Protocol (b) I4X-MC-JFCP

A Single-Arm, Multicenter, Open-Label, Phase 2 Study of nab®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

NCT02392507

Approval Date: 25-Sep-2016

1. Protocol I4X-MC-JFCP(b)
A Single-Arm, Multicenter, Open-Label, Phase 2 Study of *nab*®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

EudraCT Number: 2016-002071-96

Confidential Information

Necitumumab (LY3012211; IMC-11F8)

Single-arm Phase 2 study in patients with Stage IV squamous NSCLC. Eligible patients will receive first-line treatment of chemotherapy plus necitumumab on a 3-week cycle as follows: During the induction period, patients will receive a triplet regimen of Abraxane; hereafter referred to as *nab*-paclitaxel (100 mg/m^2 I.V. on Days 1, 8, and 15) and carboplatin (AUC 6 [mg·min/mL] I.V. on Day 1) plus necitumumab (800 mg absolute dose intravenously [I.V.] on Days 1 and 8) for a maximum of 4 cycles (or until there is radiographic documentation of progressive disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent). Only those patients with a disease response of complete response (CR), partial response (PR), or stable disease (SD) (radiographic evidence of response, not necessarily confirmed) after 4 cycles of induction regimen are eligible to then receive the maintenance (doublet) regimen of necitumumab (800 mg absolute dose on Days 1 and 8) plus *nab*-paclitaxel (100 mg/m^2 on Days 1 and 8) every 3 weeks until disease progression occurs or other discontinuation criteria are met.

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Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on 06 January 2015
Amendment (a) Electronically Signed and Approved by Lilly on 07 June 2016
Amendment (b) Electronically Signed and Approved by Lilly on approval date provided below

Approval Date: 25-Sep-2016 GMT

2. Synopsis

Study Rationale

Necitumumab (LY3012211; IMC-11F8; Portrazza®) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1, that blocks the ligand binding site of the epidermal growth factor receptor (EGFR). The EGFR is a member of the human EGFR family of tyrosine kinases. Epidermal growth factor receptor activation leads to stimulation of tyrosine kinase-dependent signal transduction pathways that can contribute to neoplastic transformation and tumor growth.

Necitumumab has shown in vivo antitumor activity against a variety of human xenograft tumors, including non-small cell lung cancer (NSCLC). In clinical setting, the feasibility of administering necitumumab in combination with a standard platinum-based doublets in the first-line treatment of advanced NSCLC has been demonstrated in 2 randomized Phase 3 trials. In the Phase 3 SQUIRE study, which was performed in patients with first-line, Stage IV squamous disease, the combination of necitumumab plus gemcitabine and cisplatin showed a statistically significant advantage over the same chemotherapy alone in overall survival (OS), progression-free survival (PFS), and disease control rate (DCR). Necitumumab has recently been approved in the United States (US) and European Union (EU) for treatment of patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin.

A randomized Phase 3 trial, Study BMS099, conducted with another EGFR-directed mAb, cetuximab, in combination with taxane and carboplatin (TC) as the chemotherapy backbone demonstrated that the addition of cetuximab to TC regimen in patients with advanced NSCLC resulted in a statistically significant improvement in the best objective response rate (ORR; complete response [CR] + partial response [PR]), but not in PFS. The analysis of this study by histologic subtypes revealed major advantages in patients with squamous cell carcinoma for the cetuximab-containing regimen over the same chemotherapy alone in terms of PFS (HR=0.7).

Recently, paclitaxel protein-bound particles for injectable suspension (albumin-bound) (Abraxane), hereafter known as *nab*-paclitaxel, was approved in the United States (US) as first-line therapy for locally advanced or metastatic NSCLC. The approval was based on a randomized Phase 3 study that demonstrated statistically significant advantages for this regimen over solvent-based paclitaxel plus carboplatin (sb-PC) in terms of ORR, as well as prolonged PFS and OS that met the prespecified non-inferiority statistical analysis. The subgroup analysis of this study by tumor histology showed in squamous NSCLC a statistically significant advantage for *nab*-paclitaxel plus carboplatin (*nab*-PC) regimen in terms of best ORR (41% versus [vs] 24%, $p<.001$), and trends of improved PFS and OS.

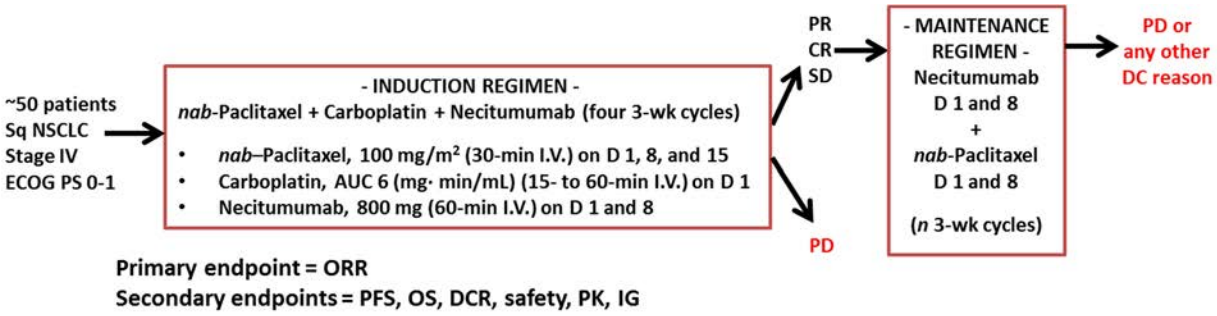
These preclinical data, the clinical efficacy of EGFR-directed mAbs in combination with taxanes and carboplatin, and the advantage of *nab*-PC over sb-PC in terms of safety and efficacy especially in squamous NSCLC together provide a strong rationale for the investigation of necitumumab in combination with *nab*-PC as first-line therapy in Stage IV squamous NSCLC.

The present single-arm Phase 2 study is being conducted to evaluate ORR, PFS, OS, DCR, and safety and tolerability associated with the study treatment of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab as first-line therapy in patients with Stage IV squamous NSCLC.

Clinical Protocol Synopsis: Study I4X-MC-JFCP(b)

Name of Investigational Products: Necitumumab (LY3012211; IMC-11F8), *nab*-paclitaxel, and carboplatin as applicable on the region	
Title of Study: A Single-Arm, Multicenter, Open-Label, Phase 2 Study of *nab*®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)	
Number of Planned Patients: Entered: 60 Enrolled: 50 Completed: 50 qualified patients	**Phase of Development:** Phase 2
Length of Study: Approximately 18 months Planned first patient visit: Apr 2015 Planned last patient visit: Oct 2016	
Objectives: The primary objective of this study is to evaluate the best objective response rate (ORR; complete response [CR] + partial response [PR]) associated with a treatment regimen of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab as first-line therapy in patients with Stage IV squamous NSCLC. The secondary objectives of the study are to: • evaluate progression-free survival (PFS), • evaluate overall survival (OS), • evaluate disease control rate (DCR), • evaluate the safety profile of necitumumab in combination with carboplatin and/or *nab*-paclitaxel chemotherapy, • determine the pharmacokinetics (PK) of necitumumab, *nab*-paclitaxel, and carboplatin, and • determine the immunogenicity of necitumumab (anti-necitumumab antibodies) The exploratory objectives of the study are to further evaluate the relationships between biomarkers related to the EGFR pathway, NSCLC etiology, and/or the mechanism of action of necitumumab and clinical outcomes.	

Study Design: This is a single-arm Phase 2 study to investigate *nab*-paclitaxel and carboplatin chemotherapy in combination with necitumumab as first-line therapy in approximately 50 patients with Stage IV squamous NSCLC (American Joint Committee on Cancer [AJCC] Staging Manual, 7th edition). Prior to screening, patient tumor tissue must be available (a formalin-fixed, paraffin-embedded [FFPE] tissue block [preferred] or 15 freshly cut unstained slides [a minimum of 6 slides] is requested). A treatment cycle is defined as 3 weeks. The treatment schema is summarized in the following figure:



Abbreviations: AUC = area under the concentration-time curve; CR = complete response; D = Day; DC = discontinuation; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; IG = immunogenicity (anti-necitumumab antibodies); I.V. = intravenous(ly); *nab*-paclitaxel = paclitaxel protein-bound particles for injectable suspension (albumin-bound); NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; sq = squamous; SD = stable disease.

Note: Figure includes Study Treatment Period only; it does not include the Continued Access Period.

Study therapy consists of an induction (triplet) regimen of *nab*-paclitaxel (100 mg/m^2 I.V. on Days 1, 8, and 15) and carboplatin (area under the concentration-time curve [AUC] 6 [mg·min/mL] intravenously [I.V.] on Day 1) plus necitumumab (800 mg absolute dose I.V. on Days 1 and 8) administered for a maximum of 4 cycles (or until there is radiographic documentation of progressive disease [PD], toxicity requiring cessation, protocol noncompliance, or withdrawal of consent). Only those patients with a disease response of CR, PR, or stable disease (SD) (radiographic evidence of response, not necessarily confirmed) after 4 cycles of induction regimen are eligible to then receive the maintenance (doublet) regimen of necitumumab (800 mg absolute dose on Days 1 and 8) plus *nab*-paclitaxel (100 mg/m^2 on Days 1 and 8) every 3 weeks until disease progression occurs or other discontinuation criteria are met. No other chemotherapy is permitted until there is radiographic documentation of PD.

If toxicity requires that necitumumab be modified by more than 2 dose reductions or delayed (held) for more than 6 weeks following Day 1 of the most recent cycle, necitumumab is to be permanently discontinued. *nab*-Paclitaxel and carboplatin are to be permanently discontinued in any of the following situations: (1) third occurrence of neutropenic fever, >7-day delay of a cycle due to absolute neutrophil count (ANC) $<1.5 \times 10^3/\mu L$, or ANC$<0.5 \times 10^3/\mu L$ for >7 days; (2) second occurrence of platelet count $<50 \times 10^3/\mu L$; or (3) third occurrence of Grade 3 or 4 sensory neuropathy. 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 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, where study completion is defined as the point when 70% of qualified patients experience a PFS event (radiographically documented PD or death), or 6 months after completing enrollment, whichever occurs first, as determined by Lilly (the sponsor).

Baseline radiographic assessment of disease will be performed within 21 days prior to first dose of study therapy. Patients will undergo radiographic assessment (computed tomography [CT] or magnetic resonance imaging [MRI]) of disease status 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, version 1.1 (RECIST 1.1).

Adverse event (AE) information will be collected until at least 30 days after the decision is made to discontinue study treatment (and, in case of AEs that are serious, considered related to study treatment or study procedures, or that caused the patient to discontinue before completing the study, until the event has resolved or is explained). A short-term postdiscontinuation follow-up visit will occur at least 30 days (+ 0-7 days; ie, at least 30 days but no more than 37 days) after the decision to discontinue. After the Short-Term Follow-up visit, only new and ongoing serious adverse events (SAEs) deemed related to protocol procedures or study treatment will be collected.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Key Inclusion Criteria

- Histologically or cytologically confirmed squamous NSCLC
- Stage IV disease at the time of study entry (AJCC Staging Manual, 7th edition)
- Measurable disease at the time of study enrollment, as defined by RECIST 1.1
- Tumor tissue (paraffin-embedded tissue block [preferred] or 15 freshly cut unstained slides [a minimum of 6 slides] is requested) available for analysis of EGFR protein expression by immunohistochemistry (IHC).

Key Exclusion Criteria

- Nonsquamous NSCLC
- Prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor
- Previous chemotherapy for advanced NSCLC
- Major surgery or received any investigational therapy in the 4 weeks prior to study entry
- Systemic radiotherapy within 4 weeks prior to study entry, or focal radiotherapy within 2 weeks prior to study entry
- Symptomatic central nervous system (CNS) malignancy or metastasis

Test Product, Dosage, and Mode of Administration:

Necitumumab drug product is a sterile, preservative-free, I.V. infusion supplied in 50-mL single-use vials containing 16 mg/mL (800 mg/50 mL) of product, and administered at a dose of 800 mg over 60 minutes on Days 1 and 8 of each 3-week cycle.

Reference Therapy, Dose, and Mode of Administration:
nab-Paclitaxel will be administered at a dose of 100 mg/m^2 I.V. over 30 minutes on Days 1, 8, and 15 of each 3-week cycle during the induction period and on Days 1 and 8 of each 3-week cycle during the maintenance period. *nab*-Paclitaxel will be used and should be prepared and administered according to the manufacturer's instructions. Carboplatin will be administered immediately after the *nab*-paclitaxel infusion. Carboplatin will be administered at AUC 6 (mg·min/mL) I.V. over a minimum of 15 minutes (maximum of 60 minutes) on Day 1 of each 3-week cycle, for a maximum of 4 cycles (approximately 12 weeks). Carboplatin will be used and should be prepared and administered according to the manufacturer's instructions.

Planned Duration of Treatment: A treatment cycle will be defined as 3 weeks, with radiographic evaluation of tumor response every 6 weeks (±3 days). Patients will be treated according to the study design described above until there is radiographic documentation of PD as assessed by the investigator, according to RECIST 1.1; toxicity requiring cessation; withdrawal of consent; or other discontinuation criteria are met.
Study Treatment Period:
Induction regimen (triplet): a maximum of 4 cycles (approximately 12 weeks), or until disease progression or unacceptable toxicity occurs
Maintenance regimen (doublet): *n* cycles following the induction period, until disease progression or unacceptable toxicity occurs
Short-Term Follow-up (postdiscontinuation): at least 30 days (+ 0-7 days; ie, at least 30 days but no more than 37 days)
Long-Term Follow-up (postdiscontinuation): until the patient's death or overall study completion, whichever occurs first

Criteria for Evaluation:

Efficacy: For these definitions, the date of study enrollment is the date of first dose of study drug (necitumumab, *nab*-paclitaxel, and/or carboplatin).

