Protocol (e) I4X-JE-JFCM

An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)

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1. Protocol I4X-JE-JFCM(e)
An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)

Necitumumab (IMC-11F8; LY3012211)
Gemcitabine (LY188011)

This is a Phase 1b/2 study in the first-line treatment of patients with advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC). The study consists of a Phase 1b part and Phase 2 part. The Phase 1b part is single arm, open-label, dose-escalation to determine the recommended dose for Phase 2 part. The Phase 2 part is open-label, randomized study to evaluate efficacy and safety of necitumumab in combination with gemcitabine-cisplatin compared with gemcitabine-cisplatin alone.

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2. Synopsis

Study Rationale

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). The EGFR is a member of the human EGFR family of tyrosine kinases. EGFR activation leads to stimulation of tyrosine kinase-dependent signal transduction pathways that can contribute to neoplastic transformation and tumor growth. Inhibition of the EGFR pathway in cells can result in disruption of cell cycle progression and mitosis, and blocks the inhibitory effect on apoptosis. Decreased angiogenesis may also occur as a result of EGFR inhibition through effects on angiogenic factor production.

Necitumumab has shown in vivo antitumor activity against a variety of human xenograft tumors, including non-small cell lung cancer (NSCLC). Phase 1 and 2 studies investigating necitumumab have provided information regarding safety and tolerability at clinically relevant doses, with preliminary evidence of clinical efficacy in a variety of human cancers.

In clinical settings, the feasibility of administering EGFR-directed Mabs in combination with a standard platinum-based doublet in the first-line treatment of advanced NSCLC has been demonstrated in several randomized studies. Two randomized Phase 3 studies were conducted with cetuximab in combination with either vinorelbine-cisplatin (FLEX; Pirker et al. 2009) or carboplatin-taxane (BMS-099; Lynch et al. 2010) as the chemotherapy backbone. The addition of cetuximab to both regimens resulted in a statistically significant improvement in the best overall response rate (complete response [CR] + partial response [PR]), but not in progression-free survival (PFS) in both studies. In FLEX, a significant prolongation of overall survival (OS) with statistical significance was observed. The analyses of both studies by histologic subtypes showed, that for cetuximab-containing regimens, a more pronounced trend in improvement of OS in squamous cell carcinoma (hazard ratio [HR] 0.80 [FLEX], HR 0.87 [BMS-099]) than in adenocarcinoma (HR 0.94 [FLEX], HR 0.89 [BMS-099]) when compared to chemotherapy alone only.

According to current National Comprehensive Cancer Network (NCCN) guidelines, the combination chemotherapy of gemcitabine-cisplatin is a preferred regimen for patients with squamous cell NSCLC. The data of treatment with combination chemotherapy suggest that patients with squamous histology may derive maximum benefit from a combination of biologic therapy with gemcitabine and cisplatin. Gemcitabine is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIa or IIIb), or metastatic (Stage IV) NSCLC, and has been shown to prolong survival. Therefore chemobackbone of global Phase 3 study (CP11-0806) is gemcitabine-cisplatin. The primary objective of global Phase 3 study (CP11-0806) is to evaluate the OS in patients with Stage IV squamous NSCLC (per the American Joint Committee on Cancer [AJCC] Staging Manual, Seventh Edition) treated with necitumumab plus gemcitabine-cisplatin chemotherapy (Arm A) vs. gemcitabine-cisplatin chemotherapy alone (Arm B) in the first-line metastatic setting.

In this study, the efficacy of necitumumab in combination with gemcitabine-cisplatin chemotherapy will be evaluated in terms of OS in Japanese patient with advanced squamous NSCLC in Phase 2 part after confirming the tolerability of necitumumab in combination with gemcitabine-cisplatin chemotherapy in Phase 1b part.

Clinical Protocol Synopsis: Study I4X-JE-JFCM

Name of Investigational Product: Necitumumab (LY3012211; IMC-11F8) and Gemcitabine (LY188011)

Title of Study: An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)

Number of Planned Patients:	**Phase of Development:**
Phase 1b Part Enrolled: 9 to 18 Phase 2 Part Enrolled: 190 Randomized: 180 (up to 190 patients will be randomized)	1b/2

Length of Study:
Planned first patient visit: Dec 2012 Planned last patient visit: Mar 2017
Planned interim analysis: Planned interim analyses are performed to monitor the safety data.

Objectives:
The primary objectives of this study are divided into two parts: the Phase 1b part and the Phase 2 part.
Phase 1b part: to investigate the safety and tolerability of necitumumab as measured by Dose-Limiting Toxicity (DLT), in combination with gemcitabine-cisplatin chemotherapy as first line treatment in patients with Stage IV squamous NSCLC and to determine the recommended dose for the subsequent Phase 2 study.
Phase 2 part: to evaluate the efficacy of necitumumab in combination with gemcitabine-cisplatin chemotherapy in terms of OS in patients with Stage IV squamous NSCLC in a first-line setting.

The secondary objectives of the study are:
Phase 1b part:

- to investigate the safety profile as assessed by clinically significant events of necitumumab in combination with gemcitabine-cisplatin chemotherapy
- to investigate the anti-tumor effect.
- to assess pharmacokinetics (PK) of necitumumab, gemcitabine, and cisplatin
- to determine the immunogenicity of necitumumab

Phase 2 part:

- to investigate the safety profile as assessed by clinically significant events of necitumumab in combination with gemcitabine-cisplatin chemotherapy
- to investigate PFS
- to investigate objective response rate (ORR)
- to investigate time to treatment failure (TTF)
- to assess PK of necitumumab in combination with gemcitabine-cisplatin
- to assess Quality of Life (QOL; Patient-reported outcomes: PROs) using Lung Cancer Symptom Scale (LCSS) and EuroQol (EQ-5D)
- to assess the relationship between EGFR protein expression (as measured by immunohistochemistry [IHC]) and each of several efficacy measures: overall survival (OS), PFS, and best tumor response (ORR)
- to determine the immunogenicity of necitumumab

Exploratory Objective is to further evaluate as follows:
Phase 1b/2 part: to explore biomarkers including HER2 and HER3 protein expression (IHC), KRAS and EGFR mutation status, fragment C gamma receptor (FCγR) polymorphisms, and/or additional biomarkers of interest related to the necitumumab, gemcitabine, and cisplatin mechanism of action.

Study Design: This is a Phase 1b/2 study in the first-line treatment of patients with advanced (Stage IV) squamous NSCLC. The study consists of a Phase 1b part and Phase 2 part. The Phase 1b part is single arm, open-label, dose-escalation to determine the recommended dose for Phase 2 part. The Phase 2 part is open-label, randomized study to evaluate efficacy and safety of necitumumab in combination with gemcitabine-cisplatin. The target enrollment is 190 patients in Phase 2 part and patients will be randomly assigned on a 1:1 basis to necitumumab plus gemcitabine-cisplatin chemotherapy (Arm A) or gemcitabine-cisplatin chemotherapy alone (Arm B). Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1) and gender (females vs. males).

Diagnosis and Main Criteria for Inclusion and Exclusions:

Key inclusion criteria at the time of enrollment (Phase 1b) or randomization (Phase 2)

- Patient has histologically confirmed squamous NSCLC.
- Patient has Stage IV NSCLC (based on the AJCC, Seventh Edition [Edge et al. 2009]).
- Patients have measurable or nonmeasurable disease documented by computed tomography (CT) scan or magnetic resonance imaging (MRI) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009).
- Patient has the ECOG PS of 0 or 1.
- The patient has not received prior anticancer therapy for NSCLC (eg, surgery, chest radiotherapy, systematic chemotherapy, and targeted therapy).
- Patient has resolution to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, of all clinically significant toxic effects of prior therapy for other than NSCLC.

Test Product, Dosage, and Mode of Administration:

- Necitumumab is a sterile, preservative-free, intravenous (I.V.) infusion supplied in 50-mL vials containing 16 mg/mL (800 mg/50 mL) of product, and administered over 50 minutes at a dose of 800 mg on Days 1 and 8 of each 3-week cycle.
- Gemcitabine is a lyophilized powder, I.V. infusion supplied in sterile vials containing 1 g as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate of product. In the Phase 1b part, gemcitabine is administered over approximately 30 minutes at a dose of 1000 or 1250 mg/m^2 on Days 1 and 8 of each cycle for a maximum of 4 cycles. In the Phase 2 part, gemcitabine is administered over approximately 30 minutes at a dose of 1250 mg/m^2 on Days 1 and 8 of each cycle for a maximum of 4 cycles.

Reference Therapy, Dose, and Mode of Administration:

Cisplatin, administered I.V. over approximately 120 minutes at a dose of 75 mg/m^2 on Day 1 for a maximum of 4 cycles.

Planned Duration of Treatment:

Baseline period: 21 days

Treatment period: 21 days for a treatment cycle. Necitumumab is administered on Days 1 and 8 of each 3-week cycle (21-day cycle), until the patient meets one or more of the discontinuation criteria. Gemcitabine is administered on Days 1 and 8 of each 3-week cycle, and cisplatin is administered on Day 1 of each 3-week cycle, for a maximum of 4 cycles.

30-day safety follow-up period (post-discontinuation): 30 days

Long-term follow-up period (post-discontinuation): Only new and ongoing serious adverse events (SAEs) deemed related to study treatment by the investigator will be collected every 90 days.

Study Completion: The point at which a 137 OS events (deaths) have been observed for final analysis

Study Extension: Patients who are on study therapy at study completion may continue to receive study therapy in the extension phase until they meet the discontinuation criteria.

Criteria for Evaluation:

Efficacy:

Overall Survival (OS): defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of study completion or are lost to follow-up will be censored at the time they were last known to be alive.

Progression-Free Survival (PFS): defined as the time from the date of randomization until the date of radiographically documented progressive disease (PD) or death due to any cause, whichever is earlier.

Time To Treatment Failure (TTF): defined as the time from the date of randomization until the date of the first observation of radiographically documented PD, death due to any cause, discontinuation of treatment for any reason, or initiation of new anticancer therapy.

Objective Response Rate (ORR): defined as the proportion of patients achieving a best response of PR or CR

Safety:

Phase 1b: DLTs, SAEs, adverse events (AEs), vital sign measurements, laboratory analyses, electrocardiograms (ECGs)

Phase 2: SAEs, AEs, vital sign measurements, laboratory analyses, ECGs

Health Outcomes:

All patients will undergo periodic evaluation of Health Outcomes, using:
(1) the LCSS; patient symptom scale only; and (2) the EQ-5D questionnaire.

Bioanalytical:

Blood concentration of necitumumab, gemcitabine, its deaminated metabolite 2',2'-difluorodeoxyuridine (dFdU), and total and free platinum from cisplatin

Pharmacokinetics:

Pharmacokinetics parameters, including, but not limited to, maximum concentration (C_{max}), area under the concentration-time curve (AUC), half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V) of necitumumab in combination with gemcitabine and cisplatin, will be estimated using noncompartmental methods of analysis. Also AUC, C_{max}, CL, $t_{1/2}$, and V of gemcitabine combination with necitumumab and cisplatin will be analyzed, and AUC and C_{max} of cisplatin combination with necitumumab and gemcitabine will be analyzed in the same manner. An exploratory population PK analysis may be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used.

Immunogenicity:

Serum for analysis of antibodies against necitumumab (immunogenicity)

Translational Research:

A tumor tissue block or minimum of 5 tumor tissue slides will be collected for the assessment of EGFR protein expression (IHC), HER2 and HER3 protein expression (IHC), KRAS and EGFR mutation status. Blood samples will be collected for the assessment of FCγR polymorphisms. Additional biomarkers related to the necitumumab, gemcitabine and cisplatin mechanism of action may also be assessed.

Statistical Methods:

The primary efficacy analyses will be conducted on the patients who are randomized and receive at least one dose of study treatment in Phase 2 part. The sample size of 180 patients (137 events) for the primary efficacy evaluation set has 68% power for a log-rank test at 0.2 one-sided alpha under the following assumptions:

- HR = 0.8 (median OS: 13.75 months vs. 11 months)
- Study period of 38 months (Enrollment: 23 months, Follow-Up: 15 months)
- Allocation 1:1

Since a dropout rate of 5% is considered, 190 patients is planned to be enrolled for Phase 2 part.

The final analysis will be performed when at least 137 events (deaths) are observed.

Efficacy: The primary efficacy analyses will be conducted on the full analysis set (FAS), defined as all patients who are randomized and receive at least one dose of study treatments, and patients will be grouped according to treatment received.

For the primary endpoint, OS, the Kaplan-Meier (KM) method will be used to generate KM curves, the medians,

quartiles and percentages of patients event-free every 3-month interval for each arm in FAS. The HR of Arm A to Arm B and its 95% confidence interval (CI) will be estimated using a stratified Cox regression model by the variables used for randomization (ECOG PS and gender), and a stratified log-rank test will be performed.
For ORR, a 95% CI of each arm will be calculated using an exact method, and the difference of ORR between two arms and its 95% CI will be estimated in FAS. The ORR will be compared between the test arm and the control arm using Fisher exact test.
As for TTF and PFS, the same analysis as ones for OS will be performed.
In Phase 1b part, the ORR and CI will be calculated on the patients who are enrolled and treated separately.
Safety: The safety analyses will be conducted on the Safety Population, defined as all treated patients in Phase 1b part and Phase 2 part.
In Phase 1b part, DLT will be summarized by cohort in the patients who are evaluable for DLT assessments and be listed by patient.
For Phase 1b part, Phase 2 part and treated patients with necitumumab (Phase 1b + Arm A in Phase 2 part), the following will be summarized and listed; TEAEs, AEs leading to dose adjustments for any study therapy, laboratory measures and vital signs.
Health Outcomes: Health Outcomes (LCSS and EQ-5D) data will be separately summarized by treatment and time points using descriptive statistics and graphic displays.
Bioanalytical: The result from PK assay and biomarker measurement will be summarized as descriptive statistics.
Pharmacokinetic: Blood concentrations of necitumumab, gemcitabine, dFdU, and total and free platinum from cisplatin at each sampling time point will be graphically summarized as time courses.
PK parameters including CL and V may be estimated by population PK analysis.
Immunogenicity: Incidence of anti-necitumumab antibodies will be tabulated.
Pharmacokinetic/Pharmacodynamic: Relationship with necitumumab drug level, efficacy, and safety will be assessed as appropriate.
Translational Research: Translational research analyses will be performed to analyze relevant biomarkers and to correlate them to clinical outcome.
Interim Analysis:
In Phase 1b part, the interim analysis will be performed after completing DLT evaluation period in Phase 1b part, and patient characteristics, laboratory values, DLTs, and AEs occurring in Cycle 1 might be summarized by cohort. Additionally, even after the above interim analysis, the Sponsor might analyze the data for scientific disclosures.
During Phase 2 part, approximately 6 interim analyses will be performed to monitor the safety data of this study. The first interim analysis for safety monitoring will be performed after 50 patients in Phase 2 part have receives at least two cycles or 6 months after enrollment of the first patient in Phase 2 part, which is earlier. After the first interim analysis, analyses will then be conducted every 6 months until all patients have discontinued all therapy (or until the study completion or the study has been terminated). The independent data monitoring committee (IDMC) members will review safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.
In addition, the Sponsor might consider the interim analysis for regulatory communication purposes. One of possible communications is a discussion of complete clinical data package with Pharmaceutical and Medical Devices Agency (PMDA), considering the results in the global Phase 3 which will be available during this study.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
adverse event (AE)	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.
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBI	average symptom burden index
AST	aspartate aminotransferase
$AUC_{0\text{-}tlast}$	Area Under the (plasma) Concentration versus time curve from time zero to time, where is the last time point with a measurable concentration
$AUC_{0\text{-}\infty}$	Area Under the (plasma) Concentration versus time curve from zero to infinity
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).
clinical research physician (CRP)/clinical research scientist (CRS)	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
CL	clearance
C_{max}	maximum observed (plasma/serum) drug concentration
C_{trough}	minimum observed (plasma/serum) drug concentration during a dosing interval
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.
CR	complete response
CRC	colorectal cancer
CrCL	creatinine clearance
CT	computed tomography
CTCAE	common Terminology Criteria for Adverse Events
CXR	chest X-ray
DCSI	Development Core Safety Information
dFdU	2',2'-difluorodeoxyuridine
DIC	disseminated intravascular coagulation
DLT	dose-limiting toxicity
DNA	Deoxyribo Nucleic Acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
electronic case report form (eCRF)	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.
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
enroll/randomize	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. Phase 1b part: Enroll Phase 2 part: Randomize
enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the Informed Consent Form directly or through their legally acceptable representatives.
ESEC	Efficacy and Safety Evaluation Committee
ethical review board (ERB)	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.

EQ-5D	EuroQol
FAS	full analysis set
FCγR	fragment C gamma receptor
FISH	fluorescence in situ hybridization
GCP	good clinical practice
HBs	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IHC	immunohistochemistry
ILD	interstitial lung disease
ILDC	Interstitial Lung Disease Committee
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
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.
IRRC	Independent Radiography Review Committee
ITT	intent-to-treat
I.V.	Intravenous
IWRS	interactive web-response system
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.
KM	Kaplan-Meier

LCSS	Lung Cancer Symptom Scale
Mab	monoclonal antibody
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MST	median survival time
NCI	National Cancer Institute
NYHA	New York Heart Association
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
per protocol set (PPS)	The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PFS	progression-free survival
PK	pharmacokinetic
PMDA	Pharmaceutical and Medical Devices Agency
PR	partial response
PRO	patient-reported outcomes
PS	performance status
QOL	quality of life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws, etc). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	stable disease
$t_{1/2}$	half-life
TPO	third-party organization
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TTF	time to treatment failure
TW	Time to Worsening
ULN	upper limits of normal
V	volume of distribution
VAS	visual analog scale
WBC	white blood cell

An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)

5. Introduction

5.1. General Introduction to Necitumumab

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 nonclinical 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 (mCRC).

The EGFR is a member of the human EGFR family of tyrosine kinases. The EGFR activation leads to stimulation of tyrosine kinase-dependent signal transduction pathways that can contribute to neoplastic transformation and tumor growth. Inhibition of the EGFR pathway in cells can result in disruption of cell cycle progression and mitosis, and blocks the inhibitory effect on apoptosis. Decreased angiogenesis may also occur as a result of EGFR inhibition through effects on angiogenic factor production.

Epidermal growth factor receptor is expressed in a variety of tumors, including colorectal, head and neck, pancreatic, lung, breast, non-small cell lung cancer (NSCLC), and renal cell carcinoma (Salomon et al. 1995). Expression of EGFR has been correlated with malignant progression, induction of angiogenesis, and inhibition of apoptosis. It has furthermore been associated with chemoresistance and radioresistance. Inhibition of EGFR function has proven to be an effective means of inhibiting tumor cell growth and proliferation (Ennis et al. 1991). Inhibiting EGFR function through the inhibition of ligand binding to EGFR-positive tumor cells is one mechanism for achieving inhibition of tumor growth (Kawamoto et al. 1984; Klohs et al. 1997; Prewett et al. 1998).

Necitumumab, which blocks ligand binding to EGFR, has shown in vivo antitumor activity against a variety of human xenograft tumors. Nonclinical pharmacology studies have demonstrated the ability of necitumumab to offer additive to synergistic antitumor effects to those of irinotecan and oxaliplatin in colorectal cancer (CRC) models, with similar effects on cisplatin-based chemotherapy in NSCLC models. This demonstrated capability to inhibit tumor growth as a single agent, and the ability to significantly complement the antitumor effects of cytotoxic therapy, support the development of necitumumab for the treatment of cancer.

