Protocol I4X-MC-JFCQ(d)

An Open-Label, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of the Combination of Necitumumab with Pembrolizumab in Patients with Stage IV Non-Small Cell Lung Cancer

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Approval Date: 17-Sep-2018

1. Protocol I4X-MC-JFCQ(d)
An Open-Label, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of the Combination of Necitumumab with Pembrolizumab in Patients with Stage IV Non-Small Cell Lung Cancer

Necitumumab (LY3012211), Pembrolizumab (MK3475)

This is an open-label, multicenter, Phase 1b study with an expansion cohort in patients with Stage IV non-small cell lung cancer (NSCLC). The study consists of 3 parts (Part A, Part B, and Part C). Part A is a single-arm, open-label, dose-escalation study to determine the recommended dose of necitumumab in combination with pembrolizumab. Part B is an open-label study to evaluate the efficacy and safety of necitumumab in combination with pembrolizumab. Part C is an open-label study to evaluate the safety of necitumumab at the recommended dose from Part A in combination with pembrolizumab in Japanese patients.

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Protocol Electronically Signed and Approved by Lilly on 27 May 2015.
Amendment (a) Electronically Signed and Approved by Lilly on 03 March 2016.
Amendment (b) Electronically Signed and Approved by Lilly on 11 July 2016.
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Amendment (d) Electronically Signed and Approved by Lilly on date provided below.

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2. Synopsis

Study Rationale

Necitumumab (IMC-11F8; LY3012211; Portrazza®) is a recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 (IgG1) that blocks the ligand-binding site of the epidermal growth factor receptor (EGFR). EGFR is detectable in approximately 85% to 90% of patients with advanced, metastatic non-small cell lung cancer (NSCLC). Necitumumab has shown signals of antitumor activity in 2 Phase 1 trials when administered as monotherapy in heavily pretreated patients including but not limited to patients with NSCLC. Portrazza has recently been approved in the US and EU for the treatment of adult patients with metastatic squamous NSCLC in combination with gemcitabine and cisplatin.

Pembrolizumab (MK-3475, Keytruda®) is a humanized IgG4 mAb directed against programmed death-1 (PD-1) T-cell co-receptor, thus blocking its interaction with ligands, PD-L1 and PD-L2. Pembrolizumab is approved for treatment of melanoma in several countries; in the US and EU it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

The rationale for combining both agents is based on clinical single-agent data that show activity of EGFR-directed mAbs and pembrolizumab in NSCLC, and preclinical data suggesting that the antitumor activity of EGFR antibodies can be attributed, at least in part, to various immune effector mechanisms.

The individual toxicity profiles of necitumumab and pembrolizumab suggest that no overlapping Grade ≥3 toxicity is expected; skin rash Grade 1-2 has been seen with both agents, hence some overlap is expected.

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

The purpose of this Phase 1b study with an expansion cohort is to explore the safety and preliminary efficacy of necitumumab plus pembrolizumab in patients with Stage IV NSCLC who have progressed after 1 platinum-based chemotherapy regimen.

Clinical Protocol Synopsis: Study I4X-MC-JFCQ

Name of Investigational Products: Necitumumab (LY3012211); Pembrolizumab (MK-3475)

Title of Study: An Open-Label, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of the Combination of Necitumumab with Pembrolizumab in Patients with Stage IV Non-Small Cell Lung Cancer

Number of Planned Patients:	**Phase of Development: 1b**
Part A Enrolled: 3 to 12 Part B (Expansion Cohort) Enrolled: 54 Part C (Japanese patients) Enrolled: 6 to 12	

Length of Study: approximately 22 months
Planned first patient visit: 15-Aug-2015
Planned last patient visit: 21-Jun-2017
Planned interim analyses: first 15 evaluable patients in Part B portion of the study who have completed 2 cycles of study treatment (or otherwise discontinued study treatment) will be analyzed for safety. Interim efficacy analyses may be performed as needed to aid in the planning of future trials. Patients with squamous and nonsquamous NSCLC, from Part A, who received the recommended necitumumab dose for Part B will be included in the interim analyses.

Objectives:
The primary objectives of the study are:
Part A: to determine the dose-limiting toxicity (DLT) of necitumumab at doses of 600 mg and 800 mg on Days 1 and 8 when combined with pembrolizumab 200 mg on Day 1 every 3 weeks (Q3W), in patients with Stage IV NSCLC as measured by the number of patients with a DLT in Cycle 1.
Part B: to evaluate the efficacy of necitumumab in combination with pembrolizumab in terms of overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) in patients with Stage IV NSCLC.
Part C: to determine the DLT of necitumumab at the recommended dose from Part A in combination with pembrolizumab in Japanese patients with Stage IV NSCLC as measured by the number of patients with a DLT in Cycle 1.

The secondary objectives of the study are:
Part A and Part C:
- to investigate the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with pembrolizumab
- to determine the ORR by RECIST 1.1
- to determine the pharmacokinetics (PK) of necitumumab in presence of pembrolizumab
- to determine the immunogenicity of necitumumab in presence of pembrolizumab

Part B: to demonstrate the feasibility of necitumumab at the recommended dose in combination with pembrolizumab by:
- investigating the safety profile as assessed by clinical and laboratory significant events
- determining disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) by RECIST 1.1.
- determining PK of necitumumab in presence of pembrolizumab
- determining the immunogenicity of necitumumab in presence of pembrolizumab

The exploratory objective is to further evaluate as follows:

Parts A, B, and C: to investigate relationship between immune- and EGFR-pathway-related biomarkers and treatment outcomes. Part B: to assess immune-related (ir)ORR, irDCR, irDOR, and irPFS by adapted RECIST 1.1 (immune-related RECIST [irRECIST]).

Study Design: This is an open-label, multicenter Phase 1b study with an expansion cohort to investigate necitumumab in combination with pembrolizumab in approximately 78 patients with Stage IV NSCLC (American Joint Committee on Cancer Staging Manual, 7th edition). The study consists of 3 parts:

- Part A: Dose-escalation part with increasing doses of necitumumab (600 mg or 800 mg on Days 1 and 8 Q3W) to determine a recommended dose range for necitumumab that may be safely administered in combination with a fixed regimen of pembrolizumab 200 mg Day 1 Q3W in patients with Stage IV NSCLC.
- Part B (expansion cohort): Dose confirmation of necitumumab in combination with a fixed regimen of pembrolizumab 200 mg on Day 1 Q3W and exploration of clinical antitumor activity in patients with Stage IV NSCLC.
- Part C: DLT confirmation using the recommended dose from Part A for necitumumab in combination with a fixed regimen of pembrolizumab 200 mg on Day 1 Q3W in Japanese patients with Stage IV NSCLC.

Approximately 54 patients will be enrolled in Part B: approximately 27 patients with squamous histology and approximately 27 patients with nonsquamous histology.

Patients will be treated until progressive disease (PD), toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Patients who are on study therapy at study completion may continue to receive study therapy in the continued access period until they meet the discontinuation criteria. Part A and Part B of this study will be considered complete approximately 6 months after the last patient in Part B has been enrolled, and Part C of this study will be considered complete approximately after all the patients in Part C have completed 8 cycles or discontinued early.

Diagnosis and Main Criteria for Inclusions and Exclusions:

Key inclusion/exclusion criteria at the time of enrollment

- The patient has histologically or cytologically confirmed NSCLC.
  Part A: NSCLC Stage IV (any histological type)
  Part B: NSCLC Stage IV (squamous and nonsquamous)
  Part C: NSCLC Stage IV in Japanese patients (squamous and nonsquamous)
- The patient must have progressed after 1 platinum-based chemotherapy regimen for Stage IV NSCLC. Prior vascular endothelial growth factor (VEGF)/VEGF receptor-targeting agents and neoadjuvant/adjuvant therapies are permitted. Prior treatment with EGFR-tyrosine kinase inhibitor and anaplastic lymphoma kinase (ALK) inhibitors is mandatory in patients with NSCLC whose tumor has EGFR-activating mutations or ALK translocations, respectively.
- Measurable disease at the time of study entry as defined by RECIST 1.1.
- The patient has an evaluable tumor tissue, an archived formaldehyde fixed-paraffin embedded (FFPE) block or at a minimum 15 slides (freshly cut slides should be submitted to the central laboratory), is available for biomarker analyses, or if not available, patient is willing to undergo a tumor biopsy of an extra-central nervous system lesion (core or excisional biopsy).
- The patient has resolution to Common Terminology Criteria for Adverse Events (CTCAE) Grade $\leq$1 of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy (with the exception of alopecia).
- Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1.
- The patient has no brain metastases that are symptomatic.

Test Product, Dosage, and Mode of Administration:

- Necitumumab is a sterile, preservative-free, intravenous infusion supplied in 50-mL vials containing 16 mg/mL (800 mg/50 mL) of product, and administered over 60 minutes at a dose of 600 mg or 800 mg on Days 1 and 8 of each 21-day cycle.
- Pembrolizumab drug product is available in 2 dosage forms intended for intravenous administration: a lyophilized powder, 50 mg/vial, ready to be reconstituted with sterile water for injection prior to use, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only. Pembrolizumab is administered over 30 minutes (-5 min/+ 10 min) at a dose of 200 mg on Day 1 of each 21-day cycle.

Reference Therapy, Dose, and Mode of Administration:
Not Applicable

Planned Duration of Treatment:
Baseline period: up to 21 days
Treatment period: 21 days treatment cycle
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion
Study completion: Part A and Part B of this study will be considered complete approximately 6 months after the last patient in Part B has been enrolled, and Part C of this study will be considered complete approximately after all the patients in Part C have completed 8 cycles or discontinued early.
Continued Access Period: Patients who are on study therapy at study completion may continue to receive study therapy in the continued access period until they meet the discontinuation criteria.

Criteria for Evaluation:
Efficacy:
Objective Response Rate (ORR) is defined as the proportion of patients achieving a best overall response of partial response (PR) or complete response (CR).
Disease Control Rate (DCR) is defined as the proportion of patients achieving a best overall response of stable disease (SD), PR, or CR.
Progression-Free Survival (PFS) is defined as the time from the date of first dose of any study drug until the date of radiographically documented PD or death due to any cause, whichever is earlier.
Overall Survival (OS) is defined as the time from the date of first dose of any study drug to the date of death from any cause.

Safety:
Part A and Part C: DLTs, serious adverse events (SAEs), adverse events (AEs), vital sign measurements, laboratory analyses, and electrocardiograms (ECGs)
Part B: SAEs, AEs, vital sign measurements, laboratory analyses, and ECGs

Pharmacokinetics:
Serum concentrations of necitumumab prior to infusion (minimum concentration [C_{min}]) and at end of the necitumumab infusion (approximately maximum concentrations for necitumumab).

Bioanalytical:
Serum concentrations of necitumumab will be measured using validated enzyme-linked immunosorbent assays.

Immunogenicity:
Serum anti-necitumumab antibody titer levels will be determined.

Translational research:
A tumor tissue block or tumor tissue slides will be collected to correlate biomarker results with clinical outcomes related to the EGFR pathway, innate and adaptive immunity, and/or other biomarkers associated with the disease pathobiology and therapeutic molecules.
Blood samples will be collected for exploratory biomarker analyses.

Statistical Methods:

Efficacy: The primary Part B outcome variable in this study will be the ORR. The Part B statistical null hypothesis states that the true ORR is 20%, whereas the research hypothesis states that the true ORR is 35%. If the research hypothesis is true, there is an 83% chance of rejecting the null hypothesis. If the null hypothesis is true, then there is at most a 10% chance of rejecting the null hypothesis. Therefore, the sample size of 54 evaluable patients in Part B has a nominal one-sided alpha level of 0.10, with statistical power of 83%.

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

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

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

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

Pharmacokinetics: Summary statistics of necitumumab data will be presented graphically as well as in tabulated form. Additional exploratory analyses using population PK approach may be performed if warranted by data.