- Tumor response will be assessed by the investigator according to RECIST 1.1 every 6 weeks (±3 days), with confirmatory assessment for patients with an objective assessment of PR or CR obtained at the next routine scheduled imaging time point (that is, after 6 weeks ±3 days).
- PFS is defined as the time from the date of study enrollment to the date of first observation of objective (radiographically documented) PD or death from any cause, whichever comes first.
- OS is defined as the time from the date of study enrollment to the date of death from any cause.
- Disease control is defined as the best tumor response of PR, CR, or SD.

Safety: The safety of necitumumab in combination with carboplatin and/or *nab*-paclitaxel chemotherapy will be assessed by reported SAEs, AEs, vital signs measurements, electrocardiogram (ECG) results, and laboratory analyses. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v 4.0), will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. This collection is in addition to the verbatim text used to describe the AE. In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor (Lilly) or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA®).

Immunogenicity: Antibodies against necitumumab, assessed for all patients at the following time points:

- Prior to the administration of study treatment on Day 1 of Cycles 1, 3, and 4;
- At the (30-day) Short-Term Follow-up; and
- In the setting of any hypersensitivity/infusion-related reaction.

Pharmacokinetics: Blood for determination of serum concentrations of necitumumab, plasma concentrations of paclitaxel, and plasma concentrations of total platinum from carboplatin, assessed for all patients at the following time points:

- Prior to and following the administration of all (not each) study treatment on Day 1 of Cycles 1, 3, and 4;
- At the (30-day) Short-Term Follow-up (PK for necitumumab only); and
- In the setting of any hypersensitivity/ infusion-related reaction (PK for necitumumab only).

Translational Research:

(Tumor tissue submission for biomarkers) Collection of tumor tissue samples is mandatory for participation in this study. Formalin-fixed, paraffin-embedded tissue derived from either the primary tumor or metastatic sites will be collected and stored at a secure central laboratory. A FFPE tissue block (preferred) or 15 freshly cut unstained slides (a minimum of 6 slides) is requested and will be used for analysis of EGFR protein expression by IHC. Analysis may be performed on biomarker variants thought to play a role in the mechanism of action of necitumumab, the pathogenesis of NSCLC, cancer-related conditions, and/or the EGFR signaling pathway.

(Plasma samples for biomarkers) Analysis may be performed on biomarker variants thought to play a role in the mechanism of action of necitumumab, the pathogenesis of NSCLC, cancer-related conditions, and/or the EGFR signaling pathway.

(Whole blood for deoxyribonucleic acid [DNA] sample [pharmacogenetic analysis]) A one-time blood sample will be collected from all patients at Baseline (preferred) or later visits, for analysis that may be performed on genetic determinants that impact the mechanism of action of necitumumab and/or the etiology of NSCLC.

Statistical Methods:

Efficacy: The primary objective of this study is to estimate the ORR in qualified patients. The sample size of 50 was selected to facilitate the estimation of the ORR with reasonable precision; no power calculation was performed. With 50 qualified patients, the 95% confidence interval (CI) estimate of ORR will have a width no greater than 29 percentage points (that is, the ORR point estimate ±14.5%). There are no planned formal tests of hypotheses about ORR. However, the maximum width of the 95% CI (previously described) will permit the conclusion (with 95% confidence) that the true value of ORR does not differ from the estimated value of ORR by more than 14.5 percentage points.

Efficacy analyses for ORR and DCR will be performed for qualified patients, where a "qualified patient" is defined as an enrolled patient who has received any amount of study drug and has had a complete radiographic assessment at baseline. A patient who is alive for at least 8 weeks after first dose and has had no postbaseline radiographic assessment will be disqualified. Efficacy analyses for PFS and OS will be performed for all patients who have received any amount of study drug (necitumumab, *nab*-paclitaxel, and/or carboplatin).

The final analysis for all outcomes, primary and secondary, including the final analysis of OS, will be performed when 70% of qualified patients experience a PFS event (radiographically documented PD or death), or 6 months after completing enrollment, whichever occurs first, as determined by Lilly (the sponsor). This will provide an appropriate duration of observation from which to estimate ORR and median PFS. Overall survival will be evaluated primarily in terms of the estimated 6-month survival.

For all time-to-event variables, such as median OS and PFS, the Kaplan-Meier method will be used to estimate related parameters (for example, medians, quartiles, 6-month event rates). Exact 95% CIs will be calculated for ORR and DCR.

Safety: Safety analyses will be performed for the Safety Population (all patients who have received any amount of study drug [necitumumab, *nab*-paclitaxel, and/or carboplatin]).

Overall exposure to study treatment, 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 the entire Study 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 at least possibly related to study treatment, and repeated for events regardless of causality. The number of patients who experienced a treatment-emergent adverse event (TEAE), SAE, AE related to study treatment, died, or discontinued from the study treatment due to an AE will be summarized. The NCI-CTCAE v 4.0 will be used to report AEs by NCI-CTCAE terms. Laboratory and non-laboratory 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 deemed by the investigator to be at least possibly related to study treatment, and repeated for events regardless of causality. Adverse events will be summarized by MedDRA System Organ Class (SOC), by decreasing frequency of Preferred Term within SOC.

Reasons for death will be summarized separately for on-therapy and within 30 days after last dose of study treatment. Serious adverse events will be summarized by SOC and Preferred Term. Hospitalizations and transfusions occurring during the Study Treatment Period or (30-day) Short-Term Follow-up will be summarized.

One safety interim analysis is planned when data are available from at least the first 10 qualified patients who have completed 2 cycles of study treatment or have died. The interim analysis will be conducted to permit evaluation of safety data by the sponsor.

Immunogenicity and Pharmacokinetics: Serum concentrations of necitumumab, plasma concentrations of paclitaxel, and plasma concentrations of total platinum from carboplatin 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. 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 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.

3. Table of Contents

A Single-Arm, Multicenter, Open-Label, Phase 2 Study of *nab*®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

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4. Abbreviations and Definitions

Term	Definition
Abraxane®	trade name for paclitaxel protein-bound particles for injectable suspension (albumin-bound) (*nab*-®paclitaxel); registered trademark of Celgene Corporation
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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study required by some ethical review boards (ERBs) or institutional review boards (IRBs).
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
Att	Attachment
AUC	area under the concentration-time 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).
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CK	creatine kinase
collection database	A computer database where clinical trial data are entered and validated.

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.
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
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 therapy until one of the criteria for discontinuation is met.
CR	complete response
CrCl	creatinine clearance
CSFs	colony-stimulating factors
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	discontinuation
DCR	disease control rate
DCSI	Development Core Safety Information (part of the Investigator's Brochure)
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
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
EU	European Union
FFPE	formalin-fixed, paraffin-embedded (tumor tissue)
FSH	follicle-stimulating hormone
GCP	good clinical practice (also Good Clinical Practice, when referring to ICH E6 guideline)
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICP-MS	inductively coupled plasma–mass spectrometry
IDMC	independent data monitoring committee
IDMS	isotope dilution mass spectrometry
Ig	immunoglobulin
IG	immunogenicity (anti-drug antibodies)
IHC	immunohistochemistry
IMC-11F8	a code name for necitumumab

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.
INR	International Normalized Ratio
INSPIRE	Study I4X-IE-JFCB or ImClone (IMCL) study CP11-0805
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form. In this study, for US sites, the IPs are necitumumab (throughout the entire study) and *nab*-paclitaxel when administered as part of the maintenance regimen. In the United States, *nab*-paclitaxel and carboplatin are considered as standard of care when administered as part of the induction regimen. In this study, for sites outside the US, the IPs are necitumumab, *nab*-paclitaxel, and carboplatin throughout the entire study, when administered as part of both the induction regimen and the maintenance regimen.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRR	infusion-related reaction
IUD	intrauterine contraceptive device
I.V.	intravenous(ly)
IWRS	interactive web response system
LC-MS/MS	liquid chromatography-tandem mass spectrometry
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.
LY3012211	a code name for necitumumab
mAb	monoclonal antibody
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume

MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX-6	modified FOLFOX-6; oxaliplatin + folinic acid + 5-fluorouracil
MRI	magnetic resonance imaging
***nab*-paclitaxel**	paclitaxel protein-bound particles for injectable suspension (albumin-bound) (generic name for Abraxane)
***nab*-PC**	*nab*-paclitaxel plus carboplatin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
necitumumab	LY3012211 or IMC-11F8 (code names)
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
qualified patient	All enrolled patients who have received any amount of study drug and have had a complete radiographic assessment at baseline are qualified. (Patients who are alive for at least 8 weeks after first dose and have had no postbaseline radiographic assessment will be disqualified.)
RBC	erythrocyte (red blood cell)

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
sb-PC	solvent-based paclitaxel plus carboplatin
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
SERM	selective estrogen receptor modulators
SOC	System Organ Class (of MedDRA)
SOPs	standard operating procedures
sq	squamous
SQUIRE	Study I4X-IE-JFCC or ImClone (IMCL) study CP11-0806
study completion	This study will be considered complete when 70% of qualified patients experience a PFS event (radiographically documented disease progression or death), or 6 months after completing enrollment, whichever occurs first, as determined by Lilly (the sponsor). At this point in the study, the final analyses for all outcomes, primary and secondary, including the final analysis of OS, will be performed.
SUSARs	suspected unexpected serious adverse reactions
TC	taxane and carboplatin
TEAE	treatment-emergent adverse event 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 or a related serious AE (SAE) reported beyond 30 days after the last dose of study treatment.
TPO	third-party organization
ULN	upper limit of normal

US	United States
v	Version (of NCI-CTCAE)
VEGF	vascular endothelial growth factor
vs	versus
VTE	venous thromboembolic event
WBC	leukocyte (white blood cell)

A Single Arm, Multicenter, Open-Label, Phase 2 Study of *nab*®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

5. Introduction

Necitumumab (LY3012211; IMC-11F8) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 that blocks the ligand-binding site of the epidermal growth factor receptor (EGFR). In preclinical studies, it has proven to be similar in antitumor activity to the chimeric mouse/human anti-EGFR mAb cetuximab, which has been approved in various regions of the world for the treatment of squamous cell carcinoma of the head and neck and *KRAS* wild-type metastatic colorectal cancer.

Epidermal growth factor receptor is detectable in approximately 85% to 90% of patients with advanced, metastatic non-small cell lung cancer (NSCLC) (Fontanini et al. 1995; Pirker et al. 2009) and development of EGFR-directed mAb, necitumumab, has been primarily focused on the treatment of this disease.

In a randomized Phase 3 study, the combination of necitumumab plus gemcitabine and cisplatin chemotherapy as first-line therapy in patients with Stage IV squamous NSCLC demonstrated a statistically significant advantage over the same chemotherapy alone in measures of overall survival (OS), progression-free survival (PFS), and disease control rate (DCR) (Thatcher et al. 2014). The safety profile of the necitumumab plus gemcitabine and cisplatin triplet was acceptable. When compared with the same chemotherapy alone, there was no increase in Grade 3 or 4 toxicities, especially including hematologic toxicities associated with gemcitabine-cisplatin, with the exception of skin toxicity and hypomagnesemia, which are primarily associated with necitumumab. Based on these data, necitumumab has recently been approved in the United States (US) and European Union (EU) for treatment of patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin.

The combination of carboplatin and paclitaxel protein-bound particles for injectable suspension (albumin-bound) (Abraxane; hereafter known as *nab*-paclitaxel) (*nab*-PC) was approved in the US as first-line therapy for locally advanced or metastatic NSCLC. The approval was based on a randomized Phase 3 study (Socinski et al. 2012) that demonstrated statistically significant advantages of the *nab*-PC regimen (100 mg/m^2 *nab*-paclitaxel weekly plus carboplatin at area under the concentration-time curve [AUC] 6 [mg·min/mL] once every 3 weeks) over solvent-based paclitaxel plus carboplatin (sb-PC; 200 mg/m^2 solvent-based paclitaxel plus carboplatin AUC 6 once every 3 weeks) in terms of objective response rate (ORR) (33% versus [vs] 25%; p<.005), as well as prolonged PFS (hazard ratio [HR]=0.90) and OS (HR=0.92) that met the prespecified non-inferiority statistical analysis. Median PFS was 6.3 vs 5.8 months and median OS was 12.1 vs 11.2 months in the *nab*-PC arm vs the sb-PC arm, respectively.

The safety analysis revealed a statistically significant lower frequency of Grade 3 or 4 neutropenia, sensory neuropathy, myalgia, and arthralgia for the *nab*-PC regimen.

The subgroup analysis of this study by tumor histology demonstrated a statistically significant advantage in squamous NSCLC for the *nab*-PC regimen in terms of best ORR (41% vs 24%, p<.001), as well as trends of improved PFS (HR=0.865) and OS (HR=0.89). Median PFS was 5.6 and 5.7 months, and median OS was 10.7 and 9.5 months in *nab*-PC and sb-PC arms, respectively.

The impact of adding the EGFR-directed mAb cetuximab to the taxane and carboplatin (TC) doublet has been investigated as first-line therapy in the advanced, metastatic NSCLC setting in Study BMS099, a Phase 3 trial (Lynch et al. 2010). The addition of cetuximab resulted in a statistically significant improvement in ORR and not significant prolongation of PFS (HR=0.90) and OS (HR=0.89). The analysis of this study by histological subtypes revealed major advantages in patients with squamous cell carcinoma for the cetuximab-containing regimen over the same chemotherapy alone in terms of PFS (HR=0.7). The safety profile of cetuximab plus TC was acceptable and consistent with its individual components.

The recombinant human EGFR-directed mAb necitumumab and the chimeric EGFR mAb cetuximab have overlapping binding epitopes and compete with ligand binding to EGFR, thereby inhibiting receptor activation and downstream signaling (Li et al. 2008).