Please see the most current necitumumab Investigator's Brochure (IB) for additional information.

5.2. Clinical Studies of Necitumumab

Necitumumab (at doses ranging from 100 to 1000 mg) has been administered to patients enrolled in a total of 5 studies (Phase 1 to 3), including:

- 2 completed Phase 1 studies in non-Japanese patients and Japanese patients (necitumumab monotherapy in advanced solid tumors);
- 1 completed Phase 2 study (necitumumab in combination with modified FOLFOX-6 in locally advanced CRC or mCRC); and
- 2 ongoing Phase 3 studies (necitumumab plus pemetrexed-cisplatin or gemcitabine-cisplatin in nonsquamous or squamous NSCLC, respectively).

Table JFCM.1 summarizes design information for all 5 studies (including enrollment information, current through 12 July 2012 for ongoing studies).

Table JFCM.1. Summary of Clinical Studies

Study No. Study Title	**Design**	**Treatment Regimen**	**Patients Enrolled** [a]
CP11-0401 Phase 1 Study of the Fully Human Anti-Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody IMC-11F8 in Patients With Solid Tumors Who Have Failed Standard Therapy	Phase 1, single-agent, dose-escalation study	Necitumumab at 100 mg every week (Arm A) and every 2 weeks (Arm B), with escalation in subsequent cohorts to 200, 400, 600, 800, and 1000 mg.	60 **Study Complete [Kuenen et al. 2010]**
CP11-0907 A Phase 1 Study of IMC-11F8 in Patients with Advanced Solid Tumors	Phase 1, single-agent, dose-escalation study in Japanese patients	Patients receive necitumumab at doses of 600 mg (Days 1 and 8 of a 3-week cycle), 800 mg (every 2 weeks), or 800 mg (Days 1 and 8 of a 3-week cycle).	15 **Study Complete**
CP11-0602 Open-Label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of IMC-11F8 in Combination with 5-FU/FA and Oxaliplatin (Modified FOLFOX-6) in Patients with Treatment-Naïve, Locally Advanced or Metastatic Colorectal Cancer	Phase 2, single-arm study	All patients receive necitumumab at 800 mg plus mFOLFOX-6 chemotherapy every 2 weeks.	44 **Study Complete**

(continued)

Summary of Clinical Studies (concluded)

Study No. Study Title	**Design**	**Treatment Regimen**	**Patients Enrolled** [a]
CP11-0805 A Randomized, Multicenter, Open-Label Phase 3 Study of Pemetrexed-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Pemetrexed-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Nonsquamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3, randomized, open-label study	**Arm A** • pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (Day 1 of every 3 week cycle) • necitumumab 800 mg (Days 1 and 8 of every 3-week cycle) **Arm B** • pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (Day 1 of every 3 week cycle)	647 **Ongoing** Enrollment Stopped [b]
CP11-0806 A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)	Phase 3, randomized, open-label study	**Arm A** • gemcitabine 1250 mg/m^2 (Days 1 and 8 of every 3 week cycle) • cisplatin 75 mg/m^2 (Day 1 of every 3 week cycle) • necitumumab 800 mg (Days 1 and 8 of every 3-week cycle) **Arm B** • gemcitabine 1250 mg/m^2 (Days 1 and 8 of every 3 week cycle) • cisplatin 75 mg/m^2 (Day 1 of every 3 week cycle)	1094 **Ongoing** Enrollment Complete

[a] As of 07 July 2012.

[b] Enrollment stopped on 02 February 2011 per Independent Data Monitoring Committee (IDMC) recommendation; see also the Development Core Safety Information (DCSI) in the investigator's brochure for necitumumab.

As of 28 June 2012, the final analysis for Japanese Phase 1 study (CP11-0907) has been finished and the final study report has not been completed. In Study CP11-0907, no Dose-Limiting Toxicity (DLT) was observed. Most common adverse events (AEs) possibly related to necitumumab by the investigator were dry skin and headache (10 patients each; 66.7%), pruritus and rash (8 patients each; 53.3%), stomatitis and anorexia (7 patients each; 46.7%), nausea and pyrexia (6 patients each; 40.0%), and acne (5 patients; 33.3%). One patient in Cohort 2 (necitumumab 800 mg every 2 weeks) experienced two AEs of Grade 3 (dry skin and rash) related to necitumumab, and all other necitumumab related adverse events were of Grade ≤2. A serious adverse event (SAE) related to necitumumab was observed in one patient at Cohort 1 (necitumumab 600 mg on Days 1 and 8 of a 3-week cycle) with oropharyngeal discomfort (Grade 2).

More information about the known and expected benefits, risks and reasonably anticipated AEs may be found in the IB. Information on AEs expected to be related to the study drug may be found in Section 7 (Development Core Safety Information: DCSI) of the IB. 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 study may be found in Section 6 (Effects in Humans) of the IB.

The Sponsor and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.3. Study Rationale

The common chemotherapy regimens for advanced, metastatic NSCLC are based on cisplatin or carboplatin in combination with either taxane (docetaxel or paclitaxel), gemcitabine, vinorelbine, or pemetrexed.

The EGFR is overexpressed in 40% to 80% of NSCLC tumors, where it plays an important role in tumorgenesis. In FLEX, a recent Phase 3 study of cetuximab plus cisplatin-vinorelbine versus cisplatin–vinorelbine alone in the treatment of NSCLC, approximately 85% of 1688 patients screened for entry were positive for EGFR expression (Pirker et al. 2009).

The feasibility of administering EGFR-directed Mabs in combination with a standard platinum-based doublet in the first-line treatment of advanced NSCLC has been demonstrated in several randomized trials. Two randomized Phase 3 trials were conducted with cetuximab in combination with either vinorelbine-cisplatin (FLEX; Pirker et al. 2009) or carboplatin-taxane (BMS-099; Lynch et al. 2010) as the chemotherapy backbone. The addition of cetuximab to both regimens resulted in a statistically significant improvement in the best overall response rate (complete response [CR] + partial response [PR]) in both studies, and in a significant prolongation of survival with statistical significance in FLEX. However in both studies, progression-free survival (PFS) was not different for both treatment arms (hazard ratio [HR] 0.94 [FLEX], HR 0.90 [BMS-099]).

The analyses of both studies by histologic subtypes showed, that for cetuximab-containing regimens, a more pronounced trend in improvement of overall survival (OS) in squamous cell carcinoma (HR 0.80 [FLEX], HR 0.87 [BMS-099]) than in adenocarcinoma (HR 0.94 [FLEX], HR 0.89 [BMS-099]) when compared to chemotherapy alone only. In BMS-099, patients with squamous cell carcinoma had a favorable PFS (HR 0.7) and OS (HR 0.87) when treated with cetuximab-containing regimen compared to chemotherapy alone.

A positive impact of cetuximab on efficacy parameters was reported in 1 randomized Phase 2 study comparing cetuximab in combination with gemcitabine–cisplatin/carboplatin versus the same chemotherapy alone (Butts et al. 2007). The best overall response rate (ORR) was 28% and 18% in the cetuximab-containing arm and the control arm, respectively. Median PFS time was 5.1 versus 4.2 months, and OS time was 12 versus 9.3 months, both for the cetuximab containing-arm versus control, respectively.

Tumor histology has not been consistently associated with clinical outcome for first-line therapy in advanced/metastatic NSCLC, but has recently emerged as a potential predictive factor. In a randomized Phase 3 study by Scagliotti et al. (2008) evaluating pemetrexed-cisplatin versus gemcitabine-cisplatin as first-line treatment in 1725 patients with advanced NSCLC, the OS

associated with these 2 regimens was similar (10.3 months for each arm; HR 0.94). However there were significant differences in OS between the regimens when the patient population was retrospectively analyzed by disease histology. In patients with nonsquamous histology, OS with pemetrexed-cisplatin was significantly greater than gemcitabine-cisplatin (11.8 versus 10.4 months, respectively; HR 0.81; 95% confidence interval [CI] 0.70 to 0.94; p=0.005). Conversely, the OS among patients with squamous cell histology was 10.8 months for gemcitabine-cisplatin versus 9.4 months for pemetrexed-cisplatin (HR 1.23; 95% CI 1.00 to 1.51; p=0.05). Furthermore, in the squamous histological subgroup gemcitabine-cisplatin showed significant advantages over pemetrexed-cisplatin in PFS (HR 1.36, p=0.002) and best ORR (31% versus 23%).

Because of these data and due to the promising add-on effect of EGFR-directed Mabs on the efficacy of gemcitabine-platinum-based chemotherapy, the combination of necitumumab plus gemcitabine-cisplatin chemotherapy versus the same chemotherapy alone is being investigated in a randomized Phase 3 trial as first-line therapy in 1094 patients with Stage IV squamous NSCLC (Study CP11-0806). This study has recently completed patient enrollment.

A post-hoc analysis of the FLEX trial showed evidence that the EGFR expression measured by a semi-quantitative immunohistochemistry score (IHC H-score) may be predictive for the efficacy of EGFR-directed Mabs in combination with platinum-based chemotherapy as first-line therapy in NSCLC (Pirker et al. 2012).

The H-score for the FLEX study was based on a scale ranging from 0 to 300. The H-score of 200 was the cutoff selected to distinguish between low and high H-scores. The cutoff value of 200 was determined by using response data to select an outcome-based discrimination threshold for EGFR expression to distinguish between low versus high EGFR-expressing patients.

The clinical outcome analyses of the FLEX study on the basis of EGFR-expression level based on 1121 patients with EGFR detectable tumor tissue represented 99.6% of the intent-to-treat (ITT) population. The efficacy analysis of the FLEX study revealed no positive impact of cetuximab on cisplatin-vinorelbine in terms of all efficacy parameters (OS, PFS, and ORR) in patients with tumor tissue and an EGFR-IHC H-score <200. A positive impact was demonstrated for patients with an EGFR-IHC H-score of >200 in terms of response rate (increase 16%) and OS (HR 0.73), but the advantage in PFS (HR 0.86) was limited in comparison to the chemotherapy-alone arm.

The subgroup analysis of the FLEX study by tumor histology and EGFR IHC H-score showed, in patients with an H-score <200 for both treatment groups, a similar OS in adenocarcinoma and squamous cell carcinoma. In patients with an H-score of >200 a clinically meaningful risk reduction for death was demonstrated in both adenocarcinoma (HR 0.74) as well as squamous cell carcinoma (HR 0.62) for the cetuximab-containing arm versus the chemotherapy-alone arm. Further, important efficacy data such as PFS and best ORR were not shown for both histological subtypes.

The lack of these data and the selection of an EGFR IHC H-score cut-off value (>200) on the basis of the response rate independent from the histological subtypes raised questions in terms of

the predictive value of this test for the efficacy of EGFR-directed Mabs in combination with different platinum-based chemotherapy regimens, especially in specific histological subtypes of NSCLC.

The Japan Phase 1b/2 study, Study I4X-JE-JFCM (JFCM), is being conducted to evaluate the efficacy of necitumumab in combination with gemcitabine-cisplatin chemotherapy in terms of OS in Japanese patient with advanced squamous NSCLC. The result will be confirmed consistent efficacy trend with global Phase 3 study.

5.4. Rationale for Selection of Dose

In this study, the combination of gemcitabine-cisplatin chemotherapy with or without necitumumab will be administered at the same dose schedule as used in the ongoing Phase 3 study (CP11-0806, gemcitabine-cisplatin with or without necitumumab in first-line treatment of Stage IV squamous NSCLC).

Gemcitabine and Cisplatin

The combination of necitumumab plus gemcitabine-cisplatin chemotherapy versus the same chemotherapy alone is being investigated in a randomized Phase 3 study as first-line therapy in 1094 patients with Stage IV squamous NSCLC (Study CP11-0806). This study has recently completed patient enrollment. The dose selection of Study CP11-0806 for cisplatin in combination with gemcitabine is based on the regimen that had been used in a previous Phase 3 study comparing cisplatin (75 mg/m^2)-gemcitabine (1250 mg/m^2) with pemetrexed (500 mg/m^2)-cisplatin (75 mg/m^2) as first-line therapy in 1725 patients with advanced or metastatic NSCLC. The results of the study demonstrated superior efficacy for cisplatin-gemcitabine in patients with squamous histology, in comparison to pemetrexed-cisplatin (Scagliotti et al. 2008). In the study, the major treatment-related Grade 3 and 4 AEs for cisplatin and gemcitabine in a total of 830 patients were neutropenia (20.7%), thrombocytopenia (12.7%), anemia (9.9%), and vomiting (6.1%).

Japan Phase 1/2 study demonstrates that the combination of CDDP and gemcitabine 1250 mg/m^2 every three weeks is tolerable for Japanese patients with NSCLC (Kusaba et al. 2002). In this study, gemcitabine 1000 mg/m^2 (approved dose in Japan) will be administered to confirm the safety of necitumumab in combination with gemcitabine-cisplatin before the administration of necitumumab and cisplatin (75 mg/m^2)-gemcitabine (1250 mg/m^2).

Based on results of DLT assessment at the Phase 1b part in this study, the recommended dose for the Phase 2 part was determined as necitumumab 800 mg (Days 1 and 8 of each 3-week cycle) in combination with cisplatin 75 mg/m^2 (Day 1) and gemcitabine 1250 mg/m^2 (Days 1 and 8).

Necitumumab

Safety data from Study CP11-0401 demonstrated that the maximum tolerated dose of necitumumab is 800 mg once weekly or once every 2 weeks (Kuenen et al. 2010). The most common drug-related AEs were typical for this class of agents, and consisted of skin reactions, headache, nausea/vomiting, and fatigue (mostly of Grades 1 and 2). In addition, the results in

Study CP11-0907 showed a tolerability of the dose in Japanese patients with advanced solid tumors and could support to apply the doses to further clinical study for Japanese patients.

Nonclinical tumor xenograft models suggested that antitumor activity requires a minimum trough level of necitumumab above 40 μg/mL. Exploratory simulation using clinical pharmacokinetics (PK) data from Study CP11-0401 was conducted to predict trough levels of necitumumab following doses of 600 or 800 mg on Days 1 and 8 of a 3-week cycle, a dosing regimen that is consistent with the standard chemotherapy used in NSCLC. The simulation results suggested that only 800 mg (Days 1 and 8 of a 21-day cycle) would maintain geometric mean trough levels greater than 40 μg/mL throughout the treatment cycle, including on both Day 8 (prior to second infusion: 126 μg/mL) and Day 22 (prior to infusion on Day 1 of Cycle 2: 66 μg/mL).

For treatment regimens based on a 3-week cycle duration, the recommended dose regimen for necitumumab is 800 mg administered on Days 1 and 8 of a 3-week (21 day) cycle. This dose regimen is based on PK simulations, which predicted approximate necitumumab minimum observed drug concentrations (C_{trough}) ranging from 52 to 108 μg/mL and 70 to 112 μg/mL following 600 and 800 mg on Days 1 and 8, respectively of a 3-week day cycle. Therefore, doses of 600 mg or above on Days 1 and 8 of a 3-week cycle would attain the target minimum trough levels of necitumumab associated with antitumor activity in preclinical tumor xenograft models (40 μg/ml); thus, a dose of 800 mg on Days 1 and 8 would provide a suitable margin above target C_{trough} concentrations.

Based on PK data from Study CP11-0401, an exploratory graphical analysis was conducted to assess correlation between clearance and body weight. No apparent correlation was observed between clearance and body weight, which suggested that necitumumab clearance is independent of patient body weight. Therefore, a flat dose (that is, no dose adjustment based on body weight) of 800 mg necitumumab given on Days 1 and 8 of a 3-week cycle is recommended for this study.

This dose regimen is expected to be safe and attain targeted efficacious exposure within the entire study duration.

Necitumumab, Gemcitabine, and Cisplatin

It is considered based on the mechanism of action that the safety profiles of gemcitabine-cisplatin and necitumumab showed at the selected dose schedules no or only marginal overlapping side effects. Therefore, it is expected that necitumumab can be safely administered at the recommended dose with the full dose of gemcitabine and cisplatin. This assumption is confirmed by repeated Independent Data Monitoring Committee (IDMC) safety assessments in the ongoing Phase 3 study (CP11-0806), which revealed no safety concerns associated with the combination of necitumumab with gemcitabine-cisplatin versus the same chemotherapy alone. The Study CP11-0806 completed subject enrollment without any study modification under close safety monitoring by IDMC. EGFR-directed Mabs have been associated with an add-on effect to the efficacy of gemcitabine-cisplatin (Butts et al. 2007). At a pooled data analysis in Study CP11-0806, as of 18 December 2011, the most frequent Grade 3 AEs regardless causality were neutropenia (159 patients; 16.2%), anemia (85 patients; 8.7%),

thrombocytopenia (53 patients; 5.4%), leukopenia (43 patients; 4.4%), asthenia (38 patients; 3.9%), dyspnea (29 patients; 3.0%), and hypomagnesemia (29 patients; 3.0%). Grade ≥4 events affecting >1% of the total treated population included neutropenia (56 patients; 5.7%), thrombocytopenia (29 patients; 3.0%), pulmonary embolism (14 patients; 1.4%), and pneumonia (10 patients; 1.0 %). The IDMC has been recommending to continue the study for approximately 500 patients treated with necitumumab in combination with gemcitabine and cisplatin.

Based on these data, the benefit-risk balance for the selected combination regimen is regarded as favorable.

6. Objectives

6.1. Primary Objective

The study is divided into two parts:

Phase 1b part: to investigate the tolerability of necitumumab as measured by DLT, in combination with gemcitabine-cisplatin chemotherapy as first line treatment in patients with Stage IV squamous NSCLC and to determine the recommended dose for the subsequent Phase 2 study.

Phase 2 part: to evaluate the efficacy of necitumumab in combination with gemcitabine-cisplatin chemotherapy in terms of OS in patients with Stage IV squamous NSCLC in a first-line setting.

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

Phase 1b part

- to investigate the safety profile as assessed by clinically significant events of necitumumab in combination with gemcitabine-cisplatin chemotherapy
- to investigate the anti-tumor effect
- to assess PK of necitumumab, gemcitabine and cisplatin
- to determine the immunogenicity of necitumumab

Phase 2 part

- to investigate the safety profile as assessed by clinically significant events of necitumumab in combination with gemcitabine-cisplatin chemotherapy
- to investigate PFS
- to investigate ORR
- to investigate time to treatment failure (TTF)
- to assess PK of necitumumab in combination with gemcitabine-cisplatin
- to assess Quality of life (QOL; Patient-reported outcomes: PROs) using Lung Cancer Symptom Scale (LCSS) and EuroQol (EQ-5D)
- to assess the relationship between EGFR protein expression (as measured by immunohistochemistry [IHC]) and each of several efficacy measures: OS, PFS, and ORR
- to determine the immunogenicity of necitumumab

6.3. Exploratory Objective

Phase 1b/2 part: to explore biomarkers including HER2 and HER3 protein expression (IHC), KRAS and EGFR mutation status, fragment C gamma receptor (FCγR) polymorphisms, and/or additional biomarkers of interest related to the necitumumab, gemcitabine and cisplatin mechanism of action.

7. Study Population

7.1. Inclusion Criteria

The criteria for enrollment must be followed explicitly. Patients are eligible to be included in the study only if they meet **all** of the following criteria at the time of enrollment (Phase 1b) or randomization (Phase 2):

[1] Patient has histologically confirmed squamous NSCLC.