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

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
ADA	anti-drug(s) antibodies
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
Assent	Agreement from an individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
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).
BCG	Bacillus Calmette-Guérin
CI	confidence interval
CK	creatine kinase
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CR	complete response
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CrCl	creatinine clearance
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives

ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
ESAs	erythropoiesis-stimulating agents
EU	European Union
FFPE	formaldehyde fixed-paraffin embedded
GC	gemcitabine/cisplatin
GC+N	gemcitabine/cisplatin plus necitumumab
GCP	good clinical practice
H_0	null hypothesis
H_a	alternative hypothesis
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IgG_1	immunoglobulin G, subclass 1
IHC	immunohistochemistry
ILD	interstitial lung disease
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical trial data, that is conducted before the final reporting database is created/locked.

investigational product (IP) [hereon referred to as study treatment]	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form. In this study, the IPs are necitumumab (LY3012211; IMC-11F8) and pembrolizumab (MK-3475).
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.
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
irSD	immune-related stable disease
I.V.	intravenous(ly)
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.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAIDs	non-steroidal anti-inflammatory drugs

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.
PC	pemetrexed–cisplatin
PC+N	necitumumab plus pemetrexed–cisplatin
PD	progressive disease
PD-1	programmed death-1
PD-L	programmed death-1 ligand
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Study completion	Part A and Part B of this study will be considered complete approximately 6 months after the last patient in Part B has been enrolled, and Part C of this study will be considered complete approximately after all the patients in Part C have completed 8 cycles or discontinued early.
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TKI	tyrosine kinase inhibitor
ULN	upper limits of normal
US	United States
USPI	United States package insert
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
VTE	venous thromboembolic event

5. Introduction

5.1. Non-Small Cell Lung Cancer

Lung cancer is the most common cancer worldwide, with an estimated 1.6 million new cases per year, and the leading cause of cancer-related mortality with an estimated 1.4 million cancer-related deaths per year (Bray et al. 2012; Bunn 2012).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Patients with localized disease have a 5-year survival rate of approximately 55%; however, 5-year survival drops significantly for patients with regional (26.1%) or distant (3.9%) disease at diagnosis (Howlader et al. 2014).

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

More recently, necitumumab has been approved in the US and EU for first-line treatment of patients with metastatic squamous NSCLC (Portrazza SmPC/USPI).

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

5.2. Necitumumab

Necitumumab (LY3012211) is a recombinant human mAb of the immunoglobulin (Ig) G_1 class, which targets EGFR. Necitumumab demonstrates a high affinity to its target and blocks ligand-induced receptor phosphorylation and downstream signaling. In vitro studies further demonstrate that necitumumab inhibits EGFR-dependent tumor cell proliferation, and can exert cytotoxic effect in tumor cells through antibody-dependent cell cytotoxicity.

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

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

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

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

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

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

The pivotal, randomized Phase 3 trial SQUIRE (I4X-IE-JFCC) compared gemcitabine/cisplatin plus necitumumab (GC+N) versus gemcitabine/cisplatin (GC) as first-line therapy in 1093 patients with Stage IV squamous NSCLC (Thatcher et al. 2015). The study met its primary objective, demonstrating a statistically significant improvement in overall survival (OS) in the GC+N Arm compared with the GC Arm (hazard ratio [HR] = 0.84; p=0.012). This was supported by a statistically significant improvement in progression-free survival (PFS; HR = 0.85; p=0.02). Several prespecified subgroup analyses for OS and PFS showed a consistent treatment effect in favor of GC+N. Post-progression anticancer therapy was similar (47% vs. 45%). The safety data obtained in SQUIRE overall were consistent with the safety profile expected for an anti-EGFR mAb, with skin reactions (any grade: 79% vs. 12%, including Grade ≥3: 8.2% vs. 0.6%) and hypomagnesemia (any grade: 31% vs. 16%, including Grade ≥3: 9.3% vs. 1.1%) being the most frequently reported events (pooled terms) occurring at higher rates for patients receiving necitumumab. The Grade ≥3 TEAEs with highest incidence for which incidence was higher in the necitumumab arm than in the control arm were hypomagnesemia (8.7% vs. 1.1%), rash (3.7% vs. 0.2%), pulmonary embolism (3.5% vs. 1.8%), hypokalemia (3.0% vs. 1.5%), and vomiting (2.8% vs. 0.9%).

In another randomized Phase 3 trial, INSPIRE (I4X-IE-JFCB [JFCB]), 947 patients were planned to be randomly assigned to necitumumab plus pemetrexed-cisplatin (PC+N) versus pemetrexed-cisplatin (PC) as first-line therapy for Stage IV nonsquamous NSCLC (Paz-Ares et al. 2013). Enrollment was halted, following an independent data monitoring committee (IDMC) recommendation, after 633 patients because of safety concerns related to thromboembolism as well as the overall number of deaths from all causes that were unbalanced against the experimental group; the trial continued for patients that had been enrolled. Based on the final analysis, PC+N did not improve the efficacy outcome over PC alone in advanced nonsquamous NSCLC (OS HR = 1.01, p=0.96; PFS HR = 0.96, p=0.66). The addition of necitumumab resulted in a higher frequency of Grade ≥3 TEAEs. Grade ≥3 TEAEs occurring more frequently in the necitumumab arm included skin or subcutaneous disorders (14.1 vs. 0.3%), thromboembolic events (9.5 vs. 6.4%), hypomagnesaemia (7.6 vs. 2.2%), asthenia (6.9 vs. 1.9%), vomiting (6.6 vs. 3.2%), dyspnea (5.3 vs. 2.6%), and diarrhea (4.3 vs. 2.2%). The frequency of study drug related deaths was 4.9% and 2.9% for PC+N and PC, respectively.

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

events, including fatal events, has been identified for necitumumab in completed clinical trials when administered as monotherapy or in combination with mFOLFOX-6 (5-FU/FA and oxaliplatin) chemotherapy.

The randomized Phase 2 trial, I4X-MC-JFCL (JFCL), compared paclitaxel-carboplatin plus necitumumab versus paclitaxel-carboplatin in the first-line treatment of patients with Stage IV squamous NSCLC. The overall efficacy and safety results were generally consistent with those of SQUIRE. Study I4X-JE-JFCM is a Phase 1b/2 study in Japanese patients with Stage IV squamous NSCLC that compares necitumumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone. The trial is monitored by an IDMC and continues as planned.

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

5.2.1. Rationale for Necitumumab Dose Selection

The recommended dose and treatment schedules for necitumumab are 800 mg (weekly), 800 mg (once every 2 weeks), or 800 mg (Days 1 and 8 of a 21-day cycle), based on safety and pharmacokinetics (PK) data from 2 Phase 1 studies in heavily pretreated patients with advanced solid tumors (JFCA and JFCE). The necitumumab 800-mg dose administered I.V. on Days 1 and 8 of each 21-day cycle has also been used in the recent pivotal, randomized Phase 3 trial SQUIRE in combination with gemcitabine/cisplatin as first-line therapy in 1093 patients with Stage IV squamous NSCLC (Thatcher et al. 2015). The starting dose of necitumumab will be at Dose Level -1 of the MTD (600 mg on Days 1 and 8 every 3 weeks [Q3W]). Since this is the first time these 2 mAbs are combined in a clinical setting, the recommended, biologically active dose of pembrolizumab was selected and it was chosen to use a DLT-driven design to escalate necitumumab to MTD.

Although the exposure-response analysis of SQUIRE data showed an association between drug exposure and efficacy, the vast majority of patients had sufficient exposure of necitumumab, as 99.6% of patients had exposures superseding half-maximal effective concentration (82 μg/mL) for OS, with the median exposure resulting in close to maximum efficacy. Necitumumab disposition showed a less-than-proportional dependence on patient body weight. Simulations based on population PK (PopPK) and pharmacodynamic models show that weight- or body surface area-based dosing would not lead to a decreased PK variability or improvement of OS.

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

5.3. Pembrolizumab

Pembrolizumab [Keytruda (US)], a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co. for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in

several countries; in the US and EU it is approved for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of patients with NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, triple negative breast cancer and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

5.3.1. Rationale for Pembrolizumab Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the US and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

In Keynote-001, an open-label Phase 1 clinical trial, conducted to evaluate the safety, tolerability, PK and pharmacodynamics, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no DLTs were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified. In addition, 2 randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will

maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

5.4. Study Rationale

The purpose of this study is to explore the efficacy and safety of necitumumab plus pembrolizumab in patients with Stage IV NSCLC who have progressed after 1 platinum-based chemotherapy regimen.

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

Pembrolizumab (MK-3475, Keytruda®) is a humanized IgG4 mAb directed against PD-1 T-cell co-receptor, thus blocking its interaction with ligands, PD-L1 and PD-L2. KEYTRUDA is indicated for the treatment of: (a) patients with unresectable or metastatic melanoma (KEYTRUDA USPI/SmPC); (b) in the US, also for patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these

aberrations prior to receiving KEYTRUDA (Keytruda USPI). Pembrolizumab is also investigated as a single agent or in combination with chemotherapy or immunotherapy in the treatment of Stage IV NSCLC. So far, pooled efficacy and safety results from several ongoing single-agent Phase 1 trials with expansion cohorts in NSCLC were reported. Antitumor activity was similar in squamous and nonsquamous NSCLC. Treatment-naïve patients responded better than experienced on ORR, mPFS, and mOS (Garon et al. 2015). The analysis was also performed in relation to the biomarker using IHC assay for PD-L1 expression, identifying patients with strongly positive, weak, or negative PD-L1 expression. PFS and OS were longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (Garon et al. 2015).

The rationale for combining both agents is based on clinical single-agent data that show activity of EGFR-directed mAbs and pembrolizumab in NSCLC, and preclinical data suggesting that the antitumor activity of EGFR antibodies can be attributed, at least in part, to various immune effector mechanisms:

- EGFR signaling results in the loss of chemokine expression that mediates tumor evasion in cutaneous squamous cell carcinoma (Pivarcsi et al. 2007) and was found to positively regulate PD-L1 expression in lung cancer cells (Akbay et al. 2013).
- EGFR ligand (amphiregulin) enhances function of regulatory T cells mediated by the EGFR (Zaiss et al. 2013).
- EGFR IgG1 antibody triggers activation of natural killer and dendritic cells followed by development of tumor antigen-specific T-cell immunity (Srivastava et al. 2013).
- Human natural killer cells increase CD137 expression when exposed to colon and H&N cancer cells treated with EGFR IgG1 antibody.
- The increase in CD137-expressing NK cells is directly correlated to an increase in EGFR-specific CD8+ T cells (Kohrt et al. 2014).

Hence, combination of PD-1 and EGFR blockade may be a promising therapeutic strategy to extend the duration of treatment response and delay development of resistance.

The individual toxicity profiles of necitumumab and pembrolizumab suggest that no overlapping Grade ≥3 toxicity is expected; skin rash Grade 1-2 has been seen with both agents, hence some overlap is expected.

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

More detailed information about the known and expected benefits and risks of pembrolizumab may be found in the Keytruda USPI and pembrolizumab IB.

6. Objectives

6.1. Primary Objective

This study is divided into 3 parts:

Part A: to investigate safety and tolerability of pembrolizumab 200 mg Q3W when combined with necitumumab administered at the doses of 600 mg and 800 mg on Days 1 and 8 of 21-day cycles in patients with Stage IV NSCLC (all histologies) as measured by number of patients with a DLT during Cycle 1

Part B: to evaluate the efficacy of necitumumab in combination with pembrolizumab in terms of ORR by RECIST 1.1 in patients with Stage IV NSCLC of squamous and nonsquamous histology

Part C: to investigate safety and tolerability of pembrolizumab 200 mg Q3W when combined with necitumumab administered at the recommended dose from Part A in Japanese patients with Stage IV NSCLC of squamous and nonsquamous histology as measured by number of patients with a DLT during Cycle 1

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

Part A and Part C:

- to investigate the safety profile as assessed by significant clinical and laboratory events of necitumumab in combination with pembrolizumab
- to determine the ORR (by RECIST 1.1)
- to determine PK of necitumumab in presence of pembrolizumab
- to determine the immunogenicity of necitumumab in presence of pembrolizumab

Part B:

To demonstrate the feasibility of combining necitumumab with pembrolizumab at the recommended doses by:

- investigating the safety profile as assessed by clinical and laboratory significant events
- determining disease control rate (DCR), duration of response (DOR), and PFS by RECIST 1.1, and OS
- determining PK of necitumumab in the presence of pembrolizumab
- determining the immunogenicity of necitumumab in the presence of pembrolizumab

6.3. Exploratory Objectives

- to investigate biomarkers and correlate these markers to clinical outcome
- to assess immune-related (ir)ORR, irDCR, irDOR, and irPFS by adapted RECIST 1.1 (immune-related RECIST [irRECIST])

7. Study Population

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

Central laboratory testing is required for assessment of eligibility. Note that repeating laboratory tests during the 21-day screening period does not constitute rescreening. Laboratory tests may not be repeated more than once in order to meet eligibility.

