I4X-MC-JFCU(b)

A Single-Arm, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Treatment of Patients with Stage IV Non-Small Cell Lung
Cancer (NSCLC)

NCT02411591

Approval Date: 12-May-2016

1. Protocol I4X-MC-JFCU(b)
A Single-Arm, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Treatment of Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC)

Necitumumab (LY3012211), Abemaciclib (LY2835219)

This is a single-arm Phase 1b study with an expansion cohort in patients with Stage IV non-small cell lung cancer (NSCLC). The study consists of 2 parts (Part A and Part B). Part A is a single-arm, open-label, dose-escalation study to determine the recommended dose of abemaciclib in combination with necitumumab for Part B (expansion cohort). Part B is an open-label study to evaluate the efficacy and safety of necitumumab in combination with abemaciclib.

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Protocol Electronically Signed and Approved by Lilly on 11 December 2014.
Amendment (a) Electronically Signed and Approved by Lilly on 10 June 2015.
Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 12-May-2016 GMT

2. Synopsis

Study Rationale

Necitumumab (IMC-11F8; LY 3012211; Portrazza®) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 (IgG1) that blocks the ligand-binding site of the epidermal growth factor receptor (EGFR). EGFR is detectable in approximately 85% of patients with advanced, metastatic non-small cell lung cancer (NSCLC). Necitumumab has shown signals of antitumor activity in 2 Phase 1 trials when administered as monotherapy in heavily pretreated patients including but not limited to patients with NSCLC. Portrazza has recently been approved in the United States (US) and European Union (EU) for the treatment of adult patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin. The cetuximab FLEX Phase 3 trial has demonstrated a statistically significant improvement in survival for the combination of an EGFR mAb in combination with chemotherapy in the first-line treatment of patients with advanced metastatic NSCLC.

Abemaciclib, a selective and potent small molecule inhibitor of CDK4/6, prevents cell cycle progression through the G1 restriction point, thus arresting tumor growth. Abemaciclib has shown single-agent antitumor activity in a Phase 1 trial in heavily pretreated patients with NSCLC.

Necitumumab and abemaciclib inhibit tumor progression by different, independent modes of action (cell surface and cell nucleus, respectively), where necitumumab blocks the ligand-binding site of the EGFR and abemaciclib blocks DNA synthesis by prohibiting cell cycle progression from G1- to S-phase.

A xenograft tumor cell-line model has shown an add-on effect of necitumumab to abemaciclib where the combination was more effective when compared to the activity of either drug alone.

The individual toxicity profile from clinical trials with each of the compounds (that is, necitumumab and abemaciclib) suggests that no or only marginal overlapping toxicity is expected. The most common Grade 3 adverse events (AEs; > 5% of patients) for single-agent abemaciclib were leukopenia and neutropenia. For necitumumab single agent, the most frequent AEs reported were skin reactions (in terms of rash) and hypomagnesemia.

Different mode of actions, preclinical data, and the clinical efficacy of necitumumab as well as other EGFR mAbs and abemaciclib in NSCLC provide a rationale for the investigation of necitumumab in combination with abemaciclib in patients with Stage IV NSCLC.

The purpose of this Phase 1b study with an expansion cohort is to explore the safety and preliminary efficacy of necitumumab plus abemaciclib in patients with Stage IV NSCLC who have received no more than 2 lines of chemotherapy of which at least one must be platinum-based.

Clinical Protocol Synopsis: Study I4X-MC-JFCU

Name of Investigational Product: Necitumumab (LY3012211) and Abemaciclib (LY2835219)	
Title of Study: A Single-Arm, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Treatment of Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC)	
Number of Planned Patients: Part A Enrolled: 3 to 18 Part B (Expansion Cohort) Enrolled: 50	**Phase of Development: 1b**
Length of Study: approximately 21 months Planned first patient visit: 08 Sep 2015 Planned last patient visit: 19 Jun 2017 Planned interim analyses: first 15 evaluable patients in Part B portion of the study who have completed 2 cycles of study treatment (or otherwise discontinued study treatment) will be analyzed for safety. Interim analyses for efficacy may be performed as needed to aid in the planning of future trials. Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the interim analyses.	

Objectives:

The primary objectives of the study are:

Part A: to determine the dose-limiting toxicity (DLT) of abemaciclib at doses up to 200 mg when combined with necitumumab 800 mg, in patients with Stage IV NSCLC as measured by the number of patients with a DLT in Cycle 1.

Part B: to evaluate the efficacy of necitumumab in combination with abemaciclib in terms of progression-free survival (PFS) rate at 3 months in patients with Stage IV NSCLC.

The secondary objectives of the study are:

Part A:

- to investigate the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with abemaciclib
- to determine the objective response rate (ORR)
- to determine the pharmacokinetics (PK) of necitumumab and abemaciclib
- to determine the immunogenicity of necitumumab

Part B: to demonstrate the safety, efficacy, and feasibility of necitumumab in combination with abemaciclib at the recommended dose by:

- determining PFS
- determining the ORR and disease control rate (DCR)
- estimating overall survival (OS)
- investigating the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with abemaciclib
- determining the PK of necitumumab and abemaciclib
- determining the immunogenicity of necitumumab

The exploratory objective is to further evaluate as follows:

Parts A and B: to correlate biomarkers with clinical outcomes, including, but not limited to, *KRAS* mutation assessment, EGFR protein expression, and/or other biomarkers associated with the disease pathobiology, the cell cycle, EGFR pathway, and/or the mechanism of action of the therapeutic molecules.

Study Design: This is a single-arm, multicenter Phase 1b study with an expansion cohort to investigate necitumumab in combination with abemaciclib in approximately 70 patients with Stage IV NSCLC (American Joint Committee on Cancer Staging Manual, 7th edition). The study consists of 2 parts:

- Part A: Dose-escalation part with increasing doses of abemaciclib (100 mg, 150 mg, or 200 mg every 12 hours [Q12H] on Days 1 to 21) to determine a recommended dose range for abemaciclib that may be safely administered in combination with a fixed regimen of necitumumab 800 mg Days 1 and 8 every 21 days in patients with Stage IV NSCLC.
- Part B (expansion cohort): Dose confirmation of abemaciclib in combination with a fixed regimen of necitumumab 800 mg on Days 1 and 8 every 21 days and exploration of clinical antitumor activity.

Approximately 50 patients will be enrolled in Part B: approximately 25 patients with squamous histology and approximately 25 patients with nonsquamous histology.

Patients will be treated until progressive disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Patients who are on study therapy at study completion may continue to receive study therapy in the extension phase until they meet the discontinuation criteria. Study completion is expected to be approximately 5 months after the last patient has been enrolled.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Key inclusion/exclusion criteria at the time of enrollment

- The patient has Stage IV NSCLC.
  Part A: NSCLC Stage IV (any type)
  Part B: NSCLC Stage IV (squamous and nonsquamous)
- The patient must have progressed after platinum-based chemotherapy AND have received a maximum of 1 other prior chemotherapy for advanced and/or metastatic disease OR must be judged by the physician as ineligible for further standard second-line chemotherapy. Prior treatment with EGFR-tyrosine kinase inhibitor and anaplastic lymphoma kinase (ALK) inhibitors is mandatory in patients whose tumor has an EGFR activating mutations or ALK translocations. Prior targeting agents and neoadjuvant/adjuvant therapies are permitted with the exception of CDK4/6-targeting agents or necitumumab.
- Measurable disease at the time of study entry as defined by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1).
- The patient has tumor tissue available for biomarker analyses.
- The patient has resolution to Common Terminology Criteria for Adverse Events (CTCAE) Grade $\leq$1 of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy (with the exception of alopecia).
- Eastern Cooperative Oncology Group performance status score of 0-1.
- The patient has no brain metastases that are symptomatic.

Test Product, Dosage, and Mode of Administration:

- Necitumumab is a sterile, preservative-free, intravenous infusion supplied in 50-mL vials containing 16 mg/mL (800 mg/50 mL) of product, and administered at a dose of 800 mg on Days 1 and 8 of each 21-day cycle.
- Abemaciclib is administered orally as capsules (supplied for clinical trial use in strength of 50 mg/capsule) every 12 hours. In Part A, abemaciclib will be administered at increasing doses of 100, 150, or 200 mg Q12H on Days 1 to 21. In Part B, abemaciclib will be administered at a fixed dose determined in Part A of the study Q12H on Days 1 to 21.

Reference Therapy, Dose, and Mode of Administration:

Not Applicable

Planned Duration of Treatment:
Baseline period: 21 days
Treatment period: 21 days treatment cycle.
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion
Study Completion: approximately 5 months after the last patient qualified for Part B of the study has enrolled
Study Extension: Patients who are on study therapy at study completion may continue to receive study therapy in the extension phase until they meet the discontinuation criteria.

Criteria for Evaluation:
Progression-Free Survival (PFS) is defined as the time from the date of enrollment until the date of radiographically documented progressive disease (PD) or death due to any cause, whichever is earlier.
Overall Survival (OS) is defined as the time from the date of study enrollment to the date of death from any cause.
Objective Response Rate (ORR) is defined as the proportion of patients achieving a best overall response of partial response (PR) or complete response (CR).
Disease Control Rate (DCR) is defined as the proportion of patients achieving a best overall response of stable disease (SD), PR, or CR.
Safety:
Part A: DLTs, serious adverse events (SAEs), AEs, vital sign measurements, laboratory analyses, and electrocardiograms (ECGs)
Part B: SAEs, AEs, vital sign measurements, laboratory analyses, and ECGs
Pharmacokinetics:
Pharmacokinetics parameters, including, but not limited to, maximum concentration, area under the concentration-time curve, and terminal half-life for abemaciclib (Part A only). Descriptive summary of exposure for abemaciclib in Part B, as well as for necitumumab in both Part A and Part B.
Bioanalytical:
Serum concentrations of necitumumab will be measured using a validated enzyme-linked immunosorbent assay bioanalytical method. Plasma concentrations of abemaciclib and metabolites will be measured using a validated liquid chromatography–tandem mass spectrometry method.
Immunogenicity:
Serum for analysis of antibodies against necitumumab (immunogenicity)
Translational Research:
A tumor tissue block or tumor tissue slides will be collected to correlate biomarker results with clinical outcomes, including, but not limited to, *KRAS* mutation assessment, EGFR protein expression, and/or other biomarkers associated with the disease pathobiology and therapeutic molecules.

Blood samples (EDTA-anticoagulated plasma) will be collected for exploratory biomarker analyses.

Statistical Methods:

Efficacy: The primary Part B outcome variable in this study will be the 3-month PFS rate, as estimated by the Kaplan Meier method. The Part B statistical null hypothesis states that the true 3-month PFS rate is 50%, whereas the research hypothesis states that the true 3-month PFS rate is 65%. Assuming the Part B portion of the study continues to a full enrollment of 50 evaluable patients, the null hypothesis will be rejected at the final analysis only if at least 60% of evaluable patients experience PFS $\geq$ 3 months. If the research hypothesis is true, there is an 81% chance of reaching full Part B enrollment and rejecting the null hypothesis. If the null hypothesis is true, then there is a 10% chance of reaching full Part B enrollment and rejecting the null hypothesis. Therefore, the Part B portion of this study has a one-sided alpha level of 0.10, with statistical power of 81%.

Safety: Safety analyses will be performed for all patients enrolled in the study who receive any amount of study drug (necitumumab or abemaciclib). Numbers and rates of AEs will be reported by National Cancer Institute CTCAE terms. Laboratory and nonlaboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grades, including the total for maximum Grade 3 and above. These summaries will be provided for events regardless of study drug causality, and repeated for events deemed by the investigator to be possibly related to study medication. Adverse events will be summarized by Medical Dictionary for Regulatory Activities™) System Organ Class (SOC), by decreasing frequency of Preferred Term within SOC. Other safety parameters will be summarized as appropriate.

A safety interim analysis will be performed after the first 15 evaluable patients in the Part B portion of the trial have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the interim analyses. The safety interim analysis will be conducted to permit evaluation of safety data by the sponsor.

Interim analyses for efficacy may be performed as needed to aid in the planning of future trials. There is no plan to stop the study for positive efficacy. The type-1 error for final primary analysis will not be affected and hence is not adjusted.

Immunogenicity: Incidence of anti-necitumumab antibodies will be tabulated.

Pharmacokinetics: Pharmacokinetic parameters of abemaciclib and necitumumab in Part A will be calculated using noncompartmental analysis (NCA) methodology as applied in Phoenix WinNonlin (version as validated by PK/pharmacodynamic standard operating procedures at the time of analysis). Summary level data for Part B will be presented as graphics and table listings. Additional analysis of data through mixed-effects modeling through NONMEM or similar software may be applied.

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

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
assent	Agreement from an individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
AUC	area under the curve
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
CDK	cyclin dependent kinases
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.

CR	complete response
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CrCl	creatinine clearance
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been 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/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
ESAs	erythropoiesis-stimulating agents
FFPE	formaldehyde fixed-paraffin embedded
FSH	follicle-stimulating hormone
GC	gemcitabine/cisplatin

GC+N	gemcitabine/cisplatin plus necitumumab
GCP	good clinical practice
H_0	null hypothesis
H_a	alternative hypothesis
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, that is conducted before the final reporting database is created/locked.
investigational product (IP) [hereon referred to as study treatment]	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form. In this study, the IPs are necitumumab (LY3012211; IMC-11F8) and abemaciclib (LY2835219).
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
I.V.	intravenous(ly)
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
mAb	monoclonal antibody

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PC	pemetrexed - cisplatin
PC+N	necitumumab plus pemetrexed - cisplatin
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
Q12H	every 12 hours
Rb	retinoblastoma
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
SAE	serious adverse event
SAP	Statistical Analysis Plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Study completion	This study will be considered complete 5 months after the last patient in Part B of the study has been enrolled.
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TKI	tyrosine kinase inhibitor
ULN	upper limits of normal
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

A Single-Arm Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Advanced Treatment of Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC)

5. Introduction

5.1. Non-Small Cell Lung Cancer

Lung cancer is the most common cancer worldwide, with an estimated 1.6 million new cases per year, and the leading cause of cancer-related mortality with 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. Patients with localized disease have a 5-year survival rate of approximately 55%; however, 5-year survival drops significantly for patients with regional (26.1%) or distant (3.9%) disease at diagnosis (Howlader et al. 2013).

Current standard first-line chemotherapy for patients with advanced or metastatic NSCLC and a good performance status consists of a platinum-based doublet, using either cisplatin or carboplatin in combination with pemetrexed (only for nonsquamous NSCLC), taxanes, vinorelbine, or gemcitabine. The combination of a platinum-doublet with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab is a treatment option for nonsquamous patients only. Induction chemotherapy maybe followed by maintenance therapy, administered either as switch- or continuation maintenance. Second-line treatment options after failure of first-line chemotherapy with or without maintenance treatment consists of monotherapy with either docetaxel, erlotinib, or pemetrexed depending on type of prior treatment. Lately, an anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, ramucirumab, in combination with docetaxel was approved in the US and EU for the second-line treatment of metastatic NSCLC, including squamous and nonsquamous histologies (Cyramza Summary of Product Characteristics [SmPC]/US package insert [USPI]). Recently, monoclonal antibodies (mAbs) directed against programmed death-1 (PD-1) T-cell co-receptor, nivolumab and pembrolizumab, have been approved in the US for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy, whereby pembrolizumab was approved for the treatment of those NSCLC patients whose tumors express PD-L1 as determined by an FDA-approved test (Opdivo USPI, Keytruda USPI). In the EU nivolumab is available for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (Opdivo SmPC). For patients with tumors harboring epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-activating mutations, monotherapy with an EGFR TKI is used upfront, followed by osimertinib (Tagrisso PI) in patients with EGFR T790M mutation-positive cancer or a platinum-based doublet as second-line, or as second- or third-line treatment if not used previously. For patients with anaplastic lymphoma kinase (ALK)-gene arrangement, treatment should include monotherapy with an ALK inhibitor (Heigener et al. 2014).