[2] Patient has Stage IV NSCLC disease (based on the American Joint Committee on Cancer [AJCC], Seventh Edition [Edge et al. 2009]).

[3] Patients have measurable or nonmeasurable disease documented by computed tomography (CT) scan or magnetic resonance imaging (MRI) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009).

[4] Patient has the Eastern Cooperative Oncology Group (ECOG) a performance status (PS) of 0 or 1 (Attachment 4).

[5] The patient had not received prior anticancer therapy for NSCLC (eg, surgery, chest radiotherapy, systematic chemotherapy, and targeted therapy).

[6] Patient has resolution to Grade ≤1 by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, of all clinically significant toxic effects of prior therapy for other than NSCLC.

[7] Patient has adequate organ function, defined as:

- Total bilirubin ≤1.5 x the upper limit of normal value (ULN),
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN
- Serum creatinine ≤1.2 x ULN or calculated creatinine clearance (CrCL) >50 mL/min (per the Cockcroft Gault formula or equivalent and/or 24-hour urine collection).
  Cockcroft-Gault formula filtration rate

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

  a age in years, weight (wt) in kilograms.
- Absolute neutrophil count (ANC) ≥1.5 x $10^3/\mu L$
- Hemoglobin ≥10.0 g/dL
- Platelets ≥100 x $10^3/\mu L$.

[8] At least 20 years of age

[9] Patient has a life expectancy of ≥12 weeks

[10] A formalin-fixed, paraffin-embedded tumor tissue block or a minimum of 5 unstained slides of tumor sample (archived or recent) must be made available prior to randomization for the evaluation of EGFR protein expression (IHC).

[11] If women, the patient is surgically sterile, postmenopausal, or compliant with a highly effective contraceptive method (failure rate <1%) during and for 6 months after the treatment period (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method).
If men, the patient is surgically sterile or compliant with a highly effective contraceptive regimen during and for 6 months after the treatment period.

[12] Patient has provided signed informed consent and is amenable to compliance with protocol schedules and testing.

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria at the time of enrollment (Phase 1b) or randomization (Phase 2):

[13] The patient is currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product 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.

[14] Patient has undergone major surgery within 28 days or subcutaneous venous access device placement within 7 days prior to enrollment (Phase 1b) or randomization (Phase 2). Furthermore, any patient with postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months will be excluded.

[15] Patient has undergone any prior radiation therapy, except for stereotactic irradiation and palliative radiation treatment at least 14 days have elapsed from last radiation treatment prior to enrollment (Phase 1b) or randomization (Phase 2). Prior radiation therapy is allowed to less than 25% of bone marrow.

[16] The patient has brain metastases that are symptomatic or require surgery, medication and radiotherapy except for stereotactic irradiation.

Patients who have undergone previous stereotactic irradiation for brain metastases, who are now non-symptomatic and no longer require treatment with steroids or anticonvulsants at least 14 days prior to enrollment (Phase 1b) or randomization (Phase 2), are eligible.

[17] Patient has superior vena cava syndrome.

[18] Patient has clinically relevant coronary artery disease or uncontrolled congestive heart failure (New York Heart Association [NYHA] III or IV) or cardiac arrhythmia poorly controlled by medications.

[19] Patient has uncontrolled hypertension defined as systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥90 mmHg despite standard medical management.

[20] Patient has diabetes requiring insulin.

[21] Patient has an angina or has experienced myocardial infarction within 6 months prior to enrollment (Phase 1b) or randomization (Phase 2).

[22] Acquired immunodeficiency syndrome (AIDS)-related illness, or have evidence of or test positive test results for human immunodeficiency virus (HIV).

[23] Have evidence of or test positive test results for hepatitis B, or hepatitis C virus antibodies (HCVb)

- positive for hepatitis B surface antigen (HBsAg+), or
- positive for anti-hepatitis B core antibody and positive for hepatitis B deoxyribonucleic acid (HBV DNA), or
- positive for anti-hepatitis B surface antibody (HBsAB+) and positive for hepatitis B deoxyribonucleic acid (HBV DNA)

[24] Previous or concurrent malignancy except for basal or squamous cell skin cancer (non-melanoma) and/or preinvasive carcinoma of the cervix, mucosal gastrointestinal or uterine carcinoma, or other solid tumors treated curatively (ie, curative resection of tumors) and without evidence of recurrence for at least 3 years prior to enrollment (Phase 1b) or randomization (Phase 2)

[25] 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

[26] Have significant third-space fluid retention (for example, ascites or pleural effusion) requiring drainage.

[27] Have history of interstitial pneumonia, or patient who showed clinically significant diffuse shadows (interstitial pneumonia or pulmonary fibrosis) as opacity on chest X-ray (CXR) or CT.

[28] Have an ongoing or active infection (requiring systemic treatment), including active tuberculosis.

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

[30] Have a peripheral neuropathy ≥Grade 2 (NCI-CTCAE version 4.0).

[31] Are pregnant (confirmed within 7 days prior to enrollment [Phase 1b] or randomization [Phase 2]), or breastfeeding. If women who stop breastfeeding enter the study, the women must stop breastfeeding during and for at least 30 days after the treatment period.

[32] Have known history of drug abuse.

[33] Are assessed as inadequate for the study by the investigator or sub investigator.

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [13] 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 [14] to [33] help in maintaining specificity of the patient population for both efficacy and safety analyses and/or to maintain patient safety.

7.3. Discontinuations

7.3.1. Discontinuation of 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 the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

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

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - The investigator/physician decides that the patient should be withdrawn from the study or study treatment.
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study treatment occurs prior to introduction of the new agent.

- Patient Decision
  - The patient or patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study treatment.
- Sponsor Decision
  - The Sponsor stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient is significantly noncompliant with study procedures and/or treatment
- An unacceptable adverse event/toxicity (eg, a persistent moderate toxicity that is intolerable to the patient)
- A Grade 3 to 4 infusion-related reaction
- Any therapy-related event that is deemed life-threatening, regardless of grade
- Any event that 1) requires a given study therapy to be modified by more than two dose reductions in all study treatments (necitumumab, gemcitabine, and cisplatin), or 2) requires all study treatments to be discontinued for more than 6 weeks following Day 1 of the most recent cycle, would warrant discontinuation of all treatments (The discontinuation criteria for each treatment are shown in Section 9.4.1.2).
- Radiographic documentation of progressive disease (PD)
- An intercurrent 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.

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

Follow-up evaluations should be performed as described in Protocol Attachment 1. All patients will be followed for survival at regularly scheduled intervals (every 90 days), for as long as the patient remains alive until study completion.

7.3.2. Discontinuation of Study Sites

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

7.3.3. Discontinuation of the Study

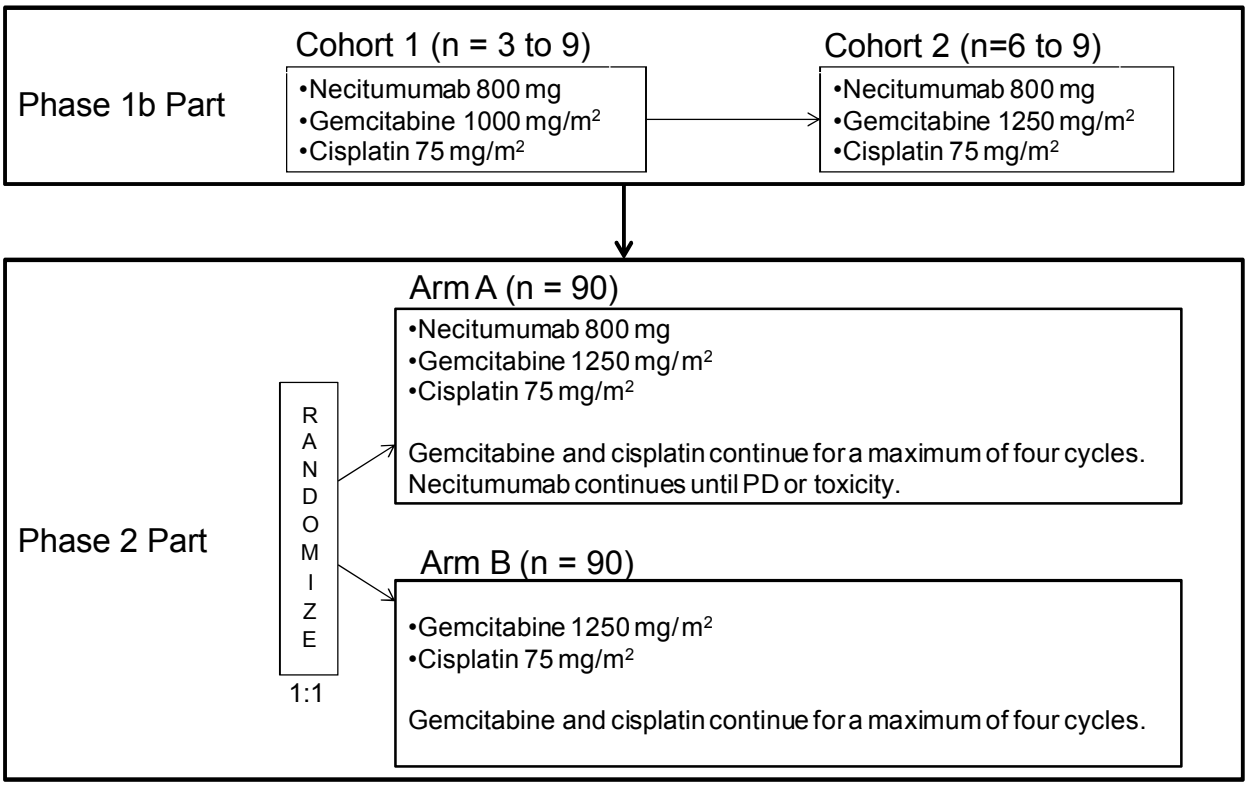
The study will be discontinued if the Sponsor judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

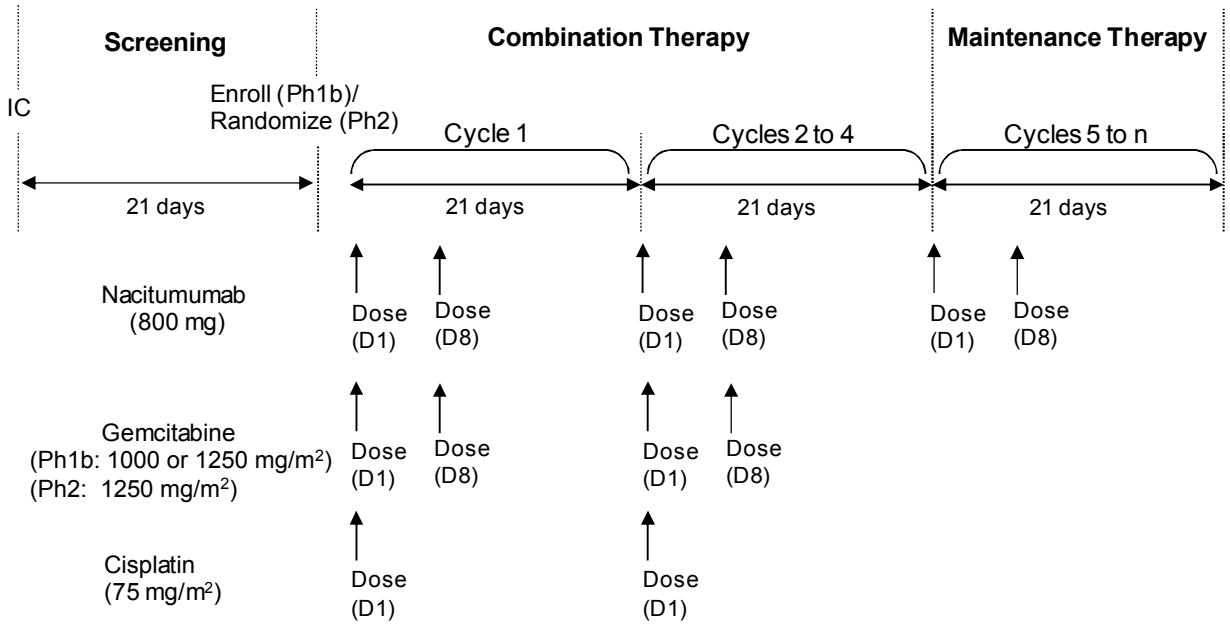
Study JFCM is an open-label, multicenter, Phase 1b/2 study in patients with Stage IV squamous NSCLC.

The study is divided into two parts: the Phase 1b part and the Phase 2 part (Figure JFCM.1).



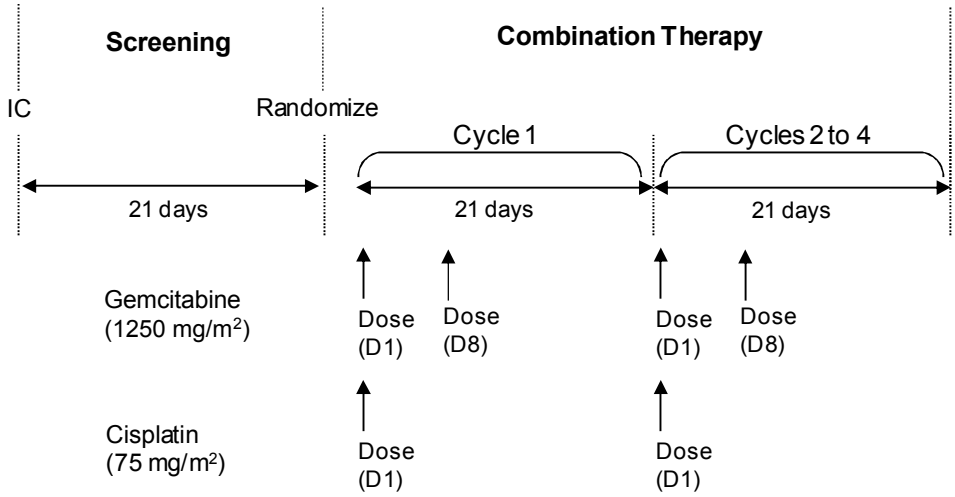
Abbreviations: n = numbers of patient, PD = progressive disease

Figure JFCM.1. Illustration of study design for Protocol I4X-JE-JFCM.



Abbreviations: IC = informed consent, D = Day

Figure JFCM.2. Illustration of study schedule in Phase 1b and Phase 2 part (Arm A)



Abbreviations: IC = informed consent, D = Day

Figure JFCM.3. Illustration of study schedule in Phase 2 part (Arm B)

Screening may occur up to 21 days prior to the enrollment (Phase 1b) or randomization (Phase 2) for each patient. Following enrollment (Phase 1b) or randomization (Phase 2), the first dose of study medication should be administered within 7 days. Patients may admit to the study site during Cycle 1 as appropriate. A treatment cycle will be defined as 3 weeks. Patients will be treated until there is radiographic PD, toxicity requiring cessation, withdrawal of consent, or until

other withdrawal criteria are met. The overviews of study schedule are shown in Figure JFCM.2 and Figure JFCM.3.

Terms used to describe the study periods are defined below:

- **Baseline:** from the time of screening to first study treatment (or discontinuation, if no treatment is given)
- **Study Treatment Period:** time from treatment start to discontinuation from study treatment
- **Post-discontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment For the patient who completed all treatments of Cycle 4 in Arm B of Phase 2 part, post-discontinuation follow-up begins the day after the Cycle 4 completion.
    - 30-Day Safety Follow-Up Period: begins one day after the decision to discontinue study treatment and lasts approximately 30 days. For the patient who completed all treatments of Cycle 4 in Arm B of Phase 2 part 30-day safety follow-up period begins one day after Cycle 4 completion and lasts approximately 30 days.
    - Long-term Follow-Up Period: begins one day after the 30-day safety follow-up period is completed and continues until death to collect additional data (for example, survival data).
- **Study Completion:** defined as the point at which a sufficient number of OS events (deaths) have been observed for final analysis, and the clinical trial database has been locked for final analysis of all endpoints.
- **Study Extension:** time following study completion and prior to the end of trial as defined in Section 8.1.6.
- **End of Trial:** Defined as the point at which a sufficient number of OS events (deaths) have been observed for final analysis, and the last patient has discontinued study treatment and completed the 30-day safety follow-up visit.

8.1.1. Phase 1b Part

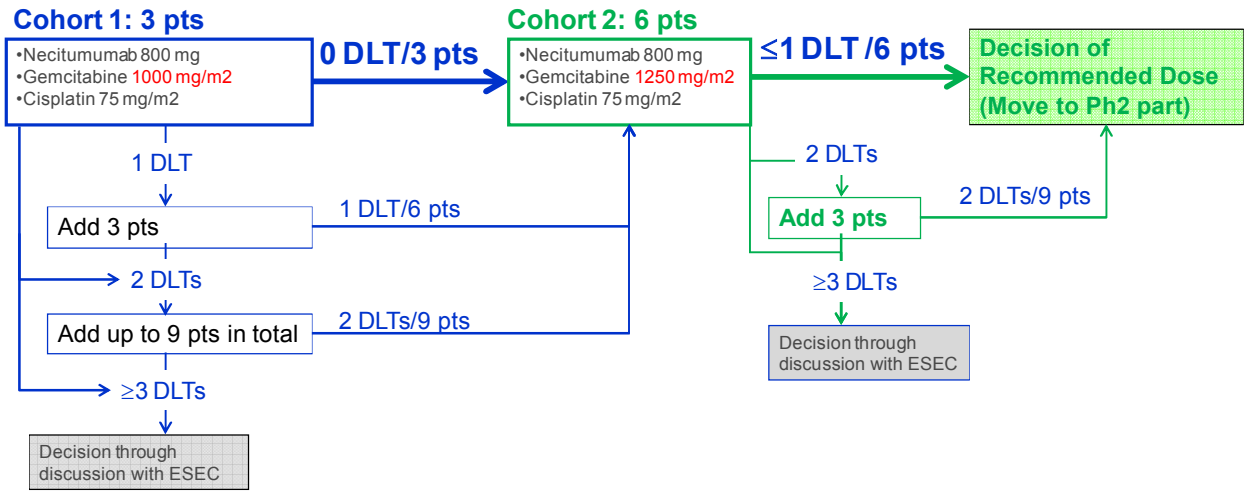
The Phase 1b part is single arm, dose-escalation to determine the recommended dose for Phase 2 part.

Following necessary premedication, all patients will receive study therapy, consisting of:

- Necitumumab, administered intravenously (I.V.) over 50 minutes at an absolute dose of 800 mg on Days 1 and 8.
- Gemcitabine, administered I.V. over approximately 30 minutes at a dose of 1000 or 1250 mg/m^2 for a maximum of 4 cycles on Days 1 and 8.
- Cisplatin, administered I.V. over approximately 120 minutes at a dose of 75 mg/m^2 on Day 1 for a maximum of 4 cycles.

Patients will receive necitumumab, followed by gemcitabine. Cisplatin will be administered to patients at least 30 minutes following the end of the gemcitabine infusion.

At least 9 patients will be enrolled to Phase 1b part (3 patients in Cohort 1 and 6 patients in Cohort 2) (Figure JFCM.4). A DLT-evaluable patient is considered to be one who has received at least one dose of gemcitabine and cisplatin and two doses of necitumumab and completed safety monitoring for DLT evaluation period (21 days in Cycle 1) (see Section 9.4.1.1). Any patient who is discontinued from the study before completing safety monitoring for DLT evaluation period will be deemed non-evaluable for assessment the tolerability of a dose level unless the patient experience a DLT before withdrawal or it can be documented that the patient doesn't experience a DLT during DLT evaluation period (21 days in Cycle 1). Additional patients may be enrolled as replacements for non-DLT evaluable patients.