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

7.1. Inclusion Criteria

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

[1] The patient has histologically or cytologically confirmed NSCLC.

- Part A: NSCLC Stage IV (any histological type)
- Part B: NSCLC Stage IV (squamous and nonsquamous)
- Part C: NSCLC Stage IV in Japanese patients (squamous and nonsquamous)
-

[2] The patient has Stage IV NSCLC (American Joint Committee on Cancer Staging Manual, [AJCC] 7th Edition [Edge et al. 2010]) at the time of study entry.

[3] The patient has measurable disease at the time of study entry as defined by RECIST 1.1 (Eisenhauer et al. 2009). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

[4] The patient must have progressed after 1 platinum-based chemotherapy regimen for Stage IV NSCLC. Prior therapy with VEGF/VEGFR targeting agents is permitted. Prior neoadjuvant/adjuvant therapy is permitted. Prior treatment with EGFR-TKI and ALK inhibitors is mandatory in patients with NSCLC whose tumor has EGFR-activating mutations or ALK translocations, respectively.

[5] The patient has an evaluable tumor tissue, an archived formaldehyde fixed-paraffin embedded (FFPE) block or at a minimum 15 slides (freshly cut slides should be submitted to the central laboratory), is available for biomarker analyses, or if not available, patient is willing to undergo a tumor biopsy of an extra-central nervous system (CNS) lesion (core or excisional biopsy). See Section 10.3.2 for further details.

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

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

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

[9] The patient has an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1 (see Attachment 3).

[10] The patient has adequate organ function prior to treatment initiation, including:

- hematologic: absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥9 g/dL. Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to study Day 1 Cycle 1 are not allowed.
- hepatic: bilirubin ≤1.5 × the upper limit of normal (ULN), alkaline phosphatase, alanine aminotransferase (ALT), and aspartate transaminase (AST) ≤3.0 times ULN. For patients with hepatic metastases, ALT and AST equaling ≤5.0 times ULN are acceptable.
- renal: serum creatinine ≤1.2 x ULN or calculated creatinine clearance (CrCl) >50 mL/min (per the Cockcroft-Gault formula as defined in Attachment 4) for patients with creatinine levels >1.2 institutional ULN
- Serum albumin level >25 g/L
- Coagulation parameters: international normalized ratio (INR) ≤1.5, or prothrombin time (PT), partial thromboplastin time (PTT), or activated partial thromboplastin time (aPTT) ≤5 seconds above ULN unless patient is receiving anticoagulant therapy as long as INR, PT, PTT, or aPTT is within therapeutic range of intended use of anticoagulants

[11] The patient is a man who is sterile (including vasectomy confirmed by post-vasectomy semen analysis) or abstains from heterosexual activity or agrees to use an adequate method of contraception and to not donate sperm starting with the first dose of study therapy, during the study and for at least 6 months following the last dose of study therapy or country requirements, whichever is longer; OR

[12] The patient is a woman of child-bearing potential who tests negative for pregnancy within 72 hours prior to receiving first dose of study medication based on a serum pregnancy test and agrees to use 2 methods of birth control or abstain from heterosexual activity during the study and for 6 months following the last dose of the study drug(s) or country requirements, whichever is longer; or be of non-child bearing potential. Non-childbearing potential is defined as (by other than medical reasons):

- ≥45 years of age and has not had menses for greater than 2 years,
- amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pretrial (screening) evaluation, or
- post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 6 months after the last dose of study therapy.

[13] The patient has an estimated life expectancy of at least 12 weeks.

7.2. Exclusion Criteria

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

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

[15] Has had a prior anti-cancer mAb within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier. Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent is not allowed.

[16] The patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

[17] The patient has undergone major surgery in the 30 days prior to study enrollment or, if earlier, they have not recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

[18] The patient has undergone chest irradiation within 2 weeks prior to Day 1 Cycle 1 study drugs administration, has not recovered from all radiation-related toxicities, requires corticosteroids, or has had radiation pneumonitis. A 2-week washout is required for focal palliative radiation to non-CNS disease.

[19] The patient has brain metastases that are symptomatic. The patients who have completed radiotherapy for brain metastases at least 4 weeks prior to receiving treatment, who are now non symptomatic and are not using steroids or anticonvulsants for at least 7 days prior to receiving treatment, are eligible. Patients with asymptomatic brain metastases without need for treatment with steroids and who have not been treated with radiotherapy are eligible. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

[20] The patient has a history of arterial thromboembolic event (ATE) or venous thromboembolic event (VTE) within 3 months prior to study enrollment. Patients with history of VTE beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with anticoagulation therapy according to the local standard.

[21] The patient has a history or evidence of clinically-relevant coronary artery disease of current ≥Class III as defined by Canadian Cardiovascular Society Angina Grading Scale (Campeau 1976) or congestive heart failure of current ≥Class III as defined by the New York Heart Association.

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

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

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

[25] The patient has a history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.

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

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

[28] The patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of trial treatment.

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

[30] The patient has a concurrent active malignancy and is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, chemo-embolization, targeted therapy, or an investigational agent. Previous history of malignancy other than NSCLC is permitted, provided that he/she has been free of disease for ≥3 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin, preinvasive carcinoma of the cervix, in situ carcinoma of the breast, or low-grade prostate cancer with no plan for treatment intervention.

[31] The patient has a history of an interstitial lung disease (ILD) or (non-infectious) pneumonitis that required steroids or current pneumonitis.

[32] The patient has an active autoimmune disease or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

[33] The patient has received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal flu vaccines that do not contain live virus are permitted.

[34] The patient is or has an immediate family member (for example, spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective institutional review board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific patient.

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [14] and [15] eliminate 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] through [26] and [28] through [34] ensure that previous or currently required treatments or conditions do not complicate on-study treatment and/or analysis of data. Exclusion Criterion [27] excludes patients who may be at elevated risk of toxicity based on the known safety profile of necitumumab and pembrolizumab.

7.3. Discontinuation

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

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

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

7.3.1. Discontinuation of Inadvertently Enrolled Patients

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

7.3.2. Discontinuation of Study Therapy

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

- Enrollment in any other clinical trial involving a study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication; discontinuation from study therapy occurs prior to introduction of the new agent.
- Investigator/Physician Decision
    - The investigator/physician decides that the patient should be withdrawn from the study due to an intercurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment in the opinion of the investigator.

  - Any study therapy-related event that is deemed life-threatening, regardless of grade, warrants discontinuation of that therapy and/or discontinuation from all therapy if appropriate in the opinion of the investigator.
  - If the patient has progressive disease (PD, confirmed by irRECIST or unconfirmed but with clinically worsening/deterioration [Section 10.1.5.1 and Table JFCQ.10.1]).
  - Any event(s) which would require a given study therapy to be modified by more than 2 dose reductions or to be held for more than 6 weeks following Day 1 of the most recent cycle warrants discontinuation of that therapy.
  - The patient becomes pregnant during treatment.
- Patient Decision
  - The patient or patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study treatment.
- Sponsor Decision
  - The sponsor stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practices (GCP).
- The patient is significantly noncompliant with study procedures and/or treatment.
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient).
- A Grade 3 to 4 IRR, and potentially other drug-related AEs, as specified in Section 9.4.1 below.
- Patients, who experience complete response (CR), that have been treated for at least 24 weeks from Cycle 1 Day 1with pembrolizumab and necitumumab or pembrolizumab alone and had at least 2 treatments with pembrolizumab with or without necitumumab beyond the date when the initial CR was declared can discontinue treatment.

7.3.3. Discontinuation from the Study

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

- enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- the investigator decides that the patient should be discontinued from the study
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- the patient or the patient's designee requests that the patient be withdrawn from the study
- Lilly 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

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

7.3.4. Patients who are Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel, or an independent third

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

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

7.3.5. Discontinuation of Study Sites

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

7.3.6. Discontinuation of the Study

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

8. Investigational Plan

8.1. Summary of Study Design

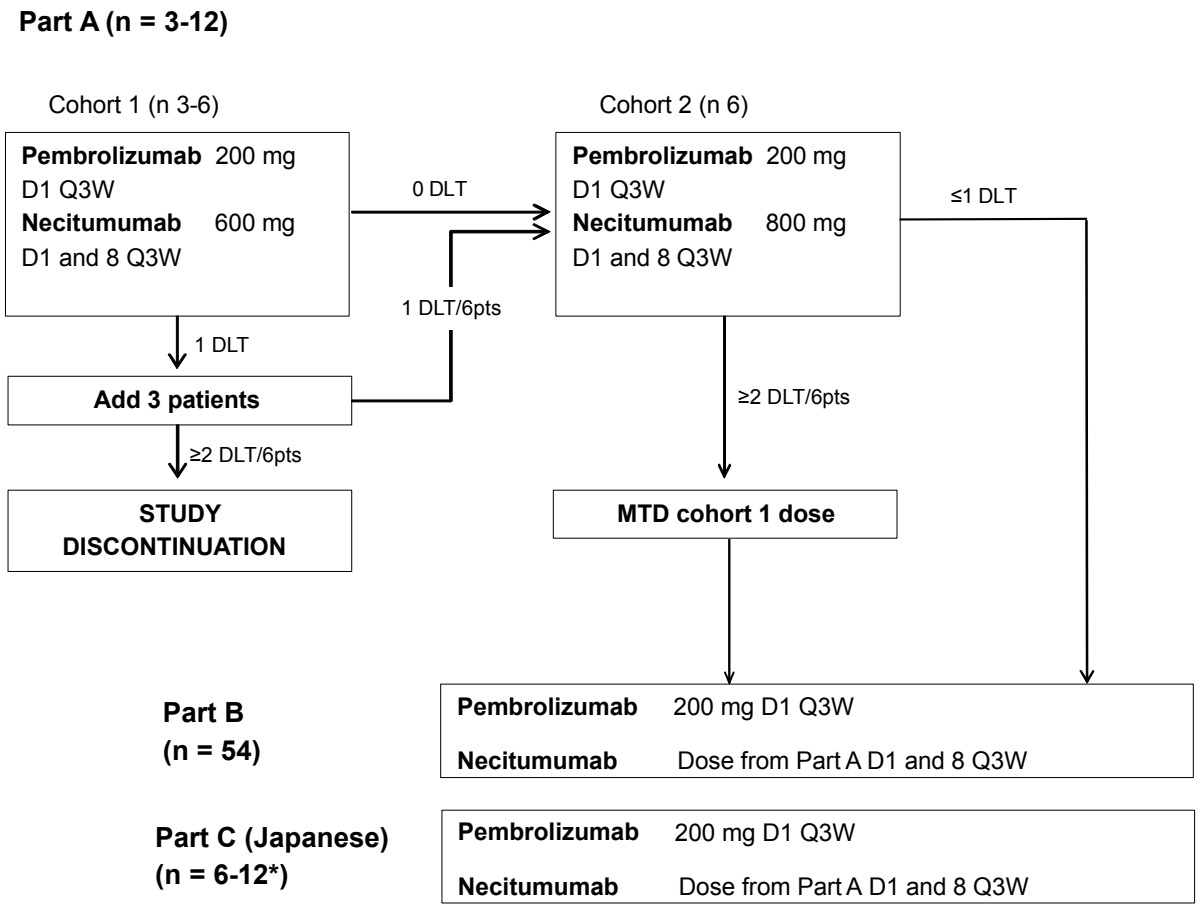
Study I4X-MC-JFCQ is an open-label, multicenter Phase 1b study with an expansion cohort to investigate necitumumab in combination with pembrolizumab in approximately 78 patients with Stage IV NSCLC (AJCC Staging Manual, 7th edition).