In preclinical studies in mice with lung cancer xenografts, necitumumab in combination with paclitaxel and cisplatin has demonstrated a significant improvement in tumor volume growth delay, compared with the same chemotherapy alone and with single-agent necitumumab (Preclinical Research, Eli Lilly and Company, 2009).

In a Phase 2 necitumumab clinical trial (Study I4X-MC-JFCL [JFCL]) of necitumumab as first-line therapy in Stage IV squamous NSCLC, the addition of necitumumab to paclitaxel-carboplatin (N+PC) resulted in an increased ORR compared to chemotherapy alone (PC) (48.9% versus 40.0%), indicating an add-on treatment effect for this combination. For PFS the treatment effect (as measured by the stratified HR) was 1.0 (95% CI: 0.71, 1.42) (median PFS: 5.4 versus 5.6 months). For OS, the median OS was 13.2 months for the N+PC Arm versus 11.2 months for the chemotherapy alone arm (PC Arm). The OS HR for the treatment effect was 0.83 (95% CI: 0.55, 1.52).

In the N+PC Arm in Study JFCL, 10 patients (9.4%) had 11 AEs with an outcome of death (where the primary cause of death may or may not be the AE). Seven of the 10 deaths occurred during the chemotherapy phase: acute respiratory failure, lung infection, septic shock, circulatory collapse, respiratory failure, pulmonary embolism, brain death, and cardiac arrest (in 1 patient). The other 3 deaths were due to hypovolemic shock, cardiac failure congestive, and pneumonia. All AEs were assessed by the investigator as not related to any study drug, with the exception of lung infection (assessed as related to chemotherapy only), respiratory failure (assessed as related to all study drugs), and circulatory collapse (unknown). In the PC Arm, 3 patients (5.5%) had 4 AEs with an outcome of death (all were assessed as not related to any study drugs) (one report each) of: death; sudden death; and pneumonia and sepsis (in 1 patient).

The OS analysis showed a higher rate of events for the necitumumab-containing arm during the first 4 months, with a later trend toward improved survival after 4 months.

The preclinical data, the clinical efficacy of EGFR-directed mAbs in combination with taxanes and carboplatin, and the advantage of *nab*-PC over sb-PC in terms of safety and efficacy especially in squamous NSCLC together provide a strong rationale for the investigation of *nab*-PC in combination with necitumumab as first-line therapy in Stage IV squamous NSCLC.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of necitumumab may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to necitumumab may be found in Section 7 (Development Core Safety Information [DCSI]) 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 (Lilly) in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of *nab*-paclitaxel may be found in the following: Package Insert (Abraxane package insert, 2015) or Section 9.4.1.

More detailed information about the known and expected benefits and risks of carboplatin may be found in the following: Package Insert (Carboplatin package insert, 2006 and 2015) or Section 9.4.1.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to evaluate the best objective response rate (ORR; complete response [CR] + partial response [PR]) associated with a treatment regimen of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab as first-line therapy in patients with Stage IV squamous NSCLC.

6.2. Secondary Objectives

The secondary objectives of the study are to:

- evaluate progression-free survival (PFS),
- evaluate overall survival (OS),
- evaluate disease control rate (DCR),
- evaluate the safety profile of necitumumab in combination with carboplatin and/or *nab*-paclitaxel chemotherapy,
- determine the pharmacokinetics (PK) of necitumumab, *nab*-paclitaxel, and carboplatin, and
- determine the immunogenicity of necitumumab (anti-necitumumab antibodies)

6.3. Exploratory Objectives

The exploratory objectives of the study are to further evaluate the relationships between biomarkers related to the EGFR pathway, NSCLC etiology, and/or the mechanism of action of necitumumab and clinical outcomes.

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Patients may be considered for re-screening after discussion with the Lilly clinical research physician (CRP) or designee. Each time re-screening is performed, 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 21-day screening period (Baseline) does not constitute re-screening. 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] have given written informed consent or assent prior to any study-specific procedures. Written consent may also be given by a legal representative.

[2] have histologically or cytologically confirmed squamous NSCLC.

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

[4] have measurable disease at the time of study enrollment as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009) (see Attachment 6).

[5] have tumor tissue (primary tumor or metastatic site; a paraffin-embedded tissue block [preferred] or 15 freshly cut unstained slides [a minimum of 6 slides] is requested) available for analysis of EGFR protein expression by immunohistochemistry (IHC).

[6] are ≥18 years of age (or of an acceptable age according to local regulations, whichever is older).

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

[8] have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (see Attachment 4).

[9] have an estimated life expectancy of at least 12 weeks.

[10] will be able to complete at least 2 cycles of treatment, in the judgment of the investigator.

[11] have adequate hepatic function as defined by a total bilirubin ≤1.25 × the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5.0 × ULN in the presence of liver metastases or ≤2.5 × ULN in the absence of liver metastases.

[12] have adequate renal function as defined by serum creatinine ≤1.2 × ULN or calculated creatinine clearance (CrCl) ≥50 mL/min for patients with creatinine >1.2 x ULN.

[13] have adequate hematologic function as evidenced by white blood cell count ≥3.0 × 10^3/μL, absolute neutrophil count (ANC) ≥1.5 × 10^3/μL, hemoglobin ≥9.5 g/dL, and platelets ≥100 × 10^3/μL.

[14a] are men who are either: (a) surgically sterile; or (b) agree to use a reliable method of birth control[†] and to not donate sperm during the study and for at least 6 months following last dose of study drug(s) or per country requirements, whichever is longer.

[14b] are women who are either: (a) not of childbearing 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 childbearing potential who have a negative serum pregnancy test within 14 days prior to first dose 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 [GnRH], antiestrogens, selective estrogen receptor modulators [SERMs], 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.

7.2. Exclusion Criteria

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

[15] are currently enrolled in a clinical trial involving an investigational product (IP) or non-approved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[16] have nonsquamous NSCLC (including adenocarcinoma, large cell, and not otherwise specified [NOS]).

[17] have received prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor.

[18] have received previous chemotherapy for advanced NSCLC. Patients who have received adjuvant or neoadjuvant chemotherapy are eligible if the last administration of the prior regimens occurred at least 1 year prior to study entry.

[19] have undergone major surgery or received any investigational therapy in the 4 weeks prior to study entry.

[20] have undergone systemic radiotherapy within 4 weeks prior to study entry, or focal radiotherapy within 2 weeks prior to study entry.

[21] have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required). Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants, and their disease is asymptomatic for at least 30 days prior to study entry.

[22] have a history of arterial or venous embolism within 6 months prior to study entry.

[23] have current clinically relevant coronary artery disease (Canadian Cardiovascular Society Angina Grading Scale > class II[‡]) or congestive heart failure (New York Heart Association [NYHA] Congestive Heart Failure Classification class III or IV[§]).

[24] have experienced myocardial infarction within 6 months prior to study entry.

[25] have clinical evidence of concomitant infectious conditions, including early signs of ongoing or active infection, tuberculosis, or known infection with the human immunodeficiency virus (HIV).

[26] have a history of significant neurological or psychiatric disorders, including dementia, seizures, or bipolar disorder, potentially precluding protocol compliance.

[27] have any NCI-CTCAE v 4.0 Grade ≥2 peripheral neuropathy.

[28] have any other serious uncontrolled medical disorders or psychological conditions that would, in the opinion of the investigator, limit the patient's ability to complete the study or sign an ICF.

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

[30] are pregnant or breastfeeding.

[31] have a known history of drug abuse.

[32] have a concurrent active malignancy. Patients with a history of malignancy are eligible provided the patient has been disease-free for ≥3 years, with the following exception: Patients with adequately treated basal or squamous cell carcinoma of the skin, preinvasive carcinoma of the cervix, or any cancer that in the judgment of the investigator and Lilly CRP/designee may not affect the interpretation of results (for example, prostate, bladder) are eligible.

[33] are receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, radiotherapy, chemo-embolization, targeted therapy, or an investigational agent.

[34] are unwilling or unable to participate in, or do not have tissue adequate for participation in the translational research portion of the study.

[35] have discontinued IP or nonapproved use of a drug or device from a clinical trial within 30 days before the first day of study treatment.

[36] have previously completed or discontinued from this study or any other study investigating necitumumab. (This exclusion criterion does not apply to patients who are re-screened prior to enrollment.).

[‡]Canadian Cardiovascular Society Angina Grading Scale (Campeau 1976):

Class I – Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Class II – Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III – Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.

Class IV – Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

[§]NYHA Congestive Heart Failure Classification (NYHA 1994):

Class I – Patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II – Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III – Patients with marked limitation of activity; they are comfortable only at rest.

Class IV – Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

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 [16] to [36] help in maintaining specificity of the patient population for both efficacy and safety analyses and/or to maintain patient safety.

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 drug, will have procedures performed as shown in the Study Schedule (Attachment 1).

Patients who are discontinued from all study drugs 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 (the sponsor) 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 CRP and the investigator to determine whether it is medically appropriate for the patient to continue in the study, with or without study treatment. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study, with or without study treatment.

7.3.2. Discontinuation of Study Treatment

This section lists the reasons for permanent discontinuation of study treatment.

Section 7.3.2.1 lists reasons for permanent discontinuation of all study treatment. Patients who are discontinued from all study treatment will be followed (for progressive disease [PD] and/or survival, as applicable) until study completion.

Section 7.3.2.2 lists reasons for permanent discontinuation of one or more study treatment components (that is, one or more study drugs that are part of the regimen being administered to the patient in this study).

For details regarding treatment delays and dose modifications, refer to Section 9.4.1.

7.3.2.1. Discontinuation of All Study Treatment

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

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- 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 drug(s) occurs prior to introduction of the new agent.

- The patient is significantly noncompliant with study procedures and/or treatment.
- Radiographic documentation of disease progression.
- A concurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment, in the opinion of the investigator.
- The patient becomes pregnant during treatment.

7.3.2.2. Discontinuation of One or More Study Treatment Components

Patients will be discontinued from one or more of the study treatment components in the following circumstances (Note that patients who have been discontinued from one or more of the study treatment components should continue to receive the remaining study treatment component[s] that has [have] not been discontinued, according to this protocol):

- The investigator decides that the patient should be discontinued from one or more of the study treatment components.
- The patient or the patient's designee (for example, parent, legal guardian, or caregiver) requests that the patient be discontinued from one or more study treatment components.
    - If the patient withdraws consent to treatment, he or she may still enter Short-Term and/or Long-Term Follow-up if consent for follow-up is not also withdrawn. It should be clarified with the patient and documented in the patient's file whether follow-up information on tumor assessment and survival can be still obtained, and if so, to what extent. Investigations scheduled for the Postdiscontinuation Follow-up should be carried out to the extent possible.
- Unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient).
- Any study treatment-related event that is deemed life-threatening, regardless of grade, warrants discontinuation of that study treatment and/or discontinuation from all study treatment, if appropriate, in the opinion of the investigator.
- Any event(s) that would require that necitumumab be modified by more than 2 dose reductions or delayed (held) for more than 6 weeks following Day 1 of the most recent cycle warrants permanent discontinuation of necitumumab.
- *nab*-Paclitaxel and carboplatin are to be permanently discontinued in any of the following situations: (1) third occurrence of neutropenic fever, >7-day delay of a cycle due to ANC $<1.5 \times 10^3/\mu L$, or ANC$<0.5 \times 10^3/\mu L$ for more than 7 days; (2) second occurrence of platelet count $<50 \times 10^3/\mu L$; or (3) third occurrence of Grade 3 or 4 sensory neuropathy (Abraxane package insert, 2015).
- A Grade 3 or 4 hypersensitivity/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.
- Screen failure or failure to meet enrollment criteria.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

- The patient or the patient's designee (for example, parent, legal guardian, or caregiver) 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

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

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 drug(s), 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

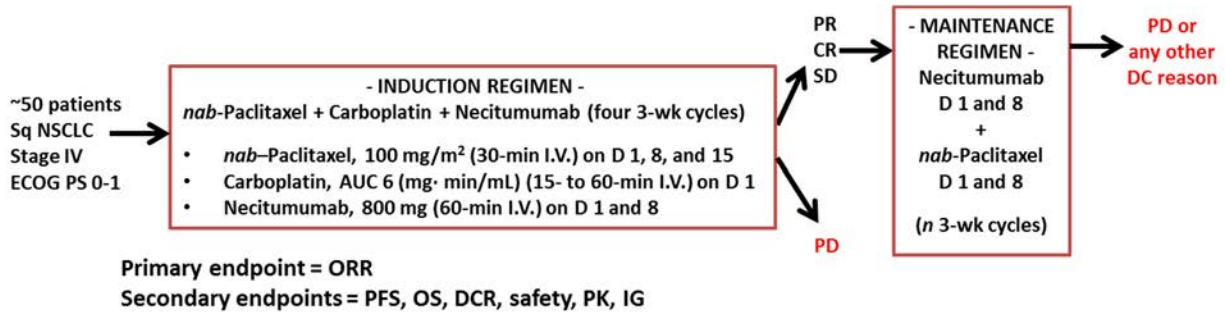
The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study I4X-MC-JFCP is a single-arm Phase 2 study to investigate *nab*-paclitaxel and carboplatin chemotherapy in combination with necitumumab as first-line therapy in patients with Stage IV squamous NSCLC.

Figure JFCP.1 illustrates the study design for the Study Treatment Period of Study I4X-MC-JFCP.



Abbreviations: AUC = area under the concentration-time curve; CR = complete response; D = Day; DC = discontinuation; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; IG = immunogenicity (anti-necitumumab antibodies); I.V. = intravenous(ly); *nab*-paclitaxel = paclitaxel protein-bound particles for injectable suspension (albumin-bound); NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; sq = squamous; SD = stable disease.
Note: Figure JFCP.1 includes the Study Treatment Period only; it does not include the Continued Access Period.

