateral oophorectomy or tubal ligation with or without hysterectomy. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the patient must be willing to use an adequate barrier method throughout the study, starting with the screening visit through 6 months after the last dose of study treatment.

Refer to Appendix 1 for definitions of *effective method of contraception* and *highly effective method of contraception*.

Patients should start using contraception from study Visit 1 throughout the study period up to 6 months after the last dose of study treatment.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, only after discussion with and permission from the Lilly clinical research physician (CRP).

Repeating laboratory tests during the screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the screening period.

7. Treatments

7.1. Treatments Administered

Ramucirumab or necitumumab, and osimertinib will be administered per Table JVDL.6.

For the Dose-Finding Portion, the DLT observation period is for up to 2 treatment cycles for Arm A (4 weeks) and 1 treatment cycle for Arm B (3 weeks).

For the Dose-Expansion Portion, each patient will be treated until confirmed objective PD (see Section 9.1.3), unacceptable toxicity, or discontinuation for any other reason.

Across all study periods, including the continued access period (Section 7.8.1), patients will be treated with ramucirumab or necitumumab and/or osimertinib until confirmed PD, unacceptable toxicity, or discontinuation for any other reason.

Table JVDL.6. Dose Finding Portion Treatment Regimens/ Dosing Schedule

	Study Drug	Dose	Route	Timing
ARM A	Ramucirumab[a]	Level 0: 10 mg/kg Level -1: 8 mg/kg	I.V.	Over 60 minutes infusion Day 1 of each 2-week cycle
	1-hour observation period[b]			
	Osimertinib[c]	80 mg	PO	Daily
	OR			
ARM B	Necitumumab[d]	Level 0: 800 mg Level -1: 600 mg	I.V.	Over 60 minutes infusion Days 1 and 8 of each 3-week cycle
	1-hour observation period[e]			
	Osimertinib[c]	80 mg	PO	Daily

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

[a] Premedication is required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 IRR, as detailed in Table JVDL.8. All premedication administered must be adequately documented in the electronic case report form.

[b] A 1-hour observation period is required after the administration of the first and second doses of ramucirumab. If there is no evidence of an IRR during the initial 2 infusions of ramucirumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour observation period should be reinstituted. Refer to Section 7.7.1.1 for further instructions in detail.

[c] Refer to Section 7.4.3 for further instructions on taking osimertinib.

[d] Prior to necitumumab infusion, consider premedication for possible skin reactions. Preemptive treatment with skin moisturizers, topical steroids, doxycycline, or sunscreen may be administered as clinically appropriate to patients receiving necitumumab. For additional information regarding preemptive management of skin toxicity, see Canadian recommendations (Melosky et al. 2009).

[e] Monitor patients from the start of the infusion until at least 1 hour after the end of the infusion in an area with resuscitation equipment and other agents (for example, epinephrine or prednisolone equivalents) available. Refer to Section 7.7.1.1 for further instructions in detail.

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

- explaining the correct use of the drugs and planned duration of each individual's treatment to the site personnel
- verifying that instructions are followed properly
- maintaining accurate and appropriate records, including those of investigational product dispensing and collection
- ensure appropriate supply, storage, handling, distribution, and usage of trial treatments in accordance with the protocol and any applicable laws and regulations
- at the end of the study, returning all unused medication to Lilly or its designee

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

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

7.1.1. Packaging and Labelling

All investigational product materials will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements. Ramucirumab and necitumumab vials should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Osimertinib tablets in bottles should be stored at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

7.2. Method of Treatment Assignment

Patients meeting all inclusion/exclusion criteria will be enrolled to study regimen. Study drug will be allocated to patients using an 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.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 14 days for Arm A/Cohort A and 21 days for Arm B. A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 3 days and not counted as a protocol deviation.

The actual doses of ramucirumab administered will be determined by measuring the patient's weight at the beginning of each cycle. If the patient's weight fluctuates by more than ±10% from the weight used to calculate the prior dose, the dose must be recalculated. Recalculation of the ramucirumab dose for weight fluctuations of <10% is permitted but not required.

Ramucirumab will be administered, over 60-minute I.V. infusion. The maximum ramucirumab infusion rate is 25 mg/min.

Necitumumab will be administered, over 60-minute I.V. infusion, at a fixed dose.

Osimertinib will be taken by patients orally once a day, at a fixed dose. If a dose of osimertinib is missed, the missed dose should not be made up and the next dose should be taken as scheduled. For administration to patients who have difficulty swallowing solids, refer to osimertinib USPI or SmPC.

A patient may continue to receive ramucirumab or necitumumab in combination with osimertinib at the assigned dose level until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 8).

7.2.1.1. Dose-Limiting Toxicity Observation

A 3+3 dose de-escalation design will be used to assess the safety of ramucirumab (Arm A) or necitumumab (Arm B) given in combination with a fixed dose of osimertinib at 80 mg daily (QD). Eligible patients will be enrolled into either of the 2 treatment arms. If there is a DLT, a forced enrollment will be applied to push new patients towards that arm until the Dose-Finding Portion is complete. DLT observation period will last for 2 cycles (4 weeks) for Arm A and 1 cycle (3 weeks) for Arm B in this portion of the study. The following criteria will be used to determine the progress of the study:

Arm A - Ramucirumab and osimertinib 3+3 de-escalation design:

1) If none of the 3 DLT-evaluable patients treated at 10 mg/kg (Dose Level 0) of ramucirumab on Day 1 Q2W in combination with 80 mg of osimertinib QD develops a DLT, the study will open the Dose-Expansion Portion at Dose Level 0.

2) If 1 of the first 3 DLT-evaluable patients develops a DLT, 3 additional patients will be added to Dose Level 0. If ≤1 of 6 DLT-evaluable patients develops a DLT, the Dose-Expansion portion will start at Dose Level 0.
3) If ≥2 of 6 DLT-evaluable patients develop a DLT, 3 eligible subjects will be enrolled and treated at 8 mg/kg (Dose Level -1) of ramucirumab on Day 1 Q2W in combination with 80 mg of osimertinib QD.
4) Similarly, if none of the 3 DLT-evaluable patients develops a DLT, the study will open the Dose-Expansion portion at Dose Level -1.
5) If 1 of the first 3 DLT-evaluable patients at Dose Level -1 develops a DLT, 3 additional patients will be added. If ≤1 of 6 DLT-evaluable patients develops a DLT, the Dose-Expansion portion will start at Dose Level -1.
6) If ≥2 of 6 DLT-evaluable patients in Dose Level -1 develop a DLT, Arm A of the study will stop.

Arm B - Necitumumab and osimertinib 3+3 de-escalation design:

1) If none of the 3 DLT-evaluable patients treated at 800 mg (Dose Level 0) of necitumumab on Days 1 and 8 Q3W in combination with 80 mg of osimertinib QD develops a DLT, the study will open the Dose-Expansion portion at Dose Level 0.
2) If 1 of the first 3 DLT-evaluable patients develops a DLT, 3 additional patients will be added to Dose Level 0. If ≤1 of 6 DLT-evaluable patients develops a DLT, the Dose-Expansion portion will start at Dose Level 0.
3) If ≥2 of 6 DLT-evaluable patients develop a DLT, 3 eligible subjects will be enrolled and treated at 600 mg (Dose Level -1) of necitumumab on Days 1 and 8 Q3W in combination with 80 mg of osimertinib QD.
4) Similarly, if none of the 3 DLT-evaluable patients develops a DLT, the study will open the Dose-Expansion portion at Dose Level -1.
5) If 1 of the first 3 DLT-evaluable patients in Dose Level -1 develops a DLT, 3 additional patients will be added. If ≤1 of 6 DLT-evaluable patients develops a DLT, the Dose-Expansion portion will start at Dose Level -1.
6) If ≥2 of 6 DLT-evaluable patients in Dose Level -1 develop a DLT, Arm B of the study will stop.

No intrapatient dose escalation is allowed. Patients who withdraw from the study during the DLT observation period for reasons other than a treatment-related toxicity may be replaced within the same dose level.

Ramucirumab or necitumumab in combination with osimertinib may continue at the assigned dose level until there is a radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

For each arm, if dropouts, dose interruptions, or reductions occur that result in a patient being nonevaluable for DLTs, additional patients will be enrolled to achieve the minimum of 3 evaluable patients. The need for patient replacement will be determined based on consultation with the investigator and Lilly CRP/clinical research scientist (CRS).