Abbreviations: DLT = Dose limited-toxicity; ESEC = Efficacy and Safety Evaluation Committee; Ph2 = Phase 2; pts = patient

Figure JFCM.4. The scheme of dose escalation in Phase 1b part

Cohort 1 will be started at a dose level of necitumumab 800 mg, Gemcitabine 1000 mg/m^2, and Cisplatin 75 mg/m^2 , and 3 subjects will be enrolled in Cohort 1. If none of 3 DLT evaluable patients in Cohort 1 develops DLT, Cohort 2 will be started at a dose level of necitumumab 800 mg, Gemcitabine 1250 mg/m^2, and Cisplatin 75 mg/m^2. If 1 of the first 3 DLT evaluable patients develops DLT at Cohort 1, 3 more patients will be added. If 2 DLT evaluable patients develop DLT at Cohort 1, the enrollment will be continued up to total 9 patients for Cohort 1, or until 3 patients develop DLTs, whichever occurs first.

If the number of DLT evaluable patients with DLT is none out of 3, 1 out of 6, or 2 out of 9 in Cohort 1, Cohort 2 will be started after consultation with the Efficacy and Safety Evaluation Committee (ESEC). If 3 patients or more develop DLTs in Cohort 1, the Sponsor will consult the ESEC to decide whether study should be discontinued or not.

Cohort 2 will be started at a dose level of necitumumab 800 mg, Gemcitabine 1250 mg/m^2, and Cisplatin 75 mg/m^2, and 6 patients will be enrolled in Cohort 2. If ≤1 of the first 6 DLT

evaluable patients develops DLT in Cohort 2, the Phase 2 part will be started with the dose level of Cohort 2 after consultation with the ESEC.

If 2 of the first 6 DLT evaluable patients develop DLT in the Cohort 2, 3 more patients will be added. If none of the additional 3 DLT evaluable patients develops DLT, the Phase 2 part will be started with the dose level of Cohort 2 after consultation with the ESEC.

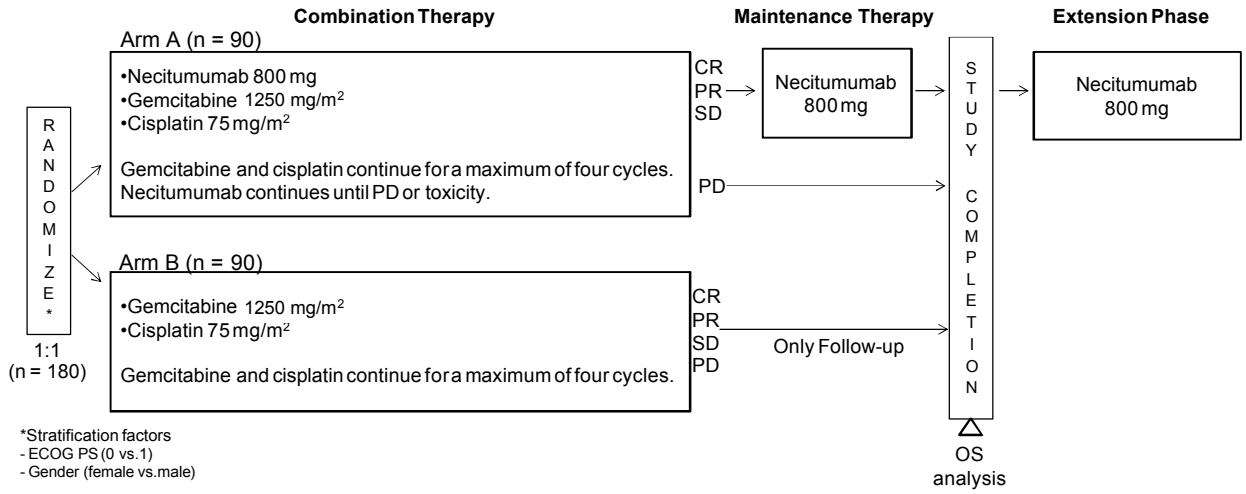
If 3 DLT evaluable patients or more develop DLTs in Cohort 2, the Phase 2 part may be started with the dose level of Cohort 1 after consultation with the ESEC. Further patients' enrollment in Cohort 1 may be considered to investigate safety and tolerability of the do se level concretely.

Patients in whom DLT occurs in Cycle 1 may still continue study treatment according to the criteria for starting the next cycle (Section 9.4.1.2) or dose modification (Section 9.4.1.3) if the patients are benefiting from study treatment in the opinion of the investigator.

Gemcitabine-cisplatin plus necitumumab may continue for a maximum of 4 cycles; patients with at least stable disease may continue to receive necitumumab until disease progression, the development of unacceptable toxicity or withdrawal of consent by the patient, or Sponsor/investigator decision.

8.1.2. Phase 2 Part

The Phase 2 part is randomized study to evaluate efficacy and safety of necitumumab in combination with gemcitabine-cisplatin (Figure JFCM.5).



Abbreviations: n = numbers of patient, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, OS = overall survival, PS = performance status

Figure JFCM.5. Illustration of study design in Phase 2 part

In the Phase 2 part, 180 patients with Stage IV squamous NSCLC will be randomized on a 1:1 basis to receive:

(1) necitumumab plus gemcitabine-cisplatin chemotherapy (Arm A); or
(2) gemcitabine-cisplatin chemotherapy alone (Arm B)

Randomization will be stratified by ECOG PS (0 vs. 1) and gender (female vs. male).

Following necessary premedication, all patients will receive study therapy, consisting of:

Arm A

- Necitumumab, administered I.V. over 50 minutes at an absolute dose of 800 mg on Days 1 and 8
- Gemcitabine, administered I.V. over approximately 30 minutes at a dose of 1250 mg/m^2 (based on the outcome of the Phase 1b part) on Days 1 and 8 for a maximum of 4 cycles; and
- Cisplatin, administered I.V. over approximately 120 minutes at a dose of 75 mg/m^2 on Day 1 for a maximum of 4 cycles.

Arm B

- Gemcitabine, administered I.V. over approximately 30 minutes at a dose of 1250 mg/m^2 (based on the outcome of the Phase 1b part) on Days 1 and 8 for a maximum of 4 cycles; and
- Cisplatin, administered I.V. over approximately 120 minutes at a dose of 75 mg/m^2 on Day 1 for a maximum of 4 cycles.

In Arm A, patients will receive necitumumab, followed by gemcitabine. In both arms, cisplatin will be administered to patients at least 30 minutes following the end of the gemcitabine infusion.

Gemcitabine and cisplatin continue for a maximum of 4 cycles. In Arm A, necitumumab continue exceeding 4 cycles, until disease progression, the development of unacceptable toxicity, protocol noncompliance or withdrawal of consent by the patient, or Sponsor/investigator decision. In Arm B, no maintenance therapy is permitted after 4 cycles of gemcitabine-cisplatin until disease progression.

8.1.3. Baseline and Study Treatment Period assessments

The Study Schedule (Attachment 1) describes the timing of baseline and study treatment period assessments.

Written informed consent must be obtained prior to any study-specific pretreatment evaluations. At baseline (within 21 days prior to dosing unless otherwise specified in Attachment 1) and during the study treatment period, medical and physical examinations, tumor measurements of palpable or visible lesions, ECOG PS evaluation, electrocardiogram (ECG) assessment, and serum chemistry, hematology, urinalysis, and coagulation laboratory tests will be completed. Blood samples for PK, biomarker, immunogenicity, and other evaluations, and tumor tissue for exploratory analyses, will be collected.

Baseline radiographic assessment of disease will be performed within 21 days prior to enrollment (Phase 1b part) or randomization (Phase 2 part); first treatment will be administered within 7 days following enrollment (Phase 1b) or randomization (Phase 2).

Patients will undergo radiographic assessment of disease status (CT or MRI) every 6 weeks (−7 to +3 business days), as calculated from the first dose of study therapy, regardless of treatment delays, until there is radiographic documentation of PD, per efficacy measurement criteria described in Section 10.1. Tumor responses will be confirmed for patients with objective assessment of PR or CR at the next routine scheduled imaging time point (no less than 4 weeks after the initial response is noted). Imaging methods used at baseline should be consistently used during study.

All enrolled patients will be assessed for toxicity at each visit.

Criteria for starting the next cycle are defined in Section 9.4.1.2. Dose reductions of investigational product and/or gemcitabine-cisplatin chemotherapy will be made in the event of specific treatment related AEs, as described in Section 9.4.1.3. Administration of one or more components of therapy (gemcitabine or cisplatin, and necitumumab in Arm A) may be delayed due to toxicity for a maximum of 6 weeks from the first dose of the previous cycle. If toxicity occurs necessitating a delay to administration of any given component of longer than 6 weeks, that component must be permanently discontinued; other components of therapy may be continued without interruption or modification if appropriate in the opinion of the investigator. Supportive care guidelines are detailed in Section 9.7.1.

8.1.4. Post-discontinuation Follow-Up Period Assessments

Post-discontinuation follow-up period begins one day after the patient and the investigator agree that the patient will no longer continue study treatment, and continues until the study completion. For the patient who completed all treatments of Cycle 4 in Arm B of Phase 2 part, Post-discontinuation follow-up begins the day after the Cycle 4 completion and continues until the study completion. Follow-up assessments will be conducted as shown in the Study Schedule (Attachment 1).

8.1.4.1. 30-Day Safety Follow-Up Period

All patients should be followed and AEs reported for a minimum of 30 days from the date of the decision to discontinue therapy (as described in Section 10.3).

A 30-day safety follow-up visit will be completed at least 30 days (+0 to 7 days) after the decision is made to discontinue therapy.

8.1.4.2. Long-term Follow-Up Period

Following discontinuation of all study treatment, patients will be followed for survival every 90 days, until death or until study completion as defined in Section 8.1.5.

Patients who discontinue study treatment for any reason other than PD will continue to undergo radiographic tumor assessments every 6 weeks (−7 to +3 business days) until PD, except when not feasible in the opinion of the investigator. Assessment will continue until radiographic

documentation of PD, as long as the patient is alive or until study completion as defined in Section 8.1.5.

Other follow-up assessments will be conducted as shown in the Study Schedule (Attachment 1).

8.1.5. Study Completion

This study will be considered complete on the date which 137 OS events (deaths) have been observed for the final analysis (approximately 15 months after the last patient starts study treatment).

8.1.6. Study Extension

Following study completion, if there are patients that have not experienced disease progression and are still receiving study therapy, the study will enter an extension period during which patients may continue to receive study therapy until there is radiographic documentation of PD, intolerable toxicity, withdrawal of consent, or until new anticancer treatment is initiated. Sites will be notified when the extension phase will begin.

During the study extension phase, the following information will be collected according to Attachment 1:

- AE assessment (including SAEs), until at least 30 days after the decision is made to discontinue study treatment;
- Administration information of study treatment;
- Reason for study therapy discontinuation (disposition); and
- Blood sampling for immunogenicity analysis in the event of an infusion-related reaction and at the 30-day Safety Follow-up visit.

During the extension phase, routine safety and efficacy monitoring, including an assessment schedule similar to that outlined in this protocol with radiographic evaluation of disease at least every 6 weeks, should be continued as necessary to confirm patient eligibility to continue in the study. The Sponsor will collect only data shown in Protocol Attachment 1 for the extension phase.

8.1.7. End of Study

The end of trial is the date when:

- A sufficient number of OS events (deaths) have been observed for final analysis (for details please see the statistical analysis plan [SAP] for this study); and
- The last patient has discontinued study treatment and completed the 30-day safety follow-up visit.

8.1.8. Committees

The following committees will be established to evaluate or patients' safety or efficacy of the study treatments. In addition, examination results such as image data and tissue samples may be

submitted to the committees to evaluate the results. For detailed information, refer to the handling procedures provided for this study.

Interstitial Lung Disease Committee (ILDC)

Interstitial Lung Disease Committee will be established. For the interstitial lung disease (ILD) and suspected ILD cases being diagnosed after starting the study treatments (on Day 1 in Cycle 1), external specialists will evaluate its related examination results such as image data and tissue samples. The assessments by the ILDC are independent from assessments by investigators and will not be collected in the clinical trial database. The assessments by the ILDC will be provided to the Sponsor and used for safety monitoring. Assessments by the ILDC will not be made available to investigators in principle.

Efficacy and Safety Evaluation Committee (ESEC)

Efficacy and Safety Evaluation Committee will be established as an independent organization for Phase 1b part. The Sponsor will consult with ESEC about DLT evaluation and cohort transition.

Independent Data Monitoring Committee (IDMC)

Independent Data Monitoring Committee will be established prior to the inclusion of the first patient in the study of Phase 2 part, and will perform the evaluation for safety.

Independent Radiography Review Committee (IRRC)

Independent Response Review Committee may review the CT scans and MRI data for tumor assessments independently if necessary (eg, inquiries from regulatory authorities).

8.2. Discussion of Design and Control

In this study, the efficacy of necitumumab in combination with gemcitabine -cisplatin chemotherapy in terms of OS in patient with advanced squamous NSCLC in Phase 2 part after confirming the tolerability of necitumumab in combination with gemcitabine -cisplatin chemotherapy in Phase 1b part.

Phase 1b part

In Study CP11-0907, the dose of 800 mg of necitumumab monotherapy which is the global recommended dose in Study CP11-0806 was tolerable for Japanese patients with solid tumors. The tolerability of necitumumab in combination with gemcitabine-cisplatin was not investigated in Japan. Therefore, Phase 1b part is planned to confirm the tolerability of necitumumab (800 mg) in combination with gemcitabine-cisplatin before Phase 2 part. The design of Phase 1b part is based on the Guidelines for Clinical Evaluation Methods of Antimalignant Tumor Drugs (Pharmaceutical and Food Safety Bureau. 2005).

The part is single arm, open-label, dose-escalation to determine the recommended dose of gemcitabine for Phase 2 part. In the first cohort of Phase 1b part, necitumumab 800 mg, gemcitabine 1000 mg/m^2 and cisplatin 75 mg/m^2 are to be examined. After confirming the tolerability of necitumumab 800 mg, gemcitabine 1000 mg/m^2, and cisplatin 75 mg/m^2,

necitumumab 800 mg, gemcitabine 1250 mg/m^2, and cisplatin 75 mg/m^2 which are the recommended doses in Study CP11-0806 are to be investigated in the second cohort.

Based on results of DLT assessment at the Phase 1b part in this study, the recommended dose for the Phase 2 part was determined as necitumumab 800 mg (Days 1 and 8 of each 3-week cycle) in combination with cisplatin 75 mg/m^2 (Day 1) and gemcitabine 1250 mg/m^2 (Days 1 and 8).

Phase 2 part

The Phase 2 part is open-label, randomized study to evaluate efficacy and safety of necitumumab in combination with gemcitabine-cisplatin.

The part will be conducted open-label, since following the first treatment session, the expected occurrence of acneform rash (common with EGFR inhibitors) in the necitumumab plus chemotherapy arm (Arm A) relative to the chemotherapy-only arm (Arm B) would unblind most patients and investigators to treatment assignment.

A randomized, controlled design is being used in this part. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this part. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects.

9. Treatment

9.1. Treatments Administered

Following necessary premedication (Section 9.1.1), patients will receive the treatment regimens in the order shown in Table JFCM.2.

Table JFCM.2. Treatment Regimens (3-week Cycle)

		Drug	Dose	Day	Infusion duration
Phase 1b	Cohort 1	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 50 minutes
		Gemcitabine	1000 mg/m^2 I.V. infusion	Days 1 and 8	over 30 minutes
		Cisplatin	75 mg/m^2 I.V. infusion	Day 1	over 120 minutes
	Cohort 2	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 50 minutes
		Gemcitabine	1250 mg/m^2 I.V. infusion	Days 1 and 8	over 30 minutes
		Cisplatin	75 mg/m^2 I.V. infusion	Day 1	over 120 minutes
Phase 2	Arm A	Necitumumab	800 mg absolute dose I.V. infusion	Days 1 and 8	over 50 minutes
		Gemcitabine	1250 mg/m^2 I.V. infusion	Days 1 and 8	over 30 minutes
		Cisplatin	75 mg/m^2 I.V. infusion	Day 1	over 120 minutes
	Arm B	Gemcitabine	1250 mg/m^2 I.V. infusion	Days 1 and 8	over 30 minutes
		Cisplatin	75 mg/m^2 I.V. infusion	Day 1	over 120 minutes

Abbreviations: I.V. = intravenous.
Gemcitabine: Administration in each 3-week cycle for a maximum of 4 cycles.
Cisplatin: Administration in each 3-week cycle for a maximum of 4 cycles, at least 30 minutes following the end of the gemcitabine infusion.
NOTE: The duration of each infusion will be based on standard procedure (eg, package insert) in standard therapeutic practice.

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, for Day 1 of every cycle, infusions administered within 5 days after the planned infusion time point will be considered acceptable. Deviations beyond this window are strongly discouraged.

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

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

9.1.1. Premedication

All premedication administered must be adequately documented in the electronic case report form (eCRF).

9.1.1.1. Premedication for Cisplatin and Gemcitabine

Premedication for cisplatin will be recommended in accordance with the package insert.

Gemcitabine will be administered on Days 1 and 8 for 30 minutes. Cisplatin will be administered on Day 1 for 120 minutes. Prophylactic antiemetics will be routinely administered. Drugs will be administered intravenously as follows. On Days 1, patients will be given I.V. hydration of normal saline. A 5-HT_3 receptor antagonist (eg, 3 mg), steroides (eg, 16 mg of dexamethasone) and a neurokinin 1 (NK_1) receptor antagonist (eg, aprepitant) will be given.

9.1.2. Investigational Product

9.1.2.1. 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 50 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 or procedure for detailed information. Necitumumab administration which is different from that outlined in the IB but described in the Investigational Product Handling Procedures is acceptable.

9.1.2.2. Gemcitabine

Gemcitabine will be supplied by the Sponsor, and should be prepared and administered according to the manufacturer's instructions. In the Phase 1b part, gemcitabine will be administered at a dose of 1000 or 1250 mg/m^2 (I.V.) over 30 minutes on Days 1 and 8 of each 3-week treatment cycle, for a maximum of 4 cycles. In the Phase 2 part, gemcitabine will be administered at a dose of 1250 mg/m^2 (I.V.) over 30 minutes on Days 1 and 8 of each 3-week treatment cycle, for a maximum of 4 cycles.

9.1.3. Cisplatin

A commercial preparation of cisplatin will be used and should be prepared and administered according to the manufacturer's instructions. Cisplatin will be administered beginning at least 30 minutes after the completion of the gemcitabine infusion on Day 1 of each 3-week treatment

cycle, at a dose of 75 mg/m2 (I.V.) administered over 120 minutes. Cisplatin will be administered for a maximum of 4 cycles.

9.2. Materials and Supplies

Clinical trial materials will be labeled according to the country's regulatory requirements.

Necitumumab is a sterile, preservative-free solution for infusion of necitumumab formulated in an aqueous solution at a concentration of 16 mg/mL (800 mg/50 mL vial). The buffer contains 10 mM citrate, 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol, 0.01% polysorbate 80. The drug product must be stored under refrigeration at 2ºC to 8ºC with protection from light.

Gemcitabine is a lyophilized powder, I.V. infusion supplied in sterile vials containing 1 g as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate of product. The drug product must be stored at controlled room temperature.

Cisplatin of a commercial product will be used and should be stored in accordance with the package insert.