Figure JFCP.1. Illustration of study design for Study I4X-MC-JFCP.

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

- **Baseline:** begins when the ICF is signed (study entry) 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 electronic case report form (eCRF) as the Date of Discontinuation from study treatment. Note that for this study, the Study Treatment Period comprises the induction treatment (triplet) regimen and the maintenance treatment (doublet) regimen, as depicted in Figure JFCP.1.

- **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 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 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.

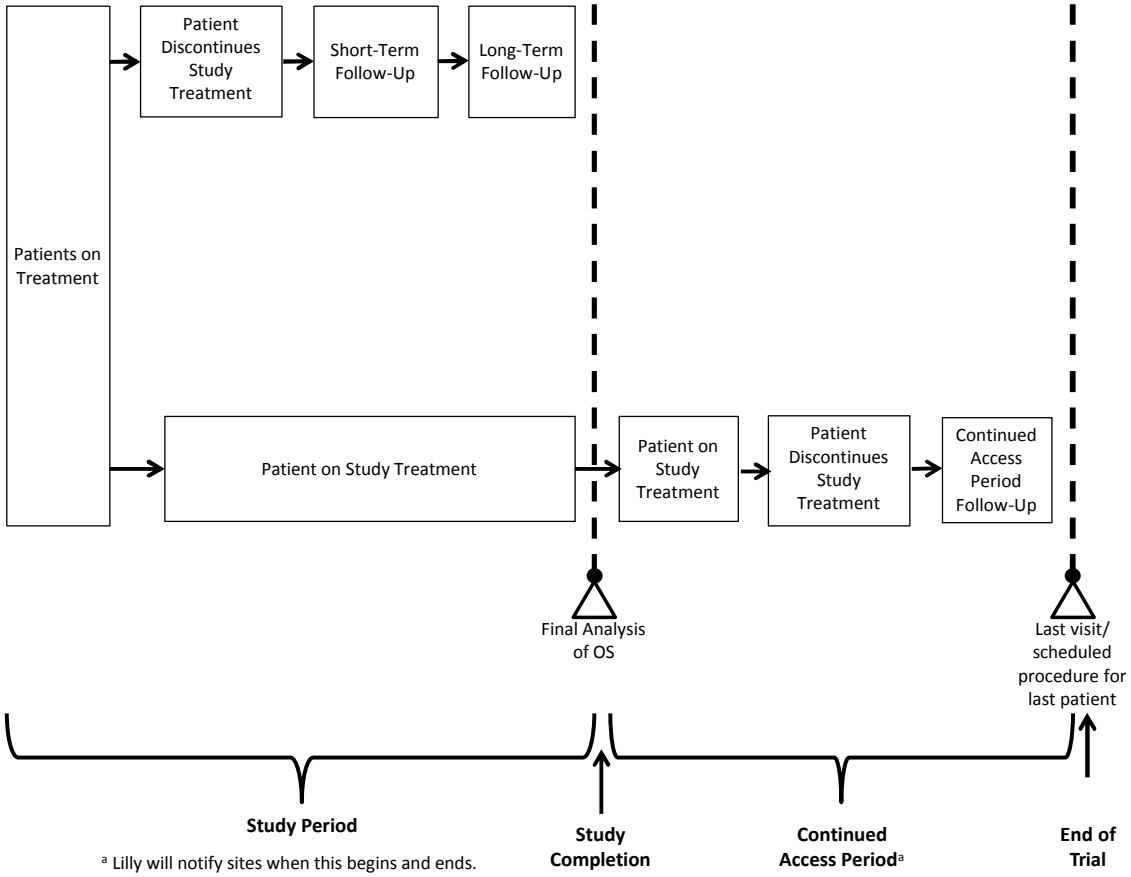
- **Continued Access Period** begins after study completion and ends at the end of trial. During the Continued Access Period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation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

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]) when 70% of qualified patients experience a PFS event (radiographically documented PD or death), or 6 months after completing enrollment, whichever occurs first, as determined by Lilly. At this point in the study, the final analyses for all outcomes, primary and secondary, including the final analysis of OS, will be performed. 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.

Figure JFCP.2 illustrates the Study Period and the Continued Access Period.



Abbreviation: OS = overall survival.

Figure JFCP.2. Study Period and Continued Access Period diagram.

8.1.2. Continued Access Period

The Continued Access Period will apply to this study only if at least one 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 exposure to study drug will be reported on the eCRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see

Section 10.2.1). 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 (anti-necitumumab antibody) analysis will be collected in the event of an infusion-related reaction during the Continued Access Follow-up.

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

8.2. Discussion of Design and Control

This study is designed as a single-arm open-label trial to estimate a potential benefit of the induction (triplet) regimen (*nab*-paclitaxel and carboplatin plus necitumumab), as well as the maintenance (doublet) regimen of necitumumab plus *nab*-paclitaxel. During the induction regimen, all participants in this trial will receive *nab*-paclitaxel and carboplatin chemotherapy at the approved dose and schedule, plus necitumumab, which may increase the total antitumor activity.

The *nab*-paclitaxel regimen administered during induction will be 100 mg/m^2 on Days 1, 8, and 15 of each 3-week cycle, until progression. The *nab*-paclitaxel regimen administered during maintenance will be reduced to (100 mg/m^2) Days 1 and 8 of each 3-week cycle to decrease potential toxicity and possibly optimize tolerability of treatment and drug exposure in patients.

9. Treatment

9.1. Treatments Administered

Following necessary premedication (Section 9.1.2), patients will receive the treatment regimen in Table JFCP.1 (in the order shown in the table). The treatment regimen comprises an induction (triplet) regimen and a maintenance (doublet) regimen. First, the induction (triplet) regimen of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab is to be administered for a maximum of four 3-week cycles, or until there is radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Then, if there is radiographic evidence of a response (not necessarily confirmed) of CR, PR, or stable disease (SD) and the patient's disease has not progressed or other discontinuation criteria have not been met, carboplatin is discontinued and the maintenance (doublet) regimen of necitumumab plus *nab*-paclitaxel is to be administered as 3-week cycles until there is radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

No other chemotherapy is permitted until radiographic documentation of PD.

Table JFCP.1. Treatment Regimens and Dosing Schedule

All treatments to be administered in the order shown in this table.		
Induction (Triplet) Regimen - Up to four 3-week cycles of the following:		
Drug	**Dose**	**Time for Administration**
Necitumumab[a]	800 mg absolute dose I.V. infusion	Administered over 60 minutes on Days 1 and 8 of each 3-week cycle.
nab-Paclitaxel[a,b]	100 mg/m^2 I.V. infusion	Administered over 30 minutes on Days 1, 8, and 15 of each 3-week cycle.
Carboplatin[a]	AUC 6 (mg·min/mL) I.V. infusion[c]	(Administered immediately after *nab*-paclitaxel.) Administered over a minimum of 15 minutes (maximum of 60 minutes) on Day 1 of each 3-week cycle, for a maximum of 4 cycles.
Maintenance (Doublet) Regimen – Every 3 weeks until disease progression occurs or other discontinuation criteria are met:		
Drug	**Dose**	**Time for Administration**
Necitumumab[a]	800 mg absolute dose I.V. infusion	Administered over 60 minutes on Days 1 and 8 of each 3-week cycle.
nab-Paclitaxel[a,b]	100 mg/m^2 I.V. infusion	Administered over 30 minutes on Days 1 and 8 of each 3-week cycle.

Abbreviations: AUC = area under the concentration-time curve; I.V. = intravenous(ly); *nab*-paclitaxel = paclitaxel protein-bound particles for injectable suspension (albumin-bound).

[a] Hypersensitivity/infusion-related reaction may occur during or following administration of necitumumab, *nab*-paclitaxel, or carboplatin. See Section 9.4.1.2.2 for a definition of Grade 3 and 4 hypersensitivity/infusion-related reaction.

[b] Source is Abraxane package insert, 2015.

[c] Refer to Section 9.1.1 for additional information on carboplatin dosing.

Refer to Section 9.4 for the selection and timing of doses.

Hypersensitivity/infusion-related reaction may occur during or following administration of necitumumab, *nab*-paclitaxel (Abraxane package insert, 2015), or carboplatin (see Section 9.4.1.2.2 for a definition of Grade 3 and 4 hypersensitivity/infusion-related reaction). 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.

It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions at precise intervals (because of holidays, travel difficulties, or other circumstances). Accordingly, infusions administered within 3 days before or after the planned infusion time point will be considered acceptable.

In the event that infusions are administered before or after a planned time point in a given cycle, the Day 1 infusion of the subsequent cycle should be administered 7 days (±3 days) after the actual Day 15 administration of the previous cycle.

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

- explaining the correct use of the drugs and planned duration of each individual's treatment to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate 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(s) so that the situation can be assessed.

9.1.1. Carboplatin Dosing

At sites where serum creatinine is determined by a method standardized to the isotope dilution mass spectrometry (IDMS) reference material, the estimated glomerular filtration rate (GFR) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. All US sites where the IDMS method is available should calculate carboplatin doses based upon serum creatinine values that were measured by the IDMS method. At sites where the IDMS method is not available, for the estimated GFR used to calculate the Calvert formula, all sites will follow the dosing guidelines outlined below and cap the GFR at 125 mL/min.

The site is responsible to consult the local lab to determine what method of serum creatinine measurement is used by that laboratory.

Calvert Formula

Total Dose (mg) = (target AUC) × (GFR + 25)

Maximum carboplatin dose (mg) = target AUC 6 (mg•min/mL) × (125 + 25) = 6 × 150 mL/min = 900 mg

9.1.2. Premedication

All premedication administered must be adequately documented in the eCRF.

9.1.2.1. Premedication for Necitumumab

Prior to necitumumab infusion, consider premedication for possible skin reactions. Preemptive treatment with skin moisturizers, topical steroids, doxycycline, or sunscreen may be administered as clinically appropriate to patients receiving necitumumab (Lacouture et al. 2011). For additional information regarding preemptive management of skin toxicity, see Canadian recommendations (Melosky et al. 2009).

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

9.1.2.2. Premedication for *Nab*-Paclitaxel and Carboplatin

No premedication is required prior to administration of *nab*-paclitaxel (Abraxane package insert, 2015). Patients who have experienced a severe hypersensitivity reaction to *nab*-paclitaxel should not be re-challenged with this drug.

An antiemetic (such as ondansetron 8 mg intravenously [I.V.], or equivalent) is recommended to be administered 30 to 120 minutes before dosing with carboplatin.

9.1.3. Study Drugs

In this study, for US sites, the IPs are necitumumab throughout the study, and *nab*-paclitaxel when administered as part of the maintenance regimen. In the US, *nab*-paclitaxel and carboplatin are standard of care when administered as part of the induction regimen.

In this study, for sites outside the US, the IPs are necitumumab, *nab*-paclitaxel, and carboplatin throughout the study, when administered as part of both the induction regimen and the maintenance regimen.

Interactive web response system (IWRS) will be used for dispensing of IP.

9.1.3.1. Necitumumab

Patients will receive necitumumab at an absolute dose of 800 mg on Days 1 and 8 of each 3-week cycle, administered as an I.V. infusion over 60 minutes.

Aseptic technique is to be used when preparing and handling necitumumab. Different drug product lots must not be mixed in a single infusion. Necitumumab is compatible with commonly used infusion containers. Refer to the IB for detailed information.

Add (or remove from AVIVA I.V. bag, which comes prefilled with 0.9% normal saline) a sufficient quantity of sterile normal saline solution (0.9% weight/volume) to the container to make the volume of saline in the I.V. container 200 mL. Add 50 mL necitumumab to give a total volume of 250 mL. The container should be gently inverted to ensure adequate mixing. The infusion rate must never exceed 25 mg/minute.

The infusion set must be flushed postinfusion with sterile 0.9% normal saline equal to or exceeding the infusion line hold-up to ensure delivery of the dose.

CAUTION: Hypersensitivity/infusion-related reactions may occur during or following administration of necitumumab (see Section 9.4.1.2.2 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. Premedication for carboplatin may be administered during this 1-hour observation period.

9.1.3.2. *Nab*-Paclitaxel

nab-Paclitaxel will be used and should be prepared and administered according to the manufacturer's instructions (Abraxane package insert, 2015). (Refer to the local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions, and I.V. administration of *nab*-paclitaxel.) *nab*-Paclitaxel will be administered at a dose of 100 mg/m^2 I.V. over 30 minutes on Days 1, 8 and 15 of each 3-week treatment cycle during the induction period and on Days 1 and 8 of each 3-week cycle during the maintenance period.

9.1.3.3. Carboplatin

Carboplatin will be used and should be prepared and administered according to the manufacturer's instructions. Carboplatin will be administered immediately after the *nab*-paclitaxel infusion (during the induction period only; it is not to be administered during the maintenance period). Carboplatin will be administered at AUC 6 (mg·min/mL) I.V. over a minimum of 15 minutes (maximum of 60 minutes) on Day 1 of each 3-week treatment cycle, for a maximum of 4 cycles (approximately 12 weeks).

9.2. Materials and Supplies

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

9.2.1. Necitumumab Drug Product

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

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

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

9.2.2. Chemotherapy Agents

nab-Paclitaxel and carboplatin will be used in this study, and will be packaged, labeled, and stored according to manufacturer standards and according to the country's regulatory requirements, if supplied by Lilly.

9.3. Method of Assignment to Treatment

Not applicable. This is a single-arm open-label study.

9.4. Selection and Timing of Doses

Local laboratory values will be used to determine the patient dose and/or dose adjustments.

A cycle is defined as an interval of 3 weeks (a delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not counted as a protocol deviation).