7.2.1.1.1. Definition of Dose-Limiting Toxicities

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

1. Any nonhematologic toxicity Grade ≥3 will be considered as DLT with the following exceptions:

   a) Liver function abnormality: Grade ≥3 elevation in aminotransferase (AST) or alanine aminotransferase (ALT) that persists for less than 7 days. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, either one of the level ≥10x upper limit of normal (ULN) lasting for ≥7 days will be considered a DLT.
   b) Renal function abnormality: Grade ≥3 renal function test elevation that persists for less than 7 days
   c) Skin rash: Grade 3 rash that resolves to Grade ≤2 within 14 days with appropriate supportive therapy
   d) The following are not considered a DLT if they are transient (<7 days) and, after treatment, decrease to Grade 2 or lower:
      - Grade ≥3 hypersensitivity and injection site reactions
      - Grade ≥3 myalgia, fatigue, and constipation, with full supportive therapy
      - Grade ≥3 electrolyte imbalance, nausea, vomiting, and diarrhea

2. Hematologic toxicity will be considered a DLT as the following:

   a) Grade 4 toxicity lasting ≥7 days, or

   b) Grade 3 or 4 thrombocytopenia if associated with bleeding or requires platelet transfusion, or

   c) Febrile neutropenia

3. Grade 5 toxicity (that is, death) if considered related to study treatment

4. Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting, for example:

   a) Any toxicity (such as confirmed ILD/pneumonitis) that is possibly related to study treatment that requires the withdrawal of the patient from the study during observation period, or

   b) A delay of >14 days due to persistent Grade ≥2 treatment-related toxicities in the initial 2 cycles, or

c) If a total at least 75% of the planned dose for either agent cannot be administered in the first 2 cycles due to toxicity

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

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

After each of the 3 patients in a dose schedule completes the observation period, a safety analysis will occur; the data will be reviewed by study investigators and the Lilly CRP/CRS, and the findings documented, indicating whether each dose schedule is or is not well tolerated. The results will inform the decision whether or not to move onto the Dose-Expansion portion.

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Doses of study drugs may need to be delayed, reduced, or discontinued to manage specific AEs or other toxicities.

7.4.1. Ramucirumab Dose Adjustments, Delays, and Discontinuation

The ramucirumab dose may need to be delayed and/or reduced if the patient experiences an AE, including an adverse event of special interest (AESI) (Section 9.2.1). Doses may be delayed to allow time for the patient to recover from the event. Certain AEs require immediate and permanent discontinuation of study treatment (see Table JVDL.8). If administration of ramucirumab is delayed for more than 4 weeks (2 cycles) after Day 1 of the most recent treatment cycle, the patient should be discontinued from ramucirumab treatment. Any patient who requires a dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study. Any patients requiring dose reduction to less than 6 mg/kg of ramucirumab will have ramucirumab discontinued. Such patients may continue with osimertinib as a single agent.

Table JVDL.7 presents the ramucirumab dose reductions for each treatment cohort.

Table JVDL.8 presents the criteria for dose modifications and dose discontinuations applicable if the patient experiences a ramucirumab AESI or other AEs at least possibly related to ramucirumab. Dose re-escalation for ramucirumab is not permitted.

Table JVDL.7. Ramucirumab Dose Reductions[a]

	Dose Schedule 1: (14-day Cycle)	Dose Schedule 2: (14-day Cycle)
Recommended Dose for Expansion Cohort	8 mg/kg on Day 1	10 mg/kg on Day 1
First dose reduction	6 mg/kg on Day 1	8 mg/kg on Day 1
Second dose reduction	Not allowed	6 mg/kg on Day 1

[a] Ramucirumab dose reductions are allowed between cycles and within a given cycle.

Table JVDL.8. Dose-Modification Guidelines for Ramucirumab for Adverse Events at Least Possibly Related to Ramucirumab, including Adverse Events of Special Interest

	Adverse Event ***NOTE: All Specific Adverse Events Listed are defined as AESIs in Section 9.2.1).***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in*** Table JVDL.7. *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
1.	**Infusion-related reaction**		
1.a.	Infusion-related reaction	2	Interrupt and reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions of ramucirumab, premedicate with: • an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride • dexamethasone or equivalent • acetaminophen/paracetamol
1.b.	Infusion-related reaction	3-4	Immediately and permanently discontinue ramucirumab
2.	**Hypertension**		
2.a.	Hypertension (non-life-threatening and associated with symptoms) NOTE: Hypertension should be monitored prior to each ramucirumab infusion.	3	• Delay ramucirumab until the hypertension is controlled with medication and is resolved to Grade 0-2. o If controlled with medication and resolved to Grade 0-2, then may resume ramucirumab at current dose. o If NOT controlled with medication and not resolved to Grade 0-2 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.
2.b.	Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy	4	Immediately and permanently discontinue ramucirumab.

Dose-Modification Guidelines for Ramucirumab for Adverse Events at least Possibly Related to Ramucirumab, including Adverse Events of Special Interest (continued)

	Adverse Event ***NOTE: All Specific Adverse Events Listed are defined as AESIs in Section 9.2.1).***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTE: Dose reductions to occur as defined in*** Table JVDL.7.
3.	**Proteinuria**		
3.a.	Proteinuria = 2+ (dipstick or routine urinalysis)[a]		• Administer ramucirumab at the current dose if clinically indicated. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 h, administer ramucirumab at the patient's current dose. o If urine protein is ≥2 g/24 h, modify the ramucirumab dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.
3.b.	Proteinuria >2+ (dipstick or routine urinalysis)[a]		• Delay ramucirumab until urine protein returns to <2 g/24 h. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 h, no further dose delay or dose reduction is required. o If urine protein remains ≥2 g/24 h and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.
3.c.	Proteinuria ≥2 g/24 h (24-hour urine collection)[a]		• **First or second occurrence**: delay ramucirumab until urine protein returns to <2 g/24 h. o If urine protein returns to <2 g/24 h, reduce ramucirumab dose. o If urine protein remains ≥2 g/24 h and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. • **Third occurrence**: discontinue ramucirumab.
3.d.	Proteinuria >3 g/24 h **or** in the setting of nephrotic syndrome[a]		Immediately and permanently discontinue ramucirumab.
4.	**Arterial thromboembolic events, venous thromboembolic events**	3 or 4	Immediately and permanently discontinue ramucirumab.
5.	**Bleeding/hemorrhage**	3 or 4	Immediately and permanently discontinue ramucirumab.
6.	**Gastrointestinal perforation**		Immediately and permanently discontinue ramucirumab.

	Adverse Event *NOTE: All Specific Adverse Events Listed are defined as AESIs in Section 9.2.1).*	CTCAE Grade	Dose-Modification Guidelines *NOTE: Dose reductions to occur as defined in* Table JVDL.7.
7.	**Reversible posterior leukoencephalopathy syndrome**		Immediately and permanently discontinue ramucirumab.
8.	**Congestive heart failure**	3-4	Immediately and permanently discontinue ramucirumab.
9.	**Fistula formation**		Immediately and permanently discontinue ramucirumab.
10.	**Impaired wound healing**		
10.a.	Prior to planned surgery		Withhold ramucirumab.
10.b	After surgery		Resume ramucirumab based on clinical judgment.
10.c.	Wound-healing complications developed during study treatment		Delay ramucirumab dosing until the wound is fully healed.
11.	Liver injury/liver failure		
11.a.	Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis		Immediately and permanently discontinue ramucirumab.
12	**Hypothyroidism**	2-4	Therapy with ramucirumab can be continued while treatment for the thyroid disorder is instituted.
13	**Other adverse events considered at least possibly related to ramucirumab**[b]		
13.a	Non-life threatening and reversible	3	May delay ramucirumab until resolved to Grade 0-1. • If resolved to Grade 0-1, may reduce ramucirumab dose. • If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.
13.b	Adverse Event	4	Permanently discontinue treatment immediately, with the exception of Grade 4 fever or Grade 4 laboratory abnormality, in which case: • **First occurrence:** Delay ramucirumab until resolved to Grade 0-1. o If resolved to Grade 0-1, may resume ramucirumab original dose at the discretion of the investigator. o If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. • **Second occurrence:** Delay ramucirumab until resolved to Grade 0-1. o If resolved to Grade 0-1, reduce ramucirumab dose. o If NOT resolved to Grade 0-1 within a reasonable timeframe, discontinue ramucirumab at investigator's discretion.

Dose-Modification Guidelines for Ramucirumab for Adverse Events at least Possibly Related to Ramucirumab, including Adverse Events of Special Interest (concluded)

Abbreviations: AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

a Perform urinalysis within 3 days prior to each infusion of ramucirumab. If 24-hour urine collection is also performed, the results of 24-hour urine collection should be used for clinical decision-making.

b Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE Version 4.0 Grade 1-2 adverse events should not necessarily have dose delays or reductions related to the persistence or mild worsening of those symptoms or laboratory values. Grade 2 toxicities which represent clinically significant worsening of symptoms from baseline, ramucirumab dose may be delayed at the discretion of the investigator. If the toxicity is resolved to Grade 0-1, then reduce ramucirumab dose. If the toxicity is not resolved to Grade 0-1, then discontinue ramucirumab.

7.4.2. Necitumumab Dose Adjustments, Delays, and Discontinuation

Prior to each administration of necitumumab, all toxicities associated with necitumumab must have resolved to Grade ≤2 (except for alopecia and skin toxicity) or baseline. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8 of each cycle).

If the criteria are not met at the time of a planned treatment, the following general rules for the management of treatment delays apply:

- In the case of reversible Grade 3-4 necitumumab-related toxicity, administration of necitumumab will be at the reduced dose or interrupted, but osimertinib will continue according to the planned schedule.
- If administration of necitumumab is delayed for more than 6 weeks (2 cycles) after Day 1 of the most recent treatment cycle, the patient should be discontinued from necitumumab treatment.