Despite the advancement of systemic treatments for patients with advanced or metastatic NSCLC, the available therapeutic options remain limited and the prognosis of the patients is poor, resulting in a continued medical need for new treatment options.

5.2. Necitumumab

Necitumumab (LY3012211) is a recombinant human mAb of the immunoglobulin (Ig) G_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.

EGFR is expressed in a variety of tumors, including colorectal, head and neck, breast, and NSCLC (Salomon et al 1995). In patients with advanced and metastatic NSCLC, EGFR is detectable in approximately 85% to 90% of patients (Fontanini et al 1995; Pirker et al 2009). Pharmacologic inhibition of EGFR signaling through competitive inhibition of ligand binding has been shown to play a role in the treatment of several cancers, leading to registration of necitumumab in squamous NSCLC and 2 other anti-EGFR mAbs in a number of other indications (Necitumumab/Portrazza SmPC, Cetuximab/Erbitux SmPC, Panitumumab/Vectibix SmPC). Moreover, another randomized Phase 3 trial, conducted with cetuximab, showed evidence that the addition of an EGFR mAb to a platinum-based doublet can significantly increase survival in patients with advanced NSCLC (Pirker et al. 2009).

The necitumumab Phase 1 program included 2 single-agent dose-escalation Phase 1 trials in Western (I4X-IE-JFCE [JFCE]) and Japanese (I4X-IE-JFCA [JFCA]) patients with advanced solid tumors or for whom no standard therapy was available.

Study JFCE included 60 patients and investigated necitumumab intravenous (I.V.) once a week (Arm A, n=29) or once every 2 weeks (Arm B, n=31) at sequential absolute dose levels from 100 mg to 1000 mg. No dose-limiting toxicities (DLTs) were observed in Arm A, which included 9 patients treated at 1000 mg. Grade 3 headache was the major DLT, occurring in 2 of 9 patients in the 1000-mg dose cohort of Arm B. Because of the timely relationship to the first dose of necitumumab, these were considered to be dose-related and the dose level of 800 mg was defined as the maximum tolerated dose (MTD) for both schedules. Grade ≥3 adverse events (AEs) considered at least possibly related to necitumumab affected 10.3% (n = 3) of patients in Arm A and 22.6% (n = 7) of patients in Arm B. Overall, the most common related Grade ≥3 AEs were fatigue (4 patients; 2 patients each in Arm A and Arm B); headache (2 patients in Arm B), and acne (2 patients, 1 patient each in Arm A and Arm B); others included anemia, diarrhea, nausea, vomiting, hypokalemia, and decreased blood magnesium (1 patient each, all in Arm B). No Grade 5 necitumumab-related AEs were observed in this study.

In Study JFCA, 15 patients were enrolled and treated (Cohort 1: 600 mg necitumumab on Days 1 and 8 of a 3-week cycle, n = 3; Cohort 2: 800 mg every 2 weeks, n = 6; and Cohort 3: 800 mg on Days 1 and 8 of a 3-week cycle, n = 6). No DLTs were observed in this study during the first 6-week cycle for any cohort. The most common treatment-emergent AEs (TEAEs) regardless of grade or relationship to study therapy were headache (n = 11; 73.3%), dry skin (n = 10; 66.7%),

pruritus (n = 9; 60.0%), and rash (n = 8; 53.3%). One patient in Cohort 2 experienced 2 related Grade 3 TEAEs of dry skin and rash; all other related events observed in the study were Grade ≤2.

Signals of antitumor activity of necitumumab monotherapy were observed in both studies with heavily pretreated patients. For Study JFCE, in total 2 partial response (PR) and 16 stable disease (SD; 1 PR, 8 SD for each treatment arm) were observed (disease control rate [DCR] Arm A 31%, Arm B 29%). For Study JFCA, SD was seen within all cohorts in a total of 10 patients (DCR 66.7%), including 1 patient with squamous NSCLC and 1 patient with nonsquamous NCLC.

Based on both Phase 1 trials, the recommended necitumumab dosing schedule is 800 mg once every week, once every 2 weeks, or on Days 1 and 8 of a 3-week cycle.

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 overall survival (OS) in the GC+N Arm compared with the GC Arm (hazard ratio [HR] = 0.84; p=0.012). This was supported by a statistically significant improvement in progression-free survival (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 ≥39.3% vs. 1.1%) being the most frequently reported events (pooled terms) occurring at higher rates for patients receiving necitumumab. The Grade ≥3 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. 2013). 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 frequency of study drug related deaths was 4.9% and 2.9% for PC+N and PC, respectively.

Based on these data, the combination of necitumumab plus pemetrexed-cisplatin is not being considered for further development. Of note, no safety signal with regard to thromboembolic or potential thromboembolic events, including fatal events, has been identified for necitumumab in completed clinical trials when administered as monotherapy or in combination with mFOLFOX6 chemotherapy.

The randomized Phase 2 trial, I4X-MC-JFCL (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. Study I4X-JE-JFCM is a Phase 1b/2 study in Japanese patients with Stage IV squamous NSCLC that compares necitumumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone. The trial is monitored by an IDMC and continues as planned.

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

5.3. Abemaciclib

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for regulation of cell division (Sherr 1996; Ortega et al. 2002). The CDK4/6 – cyclin D1 complex regulates the G1 restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein. Except for tumors with functional loss of Rb, which functions downstream of the CDK4/6 – cyclin D1 complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4/6.

Abemaciclib (LY2835219) represents a selective small molecule inhibitor of CDK4/6. It demonstrates antitumor activity in multiple mouse models of human cancer, physical and pharmacokinetic (PK) properties suitable for drug development, and an acceptable toxicity profile in nonclinical species. This compound inhibits tumor growth in multiple human xenograft models including, but not limited to, the following tumor types: 1) colorectal cancer, 2) glioblastoma multiforme, 3) acute myeloid leukemia, 4) NSCLC, and 5) mantle cell lymphoma. Recent studies with abemaciclib in murine models bearing human xenografts provide support for the relationship for lung adenocarcinomas in xenograft models, which all express an activated *KRAS* oncogene. Models that expressed an activated *KRAS* oncogene were observed to be the most sensitive to growth inhibition. Models that expressed a wild-type *KRAS* gene were observed to be among the least sensitive of the lung adenocarcinoma models to growth inhibition by abemaciclib.

In a Phase 1 study (I3Y-MC-JPBA [JPBA]), 57 patients with advanced NSCLC who progressed or relapsed after standard treatments were treated with abemaciclib at doses between 50 mg and 225 mg every 24 hours, or at doses between 75 and 275 mg every 12 hours (Q12H) (Goldman et al. 2014). The patients enrolled received a median of 4 prior regimens, and the MTD was established at 200 mg Q12H. The most common Grade 3 AEs (greater than 5% incidence) were leukopenia (14%) and neutropenia (9%). No patients in the lung cancer cohort experienced Grade 4 AEs. Less than 2% of patients discontinued due to AEs in this study cohort. Disease control rate (complete response [CR], PR, or SD) was 49 % for patients on abemaciclib,

including 2 PR and 26 patients with SD. Six patients had squamous cell NSCLC. The response assessment for these 6 patients was 1 PR, 2 SD, 1 PD, and 2 were inevaluable.

Study I3Y-MC-JPBJ (JPBJ) is an ongoing Phase 1b study in patients with previously treated NSCLC Stage IV. Patients are divided into 4 treatment arms based on prior therapy or histology and receive abemaciclib in combination with either pemetrexed, gemcitabine, ramucirumab, or PI3K/mTOR dual inhibitor. The primary objective of this study is to evaluate the safety and tolerability of abemaciclib combinations.

5.4. Study Rationale

The purpose of this study is to explore the efficacy and safety of necitumumab plus abemaciclib in patients with Stage IV NSCLC who have received no more than 2 lines of chemotherapy of which at least one must be platinum-based.

Necitumumab (LY3012211) is a recombinant human mAb of IgG_1 class, which targets EGFR. Necitumumab demonstrates a high affinity to its target and blocks ligand-induced receptor phosphorylation and downstream signaling. EGFR is detectable in approximately 85% to 90% of patients with NSCLC (Fontanini et al 1995; Pirker et al 2009). Pharmacologic inhibition of EGFR signaling through competitive inhibition of ligand binding has been shown to play a role in the treatment of several cancers, and EGFR mAbs are approved in various tumor indications (Erbitux PI/SmPC, Vectibix PI/SmPC). Portrazza has recently been approved in the United States (US) and European Union (EU) for the treatment of adult patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin (Portrazza USPI and SmPC). The necitumumab SQUIRE trial showed statistically significant improvements in OS and PFS, with an overall favorable benefit-risk profile. In addition, a recent meta-analysis investigating the addition of an EGFR mAb to platinum-based first-line therapy demonstrated a significantly improved OS and PFS in patients with advanced NSCLC (Pujol et al. 2014).

Abemaciclib, a selective and potent small molecule inhibitor of CDK4/6, prevents cell cycle progression through the G1 restriction point, thus arresting tumor growth. The data in NSCLC studies (JPBA and JPBJ) show activity for abemaciclib in both *KRAS* mutant and *KRAS* wild-type tumors. Some of the longest survivors on abemaciclib have been patients with squamous histology and *KRAS* wild-type tumors. Preliminary data suggest that more *KRAS* mutant patients have responded; however, the numbers are small and do not in any way preclude treatment of *KRAS* wild-type patients, especially in this setting (combination with necitumumab).

Necitumumab and abemaciclib inhibit tumor progression by different, independent modes of action (cell surface and cell nucleus), where necitumumab blocks the ligand-binding site of the EGFR and abemaciclib blocks DNA synthesis by prohibiting cell cycle progression from G1- to S-phase. Both agents have shown activity signals when administered as monotherapy in heavily pretreated patients, including patients with NSCLC. In a 549 xenograft model of NSCLC, the addition of necitumumab to abemaciclib improved the antitumor efficacy compared to either monotherapy (Eli Lilly, data on file).

The individual toxicity profile from clinical trials with each of the compounds (that is, necitumumab and abemaciclib) suggests that no or only marginal overlapping toxicity is expected. The most common Grade ≥3 AEs (>5% of patients) for single-agent abemaciclib were leukopenia and neutropenia. For necitumumab single agent, the most frequent AEs reported were skin reactions in terms of rash and hypomagnesemia.

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

6. Objectives

6.1. Primary Objective

This study is divided into 2 parts:

Part A: to determine the dose-limiting toxicity (DLT) of abemaciclib at doses up to 200 mg when combined with necitumumab 800 mg, in patients with Stage IV NSCLC as measured by the number of patients with a DLT in Cycle 1

Part B: to evaluate the efficacy of necitumumab in combination with abemaciclib in terms of PFS rate at 3 months in patients with Stage IV NSCLC

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

Part A:

- to investigate the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with abemaciclib
- to determine the objective response rate (ORR)
- to determine pharmacokinetics (PK) of necitumumab and abemaciclib
- to determine the immunogenicity of necitumumab

Part B:

To demonstrate the safety, efficacy, and feasibility of necitumumab in combination with abemaciclib at the recommended dose by

- determining PFS
- determining ORR and disease control rate (DCR)
- estimating OS
- investigating the safety profile as assessed by clinical and laboratory significant events
- determining PK of necitumumab and abemaciclib
- determining the immunogenicity of necitumumab

6.3. Exploratory Objectives

- to correlate biomarkers with clinical outcomes, including, but not limited to *KRAS* mutation assessment, EGFR protein expression, and/or other biomarkers associated with the disease pathobiology, the cell cycle, EGFR pathway, and/or the mechanism of action of the therapeutic molecules.

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened once. At the time of re-screening, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Central laboratory testing is required for assessment of eligibility. Note that repeating laboratory tests during the screening period does not constitute rescreening. Laboratory tests may not be repeated more than once in order to meet eligibility.

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

7.1. Inclusion Criteria

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

[1] Histologically or cytologically confirmed NSCLC

- Part A: NSCLC Stage IV (any type)
- Part B: NSCLC Stage IV (squamous and nonsquamous)

[2] Stage IV disease at the time of study entry (American Joint Committee on Cancer [AJCC] Staging Manual, 7th Edition [Edge et al. 2009])

[3] Measurable disease at the time of study entry as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009)

[4] The patient must have progressed after platinum-based chemotherapy AND have received a maximum of 1 other prior chemotherapy for advanced and/or metastatic disease OR must be judged by the physician as ineligible for further standard second-line chemotherapy. Prior treatment with EGFR-TKI and ALK inhibitors is mandatory in patients whose tumor has EGFR-activating mutations or ALK translocations. Prior targeting agents and neoadjuvant/adjuvant therapies are permitted with the exception of CDK4/6-targeting agents or necitumumab.

[5] The patient has tumor tissue available for biomarker analyses. The sample can be either 12 serially paraffin-embedded unstained tissue slides or a paraffin-embedded tissue block (see Section 10.3.2.2 for further details).

[6] The patient has given written informed consent prior to any study specific procedures. Written consent may also be provided by a legal representative.

[7] The patient is 18 years or older if required by local law or regulations.

[8] The patient has resolution to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0, of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy (with the exception of alopecia).

[9] The patient has an Eastern Cooperative Oncology Group performance status score of 0-1 (see Attachment 4).

[10] Have the following laboratory values:

- hematologic: absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥9 g/dL. Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF, or recombinant erythropoietin) within 4 weeks prior to Cycle 1 Day 1 are not allowed.
- serum albumin ≥25 g/L
- hepatic: bilirubin ≤1.5 times the upper limit of normal (ULN), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate transaminase (AST) ≤3.0 times ULN. For patients with hepatic metastases, ALT and AST equaling ≤5.0 times ULN are acceptable.
- renal: serum creatinine ≤1.2 times ULN or calculated creatinine clearance >50 mL/min (per the Cockcroft-Gault formula as defined in Attachment 5) for patients with creatinine >1.2 times ULN.

[11] Men who are sterile (including vasectomy confirmed by post-vasectomy semen analysis) or who agree to use a reliable method of birth control and to not donate sperm during the study (and for at least 12 weeks following the last dose of necitumumab and abemaciclib or country requirements, whichever is longer) OR

[12] Women who are either: (a) not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause*; or (b) of child-bearing potential who have a negative serum pregnancy test within 14 days prior to study enrollment and agree to use a highly effective method of birth control† during the study and for 6 months after the last dose of study drug(s) (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method).