Patients will receive up to 4 cycles of *nab*-paclitaxel and carboplatin chemotherapy plus necitumumab as the induction (triplet) regimen. Only those patients with a disease response of CR, PR, or SD (radiographic evidence of response, not necessarily confirmed) after 4 cycles of induction regimen are eligible to then receive the maintenance (doublet) regimen of necitumumab plus *nab*-paclitaxel every 3 weeks until disease progression occurs or other discontinuation criteria are met.

The actual dose of necitumumab administered will be an absolute dose of 800 mg.

The actual dose of *nab*-paclitaxel administered will be determined by calculating the patient's body surface area (BSA) at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the BSA will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

The actual dose of carboplatin administered will be based on the calculations described in Section 9.1.1.

A patient may continue to receive the induction (triplet) regimen until he or she has received a maximum of 4 cycles or until he or she meets at least one of the specified reasons for discontinuation (as described in Section 7.3). A patient may continue to receive the maintenance (doublet) regimen until he or she meets at least one of the specified reasons for discontinuation (as described in Section 7.3).

Study treatment will be administered as described in Section 9.1.

9.4.1. Special Treatment Considerations

9.4.1.1. Treatment Requirements and Delays

Prior to each administration of the study treatment regimen, hematology, liver function, and renal function must be adequate (see Table JFCP.2) and all other toxicities (except alopecia) must have resolved to Grade ≤2 or baseline, or, in the case of peripheral neuropathy, to Grade ≤1. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Days 8 and 15 of each cycle during the induction period and Day 8 during the maintenance period). Local laboratory results may be used to make this determination.

Table JFCP.2. Criteria for Treatment

Analyte	Criteria
Neutrophils (ANC)	$\geq 1.5 \times 10^3/\mu L$ (Day 1 of a cycle) (Days 8 or 15: $\geq 0.5 \times 10^3/\mu L$)[a]
Platelets	$\geq 100 \times 10^3/\mu L$ (Day 1 of a cycle) (Days 8 or 15: $\geq 50 \times 10^3/\mu L$)[a]
Serum creatinine	≤1.2 × ULN or calculated CrCl ≥50 mL/min[b]
Bilirubin	≤1.25 × ULN[a]
AST	≤5 × ULN in the presence of liver metastasis; ≤2.5 × ULN in the absence of liver metastasis[a]
ALT	≤5 × ULN in the presence of liver metastasis; ≤2.5 × ULN in the absence of liver metastasis

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; ULN = upper limit of normal.

[a] Adapted from Abraxane package insert, 2015.

[b] CrCl will be calculated according to Attachment 5.

If the criteria outlined in Table JFCP.2 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 9.4.1.2.1) or interrupted, but chemotherapy will continue according to the planned schedule.
- In the case of chemotherapy-related toxicity or abnormal laboratory values, the start of the next cycle of chemotherapy will be delayed until recovery to the values stated in Table JFCP.2. However, necitumumab should be administered as planned. When chemotherapy-related toxicity has resolved, chemotherapy and necitumumab will resume on the regular schedule, such that a new cycle will not start until chemotherapy resumes (see Attachment 8 for illustrative examples of dose delay management during both the induction and the maintenance regimens).
- If administration of necitumumab is delayed (held) for more than 6 weeks after Day 1 of the most recent treatment cycle , treatment with necitumumab will be permanently discontinued. Refer to Table JFCP.5 for information on *nab*-paclitaxel and carboplatin dose reductions and permanent treatment discontinuation. Note that chemotherapy dose modifications are permanent; once the dose of *nab*-paclitaxel or carboplatin has been reduced, it will remain reduced or be further reduced in subsequent cycles. Note that

patients who have been discontinued from one or more of the study treatment components should continue to receive the remaining study treatment component(s) that has (have) not been discontinued, according to this protocol.

9.4.1.2. Treatment-Emergent Adverse Events and General Dose Modifications

Note that, as stated in Section 10.2.1 (Adverse Events), 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.

9.4.1.2.1. Necitumumab Dose Modifications

This section provides general dose modification guidelines for toxicity associated with necitumumab treatment. Refer to Sections 9.4.1.2.2, 9.4.1.2.1.1, 9.4.1.2.1.2, 9.4.1.2.1.3, 9.4.1.2.1.4, and 9.4.1.2.1.5 for specific information on the management of and/or necitumumab dose adjustments due to AEs of concern that may or may not be associated with necitumumab treatment, which include hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, electrolyte abnormalities, pneumonia and sepsis, and thromboembolic events.

Apart from the necitumumab dose adjustment recommendations specific to hypersensitivity/infusion-related reactions and skin reactions (Sections 9.4.1.2.2 and 9.4.1.2.1.1, respectively), stepwise dose reductions to 600 mg and 400 mg necitumumab may be considered for non-life-threatening reversible Grade 3 and 4 toxicities after treatment interruption and resolution to Grade ≤2. After a dose reduction, the dose of necitumumab may be re-escalated to the previous dose after a minimum of 2 administrations of the reduced dose. In case of toxicities necessitating more than 2 dose reductions, treatment with necitumumab should be permanently discontinued.

9.4.1.2.1.1. Skin Reactions

9.4.1.2.1.1.1. Reactive Treatment

Recommendations for the management of skin reactions to EGFR inhibitors, based on the Canadian recommendations published by the BC Cancer Agency in 2009 (Melosky et al.), are detailed in Table JFCP.3.

Skin reactions were reported with necitumumab. The onset of events occurred mainly during the first cycle of treatment. Skin rash (any grade) should be treated, as per Table JFCP.3. 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 JFCP.3. 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 one 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.
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.**

Source: Adapted from Melosky et al. 2009.

If necitumumab treatment is delayed or discontinued due to acneiform rash, chemotherapy may be administered without interruption in the absence of disease progression.

A dermatology referral may be indicated for skin reactions that do not improve after 1 to 2 weeks of symptomatic treatment, reactions that are severely symptomatic (for example, necrosis, blistering, petechial, or purpuric lesions), reactions of NCI-CTCAE Grade ≥3, or reactions with an uncharacteristic appearance. Patients who develop skin toxicity should be monitored for early signs of infection and/or inflammation.

As with all concomitant medications/procedures, any actions taken to ameliorate skin toxic ity will be documented in the concomitant medication module of the eCRF.

9.4.1.2.1.1.2. Preemptive Treatment

Refer to Section 9.1.2.1 (Premedication for Necitumumab) for information on preemptive treatment of skin reactions. As with all concomitant medications/procedures, any actions taken to ameliorate skin toxicity with preemptive medications or procedures will be documented in the concomitant medication module of the eCRF.

9.4.1.2.1.2. Conjunctivitis

Conjunctivitis has been reported very commonly in patients receiving necitumumab. For patients with necitumumab-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.

9.4.1.2.1.3. Electrolyte Abnormalities

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

9.4.1.2.1.4. Pneumonia and Sepsis

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

In Study JFCL, a Phase 2 study to investigate carboplatin and solvent-based paclitaxel with or without necitumumab in patients with squamous NSCLC (106 versus 55 patients, 2:1 randomization), a total of 16 SAEs of pneumonia/sepsis in the necitumumab plus paclitaxel-carboplatin arm (N+PC Arm) (13 [12.3%] pneumonia, and 3 [2.8%] of sepsis) versus 5 SAEs in the paclitaxel-carboplatin alone arm (PC Arm) (3 [5.5%] pneumonia, 2 [3.6%] sepsis]) were observed, including one fatal case in each arm. No clear pattern with regard to time after first administration of trial medication (range: 4-233 days) or laboratory values for leukocytes/neutrophils could be identified.

The early occurrence of a number of cases of pneumonia/sepsis may have indicated an issue regarding enrollment of inappropriate 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, some 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 (Study JFCC; SQUIRE) did not show any evidence of an increased risk of serious lung infections or neutropenia associated with necitumumab in this combination.

9.4.1.2.1.5. Thromboembolic Events

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.

Venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs) were observed with necitumumab in combination with 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.

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

Necitumumab in Combination with Pemetrexed and Cisplatin

Administration of necitumumab in combination with pemetrexed and cisplatin is not recommended. Patients experienced an increased rate of serious thromboembolic events (including fatal events) in the necitumumab plus pemetrexed and cisplatin arm as compared to the pemetrexed and cisplatin arm. The addition of necitumumab did not improve the efficacy outcome over pemetrexed and cisplatin alone in advanced nonsquamous NSCLC.

Necitumumab in Combination with Other Agents

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 modified FOLFOX-6 chemotherapy (mFOLFOX-6; oxaliplatin + folinic acid + 5-fluorouracil).

9.4.1.2.1.6. Cardiorespiratory Disorders

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

9.4.1.2.2. Dose Modifications for 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.

Furthermore, hypersensitivity/infusion-related reactions may occur during or following administration of *nab*-paclitaxel (Abraxane package insert, 2015) or carboplatin.

Hypersensitivity/infusion-related reactions are defined according to the NCI-CTCAE v 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 and additional treatments may be utilized according to clinical symptoms and local standards at investigator discretion. Table JFCP.4 provides general treatment recommendations for hypersensitivity/infusion-related reactions to necitumumab. For hypersensitivity/infusion-related reactions to the chemotherapy, refer to the respective package insert of carboplatin or Abraxane.

Note: If a patient should have a hypersensitivity/infusion-related reaction to necitumumab, all attempts should be made to obtain an anti-necitumumab antibody (that is, immunogenicity) and 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.

Table JFCP.4. NCI-CTCAE Infusion-Related Reactions

Grade of Reaction	Recommendations for Management	
	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 or 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.**	Not applicable

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; I.V. = intravenous(ly); NCI = National Cancer Institute.

[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.

9.4.1.2.3. Chemotherapy Dose Modifications

nab-Paclitaxel and carboplatin may cause known hematologic and nonhematologic toxicities at the dose levels infused during this study; dose delays, dose reductions, or treatment discontinuation may be required (Abraxane package insert, 2015).

Refer to Table JFCP.2 for criteria pertaining to hematology, liver function, and renal function that, if not met, may require a dose delay or dose reduction of study treatment. In addition, Table JFCP.5 should be used to determine dose reductions and treatment discontinuation of *nab*-paclitaxel and carboplatin (as applicable) in case of hematologic or neurologic toxicity. NOTE: Chemotherapy dose modifications are permanent; once the dose of *nab*-paclitaxel or carboplatin has been reduced, it will remain reduced or be further reduced in subsequent cycles.

nab-Paclitaxel and carboplatin (as applicable) are to be permanently discontinued in any of the following situations: (1) third occurrence of neutropenic fever, >7-day delay of a cycle due to ANC $<1.5 \times 10^3/\mu L$, or ANC$<0.5 \times 10^3/\mu L$ for >7 days; (2) second occurrence of platelet count $<50 \times 10^3/\mu L$; or (3) third occurrence of Grade 3 or 4 sensory neuropathy (Abraxane package insert, 2015). Note that patients who have been discontinued from one or more of the study therapy components should continue to receive the remaining study therapy component(s) that has (have) not been discontinued, according to this protocol.

9.4.1.2.3.1. Hematologic and Neurologic Toxicities

General guidelines for dose modifications for hematologic and neurologic toxicities are presented in Table JFCP.5. Dose adjustments for hematologic toxicity at the start of a subsequent cycle should be based on nadir (worst) hematologic counts from the previous cycle of therapy; treatment may be delayed to allow sufficient time for recovery (to the levels defined in Table JFCP.2).

Do not administer *nab*-paclitaxel or carboplatin (as applicable) on Day 1 of a cycle until ANC $\geq 1.5 \times 10^3/\mu L$ and platelet count $\geq 100 \times 10^3/\mu L$ (Abraxane package insert, 2015). In patients who develop severe neutropenia or thrombocytopenia, withhold treatment until counts recover to ANC $\geq 1.5 \times 10^3/\mu L$ and platelet count $\geq 100 \times 10^3/\mu L$ on Day 1 or to ANC $\geq 0.5 \times 10^3/\mu L$ and platelet count $\geq 50 \times 10^3/\mu L$ on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce *nab*-paclitaxel and carboplatin doses as outlined in Table JFCP.5.

Reduce the doses of *nab*-paclitaxel and carboplatin upon a first or second occurrence of Grade 3 or 4 peripheral neuropathy, as per Table JFCP.5. Discontinue treatment with *nab*-paclitaxel and carboplatin upon a third occurrence of Grade 3 or 4 peripheral neuropathy.

Table JFCP.5. Dose Modifications for Hematologic and Neurologic Toxicities

Adverse Drug Reaction	Occurrence	Weekly *Nab*-Paclitaxel Dose (mg/m^2)	Every-3-Week Carboplatin Dose (AUC mg·min/mL)
Neutropenic fever (ANC <0.5 × 10^3/μL with fever >38°C)	First	75	4.5
OR	Second	50	3
Delay of next cycle by >7 days for ANC <1.5 × 10^3/μL OR ANC <0.5 × 10^3/μL for >7 days	Third	Discontinue treatment	Discontinue treatment
Platelet count <50 × 10^3/μL	First	75	4.5
	Second	Discontinue treatment	Discontinue treatment
Severe sensory neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue treatment	Discontinue treatment

Abbreviations: ANC = absolute neutrophil count; AUC = area under the concentration-time curve; *nab*-paclitaxel = paclitaxel protein-bound particles for injectable suspension (albumin-bound) (generic name for Abraxane).
Source: Abraxane package insert, 2015.

9.4.1.2.3.2. Nonhematologic Toxicities

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhea, or Grade 3 mucositis, interrupt treatment until the toxicity improves to Grade ≤1, then restart treatment according to the guidelines in Table JFCP.6. For Grade ≥3 peripheral neuropathy, withhold treatment until resolution to Grade ≤1. Treatment may be resumed at the next lower dose level in subsequent cycles according to the guidelines in Table JFCP.6. For any other Grade 3 or 4 non-hematologic toxicity, interrupt treatment until the toxicity improves to Grade ≤2, then restart treatment according to the guidelines in Table JFCP.6.