The following are general dose-modification guidelines for toxicity associated with necitumumab. Please see Sections 7.7.1.1 and 7.7.1.3 for specific information on the management of necitumumab-related hypersensitivity/ infusion-related reactions (IRRs), skin reactions, conjunctivitis, hypomagnesemia, and thromboembolic events.

For patients starting at necitumumab 600 mg on Days 1 and 8, one dose reduction is permitted. Patients who cannot tolerate necitumumab 400 mg should discontinue necitumumab; such patients may continue with osimertinib as a single agent.

For patients starting at dose level 800 mg on Days 1 and 8, 2 dose reductions are allowed following reversible CTCAE Grade ≥3 AEs that require delay of necitumumab treatment for up to 6 weeks following Day 1 of the most recent treatment cycle, unless DLT criteria are met. In this setting, necitumumab may be re-administered at a reduced dose (600 mg) if necessary only if AE is resolved to Grade ≤2. A second dose reduction is permitted for this level of event (Grade ≥3). Necitumumab must be discontinued if further dose reduction is required beyond 400 mg on Days 1 and 8 Q3W. The patient may continue to receive osimertinib as a single agent.

Necitumumab dose adjustments are allowed both within a cycle and between cycles.

Necitumumab may be held up to 6 weeks (2 cycles) from Day 1 of the most recent treatment cycle to permit sufficient time for recovery from the toxicity. If a dose delay occurs, the investigator may resume necitumumab dosing at the same dose level for the remainder of the study or at reduced dose (assuming resolution to at least Grade 1 for nonhematologic and at least Grade 2 for hematologic toxicity). If the patient experiences the same toxicity with the same or greater severity (CTCAE grade) requiring a dose delay within a cycle or at start of the next cycle, the patient must be dose reduced and not re-challenged a second time at the prior dose level.

If a patient experiences CTCAE Grade ≥3 hematologic toxicity possibly related to necitumumab, unless DLT criteria are met, then dosing must be delayed (until the toxicity resolves to either

baseline or at least Grade 2) and the dose of necitumumab must be reduced by 1 dose level (see below).

If a patient experiences CTCAE Grade ≥3 nonhematologic toxicity possibly related to necitumumab, unless DLT criteria are met, then dosing must be delayed (until the toxicity resolves to either baseline or at least Grade 1) and the dose of necitumumab must be reduced by 1 dose level (see below).

For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP. After re-escalation, subsequent dose adjustments should be based on the dose of necitumumab that the patient is currently receiving. Following a dose reduction, the dose of necitumumab may be re-escalated to the pre-reduction dose, provided that at least 2 administrations of the reduced dose were given, and only after consultation with the Lilly CRP.

Table JVDL.9 presents the necitumumab dose reductions.

Table JVDL.9. Dose Adjustments of Necitumumab

Dose Adjustment Level	I.V. Dose	Frequency
0	800 mg	Days 1 and 8 Q3W
-1	600 mg	Days 1 and 8 Q3W
-2	400 mg	Days 1 and 8 Q3W

Abbreviations: I.V. = intravenous; Q3W = every 3 weeks.

Events that necessitate more than 2 dose reductions warrant discontinuation from necitumumab treatment. Patients who enter the study with symptoms or laboratory values equivalent to NCI CTCAE Version 4.0 Grade 1-2 AEs should not have dose reductions related to the persistence or mild worsening (for example, from Grade 1 to Grade 2) of those symptoms or laboratory values.

In the event of alterations of necitumumab therapy due to a necitumumab-related toxicity, osimertinib need not be altered, and the planned osimertinib schedule should be maintained. Similarly, necitumumab therapy should not be delayed for osimertinib-related toxicities.

7.4.3. Osimertinib Dose Adjustments, Delays, and Discontinuation

Patients receiving ramucirumab or necitumumab plus osimertinib can have the osimertinib dose reduced if the toxicity is specifically attributable to osimertinib at the discretion of the investigator. Patients may continue treatment with ramucirumab or necitumumab if they are discontinued from osimertinib. Dose re-escalation for osimertinib is not permitted.

Patients should be treated following the recommendations, warnings, and precautions given for osimertinib.

Table JVDL.10 shows the dose-modification criteria and guidelines for management of common osimertinib toxicities.

Table JVDL.10. Recommended Dose Modifications for Osimertinib

Target Organ	Adverse Reaction[a]	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 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 4 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 Grade 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).

7.4.4. Dose Delays for Reasons Not Related to Study Treatment

Dosing interruptions of any study drug are also permitted for reasons not related to study treatment (for example, elective surgery, unrelated medical events, patient vacation, and/or holidays).

Patients should resume the delayed study drug(s) within 4 weeks for ramucirumab and 6 weeks for necitumumab of the scheduled interruption, with every effort made to start on Day 1 of the next dosing schedule, unless otherwise discussed with the Sponsor. If a dose of osimertinib is missed, the patient should not make up for the missed dose and should take the next dose at the regular time. The reason for interruption should be documented on the case report form (CRF).

7.5. Preparation/Handling/Storage/Accountability

Refer to the respective IBs for detailed information about preparation, handling, and storage of ramucirumab, necitumumab, and osimertinib.

7.6. Treatment Compliance

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

Patient compliance with osimertinib will be assessed at each visit. Compliance will be assessed by direct questioning, review of diary, and counting returned tablets. Deviations from the prescribed dosage regimen should be recorded in the CRF.

A patient will be considered significantly noncompliant if he or she missed 4 or more consecutive doses of osimertinib in a visit interval, or took <70% or >130% amount of expected study drug in a visit interval during the study. A patient will also be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

Patients who are not evaluable for pharmacokinetics, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP/CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

7.7. Concomitant Therapy

A list of restricted and excluded concomitant therapies and exceptions is provided in Appendix 7. All premedication, supportive care, and concomitant medication must be reported on the CRF at each visit.

7.7.1. Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. For the 3 study drugs, specific AEs have been identified based on past data for special monitoring and, when necessary, supportive care. For ramucirumab and necitumumab, these are referred to as AESI.

7.7.1.1. Infusion-Related Reactions - Ramucirumab and Necitumumab

IRRs have been identified as events of interest for both ramucirumab and necitumumab. In the event of an IRR, blood samples will be collected for PK and immunogenicity analysis for ramucirumab and necitumumab, respectively, at the following time points: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

IRRs may occur during or following ramucirumab or necitumumab administration. Patients should be closely monitored for signs and symptoms indicative of an IRR from the initiation of the infusion in an area where resuscitation equipment and other agents (such as epinephrine and corticosteroids) are readily available.

Signs and symptoms usually develop during or shortly after infusion and generally resolve within 24 hours. Symptoms of IRRs include rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms include bronchospasm, supraventricular tachycardia, and hypotension.

7.7.1.1.1. Infusion-Related Reactions - Ramucirumab

Table JVDL.8 presents ramucirumab dose modification for patients who experience an IRR associated with ramucirumab.

Patients must be closely monitored for a 1-hour observation period following the ramucirumab infusions for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of each study drug, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted.

For the first 2 ramucirumab infusions, measure blood pressure and pulse at the following time points: (i) within 15 minutes prior to the infusion, (ii) after completion of the infusion, and (iii) at the end of the 1-hour post-infusion observation period. For all subsequent infusions of ramucirumab, measure blood pressure and pulse prior to the infusion. Measure other vital signs as clinically indicated.

7.7.1.1.2. Infusion-Related Reactions - Necitumumab

Hypersensitivity/IRRs were reported with necitumumab. The onset of events usually occurred after the first or second administration of necitumumab. Monitor patients closely for any potential adverse effects from the start of the infusion until at least 1 hour after the end of the infusion in an area with resuscitation equipment and other agents (for example, epinephrine or prednisolone equivalents) available.

Table JVDL.11 provides general treatment recommendations for hypersensitivity/IRRs to necitumumab.

Table JVDL.11. Necitumumab Infusion-Related Reaction Treatment Guidelines

Grade of Reaction	Management Recommendations	
	First Occurrence	**Second Occurrence**
1	• Decrease infusion rate by 50% for the duration of the infusion, and monitor patient for worsening of condition.[a] • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.	• Decrease infusion rate by 50% for the duration of the infusion, and monitor patient for worsening of condition.[a] • Administer dexamethasone 10 mg I.V. (or equivalent). • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally (or equivalent), and dexamethasone 10 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.
2	• Stop the infusion, and resume the infusion when the infusion reaction has resolved to ≤ Grade 1; decrease infusion rate by 50% when the infusion resumes.[a] • Monitor patient for worsening of condition. • If necessary, administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.	• Stop the infusion, and resume the infusion when the infusion reaction has resolved to ≤ Grade 1; decrease infusion rate by 50% when the infusion resumes.[a] • Administer dexamethasone 10 mg I.V. (or equivalent). • Monitor patient for worsening of condition. • If necessary, administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally (or equivalent), and dexamethasone 10 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.
3-4	• Stop the infusion and disconnect the infusion tubing from the patient. • Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), bronchodilators for bronchospasm, epinephrine, and other medications / treatments as medically indicated. • Hospital admission may be indicated. • **Permanently discontinue necitumumab.**	N/A

Abbreviations: IRRs = infusion-related reactions; I.V. = intravenously; N/A = not applicable.

a Once the infusion rate has been reduced for a Grade 1 or 2 hypersensitivity/IRRs, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

7.7.1.2. Supportive Care for Ramucirumab

7.7.1.2.1. Supportive Care by Adverse Event of Special Interest

7.7.1.2.1.1. Hypertension

An increased incidence of severe hypertension (CTCAE Grade 3) has been reported in patients receiving ramucirumab compared with placebo. In most cases, hypertension was controlled using standard antihypertensive treatment. Preexisting hypertension should be controlled before starting ramucirumab treatment.