* A "menopausal woman" is a woman meeting either of the following criteria:

1. spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy)
2. spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level >40 mIU/mL

† A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

[13] Are able to swallow oral medications.

[14] Have an estimated life expectancy of at least 12 weeks.

7.2. Exclusion Criteria

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

[15] The patient is currently enrolled in a clinical trial involving an investigational product (IP; hereon referred to as study treatment) or non-approved use of a drug or device (other than the study treatment used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Prior treatment with CDK4/6-targeting agents or necitumumab is not permitted.

[16] The patient has undergone major surgery or received any investigational therapy in the 30-days prior to study enrollment.

[17] The patient has undergone chest irradiation within 4 weeks prior to receiving study treatment (except focal palliative irradiation, which is allowed up to 2 weeks prior to receiving study treatment).

[18] The patient has brain metastases that are symptomatic. (Patients who have completed radiotherapy for brain metastases at least 2 weeks prior to receiving study treatment, who are now non symptomatic or on stable dose of steroids or anticonvulsants during the 2 weeks prior to receiving study treatment, are eligible). Patients with asymptomatic brain metastases without need for treatment with steroids and who have not been treated with radiotherapy are eligible. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

[19] History of arterial or venous thromboembolism within 3 months prior to study enrollment. Patients with a history of venous thromboembolism beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin.

[20] History or evidence of current clinically relevant coronary artery disease ≥ Grade III by the Canadian Cardiovascular Society Angina Grading Scale or uncontrolled congestive heart failure of current > Class III as defined by the New York Heart Association.

[21] The patient has experienced myocardial infarction within 6 months prior to study enrollment.

[22] The patient has active infection requiring systemic therapy, including active tuberculosis or known history of infection with the human immunodeficiency virus (HIV 1/2 antibodies), or hepatitis B (e.g., HBsAg reactive) and/or C virus (e.g., HCV RNA qualitative is detected).

[23] The patient has a history of significant neurological or psychiatric disorders, including dementia, seizures, or bipolar disorder, potentially precluding protocol compliance.

[24] The patient has a personal 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.

[25] The patient has 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.

[26] The patient has a known allergy/history of hypersensitivity reaction to any of the treatment components, including any ingredient used in the formulation of necitumumab or abemaciclib, or any other contraindication to one of the administered treatments.

[27] The patient is pregnant or breastfeeding.

[28] The patient has a known history of drug abuse, that in the opinion of the investigator, may have an impact on the safety of the patient and/or limit the patient's ability to complete the study or adhere to any protocol procedure.

[29] The patient has a concurrent active malignancy. Previous history of malignancy is permitted, provided that the patient has been free of disease for ≥3 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin, preinvasive carcinoma of the cervix, or any cancers that in the judgment of the investigator and sponsor may not affect the interpretation of results (for example, prostate, bladder).

[30] The patient is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, chemo-embolization, targeted therapy, or an investigational agent.

[31] History of interstitial lung disease or an active non-infectious pneumonitis

[32] Recent (within 30 days before enrollment) or concurrent yellow fever vaccination

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [15] eliminates drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of AEs or drug interactions. Exclusion Criteria [15] through [25] and [27] through [32] ensure that previous or currently required treatments or conditions do not complicate on-study treatment and/or analysis of data.

Exclusion Criterion [26] excludes patients who may be at elevated risk of toxicity based on the known safety profile of necitumumab and abemaciclib.

7.3. Discontinuation

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

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

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

7.3.1. Discontinuation of Inadvertently Enrolled Patients

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

7.3.2. Discontinuation From Study Therapy

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

- Enrollment in any other clinical trial involving a study drug or enrollment in 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 study therapy occurs prior to introduction of the new agent.
- Investigator/Physician Decision
    - The investigator/physician decides that the patient should be withdrawn from the study.
    - If the patient has progressive disease (PD).
- Patient Decision
    - The patient or patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study treatment.

- Sponsor Decision
    - The sponsor stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practices (GCP).
    - The patient is significantly noncompliant with study procedures and/or treatment.
    - An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient).
    - A Grade 3 to 4 infusion-related reaction.

7.3.3. Discontinuation from the Study

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

- The investigator decides that the patient should be discontinued from the study.
- The patient or the patient's designee requests that the patient be discontinued from the study.

Patients who are discontinued from study participation will not be followed for PD or survival.

7.3.4. Patients who are Lost to Follow-Up

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

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

7.3.5. Discontinuation of Study Sites

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

7.3.6. Discontinuation of the Study

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

8. Investigational Plan

8.1. Summary of Study Design

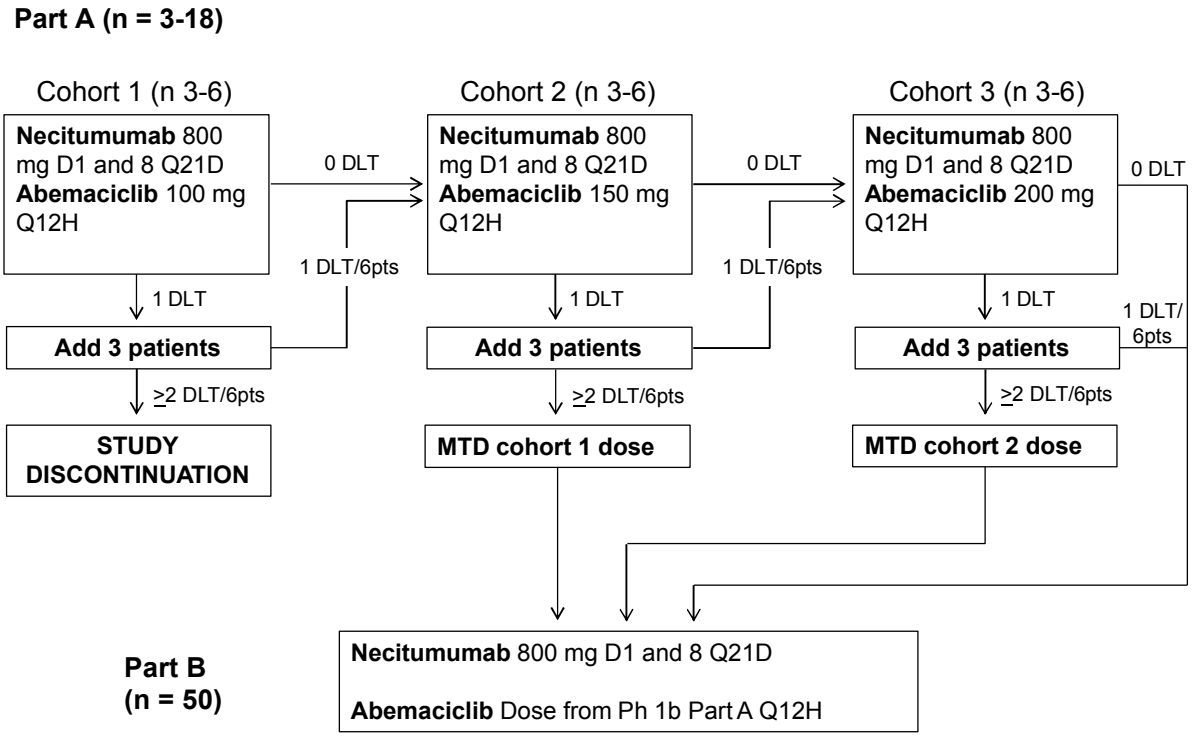
Study I4X-MC-JFCU is a single-arm, multicenter, Phase 1b study with an expansion cohort to investigate necitumumab in combination with abemaciclib in approximately 70 patients with Stage IV NSCLC (AJCC Staging Manual, 7th edition).

The study consists of 2 parts:

- Part A: Dose-escalation part with increasing doses of abemaciclib (100, 150 or 200 mg Q12H on Days 1 to 21) to determine a recommended dose range for abemaciclib that may be safely administered in combination with a fixed regimen of necitumumab 800 mg Days 1 and 8 every 21 days in patients with Stage IV NSCLC.
- Part B (Expansion Cohort): Dose confirmation of abemaciclib in combination with a fixed regimen of necitumumab 800 mg on Days 1 and 8 every 21 days and exploration of clinical antitumor activity.

In Part B, approximately 50 patients will be enrolled; approximately 25 patients with squamous and approximately 25 patients with nonsquamous histologies.

Figure JFCU.8.1 illustrates the study design.



Abbreviations: D = day; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; n = number of patients; Ph = Phase; Q12H = every 12 hours; Q21D = every 21 days.

Figure JFCU.8.1. Illustration of study design.

Part A is a single-arm, dose-escalation study to determine the recommended dose for the expansion cohort (Part B).

Part A:

Cohort 1

- Necitumumab, administered I.V. over 60 minutes at an absolute dose of 800 mg on Days 1 and 8, followed by
- Abemaciclib at a dose of 100 mg orally Q12H on Days 1 to 21

Cohort 2

- Necitumumab, administered I.V. over 60 minutes at an absolute dose of 800 mg on Days 1 and 8, followed by
- Abemaciclib at a dose of 150 mg Q12H on Days 1 to 21

Cohort 3

- Necitumumab, administered I.V. over 60 minutes at an absolute dose of 800 mg on Days 1 and 8, followed by
- Abemaciclib at a dose of 200 mg Q12H on Days 1 to 21

Note: At the time of approval of the JFCU(b) protocol amendment, all patients who are still on the study will be administered necitumumab I.V. infusion over 60 minutes.

A maximum of 18 evaluable patients will be enrolled in Part A. Any patient who is discontinued from the study before completing Cycle 1 will be excluded from the DLT population, unless a DLT was observed. Patients who do not complete Cycle 1 for reason other than DLT will be replaced.

If 1 of 3 patients in each cohort experiences a DLT during Cycle 1, 3 additional patients will be enrolled in that cohort. If 2 of 6 patients experience a DLT in Cohort 1, the study must be discontinued.

If 2 of 6 patients experience a DLT in Cohort 2 or 3, then the dose in Cohort 1 or 2 will be the MTD.

Dose escalation within a cohort will not be permitted. Patients assigned to a cohort dose level will remain at that level throughout the study. However re-escalation will be permitted as specified in Section 9.3.2.2.1.

The individual recommended dose for necitumumab is 800 mg on Days 1 and 8 every 21 days and 200 mg Q12H for abemaciclib. For this reason, further dose escalation beyond Cohort 3 will not be tested.

Patients in whom DLT occurs in Cycle 1 may still continue study treatment according to the criteria for starting the next cycle or dose modification (specified in Section 9.3.2.2.1) if the patients are benefiting from study treatment in the opinion of the investigator.

Necitumumab plus abemaciclib may be continued at the assigned dose level until disease progression, the development of unacceptable toxicity or withdrawal of consent by the patient, or sponsor/investigator decision.

Part B is a single-arm study to evaluate efficacy and safety of necitumumab in combination with abemaciclib in patients with Stage IV squamous or nonsquamous NSCLC (Figure JFCU.8.1). Patients will be treated with necitumumab 800 mg on Days 1 and 8 every 21 days and the dose of abemaciclib identified from Part A of the study Q12H on Days 1 to 21.

Provided there is an acceptable safety profile in Part A of this study, Part B will be initiated, which will include a safety interim analysis after the first 15 evaluable patients have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the safety interim analysis.

The final analysis for all outcomes will be performed approximately 5 months after completing enrollment of the study population.

A treatment cycle will be defined as 21 days. Study therapy, consisting of necitumumab plus abemaciclib will continue until there is a radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

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

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the continued access period.
    - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment.
    - **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

      Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

      Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.
- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
    - Continued access follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) approximately 5 months after the last patient in the Part B of the study has been enrolled. 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.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up (see Figure JFCU.8.2).

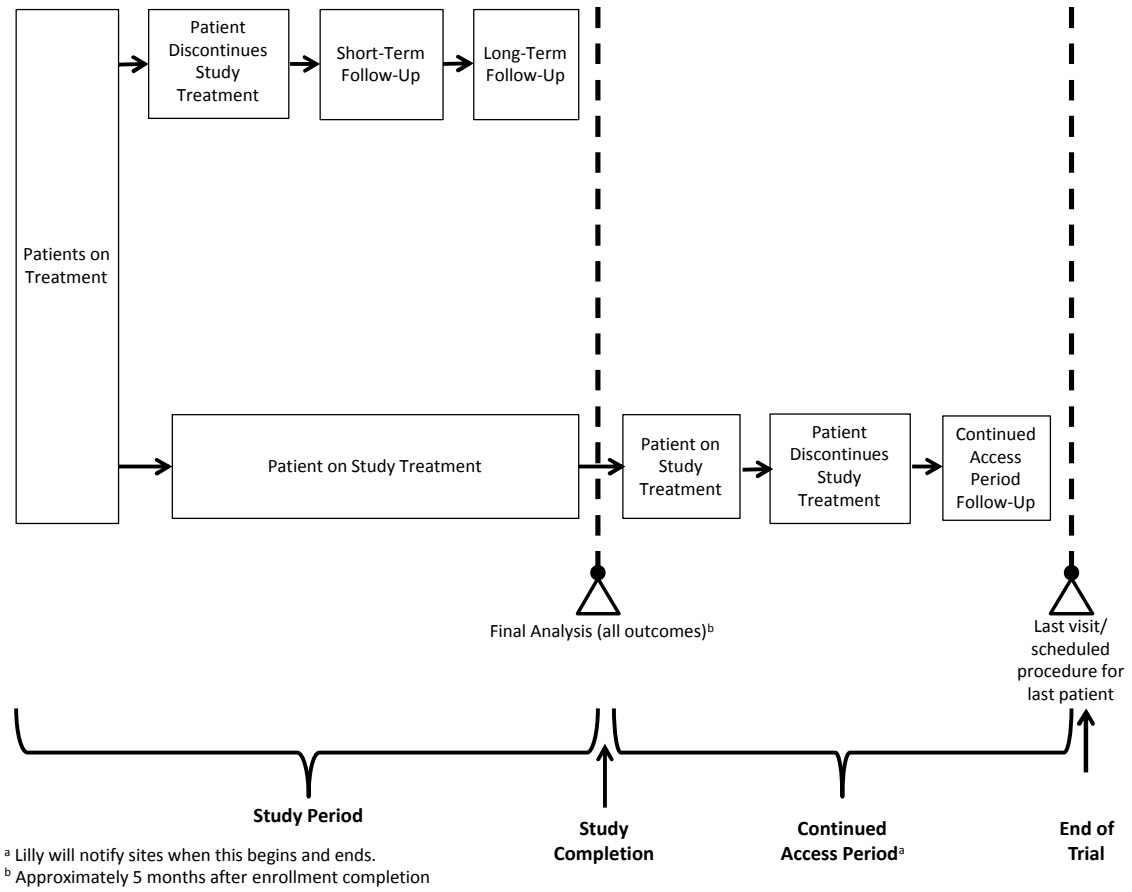


Figure JFCU.8.2. Study period and continued access diagram.

8.1.2. Continued Access Period

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the continued access period until one of the criteria for discontinuation is met (Section 7.3). Lilly will notify investigators when the continued access period begins.