Table JFCP.6. Dose Modifications for Nonhematologic Toxicities

Adverse Drug Reaction	Occurrence	Weekly *Nab*-Paclitaxel Dose (mg/m^2)	Every-3-Week Carboplatin Dose (AUC mg·min/mL)
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea Grade 3 mucositis	First	75	4.5
	Second	50	3
Grade ≥3 peripheral neuropathy Grade 3 or 4 nonhematologic toxicity	Third	Discontinue treatment	Discontinue treatment
Grade 4 cutaneous toxicity, diarrhea, or mucositis	First	Discontinue treatment	Discontinue treatment

Abbreviations: AUC = area under the concentration-time curve; *nab*-paclitaxel = paclitaxel protein-bound particles for injectable suspension (albumin-bound) (generic name for Abraxane).
Source: Abraxane Summary of Product Characteristics, 2015.

9.4.1.2.3.3. Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Abraxane package insert, 2015). Patients with moderate and severe hepatic impairment treated with *nab*-paclitaxel may be at increased risk of toxicities known to paclitaxel. Withhold *nab*-paclitaxel if the AST, ALT, and/or bilirubin criteria shown in Table JFCP.2 are not met.

9.5. Blinding

This is an open-label study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured in the eCRF at each visit. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the Short-Term Follow-up visit.

With the exceptions listed in the following subsections, 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 radiation therapy is permitted for irradiating small areas of symptomatic metastases that cannot be managed adequately. Systemic radiotherapy is not allowed. Any symptomatic deterioration or clinical disease progression requiring other forms of specific antitumor therapy, in the opinion of the investigator, will be cause for discontinuation of study therapy.

NOTE: The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. It is recommended that caution be exercised when administering *nab*-paclitaxel concomitantly with medicines known to inhibit (for example, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (for

example, rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either of these cytochrome P450 isoenzymes.

9.6.1. 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. Refer to Section 9.4.1.2 for specific information on the management of necitumumab-related hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, hypomagnesemia, and serious thromboembolic events. Guidelines regarding the use of other specific supportive care agents are presented in the following sections.

9.6.1.1. Antidiarrheal Agents

In the event of Grade 3 or 4 diarrhea, supportive measures may include antidiarrheals (loperamide), hydration, and octreotide. If diarrhea is severe (that is, requires I.V. hydration) and associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics may be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for I.V. hydration and correction of electrolyte imbalance.

9.6.1.2. Antiemetic Therapy

The use of antiemetic agents is permitted during this study. Patients with severe nausea and /or vomiting must be hospitalized for I.V. hydration and correction of electrolyte imbalance.

9.6.1.3. Analgesic Agents

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

9.6.1.4. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator.

9.6.1.5. Colony-Stimulating Factors and Erythropoiesis-Stimulating Agents

The use of colony-stimulating factors (CSFs) or erythropoiesis-stimulating agents (ESAs) are permitted during study treatment, at the discretion of the investigator.

Because recommendations on the use of CSFs and 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 [NCCN], American Society of Clinical Oncology [ASCO], American Society of Hematology [ASH], and/or Centers for Medicare and Medicaid Services Web sites) for the latest guidelines.

9.7. Treatment Compliance

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

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 following sections and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

Throughout this study, patients will be evaluated for response by the investigator, according to RECIST 1.1 (Eisenhauer et al. 2009). The preferred methods of tumor measurement are computed tomography (CT; including spiral CT scans) and magnetic resonance imaging (MRI). 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).

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Within 21 days prior to the first dose of study drug, baseline tumor measurement(s) will be performed on each patient.

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. Computed tomography of the chest and CT or MRI of the abdomen are required at each time point; CT or MRI of the brain must be performed if baseline assessment identified any lesion in this area or if clinically indicated, at the discretion of the treating physician. The method of assessment used at baseline must be used consistently for tumor assessment during the course of each patient's evaluation during the study.

If an objective response of PR or CR is observed, confirmatory scans should be obtained at the next routine scheduled imaging time point (that is, 6 weeks [±3 days]). Thereafter, a responding patient will be followed every 6 weeks (±3 days) until radiographic documentation of PD.

During the Continued Access Period, efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

10.1.2. Efficacy Assessments during Postdiscontinuation Follow-up

For patients who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and evaluate tumor response every 6 weeks (±3 days), by the same method used at Baseline and throughout the study, until the patient has radiographic documentation of PD or until study completion, whichever occurs first. After the patient has objective PD, radiographic 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 (see Section 8.1.1).

After radiographic documentation of PD, patients may receive additional anticancer therapy at the discretion of the investigator. The additional treatments should be documented in the eCRF.

10.1.3. Definitions of Efficacy Measures

Definitions of efficacy measures per patient are provided in Table JFCP.7. Summary efficacy statistics (rates, medians, etc) for study populations are defined in Section 12.2.1. For these definitions, the date of study enrollment is the date of first dose of study drug (necitumumab, *nab*-paclitaxel, and/or carboplatin).

Table JFCP.7. Definitions of Efficacy Measures per Patient

Endpoint	Definition
Best response	The best tumor response of CR or PR.
Progression-free survival	The time from the date of study enrollment to the date of first observation of objective (radiographically documented) PD or death from any cause, whichever comes first. For patients not known to have died as of the data cut-off date and who do not have objective PD, PFS will be censored at the date of the last complete radiographic assessment.
Overall survival	The time from the date of study enrollment to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS will be censored at the last contact date (last contact for patients in Postdiscontinuation Follow-up = last known alive date in mortality status).
Disease control	Best tumor response of PR, CR, or SD.

Abbreviations: CR = complete response; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

10.1.3.1. Primary Efficacy Measure

The primary efficacy measure is response as defined by RECIST 1.1 (Eisenhauer et al. 2009) provided in Attachment 6. A responder is defined as any patient who exhibits a confirmed CR or PR.

Best response is determined from the sequence of responses assessed.

A second assessment must be performed ≥28 days after the first evidence of response, such that the next scheduled scan performed 6 weeks (±3 days) after the first evidence of response would qualify for response confirmation. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. A best response of SD is defined as disease that does not meet the criteria for CR, PR, or PD and has been evaluated at least one time, at least 6 weeks after the start of study treatment.

Best response will be derived to encompass all tumor assessments from baseline until the earliest of objective progression or start of new anticancer therapy. Any responses observed after objective progression or the start of new anticancer therapy are excluded from the determination of best response.

The date of first documented objective disease progression must be recorded on the eCRF even if it occurs after the patient has started a new therapy. A brain lesion identified on a follow-up scan

is considered a new lesion and will indicate disease progression even though brain was not scanned at baseline.

The response rate (ORR) is estimated as the total number of confirmed CRs and PRs divided by the total number of qualified patients.

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 regimen 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 JFCP.8 presents a summary of AE and SAE reporting guidelines. Table JFCP.8 also shows which database or system is used to store AE and SAE data.

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

Period	Types of AEs/SAEs to Be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs[a]	x	
	SAEs related to protocol procedures	x	x
Study Treatment Period	All AEs	x	
	All SAEs	x	x
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 drug(s)	x	x
Continued Access (treatment) Period	All AEs	x	
	All SAEs	x	x
Continued Access Follow-up[a]	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 drug(s) that the investigator becomes aware of		x

Abbreviations: AE = adverse event; SAE = serious adverse event.

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, and vital signs measurements 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 immediately (within 24 hours). 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 drug must be reported to Lilly or its designee via eCRF.

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

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to study medication or study procedure, the following terminologies are defined.

- **Probably related**: a direct cause-and-effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause-and-effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to IP/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 (SOC) and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim, the CTCAE term, 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 ®).

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 AE 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 drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, 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 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 caused by disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study treatment.

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

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

10.2.1.2. Suspected Unexpected Serious Adverse Reactions

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

followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.2.2. 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 (no overread). 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 as possible after the time of ECG collection, 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 (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

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 Lilly Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- AEs, including monitoring of hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, hypomagnesemia, and thromboembolic events
- If a patient experiences elevated alanine aminotransferase (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 or weakness or asthenia, pain or chest pain, dyspnea, cough, nausea, anorexia or decreased appetite, disease progression, metastasis, hemoptysis, 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 facilitate process and product improvements.

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

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 schedules for general sample collections for this study (includes a separate schedule for the Continued Access Period).

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

Attachment 7 lists the schedules for sample collections for PK, immunogenicity, and translational research (tumor tissue, plasma for biomarker research, and whole blood for deoxyribonucleic acid [DNA] [pharmacogenetic] analysis).

A summary of the maximum number and volume of invasive samples, for all sampling, during the study, will be provided in a separate procedural manual. Fewer invasive samplings may actually occur, but this will not require a protocol amendment.

10.3.1. Samples for Standard Laboratory Testing

Standard laboratory tests, including chemistry, hematology, coagulation, and pregnancy testing (if applicable in women of childbearing potential), will be performed and analyzed centrally. The exception is urinalysis, which will be performed and analyzed locally. Attachment 2 lists the laboratory tests that will be performed for this study.

Central laboratory results, except urinalysis which will be done locally as noted above, 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).

Investigators must document their review of each laboratory safety report.

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.

Samples collected for specified laboratory tests will be destroyed within 60 days after 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 Translational Research

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

- Tumor tissue for biomarkers (see Section 10.3.2.1)
- Plasma for biomarkers (see Section 10.3.2.2)
- Whole blood for DNA sample (pharmacogenetic analysis) (see Section 10.3.2.3)

Samples will be collected at the times specified in Attachment 7.

The translational research samples will be stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor or designee. The duration allows the sponsor to respond to regulatory requests related to the study treatment.

Patients will not receive results of these investigations except where required by local law. Samples will be destroyed according to a process consistent with local regulation.

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

10.3.2.1. Tumor Tissue for Biomarkers

Collection of tumor tissue samples (primary tumor or metastatic sites) is mandatory for participation in this study. Patients must have tumor tissue (a paraffin-embedded tissue block

[preferred] or 15 freshly cut unstained slides [a minimum of 6 slides] is requested) available for analysis of EGFR protein expression by IHC.

Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying tissue may also be requested. The paraffin-embedded whole blocks will be sectioned. After testing has been completed, the paraffin-embedded whole blocks will be returned to the site. Whole blocks can be returned sooner, if requested by the sites. Partial blocks and slides will not be returned.

Mutation profiling, copy number variability, gene expression, and/or IHC may be performed on these tissue samples to assess potential associations with biomarkers relevant to pathways associated with NSCLC, the mechanism of action of necitumumab, and cancer-related conditions, and may also be used for related research methods and clinical outcomes. Additional exploratory markers studied may include, but are not limited to, markers relevant to the EGFR pathway.

10.3.2.2. Plasma for Biomarkers

Potential pharmacodynamics and/or circulating markers may include, but are not limited to, markers relevant to EGFR pathway, NSCLC etiology, and/or the mechanism of action of necitumumab.

10.3.2.3. Whole Blood for DNA Collection

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

Sampling for this analysis will be a one-time collection (refer to Attachment 7 for timing of the collection). Samples will be stored and analysis may be performed on genetic variants/copy number variations that are thought to play a role in the EGFR pathway, NSCLC etiology, and/or the mechanism of action of necitumumab.

In the event of an unexpected AE or the observation of an unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to necitumumab. 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 will only be used for investigations related to disease, cancer-related conditions, 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. Pharmacogenetic data will not be provided to the investigator or the patient except where required by local law.

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

Blood samples will also be collected to determine the plasma concentrations of paclitaxel and total platinum from carboplatin. The bioanalytical method to determine plasma concentrations of paclitaxel is a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The bioanalytical method to determine plasma concentrations of total platinum is an inductively coupled plasma–mass spectrometry (ICP-MS) method.

As noted in Attachment 1, samples will also be collected and necitumumab drug concentrations determined in the setting of an infusion-related/hypersensitivity reaction to necitumumab. The actual date and time of collection of each sample will be recorded.

Bioanalytical samples collected to measure necitumumab, paclitaxel, and total platinum 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 eCRFs, 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 eCRF 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 study. 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 Laboratory System.

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

The primary objective of this study is to estimate the ORR in qualified patients. The sample size was selected to facilitate the estimation of the ORR with reasonable precision; no power calculation was performed. With 50 qualified patients, the 95% confidence interval (CI) estimate of ORR with a width no greater than 29 percentage points (that is, the ORR point estimate ±14.5%).

There are no planned formal tests of hypotheses about ORR. However, the maximum width of the 95% CI (described in the previous paragraph) will permit the conclusion (with 95% confidence) that the true value of ORR does not differ from the estimated value of ORR by more than 14.5 percentage points.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Efficacy analyses for ORR and DCR will be performed for qualified patients, where a "qualified patient" is defined as an enrolled patient who has received any amount of study drug and has had a complete radiographic assessment at baseline. A patient who is alive for at least 8 weeks after first dose and has had no postbaseline radiographic assessment will be disqualified. Efficacy analyses for PFS and OS will be performed for all patients who have received any amount of study drug (necitumumab, *nab*-paclitaxel, and/or carboplatin).

The final analysis for all outcomes, primary and secondary endpoints, will be performed when 70% of qualified patients experience a PFS event (radiographically documented PD or death), or 6 months after completing enrollment, whichever occurs first. This will provide an appropriate duration of observation from which to estimate ORR and median PFS. Overall survival will be evaluated primarily in terms of the estimated 6-month survival.

Safety analyses will be performed for the Safety Population (all patients who have received any amount of study drug [necitumumab, *nab*-paclitaxel, and/or carboplatin]).

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 a summary of the number and percentage of patients enrolled in the study, treated, and qualified. A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient demographics including age, sex, screening height and weight, and screening body mass index (BMI) will be reported using descriptive statistics.