Monitoring of blood pressure is required during, and should occur prior to, ramucirumab therapy. Every attempt should be made to control blood pressure to systolic <140 mmHg and diastolic <90 mmHg prior to starting treatment with ramucirumab. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension.

7.7.1.2.1.2. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGFR2 pathway, including ramucirumab. In ramucirumab clinical trials, the majority of events were Grade 1 or 2. Monitoring for the development or worsening of proteinuria during ramucirumab therapy is required. Discontinue ramucirumab if the patient experiences proteinuria >3 g/24 hours or nephrotic syndrome.

7.7.1.2.1.3. Thromboembolic Events

7.7.1.2.1.3.1. Arterial Thromboembolic Events

Serious, sometimes fatal arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials.

7.7.1.2.1.3.2. Venous Thromboembolic Events

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

7.7.1.2.1.4. Bleeding/Hemorrhage

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

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (that is, variceal bleeding

from portal hypertension in hepatocellular carcinoma, lower GI hemorrhage from bowel metastases in ovarian carcinoma), although the rate of these complications varies considerably. As detailed in the ramucirumab IB, the incidences of hemorrhagic events to date, significant background incidence of bleeding in some malignancies, and use of concomitant antiplatelet therapy in some of the reported cases preclude any definitive association between bleeding and ramucirumab, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and are detailed in the inclusion/exclusion criteria.

7.7.1.2.1.5. Gastrointestinal Perforation

An infrequent incidence of GI perforations has been associated with some antiangiogenic therapeutic agents, most specifically in the context of colorectal cancer (treated with combination regimens, including anti-VEGF antibodies and cytotoxic chemotherapy) and in advanced ovarian cancer. These events may be associated with extensive abdominal/peritoneal disease burden. Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab. The incidences of these events to date and presence of significant comorbidities and risk factors preclude any definitive association with ramucirumab, although ongoing surveillance remains essential. More information about GI perforation may be found in the IB.

7.7.1.2.1.6. Reversible Posterior Leukoencephalopathy Syndrome

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

Across the clinical program to date, 2 cases of RPLS have been reported: One case occurred in each arm of the recently completed double-blind, randomized, placebo-controlled Phase 3 Study RAISE evaluating ramucirumab in combination with FOLFIRI versus FOLFIRI in combination with placebo for patients with metastatic colorectal cancer.

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

7.7.1.2.1.7. Congestive Heart Failure

An increased risk of congestive heart failure (CHF) has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines. A small number of CHF events (including fatal) were

also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies.

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

Caution should be exercised when treating patients with clinically significant cardiovascular disease, such as preexisting coronary artery disease or CHF. Ramucirumab should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

7.7.1.2.1.8. Fistula Formation

Because fistula formation has been associated with antiangiogenic agents, patients may be at increased risk for the development of fistula when treated with ramucirumab. Some fistulas can be resolved with surgical procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009).

7.7.1.2.1.9. Surgery and Impaired Wound Healing

Because ramucirumab is an antiangiogenic therapy, it may have the potential to adversely affect wound healing. Ramucirumab did not impair wound healing in a study conducted in animals; however, the impact of ramucirumab on serious or nonhealing wounds has not been evaluated in humans.

7.7.1.2.1.10. Liver Failure and Other Significant Liver Injury

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

7.7.1.2.2. Supportive Care Agents for Ramucirumab - Guidelines

Supportive care measures may include but are not limited to antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Guidelines regarding the use of specific supportive care agents are presented below.

7.7.1.2.2.1. Antiemetic Agents

Although emesis is not an expected side effect of ramucirumab, the use of antiemetic agents is permitted at the discretion of the investigator. Acceptable antiemetic agents include 5-HT_3 receptor antagonists (for example, ondansetron), dopamine receptor antagonists (for example, metoclopramide), corticosteroids (for example, dexamethasone), and others.

7.7.1.2.2.2. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. Opiate and nonopiate analgesic agents are permitted (including acetaminophen/paracetamol); however, use of NSAIDs and/or aspirin is restricted (Appendix 7).

7.7.1.2.2.3. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator. Examples include megestrol acetate, dronabinol, and others.

7.7.1.2.2.4. Granulocyte-Colony Stimulating Factors

The as-needed use of granulocyte-colony stimulating factors is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006) (Appendix 7).

7.7.1.2.2.5. Erythroid Growth Factors

The as-needed use of erythroid-stimulating factors (for example, erythropoietin) is permitted at the discretion of the investigator based on ASCO guidelines (Rizzo et al. 2008) (Appendix 7).

7.7.1.2.2.6. Other Supportive Care Agents

The use of benzodiazepines, antidepressants, laxatives, and other agents that may be helpful in controlling disease-related symptoms are also permitted and encouraged, except as prohibited in Appendix 7.

7.7.1.3. Supportive Care for Necitumumab by Adverse Event of Special Interest

7.7.1.3.1. Skin Reactions

Reactive treatment recommendations for skin reaction, based on the Canadian recommendations presented by Melosky et al. (2009), are summarized in Table JVDL.12.

Skin rash (any grade) should be treated as per Table JVDL.12. If a patient experiences a Grade 1 or 2 acne-like rash, necitumumab treatment should continue without dose modification or delay. Dose delays and or modifications for necitumumab are to be considered in case of skin reactions of Grade 3 or that are considered intolerable. If a patient experiences Grade 4 skin reactions, treatment with necitumumab should be permanently discontinued.

Table JVDL.12. Managing Skin Reactions

Grade of Reaction	Recommendations for Management
1	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity.
2	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • If clinically appropriate in the opinion of the investigator, administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity.
3	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity. • Necitumumab administration will be temporarily withheld until symptoms resolve to Grade ≤2, but not for longer than a maximum of 6 weeks following Day 1 of the most recent treatment cycle. • Following improvement to Grade ≤2, necitumumab may be re-administered, with a dose reduction of 50% but not below 400 mg. This dose may be increased to 75% of the original dose after a minimum of 1 treatment cycle (3 weeks), if symptoms do not recur. If symptoms do not recur for another treatment cycle, the dose may be re-escalated to the initial dose. • If reactions do not resolve to Grade ≤2 after 6 weeks (that is, after withholding 2 consecutive doses of necitumumab), or if reactions recur or become intolerable at 50% of the original dose, necitumumab treatment should be permanently discontinued. • Patients who experience Grade 3 skin induration / fibrosis will be immediately discontinued from necitumumab.
4	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity. • **Necitumumab administration must be immediately and permanently discontinued.**

A dermatology referral may be indicated for skin reactions that do not improve following 1-2 weeks of treatment, reactions that are severely symptomatic (for example, necrosis, blistering, or petechial or purpuric lesions), reactions of NCI CTCAE Grade ≥3, or reactions with an uncharacteristic appearance.

As with all concomitant medications/procedures, any actions taken to ameliorate skin toxicity will be documented in the concomitant medication module of the electronic CRF (eCRF).

7.7.1.3.2. Conjunctivitis

For patients with treatment-related conjunctivitis <Grade 3, the investigator is advised to initiate symptomatic treatment and follow up observation of the event. If the severity increases to Grade ≥3, or symptoms persists for >10 days after symptomatic treatment, the investigator is advised to refer the patient to an ophthalmologist for further evaluation and treatment.

7.7.1.3.3. Electrolyte Abnormalities

Consistent with observations with other EGFR mAbs, hypomagnesemia has been very commonly reported in patients treated with necitumumab in combination with cisplatin-based regimens. Hypomagnesemia is considered a class effect for EGFR mAbs. Monitor patients for hypomagnesemia, hypocalcemia, hypokalemia, and hypophosphatemia prior to each administration of necitumumab and after completion of necitumumab, until within normal limits. Prompt repletion is recommended, as appropriate.

7.7.1.3.4. Thromboembolic Events

In the Phase 3 Study JFCC, there was an increase in VTEs and ATEs in the investigational arm (necitumumab in combination with gemcitabine and cisplatin) compared to the active control arm (gemcitabine and cisplatin). The relative risk of VTEs or ATEs was approximately 3-fold higher in patients with a reported history of VTEs or ATEs.

In Study JFCB (INSPIRE), which investigated necitumumab in combination with pemetrexed and cisplatin (PC+N) in patients with nonsquamous NSCLC, patients experienced an increased rate of serious thromboembolic events (including fatal events) in the PC+N Arm as compared to pemetrexed and cisplatin (PC) alone. Furthermore, the addition of necitumumab did not improve the efficacy outcome over PC alone in advanced nonsquamous NSCLC.

Administration of necitumumab in combination with pemetrexed and cisplatin is not recommended.

Discontinuation of necitumumab in patients who experience a VTE or ATE should be considered after a thorough benefit-risk assessment for the individual patient.