9.3. Method of Assignment to Treatment

Phase 1b part:

Patients who meet all criteria for enrollment will be assigned to receive necitumumab 800 mg, gemcitabine 1000 or 1250 mg/m2, and Cisplatin 75 mg/m2 in this part. Upon confirmation of eligibility, the Sponsor will assign the treatment cohort (dose level) for each patient.

Phase 2 part:

Patients who meet all criteria for enrollment will be randomly assigned to receive either Arm A or Arm B within 7 days prior to administration of first treatment.

Upon completion of all screening evaluations to confirm a patient's eligibility, the sites will register the patient by the interactive web-response system (IWRS). The IWRS registration consists of assigning the patient a unique study identification number and randomizing the patient to 1 of the 2 treatment arms on a 1:1 basis (Arm A : Arm B).

Once the patient is registered through the IWRS, he/she is considered to be randomized in the study. The IWRS will assign patients to treatment arms according to a stratified method of randomization (that is, independent randomization within each of 4 strata, or cells), defined by all 4 combinations of the following 2 prognostic factors:

- ECOG PS at baseline (0 vs. 1); and
- gender (females vs. males).

9.4. Selection and Timing of Doses

The first treatment will be administered within 7 days of enrollment (Phase 1b) or randomization (Phase 2). Study treatment will be administered as described in Section 9.1.

9.4.1. Special Treatment Considerations

9.4.1.1. Dose-Limiting Toxicity Determination (Phase 1b part)

In Phase 1b part, DLT assessment will be performed. A DLT is defined as one of the following events, graded according to the NCI-CTCAE version 4.0, when the event occurs within 21 days from Day 1 in the Cycle 1 and is considered to be definitely or probably related to necitumumab and/or gemcitabine-cisplatin chemotherapy. DLT evaluation period is defined as 21 days from Day 1 of Cycle 1 even if next cycle treatment will be delayed due to AEs. Full supportive care may be allowed during the Cycle 1.

Advice will be obtained from the ESEC if needed, .

- Grade 4 neutropenia lasting ≥7 days
- Grade ≥3 febrile neutropenia except for transient febrile neutropenia (Grade 3 neutropenia associated with fever ≥38.0ºC for ≤24 hours)
- Grade 3 thrombocytopenia requiring platelet substitution
- Grade 4 thrombocytopenia (<25,000 /mm^3)
  If investigator consider the first data of Grade 4 thrombocytopenia (<25,000 /mm^3) would be uncertain, DLT could be judged by re-examination data. Re-examination should be done before supportive care and separate from first determination. When the result of reexamination does not match the DLT criteria, it would not be considered DLTs
- Grade ≥3 nonhematologic toxicity, with exceptions as follows:
  - The following toxicities will <u>not</u> be considered DLTs if they are transient (≤7 days) with full supportive therapy
    - Grade 3 arthralgia or myalgia
    - Grade 3 asthenia or fatigue
    - Grade 3 diarrhea, constipation, or anorexia
    - Grade 3 nausea or vomiting
  - The following toxicities will <u>not</u> be considered DLTs:
    - Grade 3 skin toxicity
    - Grade 3 or 4 hypersensitivity
    - Grade 3 injection-site reaction
    - Grade 3 elevation of transaminases lasting ≤7 days
    - Grade 3 elevation of serum-bilirubin lasting ≤7 days
    - Transient Grade 3 elevation or decrease of electrolytes

- Any toxicity leading to the omission of Day 8 or 15 of necitumumab (for those patients for whom necitumumab is delayed from Days 8 to 15) during the Cycle 1.

If a Grade 3 or 4 infusion-related reaction (hypersensitivity) occurs, due to either gemcitabine-cisplatin or necitumumab, this event will not be considered a DLT; the patient will not receive any further study therapy and will be replaced in the study by a new patient. Upon the occurrence of Grade 3 or 4 infusion-related reactions in two or more patients, enrollment will be suspended and the Sponsor will determine whether or not patient enrollment should be continued after consultation with the ESEC.

Dose-Limiting Toxicity will be decided after review of preliminary safety data by the investigator and the Sponsor.

9.4.1.2. Treatment Requirements and Delays

Cycle 1

Pretreatment local laboratory data on Day 1 in Cycle 1 may not be older than 7 days. The results at the screening test can be utilized to confirm the criteria for treatment on Day 1 if they are obtained within 7 days before the first dose of study treatment. The first cycle should be started within 7 days after the randomization. The criteria for administration of study treatment at the planned schedule are shown in Table JFCM.3 and Table JFCM.4.

Table JFCM.3. Criteria for Treatment with Necitumumab (on Day 1)

Conjunctivitis	≤Grade 2
Hypomagnemia	≤Grade 2
Skin Toxicity	≤Grade 2 (please refer to Section 9.7.1.2)
Other [a]	≤Grade 2 (for infusion-related reactions, please refer to Section 9.7.1.1)

[a]: At least possibly related to necitumumab

Table JFCM.4. Criteria for Treatment with Gemcitabine-Cisplatin (on Day 1)

Hemoglobin	≥10.0 g/dL
Neutrophils	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Serum creatinine [a]	≤1.2 x ULN or creatinine clearance >50 mL/min
Bilirubin	≤1.5 x ULN
AST	≤2.5 x ULN
ALT	≤2.5 x ULN
Other [b]	≤Grade 2, except skin toxicity

Abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase

[a]: Urine samples up to 24 hours will be used if both blood and urine samples for creatinine clearance are collected.

[b]: At least possibly related to gemcitabine.

On Day 8, pretreatment local laboratory data may be checked on the day of administration (Table JFCM.5 and Table JFCM.6).

Table JFCM.5. Criteria for Treatment with Necitumumab (on Day 8, or Day15 if delayed)

Conjunctivitis	≤Grade 2
Hypomagnemia	≤Grade 2
Skin Toxicity	≤Grade 2 (please refer to Section 9.7.1.2)
Other [a]	≤Grade 2 (for infusion-related reactions, please refer to Section 9.7.1.1)

Note: If necitumumab treatment is delayed from Day 8 to Day 15, these criteria should be met at the time of necitumumab treatment on Day 15.

[a]: At least possibly related to necitumumab

Table JFCM.6. Criteria for Treatment with Gemcitabine (on Day 8)

Neutrophils	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Serum creatinine [a]	≤1.2 x ULN or creatinine clearance >50 mL/min
Bilirubin	≤1.5 x ULN
AST	≤2.5 x ULN
ALT	≤2.5 x ULN
Other [b]	≤Grade 2, except skin toxicity

Abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase

[a]: Urine samples up to 24 hours will be used if both blood and urine samples for creatinine clearance are collected.

[b]: At least possibly related to gemcitabine.

If the criteria outlined in both Table JFCM.5 and Table JFCM.6 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 toxicity that does not meet the criteria described in Table JFCM.5, administration of necitumumab will be interrupted, but gemcitabine will continue according to the planned schedule. Specifically, in case of necitumumab-related toxicities on Day 8, gemcitabine will be administered according to the planned schedu le and necitumumab administration will be delayed for 1 week and administered on Day 15. If patient does not meet the criteria described in Table JFCM.5 on Day 15, the infusion of necitumumab will be skipped.
- If on Day 8, the criteria described in Table JFCM.6 are not met, gemcitabine administration should be skipped for this cycle.

Continuation of Therapy (Cycle 2 and Beyond)

Pretreatment laboratory data required for treatment on Day 1 in Cycle 2 and all following cycles may not be older than 3 days. Treatment on Day 8 may be administered within a ±3 day window.

Pretreatment laboratory data required for treatment on Day 8 must be collected on Day 5 or later, but 3 days or less prior to treatment.

The criteria for administration of study treatment at the planned schedule are shown in Table JFCM.7 and Table JFCM.8.

Table JFCM.7. Criteria for Treatment with Necitumumab

Conjunctivitis	≤Grade 2
Hypomagnemia	≤Grade 2
Skin Toxicity	≤Grade 2 (please refer to Section 9.7.1.2)
Other [a]	≤Grade 2 (for infusion-related reactions, please refer to Section 9.7.1.1)

[a]: At least possibly related to necitumumab

Table JFCM.8. Criteria for Treatment with Cisplatin-Gemcitabine (on Day 1) and Gemcitabine (on Day 8)

Neutrophils	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Serum creatinine [a]	≤1.2 x ULN or creatinine clearance >50 mL/min
Bilirubin	≤1.5 x ULN
AST	≤2.5 x ULN
ALT	≤2.5 x ULN
Other [b]	≤Grade 2, except skin toxicity

Abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase

[a]: Urine samples up to 24 hours will be used if both blood and urine samples for creatinine clearance are collected.

[b]: At least possibly related to cisplatin-gemcitabine

If the criteria outlined in Table JFCM.7 and Table JFCM.8 are not met at the time of a planned treatment, the following general rules for the management of treatment delays apply:

- In the case where a patient meets the criteria (Table JFCM.7 and Table JFCM.8), the administration of gemcitabine, cisplatin, and necitumumab will occur on Day 1.
- In the case of toxicity such that the patient does not meet the criteria in Table JFCM.7, administration of necitumumab will be interrupted, but gemcitabine will continue according to the planned schedule. In that case, necitumumab administration will be delayed for 1 week and administered on Day 15. If patient does not meet the criteria described in Table JFCM.7 on Day 15, the infusion of necitumumab will be skipped.
- If on Day 8 of any cycle, the criteria described in Table JFCM.8 are not met, gemcitabine administration should be skipped for this cycle.
- If administration of a given each treatment is delayed for more than 6 weeks after Day 1 of the most recent treatment cycle, this patient will discontinue of the administration of study treatment. If gemcitabine, cisplatin, or necitumumab is discontinued due to toxicity, the remaining agents should be continued according to this study protocol.

When gemcitabine-cisplatin-related toxicity has resolved, gemcitabine-cisplatin and necitumumab will resume on the regular schedule (please see Attachment 5 for illustrative examples of dose delay management).

9.4.1.3. Dose Modification

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

9.4.1.3.1. Necitumumab

The following are general dose modification guidelines for toxicity associated with necitumumab. The following sections contain specific information on the management of necitumumab related infusion-related reactions, skin reactions, conjunctivitis, hypomagnesemia, disseminated intravascular coagulation (DIC), and thromboembolic events.

Dose modifications are permitted for necitumumab following reversible Grade 3 or 4 necitumumab related AEs (ie, fatigue, anorexia, or fever) that require delay of necitumumab treatmment for up to 6 weeks following Day 1 of the most recent treatment cycle (Section 9.7.1.1 and 9.7.1.2 for infusion-related reactions and skin reactions, respectively). In this setting, necitumumab may be re-administered at a reduced dose (600 mg). A second dose reduction (to 400 mg) is permitted for this level of event (Grade 3 or 4) based on the investigator consideration. Events that necessitate more than two dose reductions warrant discontinuation of necitumumab. The dose of necitumumab may be re-escalated to the pre-reduction dose, provided that at least 3 weeks have elapsed following the first administration of the reduced dose, if appropriate in the opinion of the investigator or subinvestigator and they consult the Sponsor.

Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE version 4.0 Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening (eg, from Grade 1 to 2) of those symptoms or laboratory values. Investigators may reduce the dosage of necitumumab when Grade ≥3 necitumumab related AEs occur during the treatment cycle.

For Phase 1b, dose modifications for necitumumab are <u>not</u> permitted during the Cycle 1. If a patient experiences skin reaction, the necitumumab treatment may be modified according to Section 9.7.1.2.

9.4.1.3.2. Gemcitabine and Cisplatin

Gemcitabine and cisplatin may cause known hematologic and nonhematologic toxicities at the dose levels infused during this study; dose interruptions or reductions may be required. In such cases, the dose levels outlined in Table JFCM.9 should be used in the determination of gemcitabine and cisplatin doses. Investigators may reduce the dosage of gemcitabine and cisplatin when Grade ≥3 gemcitabine and cisplatin related AEs occur during the treatment cycle.

For Phase 1b, the dose modifications gemcitabine on Day 8 are permitted also during the Cycle 1.

NOTE: Chemotherapy dose modifications are permanent; once the dose of any agent has been reduced, it will remain reduced or be further reduced in subsequent cycles. Any patient with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction (or a reduction below the dose level associated with a second dose reduction; see the Table JFCM.9) must be discontinued from that agent. Therapy must also be discontinued if toxicity would necessitate a dose delay of more than 6 weeks following Day 1 of the most recent treatment cycle.

Table JFCM.9. Dose Reductions for Gemcitabine and Cisplatin

Dose Level	Gemcitabine		Cisplatin
Starting Dose	1000 mg/m^2	1250 mg/m^2	75 mg/m^2
First Dose Reduction	75% / 750 mg/m^2	75% / 950 mg/m^2	75% / 56 mg/m^2
Second Dose Reduction	50% / 500 mg/m^2	50% / 625 mg/m^2	50% / 38 mg/m^2

The gemcitabine and cisplatin dose levels are not linked and may be adjusted independently as summarized in Table JFCM.10 and Table JFCM.11.

9.4.1.3.2.1. Hematological Toxicity

Dose modification criteria that are the recommendation for hematologic toxicities are summarized in the Table JFCM.10. Dose adjustments for hematologic toxicity at the start of a subsequent cycle should be based on nadir hematologic counts from the previous cycle of therapy.

Table JFCM.10. Dose Reductions for Hematologic Toxicity

Drug-Related Toxicity During Previous Cycle		Gemcitabine Dose	Cisplatin Dose
ANC	Grade 4 (> 7 days)	Reduce one dose level	Reduce one dose level
Platelets	Grade 3 (requiring platelet substitution)	Reduce one dose level	Reduce one dose level
	Grade 4	Reduce one dose level	Reduce one dose level

Abbreviations: ANC = absolute neutrophil count

9.4.1.3.2.2. Nonhematological Toxicity

In any case where serum creatinine is >1.2 x ULN or calculated creatinine clearance is <50 mL/min, treatment of both gemcitabine and cisplatin must be delayed until recovery (Table JFCM.4, Table JFCM.6, and Table JFCM.8); after recovery dose adjustment is recommended. Additional guidelines for chemotherapy dose modification related to nonhematologic toxicity are summarized in Table JFCM.11. For nonhematologic toxicity not specifically covered in Table JFCM.11, dose reduction may be warranted for events if clinically appropriate in the opinion of the investigator or subinvestigator and based on worst toxicity in the previous cycle.

Table JFCM.11. Dose Reductions for Nonhematologic Toxicity

Drug-Related Toxicity During Previous Cycle		Gemcitabine Dose	Cisplatin Dose
Mucositis/Stomatitis	Grade ≥3	Reduce one dose level	-
Neurotoxicity	Grade 0 to 1	-	-
	Grade 2	-	Reduce two dose levels [a]
	Grade 3 to 4	Discontinue	Discontinue
Ototoxicity	Grade 2 to 4	-	Consider discontinuation
All Other	Grade ≥3 [b]	Reduce one dose level [c]	Reduce one dose level [c]

[a]: Reduction of two dose levels is recommended.

[b]: Excluding Grade 3 nausea/vomiting, and Grade 3 paronychia, for which no dose reduction is necessary.

[c]: If clinically appropriate in the opinion of the investigator; discontinuation of one or more agents may also be warranted in some cases.

9.5. Continued Access to Study Drug

Necitumumab may be made available after study completion to patients who are still receiving and benefitting from study treatment (see Section 8.1.6).

9.6. Blinding

This is an open-label study.

9.7. Concomitant Therapy

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

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

If any major surgery required full anesthesia should be required during the study treatment period, the patient should discontinue study treatment. However, a minor surgery performed with local anesthesia may be permitted. The time of study treatment interruption before minor surgery should be at least 7 days following the last dose of study treatment. Patients may resume all study treatment no less than 7 days following minor surgery, provided there has been adequate recovery in the opinion of the investigator. Following minor surgery that may affect the evaluable lesion, radiological evaluation of disease is required prior to resumption of study treatment.

Patients undergoing surgery before PD should be followed-up by imaging every 6 weeks until radiographically documented PD.

9.7.1. 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 study. 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 (eg, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the eCRF. Please see Section 9.4.1.3 for specific information on the management of necitumumab-related infusion reactions, skin reactions, conjunctivitis, and hypomagnesemia. Guidelines regarding the use of other specific supportive care agents are presented below.

9.7.1.1. Infusion-Related Reactions

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

- Grade 1: transient flushing or rash, drug fever <38.0ºC
- Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥38.0ºC
- 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)

Hypersensitivity/infusion-related reactions 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 infusion-related reactions with resuscitation equipment readily available. For mild or moderate (Grade 1 or 2) infusion-related reactions, adjust dose per Table JFCM.12. Immediately and permanently discontinue necitumumab for severe (Grade 3 or 4) infusion-related reactions.

Consistent with usual medical practice, selected parenteral medications may be utilized for as detailed below (Table JFCM.12). Additional treatments, chosen according to clinical symptoms and local standards, may be utilized at investigator discretion.

Table JFCM.12. Infusion-Related Reactions – Management Recommendations

Grade of Reaction	Management Recommendations
1	• Slow the infusion rate by 50%. • Monitor the patient for worsening of condition.
2	• Stop the infusion. • Administer diphenhydramine hydrochloride 50 mg oral (PO) or equivalent, acetaminophen 650 mg orally for fever, and oxygen. • Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to Grade 1; the total infusion duration should not exceed 2 hours. • Monitor for worsening of condition. • For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg PO (or equivalent) For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 10 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg PO (or equivalent), acetaminophen 650 mg orally or I.V., and dexamethasone 10 mg I.V. (or equivalent).
3	• Stop the infusion and disconnect the infusion tubing from the patient. • Administer diphenhydramine hydrochloride 50 mg PO (or equivalent), dexamethasone 10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated. • Patients who have a Grade 3 infusion-related reaction will not receive further treatment with necitumumab, but will continue to be followed on the protocol.
4	• Stop the infusion and disconnect the infusion tubing from the patient. • Administer diphenhydramine hydrochloride 50 mg PO (or equivalent), dexamethasone 10 mg I.V. (or equivalent), and other medications/treatment as indicated. • Give epinephrine or bronchodilators as indicated. • Hospital admission for observation may be indicated. • Patients who have a Grade 4 infusion-related reaction will not receive further treatment with necitumumab, but will continue to be followed on the protocol.

Abbreviations: I.V. = intravenously; PO = oral.

If a patient should have a hypersensitivity/infusion-related reaction to necitumumab, all attempts should be made to obtain an anti-necitumumab antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. In addition, these same samples may be assessed for levels of necitumumab and for biomarkers to provide information on the nature of the infusion-related reaction. The procedure for sample collection and handling is described in a separate procedural manual.

9.7.1.2. Skin Reactions

9.7.1.2.1. Reactive Treatment

Skin reactions were reported with necitumumab. The onset of events occurred mainly during the first cycle of treatment.

Based on emerging data from cetuximab, there appears to be a correlation between acneform rash and various efficacy outcomes. Therefore, if a patient experiences a Grade 1 or 2 acne-like rash, necitumumab treatment should continue without dose modification or delay. If a patient experiences acute or chronic Grade 3 rash acneiform (ie, rash associated with pain, disfigurement,

ulceration, or desquamation), pruritus, desquamation, dry skin, cheilitis, or hand-foot reaction, necitumumab treatment will be delayed for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until there is improvement to Grade ≤2. At this time, necitumumab may be re-administered (as described in Table JFCM.13). Patients who experience Grade 3 skin induration / fibrosis or any Grade 4 skin toxicity will be immediately and permanently discontinued from 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).