Baseline disease characteristics and medical history will also be summarized.

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 anticancer 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, delays, the number of cycles received, and dose intensity will be summarized for all treated patients. Summarized data will be provided for the induction period (the first 4 cycles), the maintenance period (Cycles 5 and beyond), and for the combination of the induction and maintenance periods.

12.2.6. Primary Outcome and Methodology

Refer to Section 12.1 for details of the primary analysis.

12.2.7. Analyses of Efficacy

This section provides details of planned efficacy analyses besides those described in Section 12.1. For time-to-event variables, the Kaplan-Meier method will be used to estimate parameters (for example, medians, quartiles, 6-month event rates). Refer to the SAP for additional details.

Table JFCP.9 provides definitions of key efficacy statistics used for this study. Exact 95% CIs will be calculated for ORR and DCR.

Table JFCP.9. Definitions of Key Efficacy Statistics

Efficacy Statistic	Definition
Objective response rate (ORR)	The denominator of ORR includes all qualified patients. The numerator includes those patients counted in the denominator with a best overall tumor response of CR or PR.
Median (OS, PFS)	Estimated using Kaplan-Meier method of estimation.
Disease control rate (DCR)	Using the same denominator as for ORR, the numerator of DCR includes those patients counted in the denominator with a best tumor response of SD, PR, or CR.

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

12.2.8. Pharmacokinetic and Immunogenicity Analyses

Serum concentrations of necitumumab and plasma concentrations of paclitaxel and total platinum from carboplatin 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 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.

12.2.9. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study treatment, 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 the entire Study 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 at least possibly related to study treatment or study procedure, and repeated for events regardless of 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 or a related SAE 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 study treatment due to an AE will be summarized. Refer to the SAP for details.

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 grades, including the total for maximum Grade 3 and above. These summaries will be provided for events deemed by the investigator to be at least 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 SOC and by decreasing frequency of Preferred Term within SOC.

Reasons for death will be summarized separately for on-therapy and within 30 days after last dose of study treatment. Serious adverse events will be summarized by SOC and Preferred Term.

Hospitalizations and transfusions occurring during the Study Treatment Period or (30-day) Short-Term Follow-up will be summarized.

12.2.10. Interim Analyses

One safety interim analysis is planned when data are available from at least the first 10 qualified patients who have completed 2 cycles of study treatment or have died. The interim analysis will be conducted to permit evaluation of safety data by Lilly.

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 drug.

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
- International Conference on Harmonisation (ICH) Good Clinical Practice (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 (TPO).

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 or a designee 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.

14. References

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Attachment 1. Protocol JFCP Study Schedule

Study Schedule, Protocol I4X-MC-JFCP

Perform procedures as indicated in the following schedules.

Baseline Schedule, I4X-MC-JFCP

			Baseline		
		Cycle	BL		
		Visit	0		
		Relative day to Cycle 1, Day 1	≤21	≤14	
Procedure Category	**Protocol Section or Attachment**	**Procedure**			**Comments**
Study Entry/ Enrollment	13.1	Informed consent form signed	X		ICF must be signed prior to performance of any protocol-specific tests/procedures.
	7.1, 7.2	Inclusion/exclusion evaluation and IWRS enrollment	X		To be done once all the screening (Baseline) assessments are completed.
Medical History	10.2.1	Initial history/preexisting conditions		X	
		Historical illnesses		X	
Physical Examination		Height		X	
		Weight		X	
		Blood pressure/pulse/body temperature/respiration rate		X	
	Att 4	ECOG performance status		X	
Efficacy Assessment	10.1.1, Att 6	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X		
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	9.6	Concomitant medication notation	X		

			Baseline		
		Cycle	BL		
		Visit	0		
		Relative day to Cycle 1, Day 1	≤21	≤14	
Procedure Category	**Protocol Section or Attachment**	**Procedure**			**Comments**
Laboratory/ Diagnostic Tests	10.3.1, Att 2	Hematology (central)		X	
	10.3.1, Att 2	Chemistry (central)		X	
	10.3.1, Att 2	Coagulation (central)		X	
	10.3.1, Att 2	Pregnancy test (central)		X	
	10.3.1, Att 2	Urinalysis (local)		X	
	10.3.2, Att 7	Tumor tissue sample	Refer to Attachment 7.		
	10.3.2, Att 7	Plasma sample (biomarkers)	Refer to Attachment 7.		
	10.3.2, Att 7	Whole blood for DNA sample (pharmacogenetic analysis)	Refer to Attachment 7.		
	10.2.2.1	ECG (local)		X	

Abbreviations: AE = adverse event; Att = Attachment (in the protocol); BL = baseline; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; IWRS = interactive web response system; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event.

Treatment Period Schedule, I4X-MC-JFCP

Procedure Category	Protocol Section or Attachment	Procedure	Treatment Period: Induction (Triplet) Regimen			Treatment Period: Maintenance (Doublet) Regimen		Comments
		Cycle (3-week cycle)	1-4			5-N		
		Visit	1-4			5-N		
		Relative day within a cycle	1	8	15	1	8	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Physical Examination		Weight	X			X		Body surface area to be calculated at each cycle until *nab*-paclitaxel is discontinued.
		Blood pressure/pulse/body temperature/respiration rate	X			X		
	Att 4	ECOG performance status	X			X		
Efficacy Assessment	10.1.1, Att 6	Radiologic imaging (according to RECIST 1.1) and tumor measurement	X			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 RECIST 1.1. The method of assessment used at baseline must be used consistently for tumor assessment during the course of each patient's evaluation during the study.
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X	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.
Concomitant Medications	9.6	Concomitant medication notation	X	X	X	X	X	
Study Drug	9.1, 9.1.2.1, 9.1.3.1	Necitumumab	X	X		X	X	
	9.1, 9.1.2.2, 9.1.3.2	*nab*-Paclitaxel	X	X	X	X	X	
	9.1, 9.1.1, 9.1.2.2, 9.1.3.3	Carboplatin	X					

Procedure Category	Protocol Section or Attachment	Procedure	Treatment Period: Induction (Triplet) Regimen			Treatment Period: Maintenance (Doublet) Regimen		Comments
		Cycle (3-week cycle)	1-4			5-N		
		Visit	1-4			5-N		
		Relative day within a cycle	1	8	15	1	8	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Laboratory/ Diagnostic Tests	9.4.1.1, 10.3.1, Att 2	Hematology (local and central)	X	X	X	X	X	Local lab values to be used for dosing decisions, per Table JFCP.2. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Days 8 and 15 of each cycle during the induction period and Day 8 of each cycle during the maintenance period). Central lab values to be used for the eCRF/clinical database. Hepatic monitoring tests (per Attachment 3; performed by local lab and captured on the eCRF) to be done in the event of a treatment-emergent hepatic abnormality.
	9.4.1.1, 10.3.1, Att 2	Chemistry (local and central)	X	X	X	X	X	Local lab values to be used for dosing decisions, per Table JFCP.2. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Days 8 and 15 of each cycle during the induction period and Day 8 of each cycle during the maintenance period). Central lab values to be used for the eCRF/clinical database. Hepatic monitoring tests (per Attachment 3; performed by local lab and captured on the eCRF) to be done in the event of a treatment-emergent hepatic abnormality.
	10.3.1, Att 2	Coagulation (central)	X*			X*		* Starting with Cycle 2, to be performed every second cycle (that is, Cycles 2, 4, etc).
	10.3.1, Att 2	Pregnancy test (central)	X*			X*		* Starting with Cycle 2, to be performed every second cycle in women of childbearing potential (that is, Cycles 2, 4, etc).
	10.3.1, Att 2	Urinalysis (local)	X*			X*		* Starting with Cycle 2, to be performed every second cycle (that is, Cycles 2, 4, etc).
	10.3.4, Att 7	PK	Refer to Attachment 7.					If a patient experiences an IRR to necitumumab, blood samples for both 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, Att 7	Immunogenicity: Anti-necitumumab antibodies						
	10.3.2, Att 7	Plasma sample (biomarkers)	Refer to Attachment 7.					
	10.2.2.1	ECG (local)	X*			X*		* Starting with Cycle 2, to be performed every second cycle (that is, Cycles 2, 4, etc).

Abbreviations: AE = adverse event; Att = Attachment (in the protocol); CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IRR = infusion-related reaction; PD = progressive disease; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event.

Postdiscontinuation Follow-up Schedule, I4X-MC-JFCP

			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 or Attachment**	**Procedure**			**Comments**
Physical Examination		Weight	X		
		Blood pressure/pulse/body temperature/respiration rate	X		
	Att 4	ECOG performance status	X		
Efficacy Assessment	10.1.1, Att 6	Radiologic imaging (according to RECIST 1.1) 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 or overall study completion, whichever occurs first. The method of assessment used at baseline must be used consistently for tumor assessment during the course of each patient's evaluation during the study. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed for survival every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first.
Survival Information	7.3.2, 8.1.1	Collection of survival information	X	X	Collection of survival data every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first. 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	9.6	Concomitant medication notation	X		
Laboratory/ Diagnostic Tests	10.3.1, Att 2	Hematology (central)	X		
	10.3.1, Att 2	Chemistry (central)	X		
	10.3.1, Att 2	Coagulation (central)	X		
	10.3.1, Att 2	Pregnancy test (central)	X		
	10.3.1, Att 2	Urinalysis (local)	X		
	10.3.4, Att 7	PK	Refer to Attachment 7.		
	10.3.3, Att 7	Immunogenicity: Anti-necitumumab antibodies			
	10.3.2, Att 7	Plasma sample (biomarkers)			
	10.2.2.1	ECG (local)	X		

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

Abbreviations: AE = adverse event; Attachment (in the protocol); CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAEs = serious adverse events.

Note: No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

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 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-JFCP

			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 or Attachment**	**Procedure**				**Comments**
Physical Examination		Weight	X			Body surface area to be calculated at each cycle until *nab*-paclitaxel is discontinued.
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, Att 7	PK	Refer to Attachment 7.			If a patient experiences an IRR to necitumumab, blood samples for both 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, Att 7	Immunogenicity: Anti-necitumumab antibodies				
Study Drug	9.1, 9.1.2.1, 9.1.3.1	Necitumumab	X	X		At the time of study completion, it is expected that no patients will be on the induction (triplet) regimen. Patients who are on the maintenance (doublet) regimen may continue to receive that regimen during the Continued Access (treatment) Period.
	9.1, 9.1.2.2, 9.1.3.2	*nab*-Paclitaxel	X	X		
	Not applicable	Carboplatin				

Abbreviations: AE = adverse event; Attachment (in the protocol); CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; PK = pharmacokinetics; SAE = serious adverse event.

Note: No follow-up procedures will be performed for patients who withdraw informed consent unless he or she has explicitly provided permission and consent.

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. During the Continued Access Period, required evaluations are shown in the table. Investigators will perform any other standard procedures and tests needed to treat and evaluate patients and to confirm patient eligibility to continue on treatment; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

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 JFCP Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]:	**Clinical Chemistry**[a,b]:
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[c]
	Uric acid
	Calcium
	Glucose, nonfasting
Urinalysis[a]:	Albumin
Color	Cholesterol
Specific gravity	Creatine kinase (CK)
pH	
Protein	**Pregnancy Test** (WOCBP only, serum required)[b]
Glucose	
Ketones	**Coagulation Tests**[b]**:**
Blood	INR and PT
Urine leukocyte esterase	PTT
	Fibrin D dimer
	Protein C activity (baseline only)
	Protein S activity (baseline only)

Abbreviations: AE = adverse event; CRF = case report form; IDMS = isotope dilution mass spectrometry; INR = International Normalized Ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; US = United States; WBC = white blood cells; WOCBP = women of childbearing potential.

a Assayed by local laboratory. Local laboratory results will not be collected on the CRF, except in the case of an AE.

b Assayed by Lilly-designated (central) laboratory.

c IDMS for US sites.

Attachment 3. Protocol JFCP 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 (CRP).

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	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	
Alanine aminotransferase (ALT)	**Anti-nuclear antibody[a]**
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase GGT	**Anti-smooth muscle antibody[a]**
Creatine kinase (or creatine phosphokinase) (CK [or CPK])	

Abbreviations: CRF = case report form; Ig = immunoglobulin; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

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

b Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

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

Attachment 4. Protocol JFCP ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 5. Protocol JFCP Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Attachment 6. Protocol JFCP 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, positron emission tomography (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 on the eCRF 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 eCRF (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. Magnetic resonance imaging 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 CR 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 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 PR and 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 SD in order to differentiate between response (or SD) and PD.

PET Scan (FDG-PET, PET CT): Positron emission tomography 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 CR or 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 (<10 mm 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 JFCP Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule

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

In addition, if a patient experiences an infusion-related reaction (IRR), blood samples for both 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.

Collection of tumor tissue samples (primary tumor or metastatic sites) is mandatory for participation in this study. Patients must have tumor tissue (a paraffin-embedded tissue block [preferred] or 15 freshly cut unstained slides [a minimum of 6 slides] is requested) available for analysis of EGFR protein expression by IHC.

Pharmacokinetic, Immunogenicity, and Translational Research Sampling Schedule

		Baseline	Study Treatment Period (3-wk cycles)						Post-DC Follow-up
			Cycle 1		Cycle 3		Cycle 4		
			Day 1		Day 1		Day 1		
Sample for:	**Protocol Section**	**≤14 days**	**Pre-inf**	**Post-inf**	**Pre-inf**	**Post-inf**	**Pre-inf**	**Post-inf**	**Short-Term Follow-up[a]**
Necitumumab PK[b]	10.3.4		**X[c]**	**X[d]**	**X[c]**	**X[d]**	**X[c]**	**X[d]**	**X[e]**
***nab*-Paclitaxel PK**									
Carboplatin PK									
Immunogenicity[b]	10.3.3		**X[c]**		**X[c]**		**X[c]**		**X**
Tumor tissue submission	10.3.2.1	**X**							
Plasma sample for biomarkers	10.3.2.2	**X**					**X**		**X[f]**
Whole blood sample for DNA analysis[g]	10.3.2.3	**X**							

Abbreviations: DC = discontinuation; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; inf = infusion; IRR = infusion-related reaction; PGx = pharmacogenetic; PK = pharmacokinetic(s).