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

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

During the continued access period, all AEs, SAEs, and study drug exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.2.1.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to

evaluate the reported SAE. Blood samples for PK and immunogenicity analysis will be collected in the event of an infusion-related reaction and during the continued access follow-up.

During the continued access period, the sponsor will collect only the data shown in Attachment 1. It is recommended that routine monitoring, using an assessment schedule similar to that outlined in Attachment 1 (including radiographic evaluation of disease), be continued as necessary to confirm patient eligibility to continue on treatment. However, the results of all these assessments may not be routinely collected by the sponsor, and all nonmandatory assessments (that is, all assessments not explicitly described in Attachment 1) may be performed locally rather than centrally.

8.2. Discussion of Design and Control

In this single-arm, Phase 1b study with an expansion cohort, the selected dose of necitumumab of 800 mg on Days 1 and 8 every 21 days is aligned with the MTD and the dosing schedule in the Phase 3 development program for necitumumab. The starting dose of abemaciclib will be at dose level -2 of the MTD (100 mg Q12H). This is aligned with the minimal dose applied in the dose adjustment schedule from clinical trials.

Patients with Stage IV NSCLC who have received no more than 2 lines of chemotherapy, of which at least one must be platinum-based, for advanced or metastatic disease will receive a combination of necitumumab and abemaciclib. Prior treatment with EGFR-TKI, VEGF/VEGFR-targeting agents, and ALK inhibitors is permitted.

In Part B, approximately 50 patients will be enrolled with an even split between squamous and nonsquamous histology to enable a homogenous population in the study.

Provided there is an acceptable safety profile in Part A of this study, Part B will be initiated, which will include a safety interim analysis after the first 15 evaluable patients have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the safety interim analysis.

Based on the single-arm nature of the study, the outcome will be hypothesis generating only, allowing for future consolidation of this regimen depending on the outcome.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study (Table JFCU.9.1):

In Part A, patients will receive oral abemaciclib 100 mg, 150 mg or 200 mg Q12H in combination with necitumumab 800 mg as an absolute dose on Day 1 and Day 8 every 21 days.

In Part B, the abemaciclib dose identified from Part A will be given Q12H in combination with necitumumab 800 mg as an absolute dose Day 1 and Day 8 every 21 days.

Necitumumab will be administered first followed by abemaciclib. Abemaciclib should be administered within 10 minutes of start of necitumumab infusion.

Table JFCU.9.1. Treatment Regimens/Dosing Schedule

Part A

Cohort	Drug	Dose	Day	Infusion duration
Cohort 1	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 60 minutes[a] (±5 minutes)
	Abemaciclib	100 mg Q12H	Days 1 - 21	
Cohort 2	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 60 minutes[a] (±5 minutes)
	Abemaciclib	150 mg Q12H	Days 1 - 21	
Cohort 3	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 60 minutes[a] (±5 minutes)
	Abemaciclib	200 mg Q12H	Days 1 - 21	

Part B

Drug	Dose	Day	Infusion duration
Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 60 minutes[a] (±5 minutes)
Abemaciclib	Dose from Part A Q12H	Days 1 - 21	

Abbreviations: IV= intravenously; Q12H = every 12 hours.

[a] At the time of approval of the JFCU(b) protocol amendment, all patients who are still on the study will be administered necitumumab I.V. infusion over 60 minutes (±5 minutes).

The individual recommended dose for necitumumab is 800 mg on Day 1 and Day 8 every 21 days and 200 mg Q12H for abemaciclib. For this reason, further dose escalation beyond Cohort 3 will not be tested.

Hypersensitivity/infusion-related reactions may occur during or following administration of necitumumab (see Section 9.3.2.2.3.1.1 for a definition of Grade 3 and 4 hypersensitivity/infusion-related reactions). As a routine precaution, patients treated with necitumumab should be observed closely for any potential adverse effects by the medical staff 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.

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

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

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

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

9.2. Materials and Supplies

All study treatment materials will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

Necitumumab is a sterile and preservative-free solution for I.V. infusion supplied in the following formulation:

- Necitumumab at a final concentration of 16 mg/mL (800 mg/50 mL) contained in single-use vials, in a formulation of 10 mM citrate, 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol, 0.01% polysorbate-80, pH 6.0.

All excipients used in the formulation of necitumumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of necitumumab excipients. Refer to the IB for detailed information.

Abemaciclib will be supplied by Lilly as capsules for oral administration. Abemaciclib capsules should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed.

9.3. Method of Assignment to Treatment

An interactive web response system will be used for treatment assignment in both Parts A and B of the study.

9.3.1. Selection and Timing of Doses

The first treatment will be administered within 7 days of enrollment. Study treatment will be administered as described in Section 9.1.

A cycle is defined as an interval of 21 days.

Administration of necitumumab Day 1 dose will trigger the start of a new cycle. Infusions administered within 3 days before or after the planned infusion time point due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted and not counted as a protocol deviation. The necitumumab Day 8 dose can be delayed up to 5 days. Beyond that, the Day 8 dose will have to be omitted in order to maintain the 21 day cycle. **A minimum of 7 days' interval between any necitumumab dose must be maintained.**

Abemaciclib will be taken orally every 12 (±2) hours on Days 1 through 21 of a 21-day cycle, for a total of 42 doses per cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses or vomits abemaciclib, that dose should be omitted.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue on abemaciclib treatment. If abemaciclib is interrupted as a result of not having sufficient drug supply, the treatment may be delayed up to 5 days (and not be considered a protocol violation). In exceptional circumstances, a delay >5 days is permitted upon agreement between the investigator and the Lilly CRP.

A patient may continue to receive study treatment until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3).

9.3.2. Special Treatment Considerations

9.3.2.1. Dose-Limiting Toxicity (Part A)

A dose-limiting toxicity (DLT) is defined as one of the following AEs, occurring in Cycle 1 if considered to be definitely, probably, or possibly related to necitumumab and abemaciclib. The following list will define DLT:

- Grade 3 or 4 nonhematologic toxicity according to the NCI CTCAE Version 4.0 except for nausea, vomiting, diarrhea, or electrolyte disturbance (see below)
- Grade 3 or 4 nausea, vomiting, or diarrhea that persists more than 2 days despite maximal supportive intervention
- Grade 3 thrombocytopenia with bleeding requiring transfusion
- Grade 4 thrombocytopenia with or without bleeding

- Grade 4 neutropenia that persists more than 5 days
- Grade 3 or 4 neutropenia with fever
- Grade ≥3 skin toxicity despite best supportive care
- If a total at least 75% of the planned dose for both agents cannot be administered in the first cycle due to toxicity

DLT is defined by sponsor and Principal Investigator.

The following toxicities will not be considered DLTs if they are transient <7 days) with full supportive therapy:

- Grade 3 arthralgia or myalgia
- Grade 3 asthenia or fatigue
- Grade 3 constipation

The following toxicities will not be considered DLTs:

- Grade 3 injection-site reaction
- Grade 3 elevation of transaminases lasting <7 days
- Grade 3 elevation of serum-bilirubin lasting <7 days
- Transient Grade 3 elevation or decrease of electrolytes
- Grade 3 or 4 hypersensitivity

If a Grade 3 or 4 infusion-related reaction (hypersensitivity) to necitumumab occurs, this event will not be considered a DLT; the patient will not receive any further study therapy and will be replaced in the study by a new patient.

9.3.2.2. Dose Adjustments and Delays

9.3.2.2.1. Abemaciclib

Abemaciclib dose adjustments are allowed both within a cycle and between cycles. Abemaciclib must be reduced sequentially by 1 dose level.

An abemaciclib dose level below 100 mg Q12H is not allowed. For patients starting at abemaciclib 100 mg Q12H, no further dose reduction is permitted. For patients starting at dose level 150 mg Q12H, only 1 dose reduction is allowed.

Abemaciclib may be held up to 14 days to permit sufficient time for recovery from the toxicity. If a dose suspension occurs, the investigator may resume abemaciclib 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 suspension 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 4 hematologic toxicity possibly related to abemaciclib, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib must be reduced as outlined in Table JFCU.9.2.

If a patient experiences CTCAE Grade≥3 nonhematologic toxicity possibly related to abemaciclib, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JFCU.9.2.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea) possibly related to abemaciclib that does not resolve with maximal supportive measures within 3 days (as outlined in Section 9.5.3) to either baseline or Grade 1, then dosing should be suspended (until the toxicity resolves to either baseline or at least Grade 1), and the dose of abemaciclib may be reduced as outlined in Table JFCU.9.2.

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 abemaciclib that the patient is currently receiving.

Table JFCU.9.2. Dose Adjustments of Abemaciclib

Dose Adjustment Level	Oral Dose	Frequency
0	200 mg	Every 12 hours
1	150 mg	Every 12 hours
2	100 mg	Every 12 hours

Abemaciclib must be discontinued if further dose reduction is required beyond 100 mg every 12 hours. The patient may continue to receive necitumumab as a single agent.

Patients not recovering from toxicity within 14 days should be considered for discontinuation from abemaciclib treatment.

9.3.2.2.1.1. Guidance for Monitoring of Renal Function in Patients on Abemaciclib

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. Dose alterations (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function.

9.3.2.2.2. Necitumumab

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 necitumumab-related toxicity, administration of necitumumab will be at the reduced dose (refer to Section 9.3.2.2.3) or interrupted, but abemaciclib 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.

9.3.2.2.3. Necitumumab Dose Modifications

The following are general dose-modification guidelines for toxicity associated with necitumumab. Please see Section 9.3.2.2.3.1 for specific information on the management of necitumumab-related hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, and hypomagnesemia.

Dose modifications are permitted for necitumumab following non-life threatening 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. In this setting, necitumumab may be readministered at a reduced dose (600 mg) if necessary only if AE is resolved to Grade ≤2. A second dose reduction (to 400 mg) is permitted for this level of event (Grade ≥3).

If a patient experiences CTCAE Grade ≥3 hematologic toxicity possibly related to necitumumab, then dosing must be suspended (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, then dosing must be suspended (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).

Events that necessitate more than 2 dose reductions warrant discontinuation from necitumumab treatment. Following a dose reduction, the dose of necitumumab may be re-escalated to the pre-reduction dose, provided that at least 2 administrations have elapsed following the first administration of the reduced dose, and only after consultation with the Lilly CRP. For dose modifications in response to specific AEs related to necitumumab, please see Section 9.3.2.2.3.1.

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. Dose reductions (to 400 mg) are warranted in the setting of Grade 1-2 baseline symptoms or laboratory values that worsen to Grade ≥3 during treatment.

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

9.3.2.2.3.1. Treatment Guidelines and Dose Modifications for Specific Adverse Events of Necitumumab

Adverse events of concern, which may or may not be associated with necitumumab therapy, include hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, electrolyte abnormalities, pneumonia and sepsis, and thromboembolic events.

9.3.2.2.3.1.1. Hypersensitivity/Infusion-Related Reactions

Hypersensitivity/infusion-related reactions (IRRs) were reported with necitumumab. The onset of events usually occurred after the first or second administration of necitumumab. Monitor patients during and following the infusion for signs of hypersensitivity and IRRs with resuscitation equipment readily available.

Hypersensitivity/IRRs are defined according to the NCI-CTCAE Version 4.0 definition of allergic reaction / hypersensitivity, as follows:

- Grade 1: transient flushing or rash, drug fever <38°C
- Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥38°C
- Grade 3: symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema, hypotension
- Grade 4: anaphylaxis (a life-threatening event characterized by the rapid onset [often within minutes] of airway obstruction [bronchospasm, stridor, hoarseness], urticaria, and/or hypotension)

Consistent with usual medical practice, selected parenteral medications may be utilized as detailed below. Additional treatments, chosen according to clinical symptoms and local standards, may be utilized at investigator discretion. Table JFCU.9.3 provides general treatment recommendations for hypersensitivity/IRRs to necitumumab.

Table JFCU.9.3. NCI-CTCAE 4.0 Infusion-Related Reactions

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: I.V. = intravenously; N/A = not applicable; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

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

If a patient should have a hypersensitivity/IRR to necitumumab, all attempts should be made to obtain an anti-necitumumab antibody and necitumumab PK blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. The procedure for sample collection and handling is described in a separate procedural manual.

9.3.2.2.3.1.2. Skin Reactions

9.3.2.2.3.1.2.1. Reactive Treatment

Reactive treatment recommendations for skin reaction, based on the Canadian recommendations presented by Melosky et al. (2009), are summarized in Table JFCU.9.4.

Skin rash (any grade) should be treated, as per Table JFCU.9.4. 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 JFCU.9.4. 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 readministered, with a dose reduction of 50% (400 mg). This dose may be increased to 75% of the original dose (600 mg) 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 full recommended dose (800 mg). • 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.**

If necitumumab therapy is delayed due to acneiform rash, abemaciclib may be administered without interruption in the absence of disease progression.

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).

9.3.2.2.3.1.3. 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.

9.3.2.2.3.1.4. 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.

9.3.2.2.3.1.5. 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 early signs of pulmonary infection. Treatment of any infection should be initiated according to local standards.

9.3.2.2.3.1.6. Thromboembolic Events

In the Phase 3 study JFCC, there was an increase in venous thromboembolic events (VTEs) and arterial thromboembolic events (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 the Phase 3 study JFCB, an increased rate of serious thromboembolic events, including fatal events, has been observed for the combination of necitumumab with pemetrexed and cisplatin as compared with treatment with pemetrexed and cisplatin alone in patients with nonsquamous NSCLC. Administration of necitumumab in combination with pemetrexed and cisplatin is not recommended.

No safety signal with regard to thromboembolic events, including fatal events, has been identified for necitumumab in completed clinical trials when administered as monotherapy or in combination with mFOLFOX-6 chemotherapy.

Treatment of any thromboembolic events occurring under necitumumab treatment should be as clinically indicated according to local standards, and the continuation of necitumumab therapy in these cases should be decided by the investigator after thorough risk-benefit assessment for the individual patient.

9.3.2.2.3.1.7. 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.

9.4. Blinding

This is an open-label study.

9.5. Concomitant Therapy

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

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment. Palliative radiotherapy, unless required due to progressive disease, is permitted during the study.

The results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A4. However, the extent of oxidative metabolism responsible for the systemic clearance of abemaciclib in humans is presently unknown. Based on these in vitro findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A4 should be

substituted or avoided if possible (Attachment 8). In addition, in vitro studies in primary cultures of human hepatocytes indicate that abemaciclib might inhibit the metabolism of CYP2B6 substrate drugs in vivo in human. Based on this finding, sensitive CYP2B6 substrates such as bupropion and efavirenz should be substituted or avoided if possible (Attachment 8).

Bisphosphonates or denosumab for bone metastasis are permitted.

9.5.1. Supportive Care

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Details of interventions, procedures, or blood products (for example, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the eCRF. Please see Section 9.3.2.2.3.1 for specific information on the management of necitumumab-related hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, electrolyte abnormalities, pneumonia and sepsis, and serious thromboembolic events. Guidelines regarding the use of other specific supportive care agents are presented below.

9.5.2. Colony-Stimulating Factors and Erythropoiesis-Stimulating Agents

The use of colony-stimulating factors (CSF) or erythropoiesis-stimulating agents (ESAs) are permitted during investigational therapy at the discretion of the investigator.