Table JFCM.13. Skin Reactions – Management Recommendations

Grade of Reaction	Management Recommendations
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% of the original dose (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 following Day 1, or if reactions recur or become intolerable at 50% of the original dose, necitumumab treatment should be permanently discontinued. • Patients who experience Grade 3 skin induration / fibrosis will be immediately discontinued from necitumumab.

Grade of Reaction	Management Recommendations
4	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity. • **Necitumumab administration must be immediately and permanently discontinued**.

If necitumumab therapy is delayed or discontinued due to acneform 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 following 1 to 2 weeks of treatment, reactions that are severely symptomatic (for example, necrosis, blistering, petechial, or purpuric lesions), reactions of NCI-CTCAE version 4.0 Grade ≥3, or reactions with an uncharacteristic appearance.

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

9.7.1.2.2. Pre-emptive Treatment

Recent findings have suggested that pre-emptive treatment may reduce the severity and treatment impact of EGFR-inhibitor-related skin toxicity. Please note; pre-emptive treatment for skin toxicity on only Phase 1b part may not be administered prior to the beginning of the second treatment cycle.

9.7.1.3. Conjunctivitis

Conjunctivitis has been reported very commonly in patients receiving necitumumab.

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

Serious cases of keratitis and ulcerative keratitis have been reported as uncommon or rare side effects for other anti-EGFR antibodies and are to be considered a class effect. If the diagnosis is confirmed, anti-EGFR treatment should be interrupted or discontinued, with benefits and risks of continuation of treatment to be carefully considered.

9.7.1.4. Electrolyte Abnormalities

Consistent with observations with other EGFR-targeting antibodies (as with panitumumab and cetuximab), 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-targeting antibodies. Monitor patients for hypomagnesemia, hypocalcemia, hypokalemia, and hypophosphatemia prior to each administration of

necitumumab and after completion of the treatment of necitumumab, until within normal limits. Prompt repletion is recommended, as appropriate. Hypomagnesemia is reversible following discontinuation of EGFR antibody therapy. Treatment of any hypomagnesemia should be as clinically indicated according to local standards, and necitumumab therapy should be continued unless the investigator has any related safety concern.

9.7.1.5. Interstitial Lung Disease

Cases of interstitial lung disease (ILD), including cases with fatal outcome, have been reported as an uncommon side effect for other anti-EGFR antibodies, mainly in the Japanese population. ILD may represent a class effect of such kind of drugs. If ILD is diagnosed, anti-EGFR antibody therapy is to be permanently discontinued and the patient should be treated appropriately.

9.7.1.6. Thromboembolic Events

Venous thromboembolic events and 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.

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.

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).

9.7.1.7. Cardiorespiratory Disorders

An increased frequency of cardiorespiratory arrest or sudden death was observed with necitumumab. Cardiorespiratory arrest or sudden death was reported in the pivotal Study JFCC (SQUIRE, CP11-0806) 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.

9.7.1.8. Disseminated Intravascular Coagulation (DIC)

In a preclinical study, a single case of DIC with fatal outcome was observed in a monkey exposed to 18 administrations of the highest dose (60 mg/kg) of necitumumab. Although the DIC may have been due to an underlying septicemia, a causal relationship of the event to necitumumab cannot be ruled out. Clinical safety data obtained to date do not indicate that necitumumab is associated with an increased risk of a disseminated intravascular coagulation. Nevertheless, the investigator should pay special attention to any clinical signs indicative of hemorrhage or coagulopathy, in addition to the monitoring of coagulation and hematological laboratory parameters as specified in the protocol.

9.7.1.9. Others

9.7.1.9.1. Antidiarrheal Agents

In the event of Grade 3 or 4 diarrhea, supportive measures may include antidiarrheals (loperamide), hydration etc. If diarrhea is severe (ie, 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 intravenous hydration and correction of electrolyte imbalance.

9.7.1.9.2. Granulocyte-Colony Stimulating Factors

The use of granulocyte colony stimulating factors is permitted during the study at the discretion of the investigator. Prophylaxis administration will not be performed during the DLT assessment period. The treatment for granulocyte colony stimulating factors will be recommended in accordance with the package insert.

9.7.1.9.3. Transfusion of Blood Products

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion. Prophylaxis administration will not be performed during the DLT assessment period.

9.8. 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, Health Outcome, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the study schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study

Patients may be enrolled on study with measurable or non-measurable disease based on the RECIST, version 1.1. Disease assessment will be undertaken at baseline (within 21 days prior to enrollment [Phase 1b] or randomization [Phase 2]) and then every 6 weeks (−7 to +3 business days) as calculated from the first dose of study therapy until discontinued from the study (Phase 1b) or radiographically documented PD (Phase 2). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study.

Assessment for response will be performed with confirmatory assessment for patients with an objective response of PR or CR obtained at the next routine scheduled imaging timepoint (no less than 4 weeks after the initial response is noted). Two objective status determinations of CR before progression are required for a best overall response of CR. Two determinations of PR or better before progression are required for PR. In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after the enrollment (Phase 1b) and randomization (Phase 2) at a minimum interval of 6 weeks. In cases where confirmation of response is not feasible, it should be noted in any study outcome report that the responses are not confirmed

All evaluated imaging data including CT scan and MRI will be collected and stored centrally; if necessary (eg, inquiries from regulatory authorities), independent review of all or representative sample of scans may be considered.

10.1.2. Efficacy Assessments during the Post-discontinuation Period (only Phase 2 part)

For patients who discontinue study treatment for any reason other than radiographically documented PD (for example, symptomatic deterioration) in Phase 2 part, radiographic assessments should continue as scheduled every 6 weeks (−7 to +3 business days), following the first dose of study therapy until objective radiographic evidence of PD. Follow-up will continue as long as the patient is alive, or until study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed for survival approximately every 90 days (±14 days) until death or study completion.

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

10.2. Health Outcome Measures

10.2.1. Patient-Reported Outcomes (only Phase 2 part)

All patients for whom there is a validated translation in which the patient is fluent will undergo assessment for symptoms and QOL using the LCSS and the EuroQol (EQ-5D). It is recommended that the instruments is administered together and in sequence order, with the LCSS presented first, followed by presentation of the EQ-5D.

Patients will complete the instruments at baseline (within 14 days prior to randomization), prior to the first infusion of Cycles 2 to 4, and in Arm A, every 2-cycle interval thereafter (ie, Cycle 6, Cycle 8, Cycle 10 and so on). Chemotherapy in Arm B will not continue beyond Cycle 4. The instruments will be completed every 6 weeks after discontinuation of the study treatment in Arm A until PD (ie, concurrent with radiological evaluation), and every 6 weeks after discontinuation of chemotherapy in Arm B until PD (ie, concurrent with radiological evaluation). The instruments should be completed at the beginning of the visit, before any extensive contact and consultation with the clinician/study investigator; such encounters may thereafter bias patient responses. The LCSS and the EQ-5D will be completed by all patients using the validated translated version of Japanese.

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

10.2.1.1. Lung Cancer Symptom Scale (LCSS)

Disease-related symptoms and quality of life will be assessed with the self-administered LCSS (Hollen et al. 1994). The LCSS is a validated and reliable instrument to assess lung cancer-specific symptoms and their impact on QOL. Each of the 9 symptom or summary items is assessed on a 100-mm visual analogue scale (VAS), with 0 representing no symptoms or better QOL.

10.2.1.2. EQ-5D

The EQ-5D is a standardized instrument that measures health status and is applicable to a wide range of health conditions and treatments (EuroQol Group 1990).

The EQ-5D consists of 2 parts. The first part includes 5 descriptive questions relating to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, on which the patient is required to rate his/her health. Each attribute has 3 levels: no problems, some problems, and extreme problems, thus defining 243 possible health states. Weights for Japan will be used in analysis.

The second part of the EQ-5D is a VAS that allows patients to rate their present health condition. Possible scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor 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 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).

10.3.1. Adverse Events

The Sponsor 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 ECGs, laboratories, vital sign measurements that result in a diagnosis should be reported to Sponsor or its designee.

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

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

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

In addition, all AEs occurring after the patient receives the first dose of study treatment until 30 days after the decision is made to discontinue study treatment must be reported to the Sponsor or its designee via eCRF.

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

The investigator should evaluate for AEs at each visit and will instruct to call their physician to report any AEs between visits.

The NCI-CTCAE version 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 version 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected and collected on the eCRF. This collection is in addition to 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 or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

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

10.3.1.1. Serious Adverse Events

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

Study site personnel must alert the Sponsor or its designee of any **SAE** within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. An SAE is any adverse event from this study that results in one of the following outcomes:

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

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

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Preplanned 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 therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Serious adverse events occurring after a patient has taken the last dose of study treatment will be collected in the pharmacovigilance system and clinical data collection database for 30 days after discontinuation from study treatment, regardless of the investigator's opinion of causation.

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(s), the investigator should report the SAE to the Sponsor, and the SAE will be entered in the Lilly Safety System.

10.3.1.2. Adverse Event and Serious Adverse Event Reporting

Table JFCM.14 describes AE and SAE collection with regard to the type of events to be collected in each study period.

Table JFCM.14. Adverse Event, Serious Adverse Event, and Preexisting Condition Reporting Guidelines for Study JFCM

Treatment Period	Types of Information Collected/Reported
Baseline (pretreatment)	Preexisting conditions. Procedure-related AEs/SAEs
Study treatment period (on therapy)	All AEs/SAEs
Extension period	All AEs/SAEs
30-day safety follow-up visit	All AEs/SAEs
Subsequent post-discontinuation follow-up visits, if necessary	SAEs are required to be reported only if the investigator feels the events were related to either study treatment, or a protocol procedure.

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

10.3.1.2.1. Prior to Administration of Study Treatment(s)

Adverse event and SAE collection begins after the patient has signed the ICF and has received study treatment. If a patient experiences an AE or SAE after signing informed consent, but prior to receiving study treatment, the event will NOT be collected unless the investigator believes the event may have been caused by a protocol procedure.

10.3.1.2.2. On Study

All AEs and SAEs, regardless of relatedness to study treatment(s), or protocol procedures, occurring while the patient is receiving study treatment must be reported to the Sponsor or its designee. A patient is considered to be receiving study treatment from the time he/she receives the first dose of study treatment to when he/she receives the last dose of study treatment.

10.3.1.2.3. Follow-Up Visit

All SAEs, regardless of relatedness to study treatment(s) or protocol procedures, occurring during the follow-up visit (Visit 801) must be reported to the Sponsor or its designee. The

follow-up periods begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the trial and lasts approximately 30 days. For the patient who completed all treatments of Cycle 4 in Arm B of Phase 2 part, the follow-up periods begins on the day after the Cycle 4 completion. After the 30-day follow-up, only new and ongoing SAEs deemed related to study treatment will be collected.

10.3.2. Other Safety Measures

10.3.2.1. Collection of Electrocardiograms

For each patient, 12-lead digital ECGs will be collected as ECGs according to the Study Schedule (Attachment 1). 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.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Phase 1b part

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by the Sponsor. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory if necessary (eg, inquiries from regulatory authorities). The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless an overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

Phase 2 part

Electrocardiograms will be collected locally as single ECGs in Phase 2 part.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, 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.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation.

10.3.2.2. Skin Reactions

Skin reactions are the events known as the toxicity of anti-EGFR monoclonal antibody, such as cetuximab or panitumumab. Skin reaction will be monitored under treatment in the study. The purpose of monitoring skin reactions is to enable detection of safety signals as early as possible.

Once skin reactions are reported as events, additional information will be collected at the time of toxicity assesments/AEs as shown in the Study Schedule (see Attachment 1). This aggregative assessment will result in a compilation of the characteristics of skin reactions, including frequency, duration, severity, locations, causalities and outcome, etc.

10.3.3. Safety Monitoring

The Sponsor's clinical research physician (CRP) or clinical research scientist (CRS) will monitor safety data throughout the course of the study.

Sponsor or designee will review SAEs within time frames mandated by company procedures. The Sponsor's CRP, CRS, or designee, will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review trends and laboratory analytes.

10.3.4. Complaint Handling

The Sponsor collects product complaints on study treatments and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

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

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

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

10.4. Sample Collection and Testing

Attachment 1 and Attachment 2 list the schedule for sample collections in this study.

10.4.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the study schedule (Attachment 1). Standard laboratory tests, including hematology, coagulation, and urinalysis panels, will be performed and analyzed by a local laboratory. Chemistry will be performed and

analyzed centrally. Central chemistry laboratory results will be used to determine patient eligibility at baseline. Local chemistry lab results may be used for assessment of safety and on-study dosing decisions; if so, chemistry testing scheduled on Attachment 1 must also still be performed by the central laboratory. These central chemistry 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. A serum or urine pregnancy test will be performed locally. Attachment 3 lists the specific tests that will be performed for this study.

Investigators must document their review of each laboratory safety report.

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

10.4.2. Pharmacogenetic Samples

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, a blood sample will be collected for pharmacogenetic analysis. It is a one-time collection, as noted in the Study Schedule (Attachment 1).

Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

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

10.4.3. Nonpharmacogenetic/Biomarker Stored Samples

Collection of samples for nonpharmacogenetic biomarker research is a required part of this study. A formalin-fixed, paraffin-embedded tumor tissue block or a minimum of 5 unstained slides of tumor sample (archived or recent) must be made available at baseline for evaluation of EGFR protein expression (IHC) and other biomarker assessments.

Samples may be used for research into the EGFR pathway, pathways associated with disease state, mechanism of action of necitumumab, gemcitabine, and cisplatin, research methods and/or validating diagnostic tools or assay(s) related to NSCLC and the EGFR-pathway.

The samples will be identified by the patient number (coded) and stored for up to a maximum of 15 years after the last patient visit for the study at facility selected by the Sponsor.

10.4.4. Immunogenicity Samples

Samples for immunogenicity testing will be collected at time points indicated in Study Schedule (Attachment 2). Blood samples will be used to determine antibody production against necitumumab. The actual date of each sampling will be recorded. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of necitumumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of necitumumab.

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).

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 the study treatment.

10.4.5. Samples for Drug Concentration Measurements Pharmacokinetics

At the visits and times specified in the Study Schedule (Attachment 2). Blood samples will be used to determine the serum concentrations of necitumumab and the plasma concentrations of gemcitabine, its deaminated metabolite 2',2'-difluorodeoxyuridine (dFdU) and total and free platinum from cisplatin and will be assessed by a validated assay. Determination of necitumumab drug concentrations will also be performed in the setting of an infusion-related reaction. The actual date and time (24-hour clock time) of each sampling will be recorded.

A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Sponsor. Instructions for the collection and handling of blood samples will be provided by the Sponsor.

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

10.5. Appropriateness of Measurements

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

11. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session 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, the Sponsor or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by the Sponsor 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 the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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

Electronic 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 or ECG data in Phase 1b part, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper to collect PRO measures (for example, a rating scale).

Data from complaint forms submitted to the Sponsor or designee 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 study is divided into two parts: the Phase 1b part and the Phase 2 part.

The Phase 1b part is designed based on a conventional 3+3 cohort design to investigate the tolerability of necitumumab, in combination with gemcitabine-cisplatin chemotherapy. At least 9 patients will be enrolled (3 patients in Cohort 1 and 6 patients in Cohort 2).

The purpose of Phase 2 part is to evaluate the efficacy of necitumumab in combination with gemcitabine-cisplatin chemotherapy in terms of OS. The sample size for Phase 2 part was calculated to be 180 patients based on OS. In Phase 2 part, 180 patients (up to 190 patients) will be randomized 1:1 to Arm A or B. It is assumed that the expected median survival time (MST) of Arm A and Arm B are 13.75 and 11 months (HR = 0.8), respectively, which is the similar assumption to one in Study CP11-0806. When the enrollment period is 23 months and the follow-up period is 15 months, the sample size of 180 patients (137 events) has 68% power for a log-rank test at 0.2 one-sided alpha. Additionally, the probabilities of obtaining estimated HR <0.9 or of the longer MST in necitumumab arm than one of control arm were calculated at 76% and 85% respectively, in 180 patients. The final analysis will be performed when at least 137 OS events (deaths) are observed.

Since a dropout rate of 5% is considered, 190 patients is planned to be enrolled for Phase 2 part.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

The primary efficacy analyses will be conducted on the full analysis set (FAS). This population is defined as all patients who are randomized and receive at least one dose of study treatments in Phase 2 part. Patients will be grouped according to treatment received.

If there are significant numbers of patients with major protocol violations, the Per Protocol Set (PPS) analysis will be performed for the primary and secondary efficacy endpoints. Results will serve as supportive for FAS analysis.

The safety analyses will be conducted on the Safety Population, defined as all treated patients in Phase 1b part and Phase 2 part, and patients will be grouped as follows; Phase 1b part, Arm A and Arm B in Phase 2 part, and treated patients with necitumumab (Phase 1b part + Arm A in Phase 2 part).

Pharmacogenomic analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

Missing data will generally not be imputed, except for partial dates concerning pivotal efficacy or safety parameters. Baseline is defined as the last measurement for a variable prior to the

initial dose of any investigational product. A complete description of data handling rules and planned statistical analyses is detailed in a separate SAP.

The statistical tests will be performed but p values will be shown just for reference. All CIs will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

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

A summary of all important protocol violations will be provided.

12.2.3. Patient Characteristics

Patient demographics including age, gender, race, screening height and weight, screening smoking status will be summarized.

Baseline disease characteristics will be summarized for histologic subtype, disease stage, TNM classification, ECOG PS prior to Cycle 1.

Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, the number of patients (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each of the parameters.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.4.1. Post-discontinuation Therapy

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

12.2.5. Efficacy Analyses

12.2.5.1. Primary Endpoint

The primary efficacy endpoint for the Phase 2 part of this study is OS. The OS is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at the time of study completion or are lost to follow-up will be censored at the time they were last known to be alive.

The Kaplan-Meier (KM) method will be used to generate KM curves, the medians, quartiles and percentages of patients event-free every 3-month interval for each arm. The HR of Arm A to Arm B and the CI will be estimated using a stratified Cox regression model by the variables used for randomization (ECOG PS and gender), and a stratified log-rank test will be performed.

The HR will be also estimated using the unstratified Cox regression model and an unstratified log-rank test will be performed.

12.2.5.2. Secondary Endpoints

The secondary efficacy endpoints in this study will include PFS, ORR, TTF, and Health outcomes. As for Health Outcomes, the detailed is described in Section 12.2.9.

The PFS is defined as the time from the date of randomization until the date of radiographically documented PD or death due to any cause, whichever is earlier. Patients who die without a reported progression will be considered to have progressed on the day of their death. Patients who did not progress or are lost to follow-up will be censored at the day of their last radiographic tumor assessment. If no baseline or post-baseline radiologic assessment is available, the patient will be censored at the date of randomization. If death or PD occurs after two or more consecutive missing radiographic visits, censoring will occur at the date of the last radiographic visit prior to the missed visits. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last radiographic assessment prior to initiation of new therapy.

The TTF is defined as the time from the date of randomization until the date of the first observation of radiographically documented PD, death due to any cause, discontinuation of treatment for any reason, or initiation of new anticancer therapy.

For PFS, sensitivity analyses will be conducted by including or excluding symptomatic/clinical deterioration as progression outcome or considering different censoring rules to control for missing data, patients lost to follow-up, and other censoring conditions.

The ORR is defined as the proportion of treated patients achieving a best response of PR or CR. The ORR in the patients with measurable lesions may be calculated, if deemed necessary.