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

Note: For all samples collected prior to an infusion, it is recommended that samples be collected after it is confirmed that the patient is qualified to receive the infusion at that time point.

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

b If a patient experiences an infusion-related reaction (IRR), separate blood samples for immunogenicity (anti-necitumumab antibody) and PK analysis should be drawn, within 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.

c At Cycle 1, Day 1: At any time prior to the necitumumab infusion. For all other time points: Within 4 hours prior to the beginning of the necitumumab infusion. The exact time of collection of each blood sample should be recorded. The sample taken at this time point will include serum for necitumumab PK assessment and blood for *nab*-paclitaxel and carboplatin PK assessments. Refer to the laboratory manual for details regarding the required number of blood collection tubes for any given time point.

d A postinfusion sample is to be drawn within 15 minutes after the last infusion for that study day is completed. The exact time of collection of each blood sample should be recorded. The sample taken at this time point will include serum for necitumumab PK assessment and blood for *nab*-paclitaxel and carboplatin PK assessments. Refer to the laboratory manual for details regarding the required number of blood collection tubes for any given time point.

e PK for necitumumab only.

f When applicable, EDTA plasma should be collected as near as possible to the time of disease progression, during the Study Treatment Period. If, for any reason, the post-progression sample cannot be collected at the time of progression, it should be collected at (or by) the (30-day) Short-Term Follow-up visit. The post-progression sample should be collected before the initiation of any new anticancer therapy.

g Collected at Baseline (preferred) or at later visits.

Attachment 8. Protocol JFCP Necitumumab Dosing Scenarios for Chemotherapy Delays

Induction Regimen (Cycles 1-4)			
Cycle	**Day**	**Administer Necitumumab?**	**Administer *nab*-Paclitaxel?/Carboplatin?**
Planned – No Delays			
1	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
2	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
3	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
Chemotherapy Delay of 1 Week after Cycle 1 (Preventing Start of Cycle 2)			
1	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
	22	**Yes**	**Delay of *nab*-paclitaxel and/or carboplatin**
2	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
3	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
Chemotherapy Delay of 2 Weeks after Cycle 1 (Preventing Start of Cycle 2)			
1	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
	22	**Yes**	**Delay of *nab*-paclitaxel and/or carboplatin**
	29	**Yes**	
2	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
3	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No

Induction Regimen (Cycles 1-4)			
Cycle	**Day**	**Administer Necitumumab?**	**Administer *nab*-Paclitaxel?/Carboplatin?**
Chemotherapy Delay of 3 Weeks after Cycle 1 (Preventing Start of Cycle 2)			
1	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
	22	**Yes**	**Delay of *nab*-paclitaxel and/or carboplatin**
	29	**Yes**	
	36	**No**	
2	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No
3	1	Yes	Yes/Yes
	8	Yes	Yes/No
	15	No	Yes/No

Maintenance Regimen (Cycles 5-n)			
Cycle	**Day**	**Administer Necitumumab?**	**Administer *nab*-Paclitaxel?**
Planned – No Delays			
1	1	Yes	Yes
	8	Yes	Yes
2	1	Yes	Yes
	8	Yes	Yes
3	1	Yes	Yes
	8	Yes	Yes
Chemotherapy Delay of 1 Week after Cycle 1 (Preventing Start of Cycle 2)			
1	1	Yes	Yes
	8	Yes	Yes
	15	**No**	**Delay**
2	1	Yes	Yes
	8	Yes	Yes
3	1	Yes	Yes
	8	Yes	Yes

Maintenance Regimen (Cycles 5-n)			
Cycle	**Day**	**Administer Necitumumab?**	**Administer *nab*-Paclitaxel?**
Chemotherapy Delay of 2 Weeks after Cycle 1 (Preventing Start of Cycle 2)			
1	1	Yes	Yes
	8	Yes	Yes
	15	**No**	**Delay**
	22	**Yes**	
2	1	Yes	Yes
	8	Yes	Yes
3	1	Yes	Yes
	8	Yes	Yes
Chemotherapy Delay of 3 Weeks after Cycle 1 (Preventing Start of Cycle 2)			
1	1	Yes	Yes
	8	Yes	Yes
	15	(Not applicable)	(Not applicable)
	22	**Yes**	**Delay**
	29	**Yes**	
	36	**No**	
2	1	Yes	Yes
	8	Yes	Yes
3	1	Yes	Yes
	8	Yes	Yes

Attachment 9. Protocol JFCP Protocol Amendment I4X-MC-JFCP(b) Summary
A Single-Arm, Multicenter, Open-Label, Phase 2 Study of *nab*®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

Overview

Protocol I4X-MC-JFCP, A Single-Arm, Multicenter, Open-Label, Phase 2 Study of *nab*®-Paclitaxel (Abraxane®) and Carboplatin Chemotherapy plus Necitumumab (LY3012211) in the First-Line Treatment of Patients with Stage IV Squamous 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 following additions were made as requested by the German competent authority, Paul-Ehrlich Institute:

- detailed information on the SAEs of pneumonia/sepsis occurring in Study JFCL in Section 9.4.1.2.1.4,
- the number of AEs with outcome death occurring in Study JFCL in Section 5,
- dose modification guidelines for nonhematologic toxicities according to the Abraxane Summary of Product Characteristics in Section 9.4.1.2.3.2 (Nonhematologic Toxicities), and
- guidance regarding hospitalization of patients with severe nausea and vomiting in Section 9.6.1.2 (Antiemetic Therapy).

Additionally, a deletion of the example non-life-threatening reversible Grade 3 and 4 toxicities in Section 9.4.1.2.1 was made, as fatigue and anorexia are not adverse drug reactions of necitumumab.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

5. Introduction

…

In preclinical studies in mice with lung cancer xenografts, necitumumab in combination with paclitaxel and cisplatin has demonstrated a significant improvement in tumor volume growth delay, compared with the same chemotherapy alone and with single-agent necitumumab (Preclinical Research, Eli Lilly and Company, 2009).

In a Phase 2 necitumumab clinical trial (Study I4X-MC-JFCL [JFCL]) of necitumumab as first-line therapy in Stage IV squamous NSCLC, the addition of necitumumab to paclitaxel-carboplatin (N+PC) resulted in an increased ORR compared to chemotherapy alone (PC) (48.9% versus 40.0%), indicating an add-on treatment effect for this combination. For PFS the treatment effect (as measured by the stratified HR) was 1.0 (95% CI: 0.71, 1.42) (median PFS: 5.4 versus 5.6 months). For OS, the median OS was 13.2 months for the N+PC Arm versus 11.2 months for the chemotherapy alone arm (PC Arm). The OS HR for the treatment effect was 0.83 (95% CI: 0.55, 1.52).

In the N+PC Arm, 10 patients (9.4%) had 11 AEs with an outcome of death (where the primary cause of death may or may not be the AE). Seven of the 10 deaths occurred during the chemotherapy phase: acute respiratory failure, lung infection, septic shock, circulatory collapse, respiratory failure, pulmonary embolism, brain death, and cardiac arrest (in 1 patient). The other 3 deaths were due to hypovolemic shock, cardiac failure congestive, and pneumonia. All AEs were assessed by the investigator as not related to any study drug, with the exception of lung infection (assessed as related to chemotherapy only), respiratory failure (assessed as related to all study drugs), and circulatory collapse (unknown). In the PC Arm, 3 patients (5.5%) had 4 AEs with an outcome of death (all were assessed as not related to any study drugs) (one report each) of: death; sudden death; and pneumonia and sepsis (in 1 patient).

The OS analysis showed a higher rate of events for the necitumumab-containing arm during the first 4 months, with a later trend toward improved survival after 4 months.

The ~~These~~ preclinical data, the clinical efficacy of EGFR-directed mAbs in combination with taxanes and carboplatin, and the advantage of *nab*-PC over sb-PC in terms of safety and efficacy especially in squamous NSCLC together provide a strong rationale for the investigation of *nab*-PC in combination with necitumumab as first-line therapy in Stage IV squamous NSCLC.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of necitumumab may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to necitumumab may be found in Section 7 (Development Core Safety Information [DCSI]) 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 (Lilly) in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of *nab*-paclitaxel may be found in the following: Package Insert (Abraxane package insert, 2015) or Section 9.4.1.

More detailed information about the known and expected benefits and risks of carboplatin may be found in the following: Package Insert (Carboplatin package insert, 2006 and 2015) or Section 9.4.1.

9.4.1.2.1. Necitumumab Dose Modifications

~~In t~~This section ~~are~~ provides general dose modification guidelines for toxicity associated with necitumumab treatment. Refer to Sections 9.4.1.2.2, 9.4.1.2.1.1, 9.4.1.2.1.2, 9.4.1.2.1.3, 9.4.1.2.1.4, and 9.4.1.2.1.5 for specific information on the management of and/or necitumumab dose adjustments due to AEs of concern that may or may not be associated with necitumumab treatment, which include hypersensitivity/infusion-related reactions, skin reactions, conjunctivitis, electrolyte abnormalities, pneumonia and sepsis, and thromboembolic events.

Apart from the necitumumab dose adjustment recommendations specific to hypersensitivity/infusion-related reactions and skin reactions (Sections 9.4.1.2.2 and 9.4.1.2.1.1, respectively), stepwise dose reductions to 600 mg and 400 mg necitumumab may be considered for non-life-threatening reversible Grade 3 and 4 toxicities ~~(for example, fatigue, anorexia, and fever)~~ after treatment interruption and resolution to Grade ≤2. After a dose reduction, the dose of necitumumab may be re-escalated to the previous dose after a minimum of 2 administrations of the reduced dose. In case of toxicities necessitating more than 2 dose reductions, treatment with necitumumab should be permanently discontinued.

9.4.1.2.1.4. Pneumonia and Sepsis

~~During the conduct of Study JFCL (Phase 2 study to investigate carboplatin and solvent-based paclitaxel [not the albumin-bound formulation] 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.~~

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

In Study JFCL, a Phase 2 study to investigate carboplatin and solvent-based paclitaxel with or without necitumumab in patients with squamous NSCLC (106 versus 55 patients, 2:1 randomization), a total of 16 SAEs of pneumonia/sepsis in the necitumumab plus paclitaxel-carboplatin arm (N+PC Arm) (13 [12.3%] pneumonia, and 3 [2.8%] of sepsis) versus 5 SAEs in the paclitaxel-carboplatin alone arm (PC Arm) (3 [5.5%] pneumonia, 2 [3.6%] sepsis]) were

observed, including one fatal case in each arm. No clear pattern with regard to time after first administration of trial medication (range: 4-233 days) or laboratory values for leukocytes/neutrophils could be identified.

The early occurrence of a number of cases of pneumonia/sepsis may have indicated an issue regarding ~~the~~ enrollment of ~~the~~ inappropriate 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~~ some 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 (Study JFCC; SQUIRE) did not show any evidence of an increased risk of serious lung infections or neutropenia 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.~~

9.4.1.2.3. Chemotherapy Dose Modifications

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Refer to Table JFCP.2 for criteria pertaining to hematology, liver function, and renal function that, if not met, may require a dose delay or dose reduction of study treatment. In addition, Table JFCP.5 should be used to determine dose reductions and treatment discontinuation of *nab*-paclitaxel and carboplatin (as applicable) in case of hematologic~~al~~ or neurologic toxicity. NOTE: Chemotherapy dose modifications are permanent; once the dose of *nab*-paclitaxel or carboplatin has been reduced, it will remain reduced or be further reduced in subsequent cycles.

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9.4.1.2.3.1. Hematologic~~al~~ and Neurologic Toxicities

9.4.1.2.3.2. Nonhematologic Toxicities

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhea, or Grade 3 mucositis, interrupt treatment until the toxicity improves to Grade ≤1, then restart treatment according to the guidelines in Table JFCP.6. For Grade ≥3 peripheral neuropathy, withhold treatment until resolution to Grade ≤1. Treatment may be resumed at the next lower dose level in subsequent cycles according to the guidelines in Table JFCP.6. For any other Grade 3 or 4 non-hematologic toxicity, interrupt treatment until the toxicity improves to Grade ≤2, then restart treatment according to the guidelines in Table JFCP.6.

Table JFCP.6. Dose Modifications for Nonhematologic Toxicities

Adverse Drug Reaction	Occurrence	Weekly *Nab*-Paclitaxel Dose (mg/m^2)	Every-3-Week Carboplatin Dose (AUC mg·min/mL)
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea Grade 3 mucositis	First	75	4.5
	Second	50	3
Grade ≥3 peripheral neuropathy Grade 3 or 4 nonhematologic toxicity	Third	Discontinue treatment	Discontinue treatment
Grade 4 cutaneous toxicity, diarrhea, or mucositis	First	Discontinue treatment	Discontinue treatment

Abbreviations: AUC = area under the concentration-time curve; *nab*-paclitaxel = paclitaxel protein-bound particles for injectable suspension (albumin-bound) (generic name for Abraxane).
Source: Abraxane Summary of Product Characteristics, 2015.

9.6.1.2. Antiemetic Therapy

The use of antiemetic agents is permitted during this study. Patients with severe nausea and/or vomiting must be hospitalized for I.V. hydration and correction of electrolyte imbalance.

14. References

ABRAXANE Summary of Product Characteristics, 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000778/WC500020435.pdf. Accessed on September 21, 2016.

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