Because recommendations on the use of CSFs/ESAs are rapidly evolving, investigators should frequently refer to the local, national, or international standards (for example, European Organisation for Research and Treatment of Cancer, European Society for Medical Oncology, National Comprehensive Cancer Network, American Society of Clinical Oncology, American Society of Hematology, and/or Centers for Medicare and Medicaid Services Web sites) for the latest guidelines.

9.5.3. Therapy for Diarrhea

Diarrhea may influence tolerability of abemaciclib. During therapy with abemaciclib, early treatment with antidiarrheal agents (for example, loperamide) is recommended immediately after the first loose stool and should be continued until loose bowel movements cease for 12 hours. If a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve within 24 hours to either baseline or at least Grade 1, despite maximal treatment with antidiarrheal agents, then dosing should be suspended (until the toxicity resolves to either baseline or at least Grade 1), and the dose of abemaciclib may be reduced by 1 dose level as outlined in Table JFCU.9.2 at the discretion of the investigator. If the same dose level was resumed and Grade 2 diarrhea recurs despite maximal treatment with antidiarrheal agents, the dose must be reduced by 1 dose level as outlined in Table JFCU.9.2.

A patient experiencing diarrhea requiring hospitalization (irrespective of grade) or severe diarrhea (Grade 3 or 4) must have dosing suspended (until the toxicity resolves to either baseline or at least Grade 1) and must have the abemaciclib dose reduced by 1 dose level as outlined in Table JFCU.9.2 and Section 9.3.2.2.1.

In the event of Grade 3 or 4 diarrhea, supportive measures may include hydration, loperamide, octreotide, and other antidiarrheals. If diarrhea is severe (that is, requires intravenous hydration) and/or associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics must be prescribed. Patients with Grade ≥3 diarrhea or any diarrhea associated with Grade ≥3 nausea or vomiting should be considered for hospitalization for intravenous hydration and correction of electrolyte imbalance. Events that require a patient to be hospitalized are considered SAEs (see Section 10.2.1.1).

9.5.4. Antiemetic Therapy

The use of antiemetic agents is permitted during this study.

9.5.4.1. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator.

9.5.5. Bisphosphonates and RANK-L Targeted Agents

Patients with bone metastases present on baseline imaging are allowed treatment with bisphosphonates or RANK-L targeted agents (for example, denosumab), per respective approved labels. Initiation of treatment with bone-modifying agents must begin at least 7 days prior to enrolment. Patients receiving bisphosphonates or RANK-L targeted agents should not switch treatments (for example, replace a bisphosphonate with denosumab) while on study treatment. However, exceptional cases without evidence of PD may be considered in consultation with the Lilly CRP. These exceptional cases will not incur a protocol deviation.

9.5.6. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs (see Section 10.2.1.1).

9.6. Treatment Compliance

Necitumumab will be administered intravenously at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control.

Compliance with abemaciclib will be assessed at Day 1 and Day 8 of each cycle by evaluating patient diaries and counting returned tablets.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he or she misses more than 5 consecutive days of

study medication, or more than 25% of the intended dose of study medication during any cycle (not applicable in case of omission or dose reduction of abemaciclib due to AE). Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study treatment in a cycle.

Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before any determination is made to discontinue the patient.

Patient Diaries

The study will include patient diaries to provide dosing instructions, help patients with treatment planning, and track actual doses of study treatment taken by the patient. Information from the diaries may be used for documenting study treatment compliance as well as dosing time relative to PK blood draws.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, and sample collection and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Within 21 days before the first dose of study drug, baseline tumor measurement(s) will be performed on each patient. Throughout the study, patients will be evaluated for response according to RECIST 1.1 (Eisenhauer et al. 2009).

A contrast computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at pretreatment and thereafter approximately every 6 weeks ± 3 days, if a patient had brain metastases at study entry or if clinically indicated.

Computed tomography, including spiral CT, scans and MRI are the preferred methods of measurement.

The method of assessment used at baseline must be used consistently during the course of each patient's evaluation during the study.

Imaging studies required to investigate known disease should be repeated every 6 weeks (± 3 days) following the first dose of study therapy, regardless of any treatment delays, until radiographic documentation of PD as defined by RECIST 1.1. CT of the chest and CT or MRI of the abdomen is required at each time point; CT/MRI of the brain must be performed if baseline assessment identified any lesion in this area (or if clinically indicated).

Responses (CR or PR) must be confirmed no fewer than 28 days from the first evidence of response. Thereafter, a responding patient will be followed approximately every 6 weeks (± 3 days) until objective progression is observed.

For patients continuing treatment after study completion (continued access period), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

Response assessments during the ongoing trial (and related treatment decisions) will be performed by the treating investigator at the site in cooperation with the local radiologist(s).

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

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

For those patients who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response at the same frequency and by the same method used at baseline and throughout the study until the patient has objective disease progression, starts a new anticancer therapy, or until study completion, whichever occurs first. After the patient has objective disease progression or starts a new anticancer therapy, radiologic tests are no longer required and the patient will be followed up approximately every 3 months [±7 days] until the patient's death or overall study completion, whichever comes first.

Response (CR or PR) should be confirmed before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response.

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator. These postdiscontinuation therapies should be documented on the CRF.

10.1.3. Primary Efficacy Measure (Part B only)

The primary efficacy measure is Progression Free Survival Rate as defined by RECIST 1.1 (Eisenhauer et al. 2009) provided in Attachment 6 at 3 months.

The PFS time is measured from the date of enrollment to the date of objective progression or the date of 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.

10.1.4. Secondary Efficacy Measures

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

Overall Survival (OS): OS duration is measured from the date of enrollment to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the last known alive date.

Objective Response Rate (ORR): The objective response rate is the percentage of patients with a best response of CR or PR.

10.1.5. Disease Control Rate (DCR): The proportion of patients achieving a best overall response of SD, PR, or CR. Resource Utilization

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

10.2. Safety Evaluations

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

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

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

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JFCU.10.1 presents a summary of AE and SAE reporting guidelines. Table JFCU.10.1 also shows which database or system is used to store AE and SAE data.

Table JFCU.10.1. Adverse Event and Serious Adverse Event Reporting Guidelines

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

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

Note: The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or procedures, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained.

[a] For patients who fail screening, only AEs related to protocol procedures are collected in the collection database.

10.2.1. Adverse Events

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

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from electrocardiograms (ECGs), labs, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to study treatment should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of study treatment must be reported to Lilly or its designee via eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study treatment via eCRF.

The investigator will decide whether he or she interprets the observed AEs as either reasonably possibly related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. The investigator answers Yes/No to make this assessment in relation to study treatment and study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

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

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

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

10.2.1.1. Serious Adverse Events

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

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

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

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

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

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

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

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

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

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

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

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

10.2.1.2. Suspected Unexpected Serious Adverse Reactions

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

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1) as single ECGs. 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 a qualified physician (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/corrected QT interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (for example, palpitations, near syncope, syncope) and to determine whether 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.

10.2.3. 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 or designee will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events
- If a patient experiences elevated ALT >5× ULN and elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >3 × ULN, monitoring should be triggered at ALT >2× baseline.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 3.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by Lilly in aggregate periodically during the course of the trial may be found in the IB. In the NSCLC population, the occurrence of fatigue/weakness/asthenia, pain/chest pain, dyspnea, cough, nausea, anorexia/decreased appetite, disease progression, metastasis, hemoptysis, and pleural effusion are reasonably anticipated due to the underlying malignancy.

10.2.4. Complaint Handling

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

Complaints related to concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

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

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

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

10.3. Sample Collection and Testing

Samples collected for this study will be coded with the patient number. The samples and any data generated from them can be linked back to the patient only by investigator site personnel.

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

Attachment 7 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

10.3.1. Samples for Study Qualification and Health Monitoring

Standard laboratory tests, including chemistry, hematology, coagulation, and pregnancy testing (if applicable in women of childbearing potential), will be performed and analyzed centrally. Urinalysis will be assayed by investigator-designated (local) laboratory. Attachment 2 lists the laboratory tests that will be performed for this study. Central laboratory results will be used to determine patient eligibility at baseline. Local laboratory results may be used for on-study dosing decisions; if so, testing must also still be performed by the central laboratory. These central laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database.

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1).

Based on laboratory safety values, unscheduled hepatic monitoring tests (see Attachment 3) may be performed as part of patient follow-up, in consultation with the Lilly CRP.

Investigators must document their review of each laboratory safety report.

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

10.3.2. Samples for Pharmacogenetics and Translational Research

Collection of samples for translational research is also part of this study.

Required samples for biomarker research to be collected from all patients in this study are the following:

- Whole blood
- Plasma
- Archived tumor tissue (a minimum of 12 slides is required for study eligibility)

As part of an ongoing effort by Lilly to better understand how to predict which patients are more likely to respond to necitumumab and abemaciclib treatment, whole blood, plasma, and tissue samples will be collected to explore biomarkers including but not limited to, those related to the EGFR pathway, Rb pathway, CDK4/6, cell cycle, and/or the pathogenesis of lung cancer. Analyses may include, but are not limited to, potential nucleic acid and protein markers to better understand the disease process, and to develop predictive biomarkers and diagnostics.

10.3.2.1. Samples for Pharmacogenetic Evaluation

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

Samples will be stored and analysis may be performed on genetic variants thought to play a role in the EGFR-pathway, Rb pathway, CDK4/6, cell cycle, NSCLC pathogenesis, and the mechanism of action of necitumumab or abemaciclib to evaluate their association with observed clinical outcomes (OS, PFS, and ORR).

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic

association with response to necitumumab or abemaciclib. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drugs.

Samples will be destroyed according to a process consistent with local regulation.

10.3.2.2. Archived Tumor Tissue Collection

To meet study eligibility criteria, and therefore mandatory for study participation, patients must have available formalin fixed-paraffin embedded (FFPE) tumor sample. While the tissue can be from either initial diagnosis of Stage IV NSCLC or later (for example, at relapse), the most recent sample is preferred. The sample can be either 12 serially cut unstained sections or a tissue block (preferred). Due diligence should be used to make sure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided. Available FFPE primary and/or metastatic tumor tissue should be in a whole block, partial block, or unstained slides. Archived tumor tissue must be made available for biomarker assessments. If tumor tissue (primary or metastatic site, paraffin-embedded) is available from a recent biopsy performed as a part of routine clinical care prior to screening, this may be used if archived tissue is not available. If the required amount of tumor tissue is not available, the patient may still be eligible if willing to undergo a tumor biopsy and if the procedure is considered safe and feasible at the investigator´s discretion. Cytologic samples and fine-needle aspiration specimens are not acceptable. Pathology notes accompanying archival tissue may also be requested.

In tumor tissue samples, the CDK4/6 and EGFR pathway components and markers relevant to NSCLC pathogenesis may be evaluated to assess any potential correlation with response to therapy. Tumor samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to abemaciclib and/or necitumumab therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include, but are not limited to, immunohistochemistry of proteins, FISH for copy number amplifications, RNA gene-expression profiling, and/or genetic analyses of the tumor specimen DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

Samples will be identified by the patient number (coded) and stored for up to a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor. After testing has been completed, the paraffin-embedded whole blocks will be returned to the sites. Whole blocks can be returned sooner, if requested by the sites. Partial blocks and slides will not be returned.

10.3.2.3. Plasma Sample Collection

At the visits and times specified in Attachment 7, EDTA-anticoagulated plasma will be collected for exploratory biomarker analyses that may include, but are not limited to, exosomes, nucleic acid and protein markers indicative of the pathobiology of the tumor, expected mechanisms of action of the therapy, responses to treatment, and molecular pathways.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drugs.

10.3.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected at time points specified in Attachment 7 to determine antibody production against necitumumab. The actual date and time of collection of each sample will be recorded. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the necitumumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of necitumumab.

As noted in Section 9.3.2.2.3.1, a sample for evaluation of antibodies against necitumumab will also be collected in the setting of an infusion-related/hypersensitivity reaction to necitumumab (as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event). When any immunogenicity sample is drawn, a sample for necitumumab concentration measurement (PK) should also be drawn (immunogenicity and PK samples to be collected from 2 separate blood draws, within no more than 15 minutes' time difference), to allow interpretation of immune response (see Section 10.3.4).

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

10.3.4. Samples for Drug Concentration Measurements Pharmacokinetics

Pharmacokinetic (PK) samples (venous blood) will be collected as specified in the Pharmacokinetic, Immunogenicity, and Blood Based Markers Sampling Schedule (Attachment 7). Blood samples will be collected to determine the serum concentrations of necitumumab using a validated enzyme-linked immunosorbent assay method at a laboratory approved by the sponsor.

Blood samples will also be collected to determine the plasma concentrations of abemaciclib and metabolites using a validated liquid chromatography–tandem mass spectrometry method.

Bioanalytical samples collected to measure necitumumab and abemaciclib (and metabolites) concentrations will be retained for a maximum of 1 year following last patient visit for the study.

10.4. Appropriateness of Measurements

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

11. Data Quality Assurance

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

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

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

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

11.1. Data Capture System

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

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

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect daily dosing schedule.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

A total of approximately 68 patients evaluable for either the Part A or Part B portions of the study will be enrolled. Part A requires up to 18 treated patients (3-6 per dosage cohort). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will also be part of the Part B portion of the trial. These patients will also be included in the interim analyses as described in Section 12.2.10.

An evaluable patient for Part B will include any patient enrolled in Part A and treated at the recommended doses of necitumumab and abemaciclib. In addition, patients will be entered strictly to Part B (with a total of 50 evaluable patients in Part B). To be evaluable for Part B of the study, these additional patients entered must meet the following criteria:

(1) The patient has received at least 1 dose each of necitumumab and abemaciclib.

(2) The patient has a complete radiographic assessment at baseline.

The final analysis of the study will take place approximately 5 months after the last patient evaluable for Part B portion of the study has been enrolled. The primary Part B outcome variable in this study will be the 3-month PFS rate. The Part B statistical null hypothesis states that the true 3-month PFS rate is 50%, whereas the research hypothesis states that the true 3-month PFS rate is 65%. Assuming the Part B portion of the study continues to a full enrollment of 50 evaluable patients, the null hypothesis will be rejected at the final analysis only if at least 60% of evaluable patients experience PFS ≥3 months.

If the research hypothesis is true, there is an 81% chance of reaching full Part B enrollment and rejecting the null hypothesis. If the null hypothesis is true, then there is a 10% chance of reaching full Part B enrollment and rejecting the null hypothesis. Therefore, the Part B portion of this study has a one-sided alpha level of 0.10, with statistical power of 81%.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

The primary analysis will be as described in Section 12.1.

All summary analyses, including efficacy and safety analyses, will be performed for all patients enrolled in the study who receive any amount of study drug (necitumumab and abemaciclib).

Minor changes or clarifications to any statistical analyses described in this protocol may be presented in the final statistical analysis plan (SAP) for this study.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- total number of patients enrolled; and
- total number of patients treated (safety population).

A detailed summary of reasons for patient discontinuation from treatment will be provided.
A summary of all identified major protocol violations will be provided.