The study consists of 3 parts:

- Part A: Dose-escalation part with increasing doses of necitumumab (initially 600 mg and then 800 mg on Days 1 and 8 Q3W) to determine a recommended dose for necitumumab that may be safely administered in combination with a fixed regimen of pembrolizumab 200 mg on Day 1 Q3W in patients with Stage IV NSCLC.
- Part B (Expansion Cohort): Dose confirmation of necitumumab in combination with a fixed regimen of pembrolizumab 200 mg on Day 1 Q3W and exploration of clinical antitumor activity in patients with Stage IV NSCLC.
- Part C (Japanese patients): DLT confirmation using the recommended dose from Part A for necitumumab in combination with a fixed regimen of pembrolizumab 200 mg on Day 1 Q3W in Japanese patients with Stage IV NSCLC.

In Part B, approximately 54 patients will be enrolled with an approximately even split between squamous and nonsquamous histology.

Figure JFCQ.8.1 illustrates the study design.



* Part C will first enroll 6 patients. If 2 out of 6 patients experience DLTs, the sponsor will examine the safety data and consult with an external committee as needed. The sponsor will decide if the dose is intolerable, or if additional patients will be enrolled to the same dose level (or lower dose level) for further investigation. If additional patients are needed, 6 additional Japanese patients will be enrolled (to maximum of 12 Japanese patients in Part C).

Abbreviations: D = day; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; n = number of patients; Q3W = every 21 days.

Figure JFCQ.8.1. Illustration of study design.

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

Part A:

Cohort 1

- Pembrolizumab, administered I.V. over 30 minutes (−5 min/+10 min) at an absolute dose of 200 mg on Day 1, followed by
- Necitumumab, administered I.V. over 60 minutes at a dose of 600 mg on Days 1 and 8, Q3W

Cohort 2

- Pembrolizumab, administered I.V. over 30 minutes (−5 min/+10 min) at an absolute dose of 200 mg on Day 1, followed by
- Necitumumab, administered I.V. over 60 minutes at a dose of 800 mg on Days 1 and 8, Q3W

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

A maximum of 12 evaluable patients with Stage IV NSCLC will be enrolled in Part A. Any patient who is discontinued from the study before completing Cycle 1 will be excluded from the DLT population, unless a DLT was observed. Patients who do not complete Cycle 1 for reason other than DLT will be replaced.

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

Cohort 2 will enroll 6 patients. If ≤1 of the 6 patients develops a DLT, Cohort 2 dose will be the recommended Phase 2 dose. If ≥2 of the 6 patients experience a DLT in Cohort 2, then the dose in Cohort 1 will be the MTD.

Dose escalation within a cohort will not be permitted. Patients assigned to a cohort dose level will remain at that level throughout the study. Patients who withdraw from the study during the DLT period for reasons other than a treatment-related toxicity may be replaced within the same dose level.

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

Part B:

Part B will enroll approximately 54 patients. It is a single-arm study to evaluate efficacy and safety of necitumumab in combination with pembrolizumab in patients with Stage IV squamous or nonsquamous NSCLC (Figure JFCQ.8.1). Patients will be treated with pembrolizumab 200 mg on Day 1 Q3W and the dose of necitumumab identified from Part A of the study on Days 1 and Day 8 Q3W.

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

The final analysis for all outcomes for Part B will be performed approximately 6 months after completing enrollment of the study population.

A treatment cycle will be defined as 21 days. Study therapy, consisting of necitumumab plus pembrolizumab, will continue until there is a radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Discontinuation of treatment may be considered for patients who have attained a confirmed CR that have been treated for at least 24 weeks from Cycle 1 Day 1 with pembrolizumab and necitumumab or pembrolizumab alone and had at least 2 treatments with pembrolizumab with or without necitumumab beyond the date when the initial CR was declared.

Part C:

Part C will only enroll patients from Japan. It is a single-arm study to evaluate safety and tolerability of necitumumab at the recommended dose identified from Part A of the study on Days 1 and Day 8 Q3W in combination with pembrolizumab 200 mg on Day 1 Q3W in Japanese patients with stage IV NSCLC (Figure JFCQ.8.1).

Part C will first enroll 6 patients. If 2 out of 6 patients experience DLTs, the sponsor will examine the safety data and consult with an external committee as needed. The sponsor will decide if the dose is intolerable, or if additional patients will be enrolled to the same dose level (or lower dose level) for further investigation. If additional patients are needed, 6 additional Japanese patients will be enrolled (to maximum of 12 Japanese patients in Part C).

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

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

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

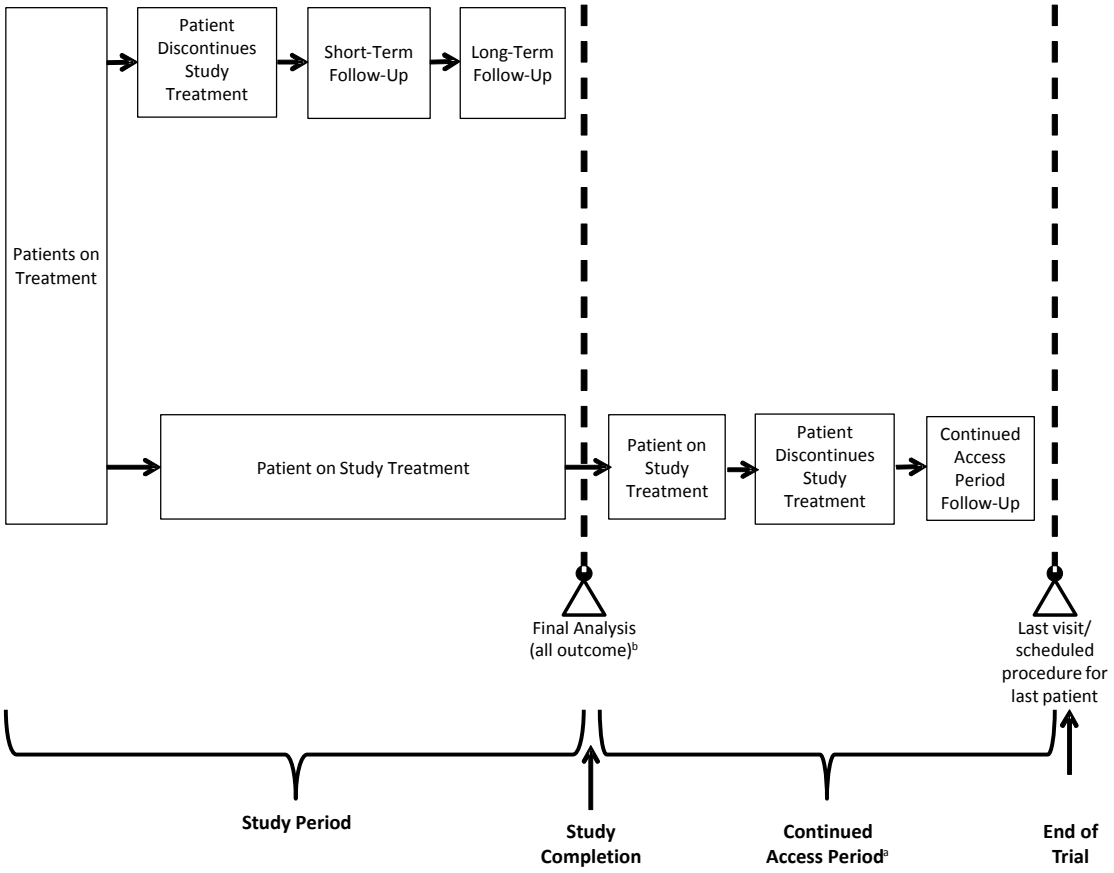
      Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.
- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who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

- Continued access follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

Part A and Part B of this study will be considered complete (that is, the scientific evaluation will be complete [study completion]) approximately 6 months after the last patient in Part B of the study has been enrolled, and Part C of this study will be considered complete approximately after all the patients in Part C have completed 8 cycles or discontinued early. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

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



[a] Lilly will notify sites when continued access period begins and ends.
[b] Part A and Part B of this study will be considered complete approximately 6 months after the last patient in Part B has been enrolled, and Part C of this study will be considered complete approximately after all the patients in Part C have completed 8 cycles or discontinued early.

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

8.1.2. Continued Access Period

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

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

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

During the continued access period, all AEs, SAEs, and study drug exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.2.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE. Blood samples for PK and immunogenicity analysis for necitumumab will be collected in the event of an IRR and during the continued access follow-up.

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

8.2. Discussion of Design and Control

In this open-label, Phase 1b study with an expansion cohort, the selected fixed-dose of pembrolizumab of 200 mg on Day 1 Q3W is an experimental dose but the differences in exposure for a 200-mg fixed-dose regimen relative to a 2-mg/kg Q3W body weight-based regimen registered currently for melanoma indication are anticipated to remain well within the established exposure margins for this compound. The starting dose of necitumumab in Part A (patients with Stage IV NSCLC) will be at dose level -1 of the MTD (600 mg on Days 1 and 8 Q3W). Since this is the first time these 2 mAbs are combined in a clinical setting, the recommended, biologically active dose of pembrolizumab was selected and it was chosen to use a DLT-driven design to escalate necitumumab to MTD.

Patients with Stage IV NSCLC who have progressed after 1 platinum-based chemotherapy regimen will receive a combination of necitumumab and pembrolizumab. Prior treatment with EGFR-TKI, VEGF/VEGFR-targeting agents, and ALK inhibitors is permitted.

In Part B, approximately 54 patients with Stage IV NSCLC with an approximately even split between squamous and nonsquamous histology will be enrolled to enable evaluation of safety and efficacy parameters by histology.

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

In Part C, 6-12 Japanese patients with Stage IV NSCLC with squamous and nonsquamous histology will be enrolled to enable evaluation of safety and efficacy parameters using a fixed

200-mg dose of pembrolizumab given Q3W and necitumumab dose as determined in the Part A of the study.

The outcome will be hypothesis generating only, allowing for future consolidation of this regimen depending on the outcome.

9. Treatment

9.1. Treatments Administered

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

In Part A, patients will receive I.V. necitumumab 600 mg or 800 mg on Day 1 and Day 8 Q3W in combination with pembrolizumab 200 mg as an absolute dose on Day 1 Q3W.

In Part B and Part C, the necitumumab dose identified from Part A will be given on Day 1 and Day 8 Q3W in combination with pembrolizumab 200 mg as an absolute dose Day 1 Q3W.

Pembrolizumab will be administered first followed by necitumumab.

Table JFCQ.9.1. Treatment Regimens/Dosing Schedule

Part A

Cohort	Drug	Dose	Day of 21-day Cycle	Infusion Duration
Cohort 1	Pembrolizumab	200 mg absolute dose I.V. infusion	Day 1	Over 30 minutes[a]
	Necitumumab	600 mg dose I.V. infusion	Days 1 and 8	Over 60 minutes[b]
Cohort 2	Pembrolizumab	200 mg absolute dose I.V. infusion	Day 1	Over 30 minutes[a]
	Necitumumab	800 mg dose I.V. infusion	Days 1 and 8	Over 60 minutes[b]

Part B and Part C

Drug	Dose	Day of 21-day Cycle	Infusion Duration
Pembrolizumab	200 mg absolute dose I.V. infusion	Day 1	Over 30 minutes[a]
Necitumumab	Recommended dose from Part A I.V. infusion	Days 1 and 8	Over 60 minutes[b]

Abbreviation: I.V. = intravenously.

[a] Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes −5 min/+10 min, i.e., between 25 to 40 minutes).

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

Based on the independent necitumumab and pembrolizumab clinical development programs, the individual recommended doses are 800 mg on Day 1 and Day 8 Q3W for necitumumab and 200 mg on Day 1 for pembrolizumab. For this reason, further dose escalation beyond Cohort 2 will not be tested.

Hypersensitivity/infusion-related reactions (IRRs) may occur during or following administration of necitumumab (see Section 9.4.1.3.1 for a definition of Grade 3 and 4 hypersensitivity/IRRs). As a routine precaution, patients treated with necitumumab should be observed closely for any potential adverse effects by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area with resuscitation equipment and other agents (for example, epinephrine or prednisolone equivalents) available.