7.7.1.3.5. Pneumonia and Sepsis

During the conduct of Study JFCL (JFCL; Phase 2 study to investigate carboplatin and soluble paclitaxel with or without necitumumab in patients with squamous NSCLC), following the non-blinded review of SAE cases that included reports related to pneumonia and sepsis, an imbalance in the number of SAEs, including fatal cases, for the necitumumab group compared with the paclitaxel-carboplatin group was found.

The early occurrence of a number of these cases may have indicated an issue regarding the enrollment of the appropriate patients. The sponsor had therefore provided clarification and reinforcement of the inclusion/exclusion criteria, requesting the investigator's particular attention with regard to infections and conditions predisposing to infections ongoing at the time of enrollment in a protocol amendment. During the further conduct of this trial, only single

additional reports were received, notably of cases reporting pneumonia and septic complications with concurrent neutropenia.

The review of the data from the Phase 3 study of necitumumab in combination with gemcitabine and cisplatin (JFCC; SQUIRE) did not show any evidence of an increased risk of serious lung infections associated with necitumumab in this combination.

Special attention should be given to patients with clinical evidence of concomitant infectious conditions including early signs of active infections. Treatment of any infection should be initiated according to local standards.

7.7.1.3.6. Cardiorespiratory Disorders

An increased frequency of cardiorespiratory arrest or sudden death was observed with necitumumab. Cardiorespiratory arrest or sudden death was reported in the pivotal Study JFCC (SQUIRE) in 2.8% (15/538) of patients treated with necitumumab plus gemcitabine and cisplatin compared to 0.6% (3/541) of patients treated with chemotherapy alone. Twelve of the 15 patients died within 30 days of the last dose of necitumumab and had comorbid conditions, including history of chronic obstructive pulmonary disease (n=7), hypertension (n=5), hypomagnesemia (n=4), and coronary artery disease (n=3). Eleven of the 12 patients had an unwitnessed death.

7.7.1.4. Supportive Care for Osimertinib by Adverse Event of Special Interest

7.7.1.4.1. Diarrhea

After 1 month treatment with osimertinib, there is an approximate 20% chance of an AE of diarrhea at any point in time. Where treatment was required, the most frequently used class of medication administered were antipropulsives (for example, loperamide).

Apply the following supportive care guidance for diarrhea:

Uncomplicated CTCAE v4.0 Grade ≤2 diarrhea:

- Dietetic measures:
  - Stop all lactose-containing products.
  - Drink 8 to 10 large glasses of clear liquids per day.
  - Eat frequent small meals.
  - Recommend low-fat regimen enriched with rice, bananas, and apple sauce.
- Pharmacological treatment:
  - Administer loperamide: initial dose 4 mg, followed by 2 mg every 4 hours of after every unformed stool.
  - Grade 1 intermittent diarrhea may not require treatment.
  - Consider continuation of loperamide until diarrhea-free for 12 hours.
  - Consider electrolyte replacement, as appropriate.

CTCAE v4.0 Grade ≥3 or any grade with complications (dehydration, fever, and/or Grade ≥3 neutropenia):

- Dietetic measures:
  - As per Grade ≤2 diarrhea
- Pharmacological treatment:
  - As per Grade ≤2 diarrhea
  - If dehydration is severe, administer octreotide and use intravenous fluids as appropriate.
  - Consider prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia.
  - Consider electrolyte replacement, as appropriate, and consider more frequent measurement of electrolytes until AE resolves.

7.7.1.4.2. Skin Reactions

Rash Treatment Guidance:

CTCAE v4.0 Grade 1:

- Emollient cream application, and/or
- Topical steroid moderate strength bid, and/or
- Topical antibiotic bid

CTCAE v4.0 Grade 2:

- Treatment same as Grade 1
- Consider using oral antibiotic for 6 weeks.

CTCAE v4.0 Grade ≥3:

- Topical steroid moderate strength bid, and
- Oral antibiotic for 6 weeks (switch to broad spectrum/gram negative cover if infection suspected [yellow crusts, purulent discharge, painful skin/nares])
- Consider skin swab for bacterial culture.

Dry Skin / Xerosis Treatment Guidance:

CTCAE v4.0 Grade 1:

- Face/Hands/Feet: over-the-counter moisturizing cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid

CTCAE v4.0 Grade 2:

- Treatment same as Grade 1

CTCAE v4.0 Grade ≥3:

- Treatment same as Grade 1/2, plus
- Eczematous areas of body: topical steroid moderate strength bid

Pruritus Treatment Guidance:

CTCAE v4.0 Grade 1:

- Topical steroid moderate strength bid or topical antipruritic bid

CTCAE v4.0 Grade 2:

- Topical steroid moderate strength bid or topical antipruritic bid
- Oral antihistamine

CTCAE v4.0 Grade ≥3:

- Oral antihistamine
- GABA agonist (gabapentin 300 mg or pregabalin 50-75 mg every 8 hours)

Paronychia Treatment Guidance:

CTCAE v4.0 Grade 1:

- Topical antibiotic bid and vinegar soaks[#]

CTCAE v4.0 Grade 2:

- Topical antibiotic bid and vinegar soaks[#]
- Topical silver nitrate weekly

CTCAE v4.0 Grade ≥3:

- Topical antibiotic bid and vinegar soaks[#]
- Topical silver nitrate weekly
- Consider nail avulsion / removal

[#] Soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 minutes every day

7.7.1.4.3. QTc

Patients with QT interval corrected by Fridericia formula (QTcF) prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is >481 msec and then restarted at a reduced dose of 40 mg. If the toxicity does not resolve to ≤ Grade 1 within 21 days, the patient will be permanently withdrawn from osimertinib.

7.7.1.4.4. Interstitial Lung Disease

If new or worsening pulmonary symptoms (for example, dyspnea) or radiological abnormality suggestive of ILD is observed, an interruption in osimertinib dosing is recommended, and the

Lilly study team should be informed. A questionnaire regarding the results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, and hematological parameters) will be sent to investigators. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and osimertinib permanently discontinued.

In the absence of a diagnosis of ILD, osimertinib may be restarted following consultation with the Lilly CRP.

Patients with a diagnosis of ILD will not be permitted to restart osimertinib.

7.8. Treatment after Study Completion

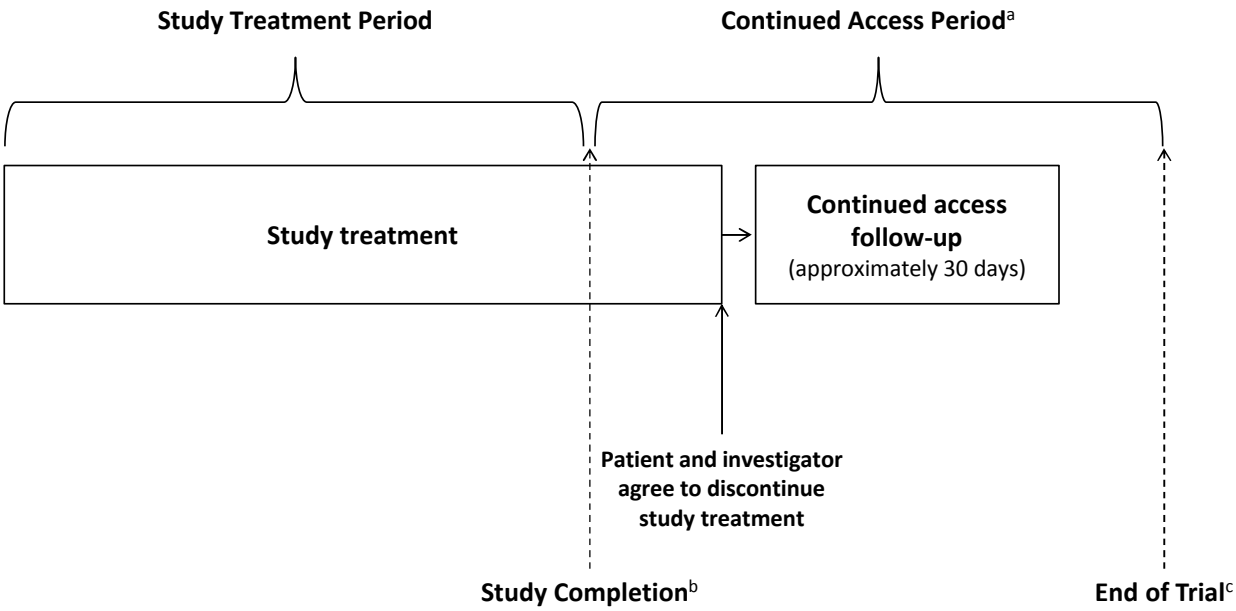
The study completion will occur approximately 2 years after last patient enrolled, or when adequate number of events are observed for survival outcome estimation, whichever comes first. Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1. Continued Access Period

Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks. The continued access period begins after study completion and ends at end of trial (Figure JVDL.3).

Continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

The patient's continued access to study treatment will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue study treatment and lasts approximately 30 (±7) days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Table JVDL.4).



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Approximately 2 years after last patient enrolled, or when adequate number of events are observed for survival outcome estimation, whichever comes first.
[c] End of trial occurs at the last visit or last scheduled procedure for the last patient.