12.2.3. Patient Characteristics

A detailed description of patient characteristics at baseline will be provided, including:

- patient demographics;
- baseline disease characteristics; and
- medical history.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.4.1. Postdiscontinuation Therapy

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

12.2.5. Treatment Compliance

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

Compliance information for abemaciclib will be collected through capsule counts at each cycle/visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \times 100$$

The actual cumulative dose taken will be determined based on counting the number of capsules returned at each visit and subtracting that number from the number of capsules dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or suspensions.

12.2.6. Primary Outcome and Methodology

Please refer to Section 12.1 for details of the primary analysis.

12.2.6.1. Analyses of Efficacy

In addition to the analyses described in Section 12.1, this section provides additional details of planned efficacy analyses. For time-to-event variables, the Kaplan-Meier method will be used to estimate parameters (for example, medians, quartiles, 1-year event rates). See also the SAP for this study for additional details.

Table JFCU.12.1 provides definitions of key efficacy statistics used for this study. Exact 95% confidence intervals will be calculated for ORR and DCR.

Table JFCU.12.1. Definitions of Key Efficacy Statistics

Efficacy Statistic	Definition
Objective Response Rate (ORR)	The denominator of ORR includes each patient enrolled who receives any amount of study drug (necitumumab or abemaciclib), who has a complete radiographic assessment at baseline, and who has at least 1 complete radiographic assessment postbaseline. The numerator includes those patients counted in the denominator with a best overall tumor response of PR or CR.
Disease Control Rate (DCR)	Using the same denominator as for ORR, the numerator of the DCR includes those patients counted in the denominator with a best tumor response of SD, PR, or CR.
Median (OS, PFS)	Estimated using Kaplan-Meier method of estimation

Abbreviations: CR = complete response; DCR = disease control rate; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.

12.2.7. Pharmacokinetic and Immunogenicity Analyses

PK analyses will be conducted on patients who have received at least 1 dose of either study drug and have had samples collected.

PK parameter estimates will be computed for abemaciclib and its metabolites. The abemaciclib PK parameters will be computed by standard noncompartmental methods of analysis using WinNonlin Professional Edition on a computer that meets or exceeds the minimum requirements for this program.

The primary parameters for analysis will be maximum concentration and area under the concentration-time curve ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as time of half-life, apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported.

Summary statistics of necitumumab PK data will be presented graphically as well as in tabulated form. Additional exploratory analyses will be performed if warranted by data, and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Serum concentrations of necitumumab and plasma concentrations of abemaciclib and metabolites at each sampling time point will be summarized using descriptive statistics. Immunogenicity (anti-necitumumab antibody) incidence will be tabulated, and correlation to necitumumab drug level, activity, and safety will be assessed, as appropriate. Additional exploratory analyses will be performed if warranted by data, using validated PK software programs (for example, NONMEM) and if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet Lilly requirements for software validation.

Interim analysis may be conducted to facilitate exploratory analyses of PK, safety, and immunogenicity through PK/pharmacodynamic modeling. Interim data may also be pooled with final and interim data from other clinical studies of necitumumab or abemaciclib to facilitate

meta-analysis using non-linear mixed effects modeling. Since the study is unblinded, study objectives will not be compromised by the interim access to data.

12.2.8. Translational Research Analyses

Biomarker results will be summarized and correlated with clinical outcomes.

12.2.9. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.2.

Overall exposure to study drugs, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

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

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened between the first dose of study treatment and 30 days after the last dose of study treatment and related SAEs reported beyond 30 days after the last dose of study treatment.

The number of patients who experienced a TEAE, SAE, AE related to study treatment, died, or discontinued from the study therapy due to an AE will be summarized.

Common Terminology Criteria for Adverse Events v 4.0 will be used to report AEs by CTCAE terms.

Laboratory and non-laboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grade 3 and above. These summaries will be provided for events deemed by the investigator to be possibly related to study treatment and repeated for events regardless of causality.

MedDRA Version 17.0 (or higher) will be used when reporting AEs by MedDRA terms. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC.

Reasons for death will be summarized separately for on-therapy and within 30 days of last dose of study drug. Serious adverse events will be summarized by PT.

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

12.2.10. Interim Analyses

A safety interim analysis will be performed after the first 15 evaluable patients in the Part B portion of the trial have completed 2 cycles of study treatment (or otherwise discontinued study treatment).

The safety interim analysis will be conducted to permit evaluation of safety data by Lilly.

The results from the safety interim analysis will be examined by an internal assessment committee, which will be established prior to enrollment of the first patient in the trial. The internal assessment committee will consist of a Lilly medical director, a Lilly CRP/clinical research scientist, a PK scientist, and a statistician and will make recommendations about the trial. Enrollment will continue while the safety interim analysis is being performed. The safety interim analysis results (including all tables, figures, and listings) will not be disseminated outside of the assessment committee, unless emerging safety outcomes warrant such a disclosure. In case a disclosure is warranted, the outcome of the safety interim analysis will be documented and a written letter will be submitted to the ERB(s) and the investigators for documentation purposes.

Interim analyses for efficacy may be performed as needed to aid in the planning of future trials. There is no plan to stop the study for positive efficacy. The type-1 error for final primary analysis will not be affected and hence is not adjusted.

Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the interim analyses.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

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

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

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

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

13.2. Ethical Review

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

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

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

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

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

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

13.3.1. Investigator Information

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

13.3.2. Protocol Signatures

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

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

13.3.3. Final Report Signature

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

The investigator chosen by Lilly will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

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

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Attachment 1. Protocol JFCU Study Schedule

Study Schedule, Protocol I4X-MC-JFCU

Perform procedure as indicated in the following schedules.

Baseline Schedule, I4X-MC-JFCU

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative day within a cycle	≤21	≤14	≤7	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Study Entry/ Enrollment	13.1	Informed consent form signed				ICF must be signed prior to performing any protocol-specific tests/procedures.
	7.1, 7.2	Inclusion/exclusion evaluation	X			
Medical History	12.2.3	Initial history/preexisting conditions		X		
	12.2.3	Historical illnesses		X		
		Habits assessment		X		Smoking
Physical Examination		Height		X		
		Weight		X		
		Blood pressure/pulse/temperature		X		
	Att. 4	ECOG performance status		X		
Efficacy Assessment	10.1.1	Radiologic imaging/Tumor Assessment (according to RECIST v1.1)	X			A contrast CT scan or MRI of the brain will be performed if the patient is known to have CNS metastasis.
Adverse Events	10.2.1	AE collection and CTCAE grading	X			Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant Medications	9.5	Concomitant medication notation	X			

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative day within a cycle	≤21	≤14	≤7	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Laboratory/ Diagnostic Tests	Att. 2	Hematology (central)		X		
	Att. 2	Chemistry (central)		X		
	Att. 2	Coagulation (central)		X		
	Att. 2	Urinalysis (local)		X		
	Att. 2	Pregnancy test (central)		X		In women of childbearing potential
	10.3.2.1	Whole blood for pharmacogenetic analysis	Refer to Attachment 7			
	10.3.4	PK sampling (central)	Refer to Attachment 7			
	10.3.3	Immunogenicity: Anti-necitumumab antibodies	Refer to Attachment 7			
	10.3.2.3	Plasma sample for Biomarker Analysis	Refer to Attachment 7			
	10.3.2.2	Tumor tissue sample	X			To meet study eligibility criteria, and therefore mandatory for study participation, patients must have available FFPE tumor sample. Previously archived Stage IV NSCLC tissue from the initial diagnosis may be used but the most recent sample is preferred (for example, at relapse). The sample can be either 12 serially cut unstained sections or a tissue block (preferred). See Section 10.3.2.2 for further details.
	10.2.2.1	ECG (local)		X		

Abbreviations: AE = adverse event; BL = baseline; CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formaldehyde fixed-paraffin embedded; ICF = informed consent form; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events.

Treatment Period Schedule, I4X-MC-JFCU

			Comments			
			Repeat every 3 weeks			
		Cycle (3-week cycle)	1-X			
		Visit	1-X			
		Relative day within a cycle	1	8		Except for the Cycle 1, Day 1 visit, allowable cycle windows are ±3 days, unless indicated otherwise (see Section 9.3.1)
Procedure Category	**Protocol Section**	**Procedure**				
Physical Examination		Weight	X			
		Blood pressure/pulse	X	X		
	Att. 4	ECOG performance status	X			
Tumor Assessment	10.1.1	Radiologic imaging (according to RECIST v1.1) and tumor measurement	X			To be performed every 6 weeks ±3 days after the first dose of study therapy, regardless of treatment delays, until there is radiographic documentation of PD as defined by the Response Evaluation Criteria In Solid Tumors (RECIST 1.1). A contrast CT scan or MRI of the brain will be performed if the patient is known to have CNS metastasis or if clinically indicated.
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X		Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant Medications	9.5	Concomitant medication notation	X	X		
IP	9.2	Necitumumab	X	X		
	9.2	Abemaciclib	X	X		Every 12 hours (+2) D1-21. Oral administration of abemaciclib should take place within 10 minutes of start of necitumumab infusion.

						Comments
			Repeat every 3 weeks			
		Cycle (3-week cycle)	1-X			
		Visit	1-X			
		Relative day within a cycle	1	8		Except for the Cycle 1, Day 1 visit, allowable cycle windows are ±3 days, unless indicated otherwise (see Section 9.3.1)
Procedure Category	**Protocol Section**	**Procedure**				
Laboratory/ Diagnostic Tests	Att. 2	Hematology (central)	X	X		Investigator-designated (local) laboratory can be used to perform additional tests for on-study dosing decisions. If so, the test must also still be performed by the central laboratory. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8). Pretreatment laboratory tests at Day 1 Cycle 1 may not be repeated if the baseline data are not older than 72 hours from Day 1 Cycle 1. Hepatic monitoring tests (per Attachment 3; assayed by central laboratory. Can be performed locally, if needed or per discretion of the investigator) to be done in the event of a treatment-emergent hepatic abnormality. In case of neutropenia, thrombocytopenia Grade 4 during Cycle 1 (dose finding part only), repeat every 2 days until recovery
	Att. 2	Chemistry (central)	X	X		Investigator-designated (local) laboratory can be used to perform additional tests for on-study dosing decisions. If so, the test must also still be performed by the central laboratory. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8). Pretreatment laboratory tests at Day 1 Cycle 1 may not be repeated if the baseline data are not older than 72 hours from Day 1 Cycle 1. Hepatic monitoring tests (per Attachment 3; assayed by central laboratory. Can be performed locally, if needed or per discretion of the investigator) to be done in the event of a treatment-emergent hepatic abnormality. Grade 3 elevation of transaminases, bilirubin, change of electrolytes (see DLT criteria), repeat every 2 days until recovery (Cycle 1, dose-finding part only).
	Att. 2	Coagulation (central)	X*			* To be performed every second cycle starting from Cycle 2
	Att. 2	Urinalysis (local)	X*			* To be performed every second cycle starting from Cycle 2
	Att. 2	Pregnancy test (central)	X*			* To be performed every cycle in women of childbearing potential
	10.3.4	PK sampling (central)	Refer to Attachment 7 Note: If a patient experiences an IRR to necitumumab at any time during the study, blood samples for necitumumab immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.			
	10.3.3	Immunogenicity: Anti-necitumumab antibodies				
	10.3.2.3	Plasma sample for Biomarker Analysis	Refer to Attachment 7			
	10.3.2.1	Whole blood for Pharmacogenetic evaluation	Refer to Attachment 7			
	10.2.2.1	ECG (local)	X*			* To be performed every second cycle starting from Cycle 2

Abbreviations: AE = adverse event; Att. = Attachment; CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; IP = investigational product; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events.

Postdiscontinuation Follow-up Schedule, I4X-MC-JFCU

			Postdiscontinuation Follow-up		
		Cycle	Short-Term Follow-up	Long-Term Follow-up	
		Visit	801	802-8XX	
		Relative day within a cycle			
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Physical Examination		Weight	X		
		Blood pressure/pulse	X		
	Att. 4	ECOG performance status	X		
Tumor Assessment	10.1.2	Radiologic imaging (according to RECIST v1.1) and tumor measurement	X	X	Patients who discontinue study treatment for any reason other than PD will continue to undergo radiographic tumor assessments every 6 weeks (±3 days) until PD, the initiation of a new anticancer therapy or overall study completion, whichever occurs first. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first.
Survival information	10.1.4	Collection of survival information		X	Collection of survival data every 3 months (±7 days). Whenever possible, survival follow-up is conducted in person. If an in-person visit is not possible, the site may confirm survival by contacting the patient directly via telephone.
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. During Postdiscontinuation long-term follow-up, only SAEs that are related to protocol procedures or study treatment will be collected.
Concomitant Medications	9.5	Concomitant medication notation	X		
Laboratory/ Diagnostic Tests	Att. 2	Hematology (central)	X		
	Att. 2	Chemistry (central)	X		
	10.3.2.3	Plasma sample for Biomarker Analysis	X		When applicable, EDTA plasma should be collected as near as possible to the time of progression disease, 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 at (or by) the short-term follow-up visit. The post progression sample should be collected before the initiation of any new anticancer therapy.
	Att. 2	Pregnancy test (central)	X		In women of childbearing potential.
	Att. 2	Urinalysis (local)	X		
	10.3.4	PK	Refer to Attachment 7		If a patient experiences an IRR to necitumumab at any time during the study, blood samples for necitumumab immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
	10.3.3	Immunogenicity: Anti-necitumumab antibodies			
	10.2.2.1	ECG (local)	X		

Postdiscontinuation Follow-up Schedule, I4X-MC-JFCU (concluded)

Abbreviations: AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IRR = infusion-related reaction; PD = progressive disease; PK = pharmacokinetic; RECIST= Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events.

Short-Term Follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts at least 30 days (+ 0-7 days; ie, at least 30 days but no more than 37 days).

Long-Term Follow-up begins the day after Short-Term Follow-up is completed and continues until the patient's death or overall study completion. Patients who discontinue study treatment for reasons other than PD will continue to undergo radiographic tumor assessments every 6 weeks (±3 days) until PD, the initiation of a new anticancer therapy or overall study completion, whichever occurs first. Patients will be followed for survival every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first.

Continued Access Schedule, I4X-MC-JFCU

			Continued Access Period				
			Treatment Period			Continued Access Follow-up	
		Cycle	X-Y			Follow-up	
		Visit	501-5XX			901	
		Relative day within a cycle	1	8			
Procedure Category	**Protocol Section**	**Procedure**					**Comments**
Physical Examination		Weight	X				
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X		X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.
Laboratory/ Diagnostic Tests	10.3.4	PK	Refer to Attachment 7				If a patient experiences an IRR to necitumumab, blood samples for necitumumab immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
	10.3.3	Immunogenicity: Anti-necitumumab antibodies					
Study Treatment	9.2	Necitumumab	X	X			
	9.2	Abemaciclib	X	X			Every 12 hours (±2) D1-21. Oral administration of abemaciclib should take place within 10 minutes of start of necitumumab infusion.

Abbreviations: AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; PK = pharmacokinetic; SAEs = serious adverse events.

Continued Access Period begins after study completion and ends at the end of trial. During the Continued Access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The Continued Access period includes Continued Access Follow-up.