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

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

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

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

9.2. Materials and Supplies

Necitumumab will be provided by Lilly and pembrolizumab will be provided by Merck (all materials will be packaged and shipped from Lilly, and will bear Lilly clinical trial material labeling). Clinical trial materials will be labeled according to the country's regulatory requirements.

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

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

All excipients used in the formulation of necitumumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of necitumumab excipients. The drug product must be stored under refrigeration at 2°C to 8°C with protection from light. Refer to necitumumab IB for detailed storage information.

Pembrolizumab drug product is available in 2 dosage forms: a white to off-white lyophilized powder, 50 mg/vial, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only.

- Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is a lyophilized powder that is reconstituted with sterile water for injection prior to use. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (if necessary).
- Pembrolizumab Solution for Infusion 100 mg/vial is a liquid, manufactured fully formulated with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier.

Both pembrolizumab product dosage forms are stored under refrigerated conditions 2°C to 8°C (36-46°F) and protected from light. Refer to pembrolizumab IB for detailed storage information.

9.3. Method of Assignment to Treatment

An interactive web response system (IWRS) will be utilized for drug dispensing for Parts A, B, and C of the study.

For patients in Part B, enrollment will be balanced to include approximately 50% squamous and 50% nonsquamous patients. Patients will be registered in the IWRS, which consists of assigning a unique study identification number and entering the patient's tumor histology type (squamous vs. nonsquamous). Once the patient is registered in the IWRS, he or she is considered being enrolled in the study. Enrollment into the IWRS will be disabled once enrollment goals have been met for both histology types.

9.4. Selection and Timing of Doses

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

A cycle is defined as an interval of 21 days.

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

A patient may continue to receive study treatment until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3), or complete remission is diagnosed (as described in Section 8.1).

9.4.1. Special Treatment Considerations

9.4.1.1. Dose-Limiting Toxicity (Parts A and C)

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

- Grade 3 or 4 nonhematologic toxicity according to the NCI-CTCAE Version 4.0, except for skin toxicity, nausea, vomiting, diarrhea, or electrolyte disturbance (see below). For patients with ≤ Grade 2 hepatic transaminase levels at baseline as a result of liver metastases, a transaminase level ≥10x ULN lasting for >7 days will be considered a DLT.
- Grade 4 nausea, vomiting, or diarrhea that persists more than 3 days despite maximal supportive intervention
- Grade 3 thrombocytopenia with bleeding requiring transfusion
- Grade 4 thrombocytopenia with or without bleeding
- Grade 4 neutropenia that persists more than 5 days
- Grade 3 or 4 neutropenia with fever, defined as single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour
- Grade ≥3 skin toxicity despite best supportive care, with exception of Grade 3 rash that resolves to Grade ≤2 within 14 days with appropriate supportive therapy
- If a total at least 75% of the planned dose for both agents cannot be administered in the first cycle due to toxicity
- Prolonged delay (>2 weeks) in initiating cycle 2 due to treatment-related toxicity
- Grade 5 toxicity

DLT is defined by sponsor and principal investigator.

The following toxicities will not be considered DLTs if they are transient (<7 days):

- Hypersensitivity and injection site reactions (If a Grade 3 or 4 hypersensitivity/ IRR to necitumumab or pembrolizumab occurs, this event will not be considered a DLT; the patient will not receive any further study therapy and will be replaced in the study by a new patient.)
- Grade ≥3 myalgia, fatigue, or constipation, with full supportive therapy
- Grade ≥3 increase or decrease of electrolytes
- Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤1 within 7 days of appropriate supportive therapy
- Grade ≥3 elevation of serum creatine kinase level that is asymptomatic that returns to Grade ≤2 within 21 days of necitumumab treatment interruption

9.4.1.2. Dose Adjustments and Delays

9.4.1.2.1. Pembrolizumab

9.4.1.2.1.1. Pembrolizumab Dose Modifications

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several

months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table JFCQ.9.2.

Table JFCQ.9.2. Dose Modification Guides for Pembrolizumab Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IRR = infusion-related reaction; T1DM = type 1 diabetes mellitus.

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

a For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, then patients should be discontinued.
b If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be given premedication for the next scheduled dose. Refer to Table JFCQ.9.5 – IRR Treatment Guidelines for further management details.
c Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

9.4.1.2.2. Necitumumab

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

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

- In the case of reversible Grade3-4 necitumumab-related toxicity (for example, fatigue, anorexia, and fever), administration of necitumumab will be at the reduced dose (refer to Section 9.4.1.2.2.1) or interrupted, but pembrolizumab will continue according to the planned schedule.
- If administration of necitumumab is delayed for more than 6 weeks (2 cycles) after Day 1 of the most recent treatment cycle, the patient should be discontinued from necitumumab treatment.

9.4.1.2.2.1. Necitumumab Dose Modifications

The following are general dose-modification guidelines for toxicity associated with necitumumab. Please see Section 9.4.1.3 for specific information on the management of necitumumab-related hypersensitivity/IRRs, skin reactions, conjunctivitis, and hypomagnesemia.

For patients starting Cycle 1 in Part A and possible Part B of the study at necitumumab 600 mg on Days 1 and 8, one dose reduction is permitted. Patients who cannot tolerate necitumumab 400 mg should discontinue necitumumab; such patients may continue with pembrolizumab as a single agent.

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

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

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

If a patient experiences CTCAE Grade ≥3 hematologic toxicity possibly related to necitumumab, unless DLT criteria are met, then dosing must be delayed (until the toxicity resolves to either baseline or at least Grade 2) and the dose of necitumumab must be reduced by 1 dose level (see below).

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

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

Table JFCQ.9.3. Dose Adjustments of Necitumumab

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

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

Events that necessitate more than 2 dose reductions warrant discontinuation from necitumumab treatment. For dose modifications in response to specific AEs related to necitumumab, please see Section 9.4.1.3.

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

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

9.4.1.3. Treatment Guidelines and Dose Modifications for Specific Adverse Events

Adverse events of special interest, which may or may not be associated with necitumumab and/or pembrolizumab therapy, include hypersensitivity/IRR, skin reactions, conjunctivitis, electrolyte abnormalities, pneumonia and sepsis, pneumonitis, diarrhea/colitis, type 1 diabetes mellitus, hypophysitis, hyper- or hypothyroidism, liver injury, renal failure/nephritis, and thromboembolic events.

9.4.1.3.1. Hypersensitivity and Infusion-Related Reactions

Refer to the NCI-CTCAE Version 4.0 for grading for hypersensitivity and IRRs.

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

9.4.1.3.1.1. Management of Infusion Reactions for Necitumumab

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

Table JFCQ.9.4 provides general treatment recommendations for hypersensitivity/IRRs to necitumumab.

Table JFCQ.9.4. Necitumumab Infusion-Related Reaction Treatment Guidelines

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

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

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

9.4.1.3.1.2. Management of Infusion Reactions for Pembrolizumab

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table JFCQ.9.5 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table JFCQ.9.5. Pembrolizumab Infusion-Related Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: I.V. fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patient may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: I.V. fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

Abbreviations: I.V. = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = non-steroidal anti-inflammatory drugs; po = oral.

If a patient should have a hypersensitivity/IRR to necitumumab or pembrolizumab, all attempts should be made to obtain an anti-necitumumab antibody and PK blood samples for necitumumab as close to the onset of the event as possible, at the resolution of the event, and 30 days following

the event. The procedure for sample collection and handling is described in a separate procedural manual.

9.4.1.3.2. Skin Reactions

9.4.1.3.2.1. Reactive Treatment

Reactive treatment recommendations for skin reaction, based on the Canadian recommendations presented by Melosky et al. (2009), are summarized in Table JFCQ.9.6.

Skin rash (any grade) should be treated as per Table JFCQ.9.6. If a patient experiences a Grade 1 or 2 acne-like rash, necitumumab treatment should continue without dose modification or delay. Dose delays and or modifications for necitumumab are to be considered in case of skin reactions of Grade 3 or that are considered intolerable. If a patient experiences Grade 4 skin reactions, treatment with necitumumab should be permanently discontinued.

Table JFCQ.9.6. Managing Skin Reactions

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

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

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

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

9.4.1.3.3. Conjunctivitis

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

9.4.1.3.4. Electrolyte Abnormalities

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

9.4.1.3.5. Thromboembolic Events

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

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

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

9.4.1.3.6. Pneumonia and Sepsis

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

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

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

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

9.4.1.3.7. Cardiorespiratory Disorders

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

9.4.2. Supportive Care Guidelines for Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 9.4.1.2.1.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

9.4.2.1. Immune-Mediated Pneumonitis

Patients who experience **Grade 2** events shall be treated with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over at least 4 weeks.

Grade 3-4 events shall immediately be treated with intravenous steroids. Additional anti-inflammatory measures can be administered, as needed. Pembrolizumab shall be withheld for moderate (Grade 2) pneumonitis, and permanently discontinued pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis.

Prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration shall be considered.

9.4.2.2. Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA) or T1DM or Grade 3-4 Hyperglycemia

Insulin replacement therapy is recommended for type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

Patients shall be evaluated with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

9.4.2.3. Immune-Mediated Hypophysitis

Grade 2 events shall be treated with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Grade 3-4 events shall be treated with an initial dose of I.V. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over at least 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Pembrolizumab must be withheld for moderate (Grade 2) hypophysitis, withhold or discontinued for severe (Grade 3) hypophysitis, and permanently discontinued for life-threatening (Grade 4) hypophysitis.

9.4.2.4. Immune-Mediated Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Patients shall be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Grade 2 hyperthyroidism events (and **Grade 2-4** hypothyroidism):

In hyperthyroidism, non-selective beta-blockers (for example, propranolol) are suggested as initial therapy. Thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. Isolated hypothyroidism may be managed without treatment interruption and without corticosteroids.

Grade 3-4 hyperthyroidism

Treatment with an initial dose of I.V. corticosteroid followed by oral corticosteroids is recommended. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Pembrolizumab must be withheld for severe (Grade 3) hyperthyroidism, and permanently discontinued for life-threatening (Grade 4) hyperthyroidism.

9.4.2.5. Hepatic Injury

For **Grade 2** immune-mediated hepatitis, liver function tests must be monitored more frequently until returned to baseline values (consider weekly). Treatment with I.V. or oral corticosteroids shall be considered.

For **Grade 3-4** immune-mediated hepatitis, intravenous corticosteroids are recommended for 24 to 48 hours.

When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

If a patient experiences elevated ALT >3× ULN and/or elevated total bilirubin >2× ULN, clinical and laboratory monitoring may be initiated, at the discretion of the investigator. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, then patients should be discontinued.
Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Site Guidance Document for Drug-Induced Liver Injury (DILI).

9.4.2.6. Renal Failure or Immune-Mediated Nephritis

In case of **Grade 2** events, treatment with corticosteroids is recommended.

Patients that experience **Grade 3-4** events shall be treated with systemic corticosteroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Pembrolizumab must be withheld for moderate (Grade 2) nephritis, and permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) nephritis.

9.5. Blinding

This is an open-label study.

9.6. Concomitant Therapy

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

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy or biological therapy, immunotherapy not specified in this protocol, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

Palliative radiotherapy, unless required due to PD, is permitted during the study.

- Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial are not allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed-virus vaccines and are allowed. However, intranasal influenza vaccines (for example, Flu - Mist®) are live attenuated vaccines and are not allowed.

Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology are not permitted. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor. Inhaled steroids are allowed for management of asthma; similarly, intranasal steroids for rhinitis and/or sinusitis are allowed.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describe other medications that are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

9.6.1. Supportive Care

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Details of interventions, procedures, or blood products (for example, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the eCRF. Please see Section 9.4.1.3 for specific information on the management of necitumumab-related hypersensitivity/IRRs, skin reactions, conjunctivitis, electrolyte abnormalities, pneumonia and sepsis, and serious thromboembolic events. Guidelines regarding the use of other specific supportive care agents are presented below.

9.6.2. Colony-Stimulating Factors and Erythropoiesis-Stimulating Agents

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

Because recommendations on the use of CSFs/ESAs are rapidly evolving, investigators should frequently refer to the local, national, or international standards (for example, European

Organisation for Research and Treatment of Cancer, European Society for Medical Oncology, National Comprehensive Cancer Network, American Society of Clinical Oncology, American Society of Hematology, and/or Centers for Medicare and Medicaid Services Web sites) for the latest guidelines.