Figure JVDL.3. Continued access diagram.

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

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

- The patient is enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
- 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.
- The investigator decides that the patient should be discontinued from study treatment.
- The patient requests that the patient be withdrawn from study treatment.
- The patient is significantly noncompliant with study procedures and/or treatment.
- disease progression

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug(s).

8.2. Discontinuation from the Study

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

- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.
- The patient becomes pregnant during the study. See Section 9.2.3 regarding regulatory reporting requirements on fetal outcome and breast-feeding.
- The investigator decides that the patient should be discontinued from the study.
- The patient requests to be discontinued from the study.
- The patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from the study.

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make

diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 3 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 2).

9.1.1. Efficacy Assessments at Baseline and during Study Treatment

RECIST 1.1 (Eisenhauer et al. 2009) will be applied as the primary measure for assessment of tumor response and date of disease progression. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Tumor imaging should be performed by computed tomography (CT), which is preferred for the majority of patients, as the more commonly used modality. Magnetic resonance imaging (MRI) should only be used when CT is contraindicated or for imaging in the brain. The same imaging technique should be used for a patient throughout the trial. CT scan or MRI of chest and upper abdomen including both adrenal glands are required, with pelvic imaging performed if clinically indicated.

The subsections below describe in detail the tumor imaging and assessment measures at baseline and during study treatment.

9.1.1.1. Baseline Tumor Imaging

Initial tumor imaging at screening must be performed within 21 days prior to the date of enrollment (assignment to treatment) or within 28 days of the first dose of study treatment. The site study team must review screening images to confirm the patient has measurable disease per RECIST 1.1.

A contrast CT scan or MRI of the brain will be performed at baseline prior to enrollment for all patients (per Exclusion Criterion [21] regarding brain metastases), and thereafter every 6 weeks (±7 days) despite any treatment delays, if a patient had brain metastases at study entry or if clinically indicated. Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within the protocol-required time frame as described above.

9.1.1.2. Tumor Imaging during Study Treatment

During study treatment, tumor response will be assessed every 6 weeks (± 7 days) by investigator, with confirmatory assessment obtained at the next routine scheduled imaging time point (that is, after 6 weeks ± 7 days), despite any treatment delays. After 24 weeks, tumor assessment will be conducted every 12 weeks (± 7 days). The start of treatment will be considered Cycle 1 Day 1 (C1D1) or the day that the first dose of any study treatment is administered.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor-imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan (that is, 6 weeks ± 7 days later), whichever is clinically indicated.

Continue to perform imaging until whichever of the following occurs first:

- disease progression confirmed by the second radiographic exam
- the start of new anticancer treatment
- withdrawal of consent
- death
- end of trial

9.1.2. Efficacy Assessments during Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted per the Schedule of Activities (Section 2).

Tumor assessments may continue for patients who discontinue from the study treatment for reasons other than disease progression every 6 to 12 weeks depending on standard of care.

9.1.3. Efficacy Measures

The objective response rate (ORR) is the proportion of enrolled patients who have received any amount of either study drug, have at least 1 postbaseline tumor image, and achieve a best overall response of complete response (CR) or partial response (PR).

Duration of response (DOR) is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of a confirmed CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DOR will be censored at the date of the last complete objective progression-free disease assessment.

Disease Control Rate (DCR) is defined as the proportion of enrolled patients who have a best overall response of CR, PR, or stable disease.

Progression-free survival (PFS) is defined as the time from the date of first study treatment until the date of the first observed radiographically documented PD or death due to any cause, whichever is earlier. The censoring is taken in the following order:

- if a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- if a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last complete objective progression-free disease assessment date.

ORR, DOR, DCR, and PFS will be assessed based on RECIST 1.1 (Eisenhauer et al. 2009).

Overall survival (OS), including 1- and 2- year survival rates, is determined from the date of first study treatment until death due to any cause. If the patient was alive at the data inclusion cutoff date for the analysis (or was lost to follow-up), OS will be censored on the last date the patient was known to be alive.

9.1.4. Appropriateness of Assessments

The measures used in this study are consistent with those used in most conventional oncology trials.

9.2. Adverse Events

The investigator will use CTCAE Version 4.0 (NCI 2009) to assign AE terms and severity grades.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study drug(s) before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via CRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or study treatment via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Adverse Events of Special Interest

9.2.1.1. Infusion-Related Reactions - Ramucirumab and Necitumumab

Any treatment-related IRRs are defined according to the CTCAE Version 4.0 definition (*General Disorders and Administration Site Conditions*). Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (*Immune System Disorders*). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

9.2.1.2. Adverse Events of Special Interest - Ramucirumab

Section 7.7.1.2.1 describes supportive care measures for each ramucirumab AESI. Table JVDL.8 presents the dose-modification guidelines for ramucirumab AESIs. Contact the Lilly CRP if questions arise concerning AESIs.

9.2.1.3. Adverse Events of Special Interest - Necitumumab

Section 7.7.1.3 describes supportive care for necitumumab AESIs. Table JVDL.11 provides general treatment recommendations for hypersensitivity/IRRs to necitumumab. Contact the Lilly CRP if questions arise concerning AESIs.

9.2.1.4. Adverse Events of Special Interest – Osimertinib

Section 7.7.1.4 describes supportive care for osimertinib AESIs. Contact the Lilly CRP if questions arise concerning AESIs.

9.2.2. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

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

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

9.2.3. Pregnancy

Cases of pregnancy that occur during maternal or paternal exposures to investigational products (ramucirumab, necitumumab, and osimertinib) should be reported within 24 hours. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, congenital abnormality, fetal death, intrauterine death, miscarriage and stillbirth, or other disabling or life-threatening complication to the mother or newborn must be reported as AEs. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. The following additional measures will be taken in the case of pregnancy:

- A patient who becomes pregnant will be immediately removed from the study.

- It is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier.
- All patients who become pregnant must be contacted by the site at least monthly and the patient's status documented to the completion/termination of the pregnancy; the investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

9.2.4. Suspected Unexpected Serious Adverse Reactions

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

9.2.5. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the ramucirumab, necitumumab, and osimertinib IBs.

9.4. Safety

9.4.1. Other Safety Measures

For each patient, ECGs, vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

9.4.1.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Schedule of Activities (Section 2) as triplicate ECGs at baseline and single ECGs in subsequent cycles. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/ QTcF interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, or syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation. Local ECG findings at baseline and end of treatment, and any on study clinically significant abnormal findings, will be reported into the eCRF and any alert reports.

9.4.2. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes (Appendix 3)
- adverse events, including ramucirumab and necitumumab AESI (Section 9.2.1).
- If a patient experiences elevated ALT ≥5× ULN and elevated total bilirubin ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 5.

Safety data will be reviewed during the study. A safety review committee (SRC) consisting of the Lilly CRP, Global Patient Safety physician, statistician, the primary investigator, and ad hoc SRC members as needed will be responsible for review of safety data.

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected as shown in Appendix 4.

Blood samples will be drawn for all patients for the assessment of ramucirumab and necitumumab concentrations in serum (also known as bioanalytical samples). Sampling times

were selected to coincide with expected C_{max} and C_{min} and with consideration to draw minimum volume of blood from patients and ensuring that the patients do not to need to make an extra visit to provide these samples.

Instructions for the collection and handling of bioanalytical blood samples will be provided by the Sponsor. The actual start and end date and time of ramucirumab and necitumumab infusion administration must be recorded on the eCRF. The actual date and time that each bioanalytical blood sample was drawn must be recorded on the laboratory accession page after the sample is drawn.

Ramucirumab and necitumumab concentrations in bioanalytical serum samples will be measured using a validated assay methodology in a laboratory designated by the Sponsor.

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

9.6. Pharmacodynamics

Pharmacodynamics has been included in Section 9.8.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in NSCLC. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs) impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in drug development or when the drugs become commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to study treatment, angiogenesis, immune functioning, and/or NSCLC and/or for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow. It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.8.1 and 9.8.2.

9.8.1. Samples for Non-pharmacogenetic Biomarker Research

Plasma samples for nonpharmacogenetic biomarker research will be collected as specified in Appendix 4, where local regulations allow.

Samples will be examined for biomarkers related to NSCLC, variable response to study treatment, the mechanism of action of ramucirumab (for Cohort A), the *EGFR* pathway, immune functioning, and/or for research-related methods or validating diagnostic tools or assays.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in drug development or when the drugs become commercially available.

9.8.2. Tumor Tissue Samples

Tumor tissue will be examined for biomarkers related to NSCLC, ramucirumab, necitumumab, the *EGFR* pathway, immune functioning, and/or research-related methods or validating diagnostic tools or assay.

Collection of the following tumor tissue sample(s) is **required** for all patients in order to participate in this study:

Formalin-fixed paraffin-embedded tumor tissue obtained from a biopsy taken after disease progression on the most recent *EGFR* TKI treatment from the primary tumor or metastatic site

should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology report accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the Sponsor. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in drug development or when the drugs become commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies, including mutation profiling, copy number variability, gene expression, and/or immunohistochemistry, may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

In addition to the required tumor tissue and biomarker samples discussed in Sections 9.8.1 and 9.8.2, patients may be asked to undergo optional collection of an additional biopsy specimen and blood sample after treatment with study drug(s) has been initiated, including potentially after disease progression. Such additional biopsies should be performed only if they do not create undue risk to the patient. If these additional samples are requested, they will be used to further investigate molecular features that may explain treatment response and resistance mechanisms.