Continued Access Follow-up begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the Continued Access period and lasts at least 30 days (+ 0-7 days; ie, at least 30 days but no more than 37 days).

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Attachment 2. Protocol JFCU Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[a]:
Hemoglobin	**Serum concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Magnesium
Mean cell volume (MCV)	Potassium
Mean cell hemoglobin concentration (MCHC)	Phosphate
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented and bands	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine[b]
	Uric acid
	Calcium
	Glucose, nonfasting
Urinalysis[c]	Albumin
Color	Cholesterol
Specific gravity	Creatine kinase (CK)
pH	
Protein	**Pregnancy Test** (females of childbearing
Glucose	potential only, serum required)[d]
Ketones	
Blood	**Coagulation Tests**[d]**:**
Urine leukocyte esterase	INR and PT
	PTT
	Fibrin D dimer
	Protein C activity (baseline only)
	Protein S activity (baseline only)

Abbreviations: IDMS = isotope dilution mass spectrometry; INR = International Normalized Ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated (central) laboratory. Investigator-designated (local) laboratory can be used to perform additional tests for on-study dosing decisions. If so, the test must also still be performed by the central laboratory.

[b] IDMS for United States sites.

[c] Assayed by investigator-designated (local) laboratory.

[d] Assayed by Lilly-designated (central) laboratory.

Attachment 3. Protocol JFCU 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, segmented and bands	
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]**
CK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by central laboratory (can be performed locally, if needed or per discretion of the investigator).

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

Attachment 4. Protocol JFCU ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 5. Protocol JFCU 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:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Attachment 6. Protocol JFCU RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements.. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 7. Protocol JFCU Pharmacokinetic, Immunogenicity, and Blood-Based Markers Sampling Schedule

It is essential that the exact infusion start and stop times (actual clock readings), as well as infusion parameters (such as 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 I.V. site as the drug infusion.

Oral administration of abemaciclib should take place within 10 minutes of start of necitumumab infusion.

Preinfusion samples should be taken as close as possible to the start of infusion, but can be drawn up to 1 hour (60 minutes) prior the infusion, and exact clock reading should be recorded. End-of-infusion samples should be drawn as soon as possible after the end of infusion, and no later than within 15 minutes, and exact clock reading should be recorded.

In addition, if a patient experiences an infusion-related reaction (IRR) to necitumumab, blood samples for necitumumab immunogenicity (anti-necitumumab antibody) and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples 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.

Part A:

Pharmacokinetic, Immunogenicity, and Blood-Based Markers Sampling Schedule

PK Sample Number	Cycle and Day	Time	Dosing of Study Drugs		Sampling Time for necitumumab PK [a]	Sampling time for necitumumab Immunogenicity [a]	Sampling for abemaciclib PK	Sampling for Plasma biomarkers	Whole blood Sampling for Pharmaco-genetic evaluation
	C1D1	0-4 h pre-dose			X	X	X	X	X
	C1D1	Dose event	Abemaciclib	Necitumumab					
1	C1D1	Up to 15 min after end of necitumumab dose			X		X		
2	C1D1	2 h ± 10 min after LY2835219 dose			X		X		
3	C1D1	4 h ± 20 min after LY2835219 dose			X		X		
4	C1D1	6 h ± 20 min after LY2835219 dose					X		
5	C1D1	8 h± 20 min after LY2835219 dose					X		
6	C1D1	10 h ± 20 min after LY2835219 dose[b]			X		X		
7	C1D8	Predose (0-1 hour pre-dose)			X		X		
	C1D8	Dose event	Abemaciclib	Necitumumab					
8	C1D8	Up to 15 min after end of necitumumab dose			X		X		
9	C2D1	Predose (0-1 hour pre-dose)			X		X		
	C2D1	Dose event	Abemaciclib	Necitumumab					
10	C2D1	Up to 15 min after end of necitumumab dose			X		X		

PK Sample Number	Cycle and Day	Time	Dosing of Study Drugs		Sampling Time for necitumumab PK [a]	Sampling time for necitumumab Immunogenicity [a]	Sampling for abemaciclib PK	Sampling for Plasma biomarkers	Whole blood Sampling for Pharmaco-genetic evaluation
11	C2D1	2 h ± 10 min after LY2835219 dose			X		X		
12	C2D1	4 h ± 20 min after LY2835219 dose			X		X		
13	C2D1	6 h ± 20 min after LY2835219 dose					X		
14	C2D1	8 h± 20 min after LY2835219 dose					X		
15	C2D1	10 h ± 20 min after LY2835219 dose[b]			X		X		
16->	Day 1 of Cycle 3, 5, and 7	Predose (0-1 hour pre-dose)			X	X	X	X[c]	
	Day 1 of Cycle 3, 5, and 7	Dose event	Abemaciclib	Necitumumab					
17->	Day 1 of Cycle 3, 5, and 7	Up to 15 min after end of necitumumab dose			X				
	30-day follow-up				X	X		X[d]	

Abbreviations: C = Cycle; D = Day; PK = pharmacokinetics.

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

[b] To omit the collection of the 10 hour "postdose" PK sample for that day does not constitute a protocol violation.

[c] Cycle 3 only.

[d] When applicable, EDTA plasma should be collected as near as possible to the time of progression disease, 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 at (or by) the 30-day follow-up visit. The post-progression sample should be collected before the initiation of any new anticancer therapy.

Part B:

Pharmacokinetic, Immunogenicity, and Blood-Based Markers Sampling Schedule

PK Sample Number	Cycle and Day	Time	Dosing of Study Drugs		Sampling Time for necitumumab PK[a, c]	Sampling time for necitumumab Immunogenicity[c]	Sampling for abemaciclib PK[b, c]	Sampling for Plasma biomarkers	Whole blood Sampling for Pharmaco-genetic evaluation
1	C1D1	0-4 h pre-dose			X	X	X	X	X
	C1D1	Dose event	Abemaciclib	Necitumumab					
2	C1D1	Up to 15 min after end of necitumumab dose			X		X		
3->	Day 1 of Cycle 3, 5, and 7	Predose (0-1 hour pre-dose)			X	X	X	X[d]	
	30-day follow-up				X	X		X[e]	

Abbreviations: C = Cycle; D = Day; PK = pharmacokinetics.

[a] Samples of approximately 2.5 mL of whole blood will be drawn into serum separator tubes for the measurement of necitumumab concentrations.

[b] For the abemaciclib and metabolites assay, approximately 2 mL of whole blood will be drawn into tubes containing K2EDTA and processed to plasma.

[c] In the event of a necitumumab infusion-related reaction, blood samples will be collected for analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

[d] Cycle 3 only.

[e] When applicable, EDTA plasma should be collected as near as possible to the time of progression disease, 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 at (or by) the 30-day follow-up visit. The post progression sample should be collected before the initiation of any new anticancer therapy.

Attachment 8. Protocol JFCU Inducers and Strong Inhibitors of CYP3A4 or Substrates of CYP2B

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Inducers of CYP3A4

Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

Strong inhibitors of CYP3A4

All HIV protease inhibitors
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated. A patient who develops brain metastases may receive acute or chronic therapy with dexamethasone, if clinically indicated. Development of brain metastases is considered progressive disease and the patient should discontinue study treatment.

Substrates of CYP2B6

Alfentanil
Bupropion
cyclophosphamide
Efavirenz
Ifosfamide
methadone
Nevirapine
Propofol
Sertraline
sorafenib
tamoxifen
Valproic acid

Attachment 9. Protocol JFCU Amendment (b) Summary

Overview

Protocol I4X-MC-JFCU (A Single-Arm, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Treatment of Patients with Stage IV Non-Small Cell Lung Cancer [NSCLC]) has been amended. The new protocol is indicated by amendment (b) 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:

- Interim efficacy analyses (as needed) have been added to aid in the planning of future trials.
- Specific AEs of necitumumab have been amended according to the new necitumumab IB.
- The infusion time for necitumumab has been updated to 60 minutes in accordance with the new necitumumab IB and Portrazza PI.
- Some changes in Section 5. Introduction have been made for updated approval and clinical trial information.

Other change points are as follows:

- A few additional minor changes were made for clarity.
- Minor editorial changes were made for clarity.

Revised Protocol Sections

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

2. Synopsis

Necitumumab (IMC-11F8; LY 3012211; Portrazza®) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 (IgG1) that blocks the ligand-binding site of the epidermal growth factor receptor (EGFR). EGFR is detectable in approximately 85% of patients with advanced, metastatic non-small cell lung cancer (NSCLC). Necitumumab has shown signals of antitumor activity in 2 Phase 1 trials when administered as monotherapy in heavily pretreated patients including but not limited to patients with NSCLC. ~~Two Phase 3 trials, the necitumumab SQUIRE trial and~~ Portrazza has recently been approved in the United States (US) and European Union (EU) for the treatment of adult patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin. ~~the~~ The cetuximab FLEX Phase 3 trial~~,~~ ~~have~~ has demonstrated a statistically significant improvement in survival for the combination of an EGFR mAb in combination with chemotherapy in the first-line treatment of patients with ~~metastatic squamous NSCLC and~~ advanced metastatic NSCLC~~, respectively~~.

Length of Study: approximately 21 months Planned first patient visit: 08 Sep 2015 Planned last patient visit: 19 Jun 2017 Planned interim ~~analysis~~analyses: first 15 evaluable patients in Part B portion of the study who have completed 2 cycles of study treatment (or otherwise discontinued study treatment) will be analyzed for safety. Interim analyses for efficacy may be performed as needed to aid in the planning of future trials. Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the ~~safety~~ interim ~~analysis~~analyses.
Objectives: The secondary objectives of the study are: Part A: • to investigate the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with abemaciclib • to determine the ~~overall~~ objective response rate (ORR) • to determine the pharmacokinetics (PK) of necitumumab and abemaciclib • to determine the immunogenicity of necitumumab
Test Product, Dosage, and Mode of Administration: • Necitumumab is a sterile, preservative-free, intravenous infusion supplied in 50-mL vials containing 16 mg/mL (800 mg/50 mL) of product, and administered ~~over 50 minutes~~ at a dose of 800 mg on Days 1 and 8 of each 21-day cycle. • Abemaciclib is administered orally as capsules (supplied for clinical trial use in strength of 50 mg/capsule) every 12 hours. In Part A, abemaciclib will be administered at increasing doses of 100, 150, or 200 mg Q12H on Days 1 to 21. In Part B, abemaciclib will be administered at a fixed dose determined in Part A of the study Q12H on Days 1 to 21.
Statistical Methods: A~~n~~ safety interim ~~safety~~ analysis will be performed after the first 15 evaluable patients in the Part B portion of the trial have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the ~~safety~~ interim ~~analysis~~analyses. The safety interim analysis will be conducted to permit evaluation of safety data by the sponsor. Interim analyses for efficacy may be performed as needed to aid in the planning of future trials. There is no plan to stop the study for positive efficacy. The type-1 error for final primary analysis will not be affected and hence is not adjusted.

4. Abbreviations and Definitions

Term	Definition
ATE	arterial thromboembolic event
ORR	~~overall~~ objective response rate
VTE	venous thromboembolic event

5.1. Non-Small Cell Lung Cancer

Current standard first-line chemotherapy for patients with advanced or metastatic NSCLC and a good performance status consists of a platinum-based doublet, using either cisplatin or carboplatin in combination with pemetrexed (only for nonsquamous NSCLC), taxanes, vinorelbine, or gemcitabine. The combination of a platinum-doublet with the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab is a treatment option for nonsquamous patients only. Induction chemotherapy maybe followed by maintenance therapy, administered either as switch- or continuation maintenance. Second-line treatment options after failure of first-line chemotherapy with or without maintenance treatment consists of monotherapy with either docetaxel, erlotinib, or pemetrexed depending on type of prior treatment. Lately, an anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, ramucirumab, in combination with docetaxel was approved in the US and EU for the second-line treatment of metastatic NSCLC, including squamous and nonsquamous histologies (Cyramza Summary of Product Characteristics [SmPC]/US package insert [USPI]). Recently, monoclonal antibodies (mAbs) directed against programmed death-1 (PD-1) T-cell co-receptor, nivolumab and pembrolizumab, have been approved in the US for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy, whereby pembrolizumab was approved for the treatment of those NSCLC patients whose tumors express PD-L1 as determined by an FDA-approved test (Opdivo USPI, Keytruda USPI). In the EU nivolumab is available for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy (Opdivo SmPC). For patients with tumors harboring epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-activating mutations, monotherapy with an EGFR TKI is used upfront, followed by osimertinib (Tagrisso PI) in patients with EGFR T790M mutation-positive cancer or a platinum-based doublet as second-line, or as second- or third-line treatment if not used previously. For patients with anaplastic lymphoma kinase (ALK)-gene arrangement, treatment should include monotherapy with an ALK inhibitor (Heigener et al. 2014).

5.2. Necitumumab

Necitumumab (LY3012211) is a recombinant human ~~monoclonal antibody (~~mAb~~)~~ of the immunoglobulin (Ig) G_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.

EGFR is expressed in a variety of tumors, including colorectal, head and neck, breast, and NSCLC (Salomon et al 1995). In patients with advanced and metastatic NSCLC, EGFR is detectable in approximately 85% to 90% of patients (Fontanini et al 1995; Pirker et al 2009). Pharmacologic inhibition of EGFR signaling through competitive inhibition of ligand binding has been shown to play a role in the treatment of several cancers, leading to registration of necitumumab in squamous NSCLC and 2 other anti-EGFR mAbs in a number of other indications (Necitumumab/Portrazza SmPC, Cetuximab/Erbitux ~~package insert [PI]/ Summary of~~

~~Product Characteristics [~~SmPC~~]~~, Panitumumab/Vectibix ~~PI/~~ SmPC). ~~At present, no anti-EGFR mAb is approved for the use in patients with NSCLC; however, 2~~ Moreover, another randomized Phase 3 trial~~s~~, ~~one~~ conducted with cetuximab ~~another with necitumumab~~, showed evidence that the addition of an EGFR mAb to a platinum-based doublet can significantly increase survival in patients with advanced NSCLC (Pirker et al. 2009) ~~and metastatic squamous NSCLC (Thatcher et al. 2014)~~.

The necitumumab Phase 1 program included 2 single-agent dose-escalation Phase 1 trials in Western (I4XT-IE-JFCE [JFCE]) and Japanese (I4XT-IE-JFCA [JFCA]) patients with advanced solid tumors or for ~~which~~ whom no standard therapy was available.

The pivotal, randomized Phase 3 trial SQUIRE (I4XT-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. 20154). The study met its primary objective, demonstrating a statistically significant improvement in overall survival (OS) in the GC+N Arm compared with the GC Arm (hazard ratio [HR] = 0.84; p=0.012). This was supported by a statistically significant improvement in progression-free survival (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 ≥39.3% vs. 1.1%) being the most frequently reported events (pooled terms) occurring at higher rates for patients receiving necitumumab. The Grade ≥3 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 (I4XT-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. 2013). 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 frequency of study drug related deaths was 4.9% and 2.9% for PC+N and PC, respectively.