9.6.3. Therapy for Diarrhea/Colitis

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

In the event of diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via I.V. infusion. For Grade 2 or higher diarrhea, consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis**, oral corticosteroids are recommended.
- For **Grade 3 or 4 diarrhea/colitis**, intravenous steroids followed by high dose oral steroids are recommended.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics must be prescribed. Patients with Grade ≥3 diarrhea or any diarrhea associated with Grade ≥3 nausea or vomiting **must be hospitalized** for intravenous hydration and correction of electrolyte imbalances. Events that require a patient to be hospitalized are considered SAEs (see Section 10.2.1.1).

Pembrolizumab shall be withheld for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinued for life-threatening (Grade 4) colitis.

9.6.4. Antiemetic Therapy

The use of antiemetic agents is permitted during this study.

9.6.5. Analgesic Agents

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

9.6.6. Bisphosphonates and RANK-L Targeted Agents

Patients with bone metastases present on baseline imaging are allowed treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents (for example, denosumab), per respective approved labels. Initiation of treatment with bone-modifying agents must begin at least 7 days prior to enrollment. Patients receiving bisphosphonates or RANK-L targeted agents should not switch treatments (for example, replace

a bisphosphonate with denosumab) while on study treatment. However, exceptional cases without evidence of PD may be considered in consultation with the Lilly CRP. These exceptional cases will not incur a protocol deviation.

9.6.7. Therapy for Febrile Neutropenia

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

9.7. Treatment Compliance

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

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he or she delays therapy for more than 6 weeks following Day 1 of the most recent cycle during the study.

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

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

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

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

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

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Within 21 days before the first dose of study drug, baseline tumor measurements will be performed on each patient. Throughout the study, patients will be evaluated for response according to RECIST 1.1 (Eisenhauer et al. 2009). For the purpose of patient management, RECIST 1.1 with adaptation (irRECIST) will be used to assess tumor response (see Section 10.1.5.1).

A contrast computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at pretreatment only, and thereafter approximately every 6 weeks ± 5 days, if a patient had brain metastases at study entry or if clinically indicated.

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

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

Imaging studies required to investigate known disease should be repeated every 6 weeks (± 5 days) following the first dose of study therapy, regardless of any treatment delays, until radiographic documentation of PD as defined by RECIST 1.1, with adaptation described below in more detail (irRECIST; see Section 10.1.5.1).

CT of the chest and CT or MRI of the abdomen and pelvis is required at each time point; CT/MRI of the brain must be performed if baseline assessment identified any lesion in this area (or if clinically indicated).

Responses (CR or PR) must be confirmed at least 28 days from the first evidence of response. Thereafter, a responding patient will be followed approximately every 6 weeks (±5 days) until objective progression is observed.

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

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

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

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

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

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

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

10.1.3. Primary Efficacy Measure (Part B only)

10.1.3.1. Tumor Imaging and RECIST Assessment

Local site study team reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine patient eligibility. Tumor imaging should be performed by CT (preferred). MRI should only be used when CT is contraindicated or for imaging in the brain, but the same imaging technique should be used in a patient throughout the trial.

Imaging should include the chest, abdomen, and pelvis.

10.1.3.1.1. Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 21 days prior to the date of the first dose of trial treatment. The site study team must review screening images to confirm the patient has measurable disease per RECIST 1.1. Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 21 days prior to the date of first dose.

10.1.3.1.2. On Study Tumor Imaging

The first on-study imaging assessment should be performed at 6 weeks (±5 days) from the date of first dose of trial treatment. Subsequent tumor imaging should be performed every 6 weeks (±5 days) or more frequently only if clinically indicated. Imaging should not be delayed for delays in any of the study drug dosing. Continue to perform imaging until whichever of the following occurs first:

- Initial site-assessed disease progression is confirmed (Section 10.1.5.1)
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study

10.1.3.2. Tumor Response Assessment

The primary efficacy measure is ORR as defined by RECIST 1.1 (Eisenhauer et al. 2009) provided in Attachment 5. A responder is defined as any patient who exhibits a confirmed CR or PR.

Best response is determined from the sequence of responses assessed.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment. A second assessment must be performed ≥28 days after the first evidence of response or at the next scheduled scan (that is, 6 weeks later), whichever is clinically indicated. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Best response of SD is defined as disease that does not meet the criteria for CR, PR, or PD and has been evaluated at least 1 time, at least 6 weeks after the start of study treatment.

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

The date of first documented objective disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy.

10.1.4. Secondary Efficacy Measures

The secondary efficacy measures, including DCR, DOR, PFS, and OS, will be collected at the times shown in the Study Schedule (Attachment 1).

10.1.5. Exploratory Efficacy Measures

10.1.5.1. Adapted RECIST 1.1 (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 assessment may not

provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

- If radiologic imaging verifies initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per Table JFCQ.10.1 below while awaiting radiologic confirmation of progression.
- If repeat imaging shows <20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed.
- If repeat imaging confirms PD due to any of the scenarios list below, patients will be discontinued from study therapy and proposed best alternative available.

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥20% and at least 5-mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive pembrolizumab and necitumumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG PS, apart from change from PS0 to PS1
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (for example, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued from study therapy until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients that are deemed clinically worsening/deteriorating are not required to have repeat imaging for confirmation of progressive disease (see Table JFCQ.10.1).

Table JFCQ.10.1. General Guidance for Decision Making on Repeated Radiologic Assessment in Patients with Initial PD based on Clinical Status

	Clinically Stable		Clinically Worsening/Deterioration	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory scan by irRECIST	Repeat imaging at ≥4 weeks to confirm PD if possible	Discontinue study treatment
Repeat scan confirms PD by irRECIST at the local site	No additional imaging required	Discontinue study treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR (compared to scan showing first radiologic evidence of PD) by irRECIST at the local site	Continue regularly scheduled imaging assessments every 6 weeks (± 5 days)	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks (± 5 days)	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

Abbreviations: CR = complete response; N/A = not applicable; PD = progressive disease; PR = partial response; SD = stable disease.

NOTE:

- If a patient has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the patient is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor.
- Any patient deemed clinically unstable should be discontinued from trial treatment at first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.
- In patients who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment every 6 weeks (± 5 days), until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

The following exploratory efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1). Confirmation by 2 consecutive observations at least 4 weeks apart is required for CR, PR, and PD for both assessments to assign best response for each patient:

- immune-related CR (irCR): disappearance of all lesions
- immune-related PR (irPR): ≥30% decrease of total tumor burden from baseline
- immune-related PD (irPD): ≥20% increase of total tumor burden from the nadir
- immune-related SD (irSD): fail to meet criteria for irCR or irPR in the absence of irPD

10.1.6. Resource Utilization

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

10.2. Safety Evaluations

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

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

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

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JFCQ.10.2 presents a summary of AE and SAE reporting guidelines. Table JFCQ.10.2 also shows which database or system is used to store AE and SAE data.

Table JFCQ.10.2. Adverse Event and Serious Adverse Event Reporting Guidelines

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

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

10.2.1. Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

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

10.2.1.1. Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

10.2.1.2. Suspected Unexpected Serious Adverse Reactions

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

10.2.1.3. Events of Clinical Interest - Pembrolizumab

The 2 categories of events of clinical interests (ECIs) for pembrolizumab include:

1. an overdose of pembrolizumab (≥1000 mg [5 times the dose]) not associated with clinical symptoms or abnormal laboratory results, and

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal (ULN) and an elevated total bilirubin lab value that is greater than or equal to 2X ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. Please refer to the Site Guidance Document for Drug-induced Liver Injury.

Section 9.4.2 describes supportive care measures for each selected pembrolizumab nonserious and serious adverse events.

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1) as single ECGs. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs 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.

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

After enrollment, if a clinically significant increase in the QT/corrected QT interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is 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, and any alert reports.

10.2.3. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- adverse events
- If a patient experiences elevated ALT >3× ULN and/or elevated total bilirubin >2× ULN, clinical and laboratory monitoring may be initiated, at the discretion of the investigator (see Section 9.4.2.5).

- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Site Guidance Document for DILI.

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

10.2.4. Complaint Handling

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

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

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

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

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

10.3. Sample Collection and Testing

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

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

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

Attachment 6 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

10.3.1. Samples for Study Qualification and Health Monitoring

Standard laboratory tests, including chemistry, hematology, coagulation, and pregnancy testing (if applicable in women of childbearing potential), will be performed and analyzed centrally. Urinalysis will be assayed by investigator-designated (local) laboratory. Attachment 2 lists the laboratory tests that will be performed for this study. Central laboratory results will be used to

determine patient eligibility at baseline. Local laboratory results may be used for on-study dosing decisions; if so, testing must also still be performed by the central laboratory. These central laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database.

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

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

Investigators must document their review of each laboratory safety report.

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

10.3.2. Samples for Pharmacogenetics and Translational Research

Collection of samples for translational research is also part of this study (see Attachment 1 and Attachment 6).

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

- Tumor tissue: archived tumor tissue available for biomarker analyses, or patient is willing to undergo a tumor biopsy of an extra-CNS lesion. Submission of FFPE tumor tissue sample blocks is preferred.
- Whole blood samples
- Plasma samples

Whole blood, plasma, and tissue samples will be collected to explore biomarkers related to variable response to necitumumab and/or pembrolizumab, the EGFR pathway, innate and adaptive immunity, immune functioning, and/or the pathogenesis of lung cancer. Analyses may include potential nucleic acid and protein markers to better understand the disease process, and to develop predictive biomarkers and diagnostics.

10.3.2.1. Whole Blood Sample for Genetic Research

A blood sample will be collected for pharmacogenetic analysis as specified in the Study Schedule (Attachment 1), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in NSCLC. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to EGFR pathway, immune cells/function, and the mechanism of action of necitumumab and pembrolizumab to evaluate their association with observed response to study treatment.

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

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

10.3.2.2. Tumor Tissue Collection

The availability of tumor tissues is important to better characterize the relationship of tumor biology and response evaluation in this study.

- If a prior archived tumor specimen is available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory. If an archived specimen is not available, submission of a newly obtained biopsy (obtained at baseline, during elective surgery, or at the specified time points) is required.
- Tumor tissue should be provided in formalin or as an FFPE block, or unstained slides. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes/report accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. FFPE blocks will be sectioned and returned to the site. Newly obtained blocks or tissue submitted in formalin and slides will not be returned.

Tumor tissue will be examined for biomarkers related to NSCLC, necitumumab, pembrolizumab, and/or the mechanism of action under investigation (for example, EGFR pathway and immune cells/function).

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to

regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

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

10.3.2.3. Plasma and Whole Blood Samples for Biomarker Research

Plasma and whole blood samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Sampling Schedule (Attachment 6), where local regulations and ERBs allow.

Samples will be used for research on EGFR pathway and immune cells/function associated with NSCLC, mechanism of action of necitumumab and pembrolizumab, and/or research method or in validating diagnostic tools or assay(s) related to NSCLC.

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

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

10.3.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against necitumumab. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the necitumumab and pembrolizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of necitumumab.

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

10.3.4. Samples for Drug Concentration Measurements Pharmacokinetics

Pharmacokinetic (PK) venous blood samples (also known as bioanalytical samples) for measurement of necitumumab serum concentrations will be collected as specified in the Pharmacokinetic, Immunogenicity, and Blood-Based Markers Sampling Schedule (Attachment 6).

Sampling times were selected to coincide with expected maximum concentration and minimum concentration of necitumumab and with consideration to draw minimum volume of blood from

patients and ensuring that the patients do not to need to make an extra visit to provide these samples.

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

Serum concentrations of necitumumab will be determined using validated enzyme-linked immunosorbent assays at laboratories approved by the sponsor.

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

10.4. Appropriateness of Measurements

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

11. Data Quality Assurance

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

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

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

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

11.1. Data Capture System

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

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

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

A total of approximately 78 patients for Part A, Part B, and Part C will be enrolled. Part A requires up to 12 treated patients (3-6 for Cohort 1 and 6 for Cohort 2). Patients with squamous and nonsquamous NSCLC from Part A who received the recommended necitumumab dose for Part B will also be analyzed together with Part B. These Part A patients who received the recommended necitumumab dose for Part B will also be included in the interim analyses as described in Section 12.2.12.