Phase 1b part

The ORR and CI will be calculated on the patients.

Phase 2 part

As for PFS and TTF, the same analysis as ones for OS will be performed in FAS.

For PFS, sensitivity analyses will be conducted by including or excluding symptomatic/clinical deterioration as progression outcome or considering different censoring rules to control for missing data, patients lost to follow-up, and other censoring conditions. For ORR, a CI of each arm will be calculated based on binominal distribution, and the difference of ORR between two arms and the CI will be estimated in FAS. The ORR will be compared between the test arm and the control arm using Fisher exact test.

12.2.6. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study treatment and have had samples collected.

Phase 1b part

Pharmacokinetic parameter estimates for necitumumab, gemcitabine, and cisplatin, if appropriate, will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$ and/or $AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), clearance (CL), and/or volume of distribution (V) may be reported. Also C_{trough} of necitumumab will be analyzed. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global PK management. The version of any software used for the analysis will be documented and the program will meet the Sponsor requirements of software validation.

Phase 2 part

The PK parameters of necitumumab including C_{max} and C_{trough} will be summarized as descriptive statistics. An exploratory population PK analysis may be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global PK management. The version of any software used for the analysis will be documented and the program will meet the Sponsor requirements of software validation.

12.2.7. Biomarker Analyses

Descriptive statistics for biomarkers will be summarized in Phase 1b and Phase 2 part.

In Phase 2 part, for OS and PFS, survival curves of each arm will be estimated using KM method by EGFR protein expression level (IHC), EGFR and KRAS mutation status, and EGFR gene copy number (fluorescence in situ hybridization [FISH]) in tumor tissue, and FCγR polymorphisms in white blood cell (WBC). The ORR will also be summarized by biomarker characteristics.

The other exploratory biomarkers, if they are identified, will be analyzed in the same manner.

12.2.8. Pharmacokinetic/Pharmacodynamic Analyses

In addition to a standard noncompartmental assessment, and provided that the data allows, the relationship between necitumumab PK and Pharmacodynamics may also be investigated with exploratory manner. Serum data from all patients will be pooled for analyses to determine the compartmental PK parameters and between- and within-patient variability.

A population PK model will then be used to develop a PK/Pharmacodynamics model where relevant efficacy Pharmacodynamics data will be analyzed. Additional PK/ Pharmacodynamics

models may be developed using other Pharmacodynamics measures, if/when warranted. Additional exploratory analyses will be performed if warranted by the data.

12.2.9. Health Outcome Analyses

For each instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study). Percentage compliance will be summarized by treatment arm for each assessment period.

12.2.9.1. Lung Cancer Symptom Scale (LCSS)

The average symptom burden index (ASBI) is defined as the mean of six symptom-specific lung cancer questions, and the total score is defined as the mean of all 9 questions.

For each index, worsening is defined as a 15-mm increase from the corresponding baseline scores.

Descriptive statistics for the nine LCSS items will be calculated. Frequency distributions, and measures of central tendency and variability (for example, means, medians, and standard deviations) will be calculated for individual LCSS items, ASBI, and total score.

The ASBI, the total score, and each of 9 individual items will be analyzed using a mixed effects analysis of variance model to estimate treatment effect as well as time-by-treatment interaction effect. Analysis of each of the ASBI and total score will be conducted using Time to Worsening (TW) as measured from the date of randomization to the first date of a clinically meaningful worsening/change. For each patient who is not known to have had a worsening, or who is lost to follow-up, TW will be censored at the date of the patient's last LCSS assessment. The KM curves of TW for the index will be estimated using KM method and the HR and the CI will be estimated using an unstratified Cox regression model.

12.2.9.2. EQ-5D: Health State Utilities

The index score is calculated from a set of item weights to derive a score on a theoretical scale of 0 to 1, with 1 representing the best health status and zero representing death based on item weights for the Japanese population (Ikeda et al. 2002).

Descriptive statistics for the index and VAS will be calculated. Frequency distributions, including measures of central tendency and variability (for example, means, medians, and standard deviations) will be calculated for individual items and for the index score. The index scores and VAS may be analyzed using a mixed effects analysis of variance model to estimate treatment effect as well as time-by-treatment interaction effect.

12.2.10. Safety Analyses

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

12.2.10.1. Extent of Exposure

Dosing data will be summarized by treatment group to include duration of treatment (weeks), number of patients treated by cycle, number of cycles of treatment per patient received,

cumulative dose, dose intensity and relative dose intensity, and number (%) of patients with dose modifications (reduced or delayed).

12.2.10.2. Adverse Events

Treatment emergent AE is defined as any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.

In Phase 1b part, DLT will be summarized by cohort in the patients who are evaluable for DLT assessments and be listed by patient.

Safety analyses will include listings or summaries of the following for both of Phase 1b part and Phase 2 part.

- Treatment-emergent adverse events (TEAEs), including seriousness, severity, and possible relationship to study treatment
- AEs leading to dose adjustments for any study therapy
- Laboratory measures
- Vital signs

12.2.10.3. Immunogenicity

Pre- and post-treatment samples for analysis of antibodies against necitumumab (immunogenicity) will be assayed using validated assays.

Incidence of anti-necitumumab antibodies will be tabulated.

12.2.11. Subgroup Analyses

Subgroup analysis will be performed for OS, PFS, and ORR for the following subgroups: age (≤65 vs. >65 years; and ≤70 vs. >70 years); gender (male vs. female); ECOG PS (0 vs. 1).

12.2.12. Interim Analyses

In Phase 1b part, the interim analysis will be performed after completing DLT evaluation period, and patient characteristics, clinical laboratory values, DLTs, and AEs occurring in Cycle 1 might be summarized by cohort. Additionally, even after the above interim analysis, the Sponsor might analyze the data for scientific disclosures.

During Phase 2 part, approximately 6 interim analyses will be performed to monitor the safety data of this study. The first interim analysis for safety monitoring will be performed after 50 patients in Phase 2 part have receives at least two cycles or 6 months after enrollment of the first patient in Phase 2 part, which is earlier. After the first interim analysis, analyses will then be conducted every 6 months until all patients have discontinued all therapy (or until the study completion or been terminated). There will be no pre-specified rules for stopping the study due to safety concerns. The IDMC members will review safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

Only the IDMC is authorized to evaluate unblinded interim safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

In addition, the Sponsor might consider the interim analysis for regulatory communication purposes. One of possible communications is a discussion of complete clinical data package with Pharmaceutical and Medical Devices Agency (PMDA), considering the results in the global Phase 3 study (Study CP11-0806) which will be available during this study. In this case, the safety and efficacy data collected at the time will be analyzed.

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 legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatment.

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

13.2. Ethical Review

The Sponsor or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site(s).

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERB(s) should be provided with the following:

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) 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
2) the ICH GCP Guideline [E6]

3) applicable laws and regulations in Japan.

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

All or some of the obligations of the Sponsor 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 study.

13.3.2. Protocol Signatures

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

13.3.3. Final Report Signature

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

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

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

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Attachment 1. Protocol JFCM Study Schedule

Study Schedule: Study I4X-JE-JFCM

	Baseline Period (21 days prior to enrollment or randomization)			**Treatment Period** (21-day cycles)															**Post-discontinuation Follow-Up Period** (Visit 801 to 8XX)		
				Combination Therapy												Maintenance Therapy (if applied)			Summary Visit [b]	30 day Safety Follow-Up [c]	Long-Term Follow-Up Every 90 days
Cycle	Baseline [a]			1			2			3			4			5 to X			(0 to +7d)	(0 to +7d)	(±14d)
Relative day within cycle	≤21	≤14	≤7	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Procedures																					
Clinical Evaluations																					
Informed Consent [d]	X																				
In-/exclusion Criteria Review	X																				
Demography	X																				
Medical History (including smoking history)	X [e]																				
HBsAg, HCVAb [f, ζ]	X																				
ECG (Phase 1b)	X						X			X			X			X			X	X	
ECG (Phase 2) [f, g]	X									X									X		
ECOG PS	X			X[h]			X[h]			X[h]			X[h]			X[h]			X	X	
Concomitant Medication [q]	X			X[h]	X[h]		X[h]	X[h]		X[h]	X[h]		X[h]	X[h]		X[h]	X[h]		X	X	
Physical Exam, Height & Weight [i]	X			X[h]			X[h]			X[h]			X[h]			X[h]			X	X	
BSA [j]				X			X			X			X			X					
Vital Signs [k]	X			X[l]	X[l]		X[l]	X[l]		X[l]	X[l]		X[l]	X[l]		X[l]	X[l]		X	X	
Toxicity Assessments/AEs [q]	X[e]			X[h]	X[h]		X[h]	X[h]		X[h]	X[h]		X[h]	X[h]		X[h]	X[h]		X[m]	X[m]	X[n]
QOL Assessments (LCSS, EQ-5D)		X[o]					X[o]			X[o]			X[o]			X[o]			X[o]		
Laboratory Evaluations																					
Hematology Profile [f, p, q]		X		X[r]	X		X	X		X	X		X	X		X	X		X	X	
Coagulation Profile [f, p, s]		X									X[r]								X	X	
Chemistry Profile [p, q]		X		X[r]	X		X	X		X	X		X	X		X	X		X	X	
Urinalysis [f, p, s, t]		X[r]									X[r]								X	X	
Pregnancy Test [f]			X[u]																	X[u]	
Efficacy Assessments																					
Survival Information															X[v]						
Imaging [f]/Tumor Assessments [w]	X[x]														X[y]						
Contrast CT or MRI of the brain	X[z]														X[z]						

Study Schedule: Study I4X-JE-JFCM (continued)

	Baseline Period (21 days prior to randomization)			**Treatment Period** (21-day cycles)															**Post-discontinuation Follow-Up Period**		
				Combination Therapy												Maintenance Therapy (if applied)			Summary Visit [b]	30 day Safety Follow-Up [c]	Long-term Follow-Up Every 90 days
Cycle	Baseline [a]			1			2			3			4			5 to X			(0 to +7d)	(0 to +7d)	(±14d)
Relative day within cycle	≤21	≤14	≤7	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15			
Procedures																					
Additional and Exploratory Analyses																					
Whole blood samples for DNA and FCγR	X																				
Tissue Sample Confirmation α	X																				
Immunogenicity	**See Protocol Attachment for Sampling Schedule**																				
Pharmacokinetic Sample																					
Treatment Administration β																					
Necitumumab				X	X γ		X	X γ		X	X γ		X	X γ		X	X γ				
Administer Gemcitabine δ				X	X γ		X	X γ		X	X γ		X	X γ							
Administer Cisplatin δ, ε				X			X			X			X								

Study Schedule: Study I4X-JE-JFCM (continued)

Abbreviations: AE = adverse event; BSA = body surface area; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D = European Quality of Life – 5 dimensions; LCSS = Lung Cancer Symptom Scale; MRI = magnetic resonance imaging.

[a] Examination conducted before informed consent date will be accepted to use as screening data, if informed consent include such a notice and the patient consents to it.

[b] The summary visit is used when the decision is made to stop treatment and is completed up to 7 days after the decision to discontinue study treatment. For the patient who completed all treatments of Cycle 4 in Arm B of Phase 2 part or who discontinued necitumumab treatment before maintenance therapy but completed chemotherapy (gemcitabine and cisplatin) of Cycle 4 in Arm A of Phase 2 part, the summary visit is completed up to 7 days after the Cycle 4 completion (Cycle 4 Day 21 [+7 days]).

[c] The 30-day safety follow-up period begins on the day after the decision to discontinue study treatment and lasts approximately 30 days. For the patient who completed all treatments of Cycle 4 in Arm B of Phase 2 part, the 30-day safety follow-up period begins on the day after the Cycle 4 completion and lasts approximately 30 days (Cycle 4 Day 51 [+7 days]). The 30-day safety follow-up visit occurs at or near the end of the 30-day safety follow-up period (+7 days).

[d] Obtain informed consent prior to any study-related procedures or evaluations.

[e] Any preexisting and pretreatment toxicity should be documented and recorded as part of the pretreatment medical history.

[f] Performed locally.

[g] ECGs will be collected at baseline, prior to the first infusion of Cycle 3, and at the summary visit. A time window of -3 days is permitted for the Day 1 of Cycle 3 assessments.

[h] Before the treatment

[i] Height measurements to be performed at baseline only. A time window of -7 days is permitted for the physical exam on Day 1.

[j] For BSA calculation height from screening visit to be used at each subsequent cycle.

[k] Temperature, Pulse rate, Respiratory rate, and Systolic/Diastolic Blood pressure

[l] To be obtained at every treatment visit, immediately prior to and at the completion of each infusion of necitumumab, and before and at the completion of chemotherapy (gemcitabine and cisplatin) administration.

[m] All AEs/SAEs will be followed for up to 30 days after the decision is made to discontinue study treatment.

[n] After the 30-day safety follow-up, only new and ongoing SAEs deemed related to study treatment will be collected.

Study Schedule: Study I4X-JE-JFCM (continued)

o Health Outcomes will be evaluated prior to the first infusion of every cycle thereafter until PD. Self-reported health outcome assessments (LCSS and EQ-5D) will be performed pretreatment (within 14 days of randomization), prior to the first infusion of Cycles 2 to 4, and every 2-cycle interval thereafter (ie, Cycle 6, Cycle 8, Cycle 10 and so on). Chemotherapy in Arm B will not continue beyond Cycle 4. The instruments will be completed every 6 weeks after discontinuation of the study treatment in Arm A until PD (ie, concurrent with radiological evaluation), and every 6 weeks after discontinuation of chemotherapy in Arm B until PD (ie, concurrent with radiological evaluation). At every scheduled timepoint, the LCSS should be administered prior to the EQ-5D. The first assessment must be done in investigator sites to ensure that patients understand how to complete the questionnaires. Following the pretreatment assessment, patients may complete the health outcomes assessments up to 3 days prior to the scheduled assessment time and may complete them at home if patients can contact site personnel with any questions.

p Hematology, chemistry and coagulation profiles to be collected within 3 days prior to treatment on Day 1 in each cycle. Hematology and chemistry profiles will also be collected within 3 days prior to treatment on Day 8 in each cycle. The laboratory data required for treatment on Day 8 must be collected on Day 5 or later, but 3 days or less prior to treatment (e.g., if treatment scheduled on Day 8 is administered on Day 5, pretreatment laboratory data must be collected on Day 5 only). If the patient has gemcitabine and/or cisplatin-related toxicities, perform hematology and/or chemistry tests weekly based on toxicity. In this case, local chemistry laboratory results may be used for safety assessment; if so, the chemistry tests must also be performed by the central laboratory. If results of the laboratory tests obtained on planned Day 1 of the next cycle require a delay in the start of the subsequent cycle, any repeat laboratory tests should be obtained as clinically indicated. Central chemistry laboratory results will be used to determine patient eligibility at baseline. Local chemistry laboratory results may be used for safety assessment and dosing decisions; if so, the tests scheduled on the study protocol must also be performed by the central laboratory, regardless of delayed or omitted the study treatment.

q If necitumumab and/or chemotherapy are delayed or omitted, all procedures (including concomitant medication, toxicity assessments/AEs, hematology and chemistry tests) planned on Day 8 must be performed on Day 8, and the same procedures will also be conducted before the next administration of necitumumab on Day15. Regardless of delayed or omitted the study treatment, the chemistry test which scheduled on the study protocol must be performed by central laboratory.

r For the Cycle 1, it might be acceptable to use the test results of the safety laboratory values obtained during screening if these tests have been performed within 7 days of Day 1 and are deemed still clinically valid by the treating investigator. Urinalysis and BSA calculation do not have to be performed again for the Cycle 1.

s Urinalysis and coagulation profiles to be collected within 3 days prior to treatment on Day 1 in Cycle 1, and every 2 cycles thereafter (ie, Cycle 3, Cycle 5, Cycle 7 and so on).

t Routine dipstick measurements within 14 days prior to treatment on Day 1 and at the time of 30-day Safety Follow-Up.

u Pregnancy test for women of childbearing potential. Patients are not considered to be of childbearing potential if: (a) they are surgically sterile (hysterectomy, bilateral tubal ligation or bilateral oophorectomy), (b) they are postmenopausal. Pregnancy testing will occur during screening and 30-day safety follow-up periods.

v This follow-up might be a phone-call to the patient, her/his family, or local doctor. Collection of survival data and subsequent antitumor therapies. In Phase 1b part, survival information is not necessary after 30 day safety follow-up period.

[w] Disease assessment will be performed as scheduled every 6 weeks (-7 to +3 business days) from the first dose of study therapy. The method used at baseline must be used consistently for tumor assessment.

Study Schedule: Study I4X-JE-JFCM (complete)

[x] For baseline imaging, besides a CT scan or MRI of chest and upper abdomen including both adrenal glands, a contrast CT scan or MRI of the brain is required within 21 days prior to randomization.

[y] Imaging studies and tumor assessments should be performed as scheduled every 6 weeks (−7 to +3 business days) following first dose of study therapy until discontinued from the study (Phase 1b) or radiographically documented PD (Phase 2), even if therapy is delayed, except when not feasible in the opinion of the investigator due to patient's clinical status. Patients with pathological bone lesions at baseline should undergo respective assessments as well. In Phase 1b part, tumor assessment is not necessary after 30-day safety follow-up period.

[z] A contrast CT or MRI of the brain will be performed at baseline within 21 days prior to randomization for all patients. If the patient had brain metastases at baseline or if clinically indicated, a contrast CT or MRI of the brain will be performed thereafter every 6 weeks (−7 to +3 business days) weeks despite any treatment delays.

[α] Phase 1b/2 parts

[β] For treatment guidelines, refer to Section 9.1.

[γ] A time window of ±3 days is permitted for the Day 8 assessments, but the assessments should be done prior to treatment. Infusions administered within 3 days before or after the planned infusion timepoint is considered acceptable; however, infusions administered within 3 days after the planned infusion timepoint is preferable.

[δ] Subsequent doses of cisplatin and gemcitabine must be recalculated if there is a ≥10% change (increase or decrease) in body weight from the last dose calculation; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from the last dose calculation. For patients undergoing repeated palliative drainage procedures to remove pleural or peritoneal fluid, dry weight will be defined as weight obtained after the drainage procedure and before fluid reaccumulation. In such circumstances, dry weight will be used for dose calculation, if obtained within 30 days prior to dose. If no recent dry weight is available, actual weight will be used.

[ε] The administration of cisplatin will be based on standard procedure (eg, package insert) in standard therapeutic practice.

[ζ] The test conducted before the informed consent date will be accepted for use as screening data if the test result was not positive and is still deemed clinically valid by the investigator.

Data Collected by the Sponsor for the Extension Phase Only

Procedure [a]	Treatment Period (21-day cycles)	Summary Visit[b]	30 day Safety Follow-Up[c]
Toxicity Assessments/AEs	X	X	X
Immunogenicity	X[d]		X
Pharmacokinetics sample (necitumumab)	X[d]		X
Administer Study Therapy	X		
Reason for study therapy discontinuation		X	

[a] During the extension phase, routine safety and efficacy monitoring, including radiographic evaluation of disease and laboratory testing, such as pregnancy testing, should be continued as necessary to confirm patient eligibility to continue in the study. The Sponsor will collect only data shown in this table for the extension phase.

[b] The summary visit is used when the decision is made to stop treatment and is completed up to 7 days after the decision is made to discontinue treatment.

[c] The 30-day safety follow-up period begins on the day after the patient and the investigator agree to discontinue the patient from the treatment portion of the study and lasts approximately 30 days. The 30-day safety follow-up visit occurs at or near the end of the 30-day safety follow-up period (+7 days).