Based on these data, the combination of necitumumab plus pemetrexed-cisplatin is not being considered for further development. Of note, no safety signal with regard to thromboembolic or

potential thromboembolic events, including fatal events, has been identified for necitumumab in completed clinical trials when administered as monotherapy or in combination with mFOLFOX6 chemotherapy.

~~Currently, 2~~The randomized Phase 2 trial~~s, are ongoing (~~I4X~~T-IE~~MC-JFCL [~~(JFCL), ~~] and I4T-JE-JFCM [JFCM]). Study JFCL compares~~ 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. Study I4X-JE-JFCM is a Phase 1b/2 study in Japanese patients with Stage IV squamous NSCLC that compares necitumumab plus gemcitabine-cisplatin versus gemcitabine-~~-~~cisplatin alone. ~~Each~~The trial is monitored by an IDMC and continues as planned.

5.4. Study Rationale

Necitumumab (LY3012211) is a recombinant human mAb of IgG_1 class, which targets EGFR. Necitumumab demonstrates a high affinity to its target and blocks ligand-induced receptor phosphorylation and downstream signaling. EGFR is detectable in approximately 85% to 90% of patients with NSCLC (Fontanini et al 1995; Pirker et al 2009). Pharmacologic inhibition of EGFR signaling through competitive inhibition of ligand binding has been shown to play a role in the treatment of several cancers, and EGFR mAbs are approved in various tumor indications (Erbitux PI/-SmPC, Vectibix PI/-SmPC). Portrazza has recently been approved in the United States (US) and European Union (EU) for the treatment of adult patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin (Portrazza USPI and SmPC). ~~Two randomized Phase 3 trials show evidence that the addition of an EGFR mAb to a platinum-based doublet can significantly increase survival in patients with advanced/ metastatic NSCLC (Pirker et al. 2009) and metastatic squamous NSCLC (Thatcher et al. 2014).~~ The necitumumab SQUIRE trial showed statistically significant improvements in OS and PFS, with an overall favorable benefit-risk profile. In addition, a recent meta-analysis investigating the addition of an EGFR mAb to platinum-based first-line therapy demonstrated a significantly improved OS and PFS in patients with advanced NSCLC (Pujol et al. 2014).

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

6.2. Secondary Objectives

Part A:

- to investigate the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with abemaciclib

- to determine the ~~overall~~ objective response rate (ORR)
- to determine pharmacokinetics (PK) of necitumumab and abemaciclib
- to determine the immunogenicity of necitumumab

7.1. Inclusion Criteria

[10] Have the following laboratory values:

- hematologic: absolute neutrophil count ≥1.5 × 10~~9~~^{9}/L, platelets ≥100 × 10~~9~~^{9}/L, and hemoglobin ≥9 g/dL. Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF, or recombinant erythropoietin) within 4 weeks prior to Cycle 1 Day 1 are not allowed.
- ~~S~~serum albumin ≥25 g/L
- hepatic: bilirubin ≤1.5 ~~×~~times the upper limit of normal (ULN), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate transaminase (AST) ≤3.0 times ULN. For patients with hepatic metastases, ALT and AST equaling ≤5.0 times ULN are acceptable.
- renal: serum creatinine ≤1.2 ~~×~~times ULN or calculated creatinine clearance >50 mL/min (per the Cockcroft-Gault formula as defined in Attachment 5) for patients with creatinine >1.2 times ULN.

[11] ~~are m~~Men who are sterile (including vasectomy confirmed by post-vasectomy semen analysis) or who agree to use a reliable method of birth control and to not donate sperm during the study (and for at least 12 weeks following the last dose of necitumumab and abemaciclib or country requirements, whichever is longer) OR

[12] ~~are w~~Women who are either: (a) not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause*; or (b) of child-bearing potential who have a negative serum pregnancy test within 14 days prior to study enrollment and agree to use a highly effective method of birth control† during the study and for 6 months after the last dose of study drug(s) (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method).

7.2. Exclusion Criteria

[18] The patient has brain metastases that are symptomatic. (Patients who have completed radiotherapy for brain metastases at least 2 weeks prior to receiving study treatment, who are now non symptomatic or on stable dose of steroids or anticonvulsants during the 2 weeks prior to receiving study treatment, are eligible). Patients with asymptomatic brain metastases without need for treatment with steroids and who have not been treated with radiotherapy are eligible. This

exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

[22] The patient has ~~any ongoing or~~ active infection requiring systemic therapy, including active tuberculosis or known history of infection with the human immunodeficiency virus (HIV 1/2 antibodies), or hepatitis B (e.g., HBsAg reactive) and/or C virus (e.g., HCV RNA qualitative is detected).

[31] History of interstitial lung disease or an active non-infectious pneumonitis

8.1. Summary of Study Design

Cohort 1

- Necitumumab, administered I.V. over ~~50~~ 60 minutes at an absolute dose of 800 mg on Days 1 and 8, followed by
- Abemaciclib at a dose of 100 mg orally Q12H on Days 1 to 21

Cohort 2

- Necitumumab, administered I.V. over ~~50~~ 60 minutes at an absolute dose of 800 mg on Days 1 and 8, followed by
- Abemaciclib at a dose of 150 mg Q12H on Days 1 to 21

Cohort 3

- Necitumumab, administered I.V. over ~~50~~ 60 minutes at an absolute dose of 800 mg on Days 1 and 8, followed by
- Abemaciclib at a dose of 200 mg Q12H on Days 1 to 21

Note: At the time of approval of the JFCU(b) protocol amendment, all patients who are still on the study will be administered necitumumab I.V. infusion over 60 minutes.

Provided there is an acceptable safety profile in Part A of this study, Part B will be initiated, which will include a~~n~~ safety interim ~~safety~~ analysis after the first 15 evaluable patients have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the safety interim analysis.

8.2. Discussion of Design and Control

Provided there is an acceptable safety profile in Part A of this study, Part B will be initiated, which will include a~~n~~ safety interim ~~safety~~ analysis after the first 15 evaluable patients have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the safety interim analysis.

9.1. Treatments Administered

Table JFCU.9.1. Treatment Regimens/Dosing Schedule

Part A

Cohort	Drug	Dose	Day	Infusion duration
Cohort 1	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over ~~50~~ 60 minutes[a] (±5 minutes)
	Abemaciclib	100 mg Q12H	Days 1 - 21	
Cohort 2	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over ~~50~~ 60 minutes[a] (±5 minutes)
	Abemaciclib	150 mg Q12H	Days 1 - 21	
Cohort 3	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over ~~50~~ 60 minutes[a] (±5 minutes)
	Abemaciclib	200 mg Q12H	Days 1 - 21	

Part B

Drug	Dose	Day	Infusion duration
Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over ~~50~~ 60 minutes[a] (±5 minutes)
Abemaciclib	Dose from Part A Q12H	Days 1 - 21	

Abbreviations: IV= intravenously; Q12H = every 12 hours.

[a] At the time of approval of the JFCU(b) protocol amendment, all patients who are still on the study will be administered necitumumab I.V. infusion over 60 minutes (±5 minutes).

9.2. Materials and Supplies

Necitumumab is a sterile~~,~~ and preservative-free~~,~~ solution for I.V. infusion supplied in the following formulation:

- Necitumumab at a final concentration of 16 mg/mL (800 mg/50 mL) contained in single-use vials, in a formulation of 10 mM citrate, 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol, 0.01% polysorbate ~~(Tween®)~~-80, pH 6.0.

All excipients used in the formulation of necitumumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of necitumumab excipients. Refer to the IB for detailed ~~storage~~ information.

9.3.2.2.1. Abemaciclib

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (~~such as~~except diarrhea) possibly related to abemaciclib that does not resolve with maximal supportive measures within 3 days (as outlined in Section 9.5.3.) to either baseline or Grade 1, then dosing should be suspended (until the toxicity resolves to either baseline or at least Grade 1), and the dose of abemaciclib may be reduced as outlined in Table JFCU.9.2.

9.3.2.2.1.1. Guidance for Monitoring of Renal Function in Patients on Abemaciclib

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. Dose alterations (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function.

9.3.2.2.3.1.1. ~~Infusion Reactions~~Hypersensitivity/Infusion-Related Reactions

Hypersensitivity/infusion-related reactions (IRRs) were reported with necitumumab. The onset of events usually occurred after the first or second administration of necitumumab. Monitor patients during and following the infusion for signs of hypersensitivity and IRRs with resuscitation equipment readily available.

Hypersensitivity/~~infusion-related reactions~~IRRs are defined according to the NCI-CTCAE Version 4.0 definition of allergic reaction / hypersensitivity, as follows:

- Grade 1: transient flushing or rash, drug fever <38°C
- Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥38°C
- Grade 3: symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema, hypotension
- Grade 4: anaphylaxis (a life-threatening event characterized by the rapid onset [often within minutes] of airway obstruction [bronchospasm, stridor, hoarseness], urticaria, and/or hypotension)

Consistent with usual medical practice, selected parenteral medications may be utilized as detailed below. Additional treatments, chosen according to clinical symptoms and local standards, may be utilized at investigator discretion. Table JFCU.9.3 provides general treatment recommendations for hypersensitivity/~~infusion-related reactions~~IRRs to necitumumab.

If a patient should have a hypersensitivity/~~infusion-related reaction~~IRR to necitumumab, all attempts should be made to obtain an anti-necitumumab antibody and necitumumab PK blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. The procedure for sample collection and handling is described in a separate procedural manual.

9.3.2.2.3.1.4. 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.~~Hypomagnesemia occurred very commonly in patients receiving necitumumab. Only individual cases led to discontinuation of necitumumab. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia and replenish electrolytes as necessary.~~

9.3.2.2.3.1.5. ~~Cases of~~ Pneumonia and Sepsis

~~In the ongoing~~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.

~~an imbalance in the number of SAEs related to pneumonia and sepsis, including fatal cases, was observed. After an unblinded review of all data by the IDMC assigned for this study, it was recommended to continue the study as planned.~~

~~Serious infections are common complications of chemotherapy among oncology patients, due to the bone marrow suppressing effect of chemotherapy and associated in time with the occurrence of neutropenia.~~

~~It is of note that only some of the cases were associated with neutropenia and no imbalance was noted regarding events of neutropenia between the treatment arms. Furthermore, a considerable number of cases observed in this study occurred very early after start of treatment, within 8 days after the first dose of the study drugs and before the administration of the second dose of necitumumab, which does not reflect the typical time pattern expected for a regimen including platinum-based chemotherapy and may indicate an underlying infection in these patients at time of enrollment into Study JFCL.~~

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.

9.3.2.2.3.1.6. Thromboembolic Events

In the Phase 3 study JFCC, there was an increase in venous thromboembolic events (VTEs) and arterial thromboembolic events (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 the Phase 3 study JFCB, an increased rate of serious thromboembolic events, including fatal events, has been observed for the combination of necitumumab with pemetrexed and cisplatin as compared with treatment with pemetrexed and cisplatin alone in patients with nonsquamous NSCLC. Administration of necitumumab in combination with pemetrexed and cisplatin is not recommended.

~~In the Phase 3 study JFCC, a higher rate of thromboembolic events (for example, pulmonary embolism, venous thrombosis, cerebral ischemia, peripheral ischemia, and myocardial infarction) was observed in patients treated with the combination of necitumumab, gemcitabine, and cisplatin as compared to patients treated with gemcitabine and cisplatin alone. No relevant imbalance was observed with regard to fatal thromboembolic events.~~

~~In cases of sudden death, investigators are requested to record on the SAE report form as much information as possible regarding the symptoms and signs immediately preceding death and any postmortem results so that an accurate cause of death may be established (specifically so that thromboembolism may be confirmed or denied).~~

9.3.2.2.3.1.7. 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.

12.1. Determination of Sample Size

A total of approximately 68 patients evaluable for either the Part A or Part B portions of the study will be enrolled. Part A requires up to 18 treated patients (3-6 per dosage cohort). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will also be part of the Part B portion of the trial. These patients will also be included in the interim ~~safety analysis~~ analyses as described in Section 12.2.10.

The final analysis of the study will take place approximately 5 months after the last patient evaluable for Part B portion of the study has been enrolled. The primary Part B outcome variable in this study will be the 3-month PFS rate. The Part B statistical null hypothesis states that the true 3-month PFS rate is 50%, whereas the research hypothesis states that the true 3-month PFS rate is 65%. Assuming the Part B portion of the study continues to a full enrollment of 50 evaluable patients, the null hypothesis will be rejected at the final analysis only if at least 60% of evaluable patients ~~expereince~~experience PFS ≥3 months.

12.2.10. Interim Analyses

A~~n~~ safety interim analysis will be performed after the first 15 evaluable patients in the Part B portion of the trial have completed 2 cycles of study treatment (or otherwise discontinued study treatment).~~Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the safety interim analysis.~~

The safety interim analysis will be conducted to permit evaluation of safety data by Lilly.

The results from the safety interim ~~analyses~~ analysis will be examined by an internal assessment committee, which will be established prior to enrollment of the first patient in the trial. The internal assessment committee will consist of a Lilly medical director, a Lilly CRP/clinical research scientist, a PK scientist, and a statistician and will make recommendations about the trial. Enrollment will continue while the safety interim analysis is being performed. ~~Interim~~ The safety interim analysis results (including all tables, figures, and listings) will not be disseminated outside of the assessment committee, unless emerging safety outcomes warrant such a disclosure. In case a disclosure is warranted, the outcome of the safety interim

~~analyses~~ analysis will be documented~~,~~ and a written letter will be submitted to the ERB(s) and the investigators for documentation purposes.

Interim analyses for efficacy may be performed as needed to aid in the planning of future trials. There is no plan to stop the study for positive efficacy. The type-1 error for final primary analysis will not be affected and hence is not adjusted.

Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the interim analyses.

14. References

Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, Ramlau R, Galiulin RK, Bálint B, Losonczy G, Kazarnowicz A, Park K, Schumann C, Reck M, Depenbrock H, Nanda S, Kruljac-Letunic A, Kurek R, Paz-Ares L, Socinski MA, SQUIRE investigators. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomized, controlled phase 3 trial. *Lancet Oncol.* 2015;16(7):763-774.

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Attachment 2. Protocol JFCU Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[a]:
Hemoglobin	**Serum concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Magnesium
Mean cell volume (MCV)	Potassium
Mean cell hemoglobin concentration (MCHC)	Phosphate
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented and bands	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine[b]
	Uric acid
	Calcium
	Glucose, nonfasting
Urinalysis[c]	Albumin
Color	Cholesterol
Specific gravity	Creatine kinase (CK)
pH	
Protein	**Pregnancy Test** (females of childbearing
Glucose	potential only, serum required)[d]
Ketones	
Blood	**Coagulation Tests**[d]**:**
Urine leukocyte esterase	INR and PT
	PTT
	Fibrin D dimer
	Protein C activity (baseline only)
	Protein S activity (baseline only)

Attachment 8. Protocol JFCU Inducers and Strong Inhibitors of CYP3A4 or Substrates of CYP2B

Substrates of CYP2B6

Alfentanil
Bupropion
cyclophosphamide
Efavirenz
Ifosfamide
methadone
Nevirapine
Propofol
Sertraline
sorafenib
tamoxifen
Valproic acid