An evaluable patient for Part B will include any patient enrolled in Part A and treated at the recommended Phase 2 doses of necitumumab and pembrolizumab. In addition, patients will be entered strictly to Part B (with approximately 54 evaluable patients in Part B). To be evaluable for the efficacy analysis of study, these patients must meet the following criteria:

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

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

In Part C, approximately 6-12 Japanese patients will be enrolled and treated with necitumumab at the recommended dose from Part A in combination with pembrolizumab.

The primary analysis of the Part A and Part B will take place approximately 6 months after the last patient evaluable for Part B portion of the study has been enrolled. The primary Part B outcome variable in this study will be ORR. The Part B statistical null hypothesis states that the true ORR associated with the regimen of necitumumab and pembrolizumab is 20%, whereas the research hypothesis states that the true ORR associated with the combination regimen is 35%.

If the research hypothesis of a 35% ORR is true, there is an 83% chance of rejecting the null hypothesis. If the null hypothesis of a 20% ORR is true, then there is at most a 10% chance of rejecting the null hypothesis. Therefore, the sample size of 54 evaluable patients in Part B has a nominal one-sided alpha level of 0.10, with statistical power of 83%.

The analysis of Part C will take place approximately after all the patients from Part C have completed 8 cycles or discontinued early. At the same time, some of the efficacy of Part B may be updated, where appropriate.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

The primary analysis will be as described in Section 12.1.

All efficacy summary analyses will be performed for all evaluable patients (as defined in Section 12.1). All safety summary analyses will be performed for all treated patients (those enrolled in the study who receive any amount of study drug [necitumumab and/or pembrolizumab]).

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

12.2.2. Patient Disposition

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

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

A detailed summary of reasons for patient discontinuation from treatment will be provided. A summary of all identified important (as defined in the SAP) protocol violations will be provided.

12.2.3. Patient Characteristics

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

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

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.4.1. Postdiscontinuation Therapy

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

12.2.5. Treatment Compliance

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

12.2.6. Primary Outcome and Methodology

The primary efficacy endpoint of ORR and its exact 80% CI and 95% CI will be estimated.

12.2.7. Analyses of Efficacy

In addition to the analyses described in Section 12.1, this section provides additional details of planned efficacy analyses. For time-to-event variables, the Kaplan-Meier method will be used to estimate parameters (for example, medians, quartiles, 6 months, and 1-year event rates). See also the SAP for additional details.

ORR: The denominator of ORR includes each evaluable patient. The numerator includes those patients counted in the denominator with a best overall tumor response of PR or CR.

DCR: Using the same denominator as for ORR, the numerator of the DCR includes those patients counted in the denominator with a best tumor response of SD, PR, or CR.

DOR: The DOR is defined only for responders (patients with a confirmed CR or PR, as defined in Section 10.1.1). It is measured from the date of first evidence of a confirmed CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DOR will be censored at the date of the last complete objective progression-free disease assessment.

PFS: The PFS time is measured from the date of first dose to the date of objective progression or the date of death due to any cause, whichever is earlier. The censoring is taken in the following order:

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

OS: OS duration is measured from the date of first dose to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the last known alive date. ORR, DCR, DOR, and PFS will be assessed based on RECIST 1.1.

12.2.7.1. Exploratory Outcome and Methodology

The irORR, irDCR, irDOR, and irPFS accessed based on adapted RECIST 1.1 (irRECIST) will be used for exploratory analysis of ORR, DCR, DOR, and PFS. See also the SAP for additional details.

12.2.8. Pharmacokinetic and Immunogenicity Analyses

PK Analyses:

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

Summary statistics of necitumumab data will be presented graphically as well as in tabulated form. Additional exploratory analyses using PopPK approach may be performed if warranted by data. Patient or study factors that may influence the PK of necitumumab, when given in combination with pembrolizumab, may be explored. The relationship between necitumumab exposure, when given in combination with pembrolizumab, and selected safety outcomes may also be explored.

Immunogenicity Analyses:

Immunogenicity (anti-necitumumab antibody) incidence will be tabulated, and correlation to necitumumab drug level, activity, and safety will be assessed, as appropriate, respectively. The measures that will be analyzed include baseline presence and level of anti-drug(s) antibodies

(ADA), treatment-emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to IRRs.

Interim analysis:

Interim analysis may be conducted to facilitate exploratory analyses of PK, pharmacodynamics (safety), and immunogenicity. Interim data may also be pooled with final and interim data from other clinical studies of necitumumab and analyzed using a population PK/pharmacodynamic approach. Since the study is unblinded, study objectives will not be compromised by the interim analysis.

12.2.9. Translational Research Analyses

Biomarker results will be summarized and correlated with clinical outcomes.

12.2.10. Safety Analyses

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

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

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

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

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

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

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

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

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

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

12.2.11. Subgroup Analyses

Exploratory subgroup analyses by histology will be performed to look for evidence of any differences in efficacy or safety that might depend on histology.

12.2.12. Interim Analyses

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

Patients with squamous and nonsquamous NSCLC from Part A who received the recommended necitumumab dose for Part B will be included in the interim analyses.

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

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

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

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

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

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

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

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

13.2. Ethical Review

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

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

The ERB should include or consult with experts who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

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

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

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

- applicable laws and regulations

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

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

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

13.3.1. Investigator Information

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

13.3.2. Protocol Signatures

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

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

13.3.3. Final Report Signature

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

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

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

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Attachment 1. Protocol JFCQ Study Schedule

Study Schedule, Protocol I4X-MC-JFCQ

Perform procedure as indicated in the following schedules.

Baseline Schedule, I4X-MC-JFCQ

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative day within a cycle	≤21	≤14	≤7	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Study Entry/ Enrollment	13.1	Informed consent form signed	X			ICF must be signed prior to performing any protocol-specific tests/procedures.
	7.1, 7.2	Inclusion/exclusion evaluation	X			
Medical History	12.2.3	Initial history/preexisting conditions		X		
	12.2.3	Historical illnesses		X		
		Habits assessment		X		Smoking
Physical Examination		Height		X		
		Weight		X		
		Blood pressure/pulse/temperature		X		
	Att. 3	ECOG performance status		X		
Efficacy Assessment	10.1.1	Radiologic imaging/Tumor Assessment (according to RECIST v1.1)	X			A contrast CT scan or MRI of the brain will be performed if the patient is known to have CNS metastasis.
Adverse Events	10.2.1	AE collection and CTCAE grading		X		Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant Medications	9.6	Concomitant medication notation		X		

			Baseline			
		Cycle	BL			
		Visit	0			
		Relative day within a cycle	≤21	≤14	≤7	
Procedure Category	**Protocol Section**	**Procedure**				**Comments**
Laboratory/ Diagnostic Tests	Att. 2	Hematology (central)		X		
	Att. 2	Chemistry (central)		X		
	Att. 2	Coagulation (central)		X		
	Att. 2	T3, free T4, TSH (central)		X		
	Att. 2	Urinalysis (local)		X		
	Att. 2	Pregnancy test (central)		X		In women of childbearing potential
	10.3.2.1	Whole blood for genetic research	Refer to Attachment 6.			
	10.3.4	PK sampling (central)	Refer to Attachment 6.			
	10.3.3	Immunogenicity: Anti-necitumumab antibodies	Refer to Attachment 6.			
	10.3.2	Plasma and Whole blood samples for Biomarker Analysis	Refer to Attachment 6.			
	10.3.2	Tumor tissue sample	X			To meet study eligibility criteria, and therefore mandatory for study participation, patients must have an evaluable and archived FFPE block or a minimum 15 slides (freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut), available for biomarker analyses, or if not available, patient is willing to undergo a tumor biopsy of an extra-CNS lesion (core or excisional biopsy). See Section 10.3.2 for further details.
	10.2.2.1	ECG (local)	X			

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

Treatment Period Schedule, I4X-MC-JFCQ

			Comments			
			Repeat every 3 weeks			
		Cycle (3-week cycle)	1-X			
		Visit	1-X			
		Relative day within a cycle	1	8		Except for the Cycle 1, Day 1 visit, allowable cycle windows are ±3 days, unless indicated otherwise (see Section 9.4).
Procedure Category	**Protocol Section**	**Procedure**				
Physical Examination		Weight	X			
		Blood pressure/pulse	X	X		Blood pressure will be collected pre-infusion and post-infusion of pembrolizumab and necitumumab.
	Att. 3	ECOG performance status	X			
Tumor Assessment	10.1.1	Radiologic imaging (according to RECIST v1.1) and tumor measurement	X			To be performed every 6 weeks ±5 days after the first dose of study therapy, regardless of treatment delays, until there is confirmed radiographic documentation of PD as defined by the adapted RECIST 1.1, unless patient is clinically unsuitable to wait for confirmatory scan. A contrast CT scan or MRI of the brain will be performed if the patient is known to have CNS metastasis or if clinically indicated.
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X		Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Concomitant Medications	9.6	Concomitant medication notation	X	X		
IP	9.2	Necitumumab	X	X		
	9.2	Pembrolizumab	X			

			Comments			
			Repeat every 3 weeks			
		Cycle (3-week cycle)	1-X			
		Visit	1-X			
		Relative day within a cycle	1	8		Except for the Cycle 1, Day 1 visit, allowable cycle windows are ±3 days, unless indicated otherwise (see Section 9.4).
Procedure Category	**Protocol Section**	**Procedure**				
Laboratory/ Diagnostic Tests	Att. 2	Hematology	X	X		Investigator-designated (local) laboratory can be used to perform additional tests for on-study dosing decisions. If so, the test must also still be performed by the central laboratory. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8). Hepatic monitoring tests (see Site Guidance Document for DILI) to be done in the event of a treatment-emergent hepatic abnormality. In case of neutropenia, thrombocytopenia Grade 4 during Cycle 1 (dose finding part only), repeat every 2 days until recovery.
	Att. 2	Chemistry	X	X		Investigator-designated (local) laboratory can be used to perform additional tests for on-study dosing decisions. If so, the test must also still be performed by the central laboratory. Pretreatment laboratory data may not be older than 72 hours (Day 1 of each cycle) or 24 hours (Day 8). Hepatic monitoring tests (see Site Guidance Document for DILI) to be done in the event of a treatment-emergent hepatic abnormality. Grade 3 elevation of transaminases, bilirubin, change of electrolytes (see DLT criteria), repeat every 2 days until recovery.
	Att. 2	Coagulation (central)	X*			* To be performed every second cycle starting from Cycle 2
	Att. 2	T3, free T4, TSH (central)	X*			* To be performed every second cycle starting from Cycle 2
	Att. 2	Urinalysis (local)	X*			* To be performed every second cycle starting from Cycle 2
	Att. 2	Pregnancy test (local)	X*			Local urine test can be performed. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. * To be performed every cycle in women of childbearing potential
	10.3.4	PK sampling (central)	Refer to Attachment 6. Note: If a patient experiences an IRR to necitumumab at any time during the study, blood samples for both immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.			
	10.3.3	Immunogenicity: Anti-necitumumab antibodies				
	10.3.2	Plasma and Whole blood samples for Biomarker Analysis	Refer to Attachment 6.			
	10.3.2.1	Whole blood for genetic evaluation	Refer to Attachment 6.			
	10.2.2.1	ECG (local)	X*			* To be performed every second cycle starting from Cycle 2