9.8.3. Immunogenicity Assessments

Immunogenicity samples will be collected at baseline for all patients and when an IRR occurs. The immunogenicity assessments will be performed only for those patients who experienced an IRR.

Blood samples for immunogenicity testing will be collected as shown in Appendix 4 to determine antibody production against ramucirumab (for Arm A and Cohort A) or necitumumab (for Arm B). Immunogenicity will be assessed by validated immunogenicity assays designed to detect anti-ramucirumab and anti-necitumumab antibodies in the presence of ramucirumab (for Arm A and Cohort A) and necitumumab (for Arm B), respectively. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ramucirumab (for Arm A and Cohort A) or necitumumab (for Arm B).

Samples will be retained for a maximum of 15 years after last the patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to ramucirumab or necitumumab.

9.9. Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

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

The following sample sizes apply to each portion of the study:

Dose-Finding Portion: up to 12 DLT-evaluable patients each for Arms A and B
Dose-Expansion Portion: 22 patients for Cohort A

During the Dose-Expansion Portion, 22 patients in Cohort A will be treated, to provide a preliminary assessment of tumor response and an assessment of safety. All patients enrolled in the Dose-Finding Portion (Arm A) will also be included for all planned analyses. The null hypothesis is based on the assumption that the ORR is no greater than 60% and the target treatment effect (alternative response rate) of the combination treatment on ORR is greater than 70% and 75%, respectively. Based on these assumptions, a sample size of n=25 provides statistical power of approximately 58% and 78%, respectively, with a 1-sided 0.20 significance level.

10.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly.

For the Dose-Finding Portion, a 3+3 dose de-escalation design will be used to assess the safety of ramucirumab or necitumumab in combination with osimertinib. Additional patients will be enrolled in a dosing schedule to achieve the minimum of 3 evaluable patients for each arm, if dropouts or dose interruptions or reductions occur that result in a patient being nonevaluable for DLTs. Data will be reviewed by dose schedule group (3 patients) for each arm.

For the Dose-Expansion Portion, final analysis will occur upon the completion of the study. Primary analysis will be conducted approximately 6 months after last patient receives initial dose. All patients enrolled in the Dose-Finding Portion (Arm A) and the Dose-Expansion Portion (Cohort A) will be included for all planned analyses. Patients enrolled in Arm B of the Dose-Finding Portion will be analyzed separately.

Descriptive statistics will be derived where appropriate. The rate of DLTs will be summarized by arm; dose exposure for each study drug will be calculated.

Pharmacodynamics/ Biomarkers

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

General

Additional details may be provided in a separate statistical analysis plan (SAP) for the study. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

ORR and DCR (according to RECIST 1.1), and the corresponding confidence intervals, will be provided for Arm A and Cohort A. Patients enrolled in Arm B of the Dose-Finding Portion will be analyzed separately. Time-to-event variables, such as time to response, DOR, PFS, and OS, will be estimated by Kaplan-Meier (1958) methodology. Presentations of efficacy may include patients enrolled in the Dose-Finding Portion with the same treatment schedule.

10.3.2. Safety Analyses

All patients who receive at least 1 dose of ramucirumab, necitumumab, or osimertinib will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE Version 4.0.

Safety analyses will include summaries of the following:

- DLTs: the number of patients who experienced any DLTs during DLT observation period will be summarized by dose schedule in the Dose-Finding Portion for each arm.
- AEs, including severity and possible relationship to study drug
- AEs by Medical Dictionary for Regulatory Activities® System Organ Class (SOC) by decreasing frequency of Preferred Term within SOC
- Laboratory and nonlaboratory AEs by CTCAE term and maximum CTCAE grade (regardless of causality and at least possibly related to study treatment)

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

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

10.3.3.2. Patient Characteristics

Patient characteristics which will be summarized by:

- Patient demographics will be reported using descriptive statistics. Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

- Baseline disease characteristics will be summarized by presenting frequency counts and percentages (for example, for pathological diagnosis [histological or cytological] and disease stage).
- Disease-related therapies will include prior anticancer treatments and prior radiotherapies (such as type of therapy, regimen, and prior surgery).

Other patient characteristics will be summarized as deemed appropriate.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment arm will be reported.

10.3.3.4. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation anticancer therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name.

10.3.3.5. Treatment Compliance

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

10.3.3.6. Pharmacokinetic Analyses

Serum C_{min} and concentrations at 1 hour post end of infusion (approximately C_{max}) for ramucirumab and necitumumab will be summarized by descriptive statistics.

10.3.3.7. Immunogenicity Analyses

Immunogenicity samples will be collected at baseline for all patients and when an IRR occurs. The immunogenicity analyses will be performed only for those patients who experienced an IRR.

Immunogenicity (anti-ramucirumab and anti-necitumumab antibody) incidence will be tabulated for those individuals who experience an IRR, and correlation to ramucirumab and necitumumab drug level, activity, and safety will be assessed, as appropriate, respectively. The measures that will be analyzed include the presence of baseline antidrug antibodies (ADA), treatment-emergent ADA, neutralizing ADA, and incidence of ADA related to IRRs.

10.3.3.8. Biomarker Analysis

Biomarkers may be summarized and assessed for correlations with clinical outcomes.

10.3.4. Interim Analysis

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

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
AUC_{ss}	area under the plasma concentration-time curve at steady state
BCRP	breast cancer resistance protein
β-hCG	beta human chorionic gonadotropin
BICR	blinded independent central review
C1D1	Cycle 1 Day 1
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
$C_{min,ss}$	minimum concentration at steady state
CR	complete response
CRF	case report form

CRP	Clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
effective method of contraception	male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. Also see the definition of highly effective method of contraception.
EGFR	epidermal growth factor receptor
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
EU	European Union
FOLFIRI	irinotecan, 5-fluorouracil, and folic acid
FSH	follicle-stimulating hormone
GCP	good clinical practice

GEJ	gastroesophageal junction
GI	gastrointestinal
highly effective method of contraception	combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 Kg (<198 pounds), total abstinence, or vasectomy. Also see the definition of effective method of contraception.
HIV	human immunodeficiency virus
HR	hazard ratio
HRCT	high-resolution computed tomography
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IgG	immunoglobulin G
ILD	interstitial lung disease
INR	International Normalized Ratio
interim analysis	An interim analysis is an analysis of clinical trial data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRR	infusion-related reaction
I.V.	intravenous
IWRS	interactive web-response system
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer
mPFS	median progression-free survival
MRI	magnetic resonance imaging

MTD	maximal tolerated dose
MUGA	Multiple-gated acquisition
NC	not calculable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAIDs	nonsteroidal anti-inflammatory agents
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	package insert
PK	Pharmacokinetics
PopPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected by Fridericia formula
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.

re-screen	to screen a patient who was previously declared a screen failure for the same study
RNA	ribonucleic acid
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SRC	safety review committee
SUSARs	suspected unexpected serious adverse reactions
T3	triiodothyronine
T4	thyroxine
TEAE	Treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
VTE	venous thromboembolic event

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of study treatment.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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

- the current IB and updates during the course of the study
- the ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

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

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

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

Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

Protocol Signatures

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

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

Final Report Signature

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

The investigator with the most enrolled patients will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

Data Quality Assurance

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

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

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly,

applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

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

Case report form data will be encoded and stored in a clinical trial database.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology – Local lab	**Clinical Chemistry** – Local lab and Central lab[a]
Erythrocyte (RBC)	**Serum Concentrations of:**
Hemoglobin (HGB)	
Hematocrit (HCT)	Alkaline phosphatase
Platelet (PLT)	Alanine aminotransferase (ALT)
Leukocytes (WBC)	Aspartate aminotransferase (AST)
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)
Lymphocytes	Creatine kinase (CK)
Monocytes	Creatinine
Eosinophils	Uric acid
Basophils	Calcium
	Glucose
Thyroid Function Tests – Central lab	Albumin
Thyroid stimulating hormone (TSH)	Phosphorus
Total triiodothyronine (T3)	Potassium
Free thyroxine (T4)	Sodium
	Magnesium
	Total bilirubin
Urinalysis – Local lab	Direct bilirubin (if total bilirubin is elevated above
Routine dipstick measurements, and if clinically indicated, microscopic analysis.	the upper limit of normal)
	Total protein
Protein[b]	Blood urea nitrogen (BUN)
Blood	
Glucose	Chloride
Specific gravity	
Coagulation Test – Local lab	
Prothrombin time (PT) or International normalized ratio (INR)	**Pregnancy Test**[c] – Local lab
	Urine or Serum
Partial thromboplastin time (PTT) or activated PTT (aPTT)	β-human chorionic gonadotropin (β-hCG)

Abbreviations: RBC = red blood cell; WBC = white blood cell.

a Central chemistry laboratories will be required to determine patient eligibility at baseline; local chemistry laboratory testing will not be permitted for a determination of patient eligibility. Local chemistry laboratory results may be used for on-study dosing decisions; if so, chemistry testing must also still be performed by the central laboratory. These central chemistry laboratory results will be used for subsequent safety analyses.

b If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24 hour urine collection (to assess protein) must be obtained.

c Minimum sensitivity 25 IU/L or equivalent units of β-human chorionic gonadotropin (β-hCG), for women of childbearing potential (WOCBP). If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

Appendix 4. Sampling Schedule for Pharmacokinetics, Immunogenicity, Biomarkers, and Pharmacogenetics

It is essential that the exact infusion start and stop times (actual clock readings), as well as infusion parameters (such as, type of infusion pump, flow rate settings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the pharmacokinetic blood samples not be withdrawn from the same site as the drug infusion.