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

Attachment 2. Protocol JFCM Schedule for Pharmacokinetic and Immunogenicity Sampling

Schedule for Pharmacokinetic and Immunogenicity Sampling, Protocol I4X-JE-JFCM (Phase 1b)

		Pharmacokinetic sample			
		Necitumumab (Nec)	Gemcitabine (Gem)	Cisplatin (Cis)	Immunogenicity
Cycle 1					
Day 1	**Pre-inf of Nec**	X	X	X	X
	Post-inf of Nec [d]	X			
	30 min Post-inf of Nec		X (Post-inf of Gem) [c, d]		
	1 h Post-inf of Nec	X	X (30 min Post-inf of Gem) [c]		
	1h 30 min Post-inf of Nec		X (1 h Post-inf of Gem) [c]		
	2h 30 min Post-inf of Nec		X (2 h Post-inf of Gem) [c]		
	3 h Post-inf of Nec	X		X (Post-inf of Cis) [c, d]	
	6 h Post-inf of Nec	X		X (3 h Post-inf of Cis) [c]	
Day 2	**24 h Post-inf of Nec**	X		X (21 h Post-inf of Cis) [c]	
Day 5	**96 h Post-inf of Nec**	X		X (93 h Post-inf of Cis) [c]	
Day 8	**Pre-inf of Nec day 8** [a]	X		X (165 h Post-inf of Cis) [c]	
	Post-inf of Nec day 8 [a, d]	X			
Day 15	**167 h Post-inf of Nec day 8** [a]	X			
	(Pre-inf of Nec day 15) [a]	(X)			
	(Post-inf of Nec day 15) [a,d]	(X)			
Cycle 2					
Day 1	**Pre-inf of Nec**	X			X
Day 8	**Pre-inf of Nec**	X			
Cycle 3					
Day 1	**Pre-inf of Nec day 1**	X			X
	Post-inf of Nec day 1 [d]	X			
	1 h Post-inf of Nec day 1	X			
	3 h Post-inf of Nec day 1	X			
	(6 h Post-inf of Nec day 1) [b]	(X)			
(Day 2)	**(24 h Post-inf of Nec day 1)** [b]	(X)			
(Day 5)	**(96 h Post-inf of Nec day 1)** [b]	(X)			
Day 8	**Pre-inf of Nec day 8** [a]	X			
	Post-inf of Nec day 8 [a, d]	X			
(Day 15)	**(167 h Post-inf of Nec day 8)** [a, b]	(X)			
	(Pre-inf of Nec day 15) [a]	(X)			
	(Post-inf of Nec day 15) [a, d]	(X)			

		Pharmacokinetic sample			
		Necitumumab (Nec)	Gemcitabine (Gem)	Cisplatin (Cis)	Immunogenicity
Cycle 4					
Day 1	**Pre-inf of Nec**	X			X
Day 8	**Pre-inf of Nec**	X			
Visit 801					
30 days after the decision to discontinue study treatment		X			X

Note: It is essential that the draw dates and draw times are accurately recorded.
Blood samples for PK evaluation will be collected based on the starting and completion of Necitumumab administration.

Abbreviations: Nec=Necitumumab, Gem=Gemcitabine, Cis=Cisplatin, h = hour, post-inf = post-infusion, pre-inf = pre-infusion.

a If treatment for necitumumab will be postpone from Days 8 to 15, sample collection will be skipped and collected on Day 15.

b Optional

c Post-inf times are PK sample collection time points starting on completion of Gemcitabine or Cisplatin administration. If time points starting on completion of each study drug administration were different, bood samples will be collected at time points starting on the administration of Gemcitabine or Cisplatin rather than that of Necitumumab.

d "Post-infusion" blood samples for necitumumab, gemcitabine, and cisplatin will be taken immediately prior to or taken immediately after the end of infusion to ensure an accurate C_{max}.

Schedule for Pharmacokinetic and Immunogenicity Sampling, Protocol I4X-JE-JFCM (Arm A in Phase 2)

		Pharmacokinetic sample for Necitumumab (Nec)	Immunogenicity
Cycle 1			
Day 1	**Pre-inf of Nec**	X	X
	Post-inf of Nec [b]	X	
Cycle 2			
Day 1	**Pre-inf of Nec** [c]	X	
Cycle 3			
Day 1	**Pre-inf of Nec** [c]	X	X
	Post-inf of Nec [b]	X	
Cycle 4			
Day 1	**Pre-inf of Nec** [c]	X	
Cycles 5 to X			
Day 1	**Pre-inf of Nec**	X [a]	X [a]
Visit 801			
30 days after the decision to discontinue study treatment [d]		X	X

Note: It is essential that the draw dates and draw times are accurately recorded.
Blood samples for PK evaluation will be collected based on the starting and completion of Necitumumab administration.

Abbreviations: Nec=Necitumumab, h = hour, post-inf = post-infusion, pre-inf = pre-infusion.

a After 5 cycle: pharmacokinetics and immunogenicity will be examined every 2 cycles

b "Post-infusion" blood samples for necitumumab will be taken immediately prior to or taken immediately after the end of infusion to ensure an accurate C_{max}.

c If only necitumumab is discontinued before Cycle 4 (chemotherapy continues for a maximum of 4 cycles), a PK sample will be taken at Day 1 of the first cycle after the decision to discontinue necitumumab (i.e. the first cycle when only chemotherapy is administered). If this is Cycle 3 Day 1, an immunogenicity sample will also be taken. Collection of PK and/or immunogenicity samples at Day 1 of the subsequent cycle is not required.

d If only necitumumab is discontinued before Cycle 4 (chemotherapy continues for a maximum of 4 cycles), this PK and immunogenicity sampling will be taken at the nearest planned visit to 30 days after the decision to discontinue necitumumab.

Attachment 3. Protocol JFCM Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology [a]	**Clinical Chemistry** [b]
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
	Magnesium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils	Alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)
Lymphocytes	Aspartate aminotransferase/ Serum glutamic oxaloacetic transaminase (AST/SGOT)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, nonfasting
Urinalysis [a]	Albumin
Glucose	Cholesterol
Protein	Creatine kinase (CK)
Ketones	Inorganic phosphorus (IP)[a, d]
Blood	
Specific gravity	**Pregnancy Test (Urine/Serum)**[a, c]
pH	
Urine leukocyte esterase	**Coagulation Profile** [a]
	Prothrombin Time (PT)
	Partial Thromboplastin Time (PTT)
	International Normalized Ratio (INR)

Abbreviations: RBC = red blood cells; WBC = white blood cells;

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

[b] Assayed by Sponsor-designated (central) laboratory.

[c] Whichever is selected should be followed throughout.

[d] The assay result will be monitored by investigators to assess safety and be captured as an adverse event in the eCRF, if necessary. It is not necessary to record the actual assay result in the eCRF because it will not be used in the safety analysis.

Attachment 4. Protocol JFCM ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

References:

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol.* 1982;5:649-655.

Attachment 5. Protocol JFCM Necitumumab, Gemcitabine, and Cisplatin Dosing Scenarios for Chemotherapy Delays

Cycle	Day	Necitumumab	Gemcitabine	Cisplatin
No treatment delay				
1	1	X	X	X
	8	X	(X)	
	15			
2	1(22)	X	X	X
Necitumumab schedule change				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	X		
2	1(22)	X	X	X
Necitumumab schedule change and skip				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	No administration due to treatment criteria is not met		
2	1(22)	X	X	X
Treatment delay for Cycle 2 (1 week):				
1	1	X	X	X
	8	X	(X)	
	15			
	22	No administration due to treatment criteria is not met		
2	1(29)	X	X	X
Treatment delay for Cycle 2 (1 week): Necitumumab schedule change				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	X		
	22	No administration due to treatment criteria is not met		
2	1(29)	X	X	X
Treatment delay for Cycle 2 (1 week): Necitumumab schedule change and skip				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	No administration due to treatment criteria is not met		
	22	No administration due to treatment criteria is not met		
2	1(29)	X	X	X

Cycle	Day	Necitumumab	Gemcitabine	Cisplatin
Treatment delay for Cycle 2 (2 weeks):				
1	1	X	X	X
	8	X	(X)	
	15			
	22	No administration due to treatment criteria is not met		
	29	No administration due to treatment criteria is not met		
2	1(36)	X	X	X
Treatment delay for Cycle 2 (2 weeks): Necitumumab schedule change				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	X		
	22	No administration due to treatment criteria is not met		
	29	No administration due to treatment criteria is not met		
2	1(36)	X	X	X
Treatment delay for Cycle 2 (2 weeks): Necitumumab schedule change and skip				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	No administration due to treatment criteria is not met		
	22	No administration due to treatment criteria is not met		
	29	No administration due to treatment criteria is not met		
2	1(36)	X	X	X
Treatment delay for Cycle 2 (3 weeks):				
1	1	X	X	X
	8	X	(X)	
	15			
	22	No administration due to treatment criteria is not met		
	29	No administration due to treatment criteria is not met		
	36	No administration due to treatment criteria is not met		
2	1(43)	X	X	X
Treatment delay for Cycle 2 (3 weeks): Necitumumab schedule change				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	X		
	22	No administration due to treatment criteria is not met		
	29	No administration due to treatment criteria is not met		
	36	No administration due to treatment criteria is not met		
2	1(43)	X	X	X

Cycle	Day	Necitumumab	Gemcitabine	Cisplatin
Treatment delay for Cycle 2 (3 weeks): Necitumumab schedule change and skip				
1	1	X	X	X
	8	No administration due to treatment criteria is not met	(X)	
	15	No administration due to treatment criteria is not met		
	22	No administration due to treatment criteria is not met		
	29	No administration due to treatment criteria is not met		
	36	No administration due to treatment criteria is not met		
2	1(43)	X	X	X

Attachment 6. Protocol JFCM Amendment (e) Summary [An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)]

Overview

Protocol I4X-JE-JFCM [An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)] has been amended. The amended protocol is indicated by the revised study alias, Protocol 14X-JE-JFCM (e) and will be used to conduct the study in place of any preceding version of the protocol.

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

- The following changes related to patient safety were made to maintain consistency with the latest updated IB (approved 30-Mar-2016).
    - Section 9.7.1.1 Infusion-Related Reactions was updated.
    - Section 9.7.1.2.1 Reactive Treatment was updated.
    - Section 9.7.1.3 Conjunctivitis was updated.
    - Section 9.7.1.4 Hypomagnesemia was changed to Electrolyte Abnormalities and updated.
    - Section 9.7.1.6 Thromboembolic Events was updated and divided into two sections “Section 9.7.1.6 Thromboembolic Events” and “Section 9.7.1.7 Cardiorespiratory Disorders”.
    - Section 14: Added references.
    - Attachement 3: Added “inorganic phosphorus” to monitor patients for hypophosphatemia as described in Section 9.7.1.4.
- Other changes are as follows:
    - Section 8.1.8: Added the text to clarify the position of the ILDC in this study.
    - Section 10.2.1 and Attachment 1: Added the text to clarify the data collection after discontinuation of the study treatment in Arm A.

Revised Protocol Sections

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

1. Protocol I4X-JE-JFCM(e)

An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC)

8.1.8. Committees

Interstitial Lung Disease Committee (ILDC)

Interstitial Lung Disease Committee will be established. For the interstitial lung disease (ILD) and suspected ILD cases being diagnosed after starting the study treatments (on Day 1 in Cycle 1), external specialists will evaluate its related examination results such as image data and tissue samples. The assessments by the ILDC are independent from assessments by investigators and will not be collected in the clinical trial database. The assessments by the ILDC will be provided to the Sponsor and used for safety monitoring. Assessments by the ILDC will not be made available to investigators in principle.

9.7.1.1. Infusion-Related Reactions

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

- Grade 1: transient flushing or rash, drug fever <38.0ºC
- Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥38.0ºC

- 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)

Hypersensitivity/infusion-related reactions 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 infusion-related reactions with resuscitation equipment readily available. For mild or moderate (Grade 1 or 2) infusion-related reactions, adjust dose per Table JFCM.12. Immediately and permanently discontinue necitumumab for severe (Grade 3 or 4) infusion-related reactons.

Consistent with usual medical practice, selected parenteral medications may be utilized for as detailed below (Table JFCM.12). Additional treatments, chosen according to clinical symptoms and local standards, may be utilized at investigator discretion.

9.7.1.2.1. Reactive Treatment

Skin reactions were reported with necitumumab. The onset of events occurred mainly during the first cycle of treatment.

Based on emerging data from cetuximab, there appears to be a correlation between acneform rash and various efficacy outcomes. Therefore, if a patient experiences a Grade 1 or 2 acne-like rash, necitumumab treatment should continue without dose modification or delay. If a patient experiences acute or chronic Grade 3 rash acneiform (ie, rash associated with pain, disfigurement, ulceration, or desquamation), pruritus, desquamation, dry skin, cheilitis, or hand-foot reaction, necitumumab treatment will be delayed for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until there is improvement to Grade ≤2. At this time, necitumumab may be re-administered (as described in Table JFCM.13). Patients who experience Grade 3 skin induration / fibrosis or any Grade 4 skin toxicity will be immediately and permanently discontinued from necitumumab.

~~At the June 2008 World GI Congress in Barcelona, Spain, Mitchell et al presented results of a study comparing pre-emptive versus reactive treatment of skin toxicity among patients receiving panitumumab, another monoclonal antibody directed against the EGFR. In this study, pre-emptive treatment reduced the incidence of skin toxicity Grade ≥2 by more than 50% over reactive treatment, and resulted in fewer dose delays. As a recommendation, on the basis of these data, pre-emptive treatment with skin moisturizers, topical steroids, doxycycline, or sunscreen may be administered as clinically appropriate to patients receiving 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).

9.7.1.3. Conjunctivitis

Conjunctivitis has been reported very commonly in patients receiving necitumumab.

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

Serious cases of keratitis and ulcerative keratitis have been reported as uncommon or rare side effects for other anti-EGFR antibodies and are to be considered a class effect. If the diagnosis is confirmed, anti-EGFR treatment should be interrupted or discontinued, with benefits and risks of continuation of treatment to be carefully considered.

9.7.1.4. Electrolyte Abnormalities~~Hypomagnesemia~~

Consistent with observations with other EGFR-targeting antibodies (as with panitumumab and cetuximab), 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-targeting antibodies. Monitor patients for hypomagnesemia, hypocalcemia, hypokalemia, and hypophosphatemia prior to each administration of necitumumab and after completion of the treatment of necitumumab, until within normal limits. Prompt repletion is recommended, as appropriate.~~Hypomagnesemia has been reported with necitumumab therapy and is considered to be a class effect with EGFR-targeting antibodies (as with panitumumab and cetuximab).~~ Hypomagnesemia is reversible following discontinuation of EGFR antibody therapy. Treatment of any hypomagnesemia should be as clinically indicated according to local standards, and necitumumab therapy should be continued unless the investigator has any related safety concern.

9.7.1.6. Thromboembolic Events

Venous thromboembolic events and 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.

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.

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).

~~In an ongoing Study (CP11-0805) for the combination of necitumumab with pemetrexed and cisplatin in nonsquamous NSCLC, an increased rate of serious thromboembolic events, including fatal events, as compared to the treatment with pemetrexed and cisplatin alone has been observed. These cases included cases of arterial thromboembolism (for example, cerebrovascular ischemia, intestinal ischemia, or leg ischemia), venous thromboembolism (for example, pulmonary embolism) and cases where thromboembolism was not proven, but could not be excluded (for example, cases of sudden death with limited information); the latter cases mainly contributed to the excess of fatal events.~~

~~The majority of fatal cases occurred within the first two cycles of therapy, leading to the IDMC recommendation to stop enrollment and to stop treatment in patients who have not yet completed Cycle 2 of treatment. No other strategies on how to prevent serious thromboembolic events in this study could be identified from a thorough review of the data. Further analysis is ongoing.~~

~~For the combination of necitumumab with gemcitabine and cisplatin in another ongoing study, in squamous NSCLC (CP11-0806) a higher rate of serious venous thromboembolic events (mainly deep vein thrombosis and pulmonary embolism) as compared to the treatment with gemcitabine and cisplatin alone has been observed; this imbalance however, did not pertain to fatal cases. Further analysis is ongoing.~~

~~No safety signal with regard to thromboembolic events, including fatal thromboembolic events, has been identified for necitumumab when administered as monotherapy or in combination with modified FOLFOX-6 chemotherapy (5-fluorouracil, folinic acid, and oxaliplatin).Treatment of any thromboembolic events 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.~~

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

9.7.1.7. Cardiorespiratory Disorders

An increased frequency of cardiorespiratory arrest or sudden death was observed with necitumumab. Cardiorespiratory arrest or sudden death was reported in the pivotal Study JFCC (SQUIRE, CP11-0806) 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.

10.2.1. Patient-Reported Outcomes (only Phase 2 part)

All patients for whom there is a validated translation in which the patient is fluent will undergo assessment for symptoms and QOL using the LCSS and the EuroQol (EQ-5D). It is recommended that the instruments is administered together and in sequence order, with the LCSS presented first, followed by presentation of the EQ-5D.

Patients will complete the instruments at baseline (within 14 days prior to randomization), prior to the first infusion of Cycles 2 to 4, and in Arm A, every ~~2~~ 2-cycle~~s~~ interval thereafter (ie, Cycle 6, Cycle 8, Cycle 10 and so on). Chemotherapy in Arm B will not continue beyond Cycle 4. The instruments will be completed every 6 weeks after discontinuation of the study treatment in Arm A until PD (ie, concurrent with radiological evaluation), ~~in Arm A~~ and every 6 weeks after discontinuation of chemotherapy in Arm B until PD (ie, concurrent with radiological evaluation ~~after discontinuation of chemotherapy~~). The instruments should be completed at the beginning of the visit, before any extensive contact and consultation with the clinician/study investigator; such encounters may thereafter bias patient responses. The LCSS and the EQ-5D will be completed by all patients using the validated translated version of Japanese.

14. References

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Attachment 1. Protocol JFCM Study Schedule

- Health Outcomes will be evaluated prior to the first infusion of every cycle thereafter until PD. Self-reported health outcome assessments (LCSS and EQ-5D) will be performed pretreatment (within 14 days of randomization), prior to the first infusion of Cycles 2 to 4, and every 2-cycle interval thereafter (ie, Cycle 6, Cycle 8, Cycle 10 and so on). Chemotherapy in Arm B will not continue beyond Cycle 4. The instruments will be completed every 6 weeks after discontinuation of the study treatment in Arm A until PD (ie, concurrent with radiological evaluation), ~~in Arm A~~ and every 6 weeks after discontinuation of chemotherapy in Arm B until PD (ie, concurrent with radiological evaluation ~~after discontinuation of chemotherapy~~). At every scheduled timepoint, the LCSS should be administered prior to the EQ-5D. The first assessment must be done in investigator sites to ensure that patients understand how to complete the questionnaires. Following the pretreatment assessment, patients may complete the health outcomes assessments up to 3 days prior to the scheduled assessment time and may complete them at home if patients can contact site personnel with any questions.

Attachment 3. Protocol JFCM Clinical Laboratory Tests

Clinical Laboratory Tests

Clinical Chemistry [b]
Serum Concentrations of:
Inorganic phosphorus (IP)[a, d]

[d] The assay result will be monitored by investigators to assess safety and be captured as an adverse event in the eCRF, if necessary. It is not necessary to record the actual assay result in the eCRF because it will not be used in the safety analysis.

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