Sampling Schedule for Pharmacokinetics, Immunogenicity, Biomarkers, and Pharmacogenetics – Ramucirumab Arm and Cohort

Visit/Cycle Day	Sample Time	PK[a] (Serum)	IG[a] (Serum)	Biomarker (Plasma)	PG[f] (Whole Blood)
Day -14 to Day 1 of Cycle 1	Predose[b]	X	X	X	X
Day 1 of Cycle 1	1 h post end of ramucirumab infusion[c]	X			
Day 1 of Cycle 2	Predose[d]	X			
Day 1 of Cycle 4	Predose[d]	X			
Day 1 of Cycle 5	Predose[d]	X			
Day 1 of Cycle 7	Predose[d]	X		X	
Day 1 of Cycle 13	Predose[d]	X			
Short-term 30-day Safety Follow-Up Period	Anytime[e]			X	

Note: It is essential that the dosing days, dosing times, draw dates and draw times are accurately recorded.
Abbreviations: IG = immunogenicity; PG = pharmacogenetic(s); PK = pharmacokinetic(s).

a In the event of an infusion-related reaction, a blood sample 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 Prior to the first infusion (baseline; may be obtained within 14 days prior to the initial infusion of ramucirumab/placebo on Day 1 Cycle 1).

c Collection window: within 1 to 1.5 hours after the end of ramucirumab infusion.

d Collection window: within 3 hours prior to ramucirumab infusion.

e When applicable, plasma should be collected as close as possible to the time of disease progression during the study treatment period. If for any reason the post progression sample cannot be collected at the time of progression, this should be done during the 30-day follow-up period. The post progression sample should be collected before the initiation of any new anticancer therapy.

f Mandatory whole blood sample will be used for pharmacogenetic analysis. 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.

Sampling Schedule for Pharmacokinetics, Immunogenicity, Biomarkers, and Pharmacogenetics – Necitumumab Arm

Visit/Cycle Day	Sample Time	PK[a] (Serum)	IG[a] (Serum)	Biomarker (Plasma)	PG[f] (Whole Blood)
Day -14 to Day 1 of Cycle 1	Predose[b]	X	X	X	X
Day 1 of Cycle 1	1 h post end of necitumumab infusion[d]	X			
Day 1 of Cycle 3	Predose[c]	X			
	1 h post end of necitumumab infusion[d]	X			
Day 1 of Cycle 5	Predose[c]	X		X	
Day 1 of Cycle 7	Predose[c]	X			
Day 1 of Cycle 9	Predose[c]	X			
Short-term 30-day Safety Follow-Up Period	Anytime[e]			X	

Note: It is essential that the dosing days, dosing times, draw dates and draw times are accurately recorded.
Abbreviations: IG = immunogenicity; PG = pharmacogenetic(s); PK = pharmacokinetic(s).

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

b Prior to the first infusion (baseline; may be obtained within 14 days prior to the initial infusion of necitumumab on Day 1 Cycle 1).

c Prior to necitumumab infusion.

d 1 hour ±10 minutes post end of necitumumab infusion.

e When applicable, plasma should be collected as close as possible to the time of disease progression during the study treatment period. If for any reason the post progression sample cannot be collected at the time of progression, this should be done during the 30-day follow-up period. The post progression sample should be collected before the initiation of any new anticancer therapy.

f Mandatory whole blood sample will be used for pharmacogenetic analysis. 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.

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated laboratory.

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

Appendix 6. Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft and Gault 1976.

Appendix 7. Protocol JVDL Restricted and Prohibited Concomitant Therapy

The table below describes medications, treatments, and drug classes restricted or prohibited, with exceptions and conditions for use during the study treatment period (there are no prohibited therapies during the follow- up period). Patients who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should be removed from the trial. Patients may receive other supportive therapy or vaccinations that the investigator deems to be medically necessary.

In addition, there are potential interactions between osimertinib and either CYP3A4 inducers or CYP3A4 inhibitors. Drugs that induce CYP3A4, such as carbamazepine, fosphenytoin, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's wort, may reduce the effects of osimertinib through increased osimertinib metabolism and decreased plasma concentrations. Therefore, avoid strong CYP3A4 inducers if possible. For strong CYP3A4 inhibitors, avoid concurrent administration if possible; however, if no alternative exists, the patient should be closely monitored for signs of toxicity.

Therapy	As Needed	Chronic Use	Exceptions or Conditions for Use
Anti-platelet therapy	yes	no	Chronic use of aspirin up to 325 mg/day is permitted.
Anticoagulation therapy	no	Yes, with restrictions	At enrollment, patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin or similar agent. If on warfarin, the patient must have an INR ≤3 and no active bleeding or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).
Anti-cancer biological therapy	no	no	
Chemotherapy	no	no	
Colony-stimulating factors	yes	no	Follow local guidelines.
Erythroid growth factors	yes	no	Follow local guidelines.
Experimental medicines or investigational agents	no	no	Other than ramucirumab, necitumumab, or osimertinib
Glucocorticoids	no	no	Systemic glucocorticoids are permitted to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: Inhaled steroids are allowed for management of asthma.
Immunotherapy	no	no	Other than inhaled steroids and vaccinations
NSAIDs	yes	no	Chronic use of aspirin up to 325 mg/day is permitted. In addition, in certain medical situations, NSAIDs may be the best treatment option (for example, for pain management). Increased risk of bleeding should be considered by the treating physician and the patient.
Radiation therapy	no	no	Localized radiation therapy to a symptomatic, solitary lesion or to the brain may be allowed after consultation with the Sponsor.
BCRP	Yes	Yes	Monitor for AEs (including CK) of the BCRP substrate (e.g., rosuvastatin, sulfasalazine) and signs of changed tolerability of osimertinib, unless otherwise instructed in its approved labeling, when coadministered with osimertinib. If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

Abbreviations: BCRP = breast cancer resistance protein; INR = international normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs.

Appendix 8. Protocol Amendment I4T-MC-JVDLc Summary An Open-Label, Multicenter, Phase 1 Study with Expansion Cohorts of Ramucirumab or Necitumumab in Combination with Osimertinib in Patients with Advanced T790M-Positive *EGFR*-Mutant Non-Small Cell Lung Cancer after Progression on First-Line *EGFR* TKI Therapy

Overview

Protocol I4T-MC-JVDL, An Open-Label, Multicenter, Phase 1 Study with Expansion Cohorts of Ramucirumab or Necitumumab in Combination with Osimertinib in Patients with Advanced T790M-Positive EGFR-Mutant Non-Small Cell Lung Cancer after Progression on First-Line EGFR TKI Therapy, has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Study completion was redefined as occurring approximately 2 years after last patient enrolled, or when adequate number of events are observed for survival outcome estimation, whichever comes first.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Section 1. Synopsis

Length of Study Portion

The duration of the Dose-Expansion Portion (excluding the Continued Access Period) from first patient enrolled to the completion of the study is approximately ~~2.5~~ 2 years~~. The completion of the study is defined as 1 year~~ after last patient enrolled, or when ~~18 of the 22 (80%) patients in Cohort A in the Dose-Expansion Portion have confirmed progressive disease, unacceptable toxicity, or discontinuation for any other reason,~~ adequate number of events are observed for survival outcome estimation, whichever comes first.

Section 5.3. Study Completion and End of Trial Definition

There will be a database lock to report the primary data analyses approximately 6 months after last patient receives initial dose in the Dose-Expansion Portion of the study.

The completion of the study (Study Completion) is defined as ~~1 year~~ approximately 2 years after last patient enrolled, or when ~~18 of the 22 (80%) patients in Cohort A in the Dose-Expansion Portion have confirmed PD, unacceptable toxicity, or discontinuation for any other reason~~ adequate number of events are observed for survival outcome estimation, whichever comes first.

Section 7.8. Treatment after Study Completion

The study completion will occur ~~1 year~~ approximately 2 years after last patient enrolled, or when ~~18 of the 22 (80%) patients in Cohort A in the Dose-Expansion Portion have confirmed PD, unacceptable toxicity, or discontinuation for any other reason~~ adequate number of events are observed for survival outcome estimation, whichever comes first. Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1. Continued Access Period

Figure JVDL.3 Continued access diagram.

[b] ~~One year~~ Approximately 2 years after last patient enrolled, or when ~~18 of the 22 (80%) patients in Cohort A in the Dose-Expansion Portion have confirmed progressive disease, unacceptable toxicity, or discontinuation for any other reason~~ adequate number of events are observed for survival outcome estimation, whichever comes first.

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