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

Postdiscontinuation Follow-up Schedule, I4X-MC-JFCQ

			Postdiscontinuation Follow-up		
		Cycle	Short-Term Follow-up	Long-Term Follow-up	
		Visit	801	802-8XX	
		Relative day within a cycle			
Procedure Category	**Protocol Section**	**Procedure**			**Comments**
Physical Examination		Weight	X		
		Blood pressure/pulse	X		
	Att. 3	ECOG performance status	X		
Tumor Assessment	10.1.1	Radiologic imaging (according to RECIST v1.1) and tumor measurement	X	X	Patients who discontinue study treatment for any reason other than PD will continue to undergo radiographic tumor assessments every 6 weeks (±5 days) until PD, the initiation of a new anticancer therapy, or overall study completion, whichever occurs first. After the patient has objective (confirmed or unconfirmed) disease progression, radiologic tests are no longer required and the patient will be followed approximately every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first.
Survival information	10.1.4	Collection of survival information		X	Collection of survival data every 3 months (±7 days). Whenever possible, survival follow-up is conducted in person. If an in-person visit is not possible, the site may confirm survival by contacting the patient directly via telephone.
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. During Postdiscontinuation long-term follow-up, only SAEs that are related to protocol procedures or study treatment will be collected.
Concomitant Medications	9.6	Concomitant medication notation	X		
Laboratory/ Diagnostic Tests	Att. 2	Hematology	X		
	Att. 2	Chemistry	X		
	10.3.2	Plasma and Whole blood samples for Biomarker Analysis	X		When applicable, EDTA plasma should be collected as near as possible to the time of progression disease, during the study treatment period. If for any reason the post progression sample cannot be collected at the time of progression, this should be done at (or by) the short-term follow-up visit. The post progression sample should be collected before the initiation of any new anticancer therapy.
	Att. 2	Pregnancy test (local)	X		In women of childbearing potential. Local urine test can be performed. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
	Att. 2	T3, free T4, TSH (central)	X		
	Att. 2	Urinalysis (local)	X		
	10.3.4	PK	Refer to Attachment 6.		If a patient experiences an IRR to necitumumab at any time during the study, blood samples for both immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
	10.3.3	Immunogenicity: Anti-necitumumab			
	10.2.2.1	ECG (local)	X		

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

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

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

Long-Term Follow-up begins the day after Short-Term Follow-up is completed and continues until the patient's death or overall study completion. Patients who discontinue study treatment for reasons other than PD will continue to undergo radiographic tumor assessments every 6 weeks (±5 days) until PD, the initiation of a new anticancer therapy, or overall study completion, whichever occurs first. Patients will be followed for survival every 3 months (±7 days) until the patient's death or overall study completion, whichever occurs first.

Continued Access Schedule, I4X-MC-JFCQ

			Continued Access Period				
			Treatment Period			Continued Access Follow-up	
		Cycle	X-Y			Follow-up	
		Visit	501-5XX			901	
		Relative day within a cycle	1	8			
Procedure Category	**Protocol Section**	**Procedure**					**Comments**
Physical Examination		Weight	X				
Adverse Events	10.2.1	AE collection and CTCAE grading	X	X		X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.
Laboratory/ Diagnostic Tests	10.3.4	PK	Refer to Attachment 6.				If a patient experiences an IRR to necitumumab, blood samples for both immunogenicity and PK analysis should be drawn, with no more than 15 minutes' time difference. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.
	10.3.3	Immunogenicity: Anti-necitumumab antibodies					
Study Treatment	9.2	Necitumumab	X	X			
	9.2	Pembrolizumab	X				

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

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

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

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

Attachment 2. Protocol JFCQ Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry[a]:**
Hemoglobin	**Serum concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Magnesium
Mean cell volume (MCV)	Potassium
Mean cell hemoglobin concentration (MCHC)	Phosphate
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented and bands	Direct bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine[b]
	Uric acid
Thyroid Function Test[e]:	Calcium
Thyroid-stimulating hormone (TSH)	Glucose, nonfasting
Total triiodothyronine (T3)	Albumin
Free thyroxine (T4)	Cholesterol
	Creatine kinase (CK)
Urinalysis[c]:	
Color	
Specific gravity	
pH	
Protein	**Pregnancy Test** (females of childbearing potential only)[d]
Glucose	
Ketones	
Blood	**Coagulation Tests[e]:**
Urine leukocyte esterase	INR and PT
	PTT
	Fibrin D dimer
	Protein C activity (baseline only)
	Protein S activity (baseline only)

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

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

[b] IDMS for United States sites.

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

[d] For fulfilling Inclusion Criterion 12, a central serum pregnancy test is mandatory. During treatment and postdiscontinuation periods, a local urine test can be performed. If the local urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

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

Attachment 3. Protocol JFCQ ECOG Performance Status Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 4. Protocol JFCQ Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

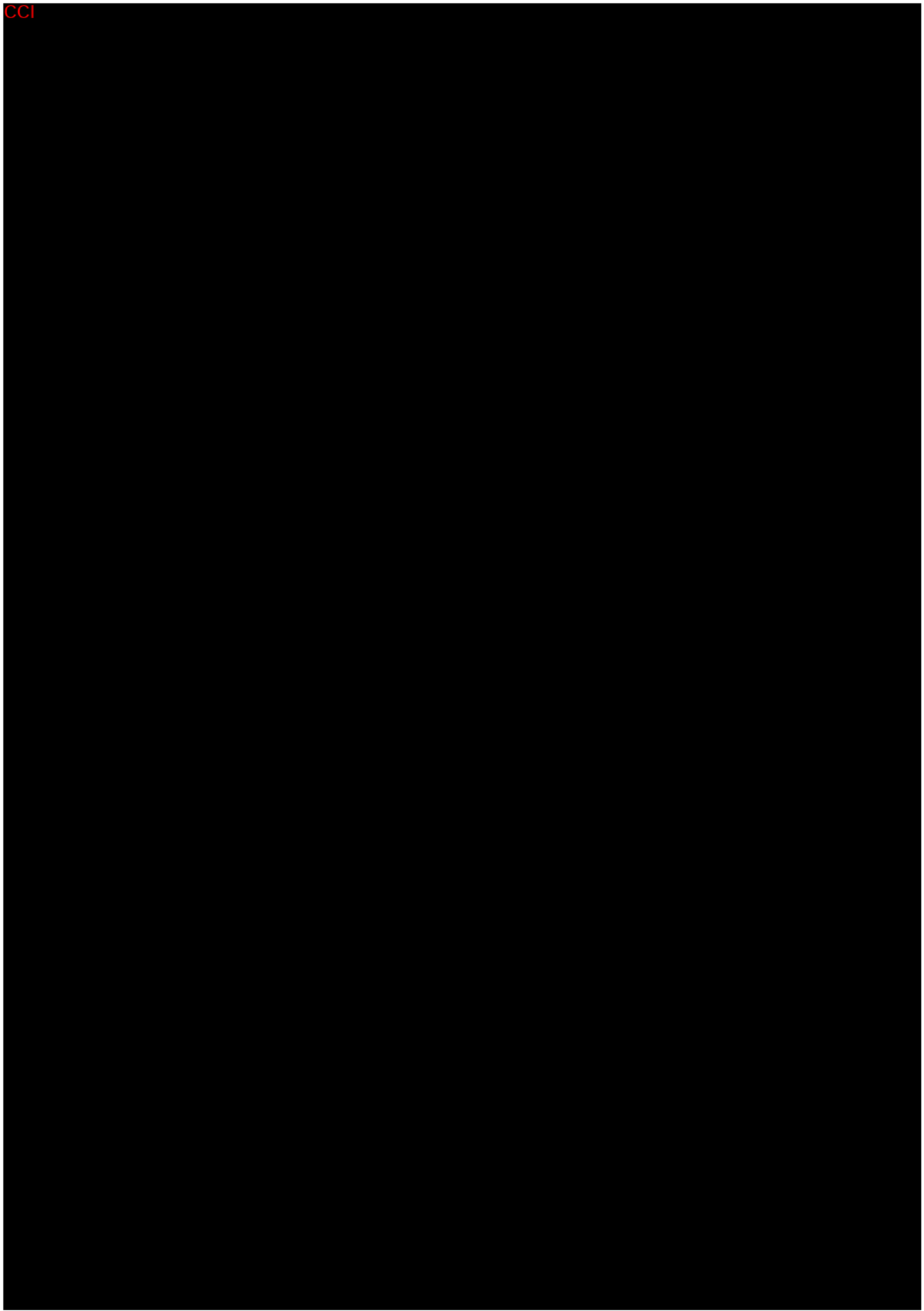
$$\textbf{CrCl} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85} \text{ (if female), or } \times \textbf{1.0} \text{ (if male)}}{\textbf{72} \times \textbf{serum creatinine } (mg/dL)} \text{ (mL/min)}$$

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.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Attachment 6. Protocol JFCQ Pharmacokinetic, Immunogenicity, and Blood-Based Markers Sampling Schedule

PK and Immunogenicity samples will be collected for necitumumab only. It is essential that the exact infusion start and stop times (actual clock readings) are recorded. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the pharmacokinetic blood samples not be withdrawn from the same I.V. site as the drug infusion.

Predose samples should be taken as close as possible to the start of first infusion, but can be drawn up to 1 hour (60 minutes) prior first infusion, and exact clock reading should be recorded. Post-dose (post-end of infusion) samples for PK for necitumumab should be drawn immediately after end of necitumumab infusion (range = after end of infusion +10 minutes) and exact clock reading should be recorded.

In addition, if a patient experiences an IRR, blood samples for both immunogenicity (anti-necitumumab antibody,) and PK (necitumumab concentration) should be drawn, with no more than 15 minutes' time difference between PK and immunogenicity samples. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.

Pharmacokinetic, Immunogenicity, Biomarker, and Pharmacogenetic Sample Collection for Part A, Part B, and Part C

Visit/Cycle Day	Study Day	Sample Time (relative to start of pembrolizumab infusion) (HR:MIN)[a]	Necitumumab PK[c] (Serum)	Necitumumab Immunogenicity[c] (Serum)	Biomarker and Pharmacogenetic	
					Plasma and Whole Blood for Biomarker	Whole Blood for Genetics
Cycle 1 Day 1 (Pembrolizumab and Necitumumab infusion)	1	**0:00 hr** Predose sample[b,e] **1:30 hr** Postdose sample[d,e]	**X** (collect prior to start of first infusion) **X** (collect immediately after Necitumumab infusion ends)	**X**	**X**	**X**
Cycle 1 Day 8 (Necitumumab infusion only)	8	**0:00 hr** Predose sample			**X**	
Cycle 2 Day 1 (Pembrolizumab and Necitumumab infusion)	22	**0:00** hr Predose sample[b,e] **1:30 hr** Postdose sample[d,e]	**X** (collect prior to start of first infusion) **X** (collect immediately after Necitumumab infusion ends)	**X**	**X**	
Cycle 4 Day 1 (Pembrolizumab and Necitumumab infusion)	64	**0:00** hr Predose sample[b,e] **1:30 hr** Postdose sample[d,e]	**X** (collect prior to start of first infusion) **X** (collect immediately after Necitumumab infusion ends)	**X**	**X**	

Visit/Cycle Day	Study Day	Sample Time (relative to start of pembrolizumab infusion) (HR:MIN)[a]	Necitumumab PK[c] (Serum)	Necitumumab Immunogenicity[c] (Serum)	Biomarker and Pharmacogenetic	
					Plasma and Whole Blood for Biomarker	Whole Blood for Genetics
Cycle 6 Day 1 (Pembrolizumab and Necitumumab infusion)	106	**0:00** hr Predose sample[b,e]	**X** (collect prior to start of first infusion)	**X**	**X**	
		1:30 hr Postdose sample[d,e]	**X** (collect immediately after Necitumumab infusion ends)			
Cycle 8 Day 1 (Pembrolizumab and Necitumumab infusion)	148	**0:00** hr Predose sample[b,e]	**X** (collect prior to start of first infusion)	**X**	**X**	
		1:30 hr Postdose sample[d,e]	**X** (collect immediately after Necitumumab infusion ends)			
30 days Post treatment DC		Anytime[f]	**X**	**X**	**X**	

Abbreviations: DC = Discontinuation; eCRF = electronic case report form; PK = pharmacodynamics; IK = immunokinetics/immunogenicity; IRR = infusion-related reaction.

Note: 30-minute pembrolizumab infusion is given first followed by 60-minute necitumumab infusion.

[a] All sample times are relative to start of first infusion.

[b] Pre-dose sample for necitumumab PK, and/or IK should be preferably collected within 1 hour prior to start of first infusion.

[c] In the event of an IRR, blood samples will be collected for necitumumab PK and IK analysis at the following time points within 15 minutes of one another: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

[d] Postdose samples should be collected after the end of necitumumab infusion, preferably within a 10 minute time window.

[e] While best effort should be done to draw the blood sample for PK/IK within the time windows provided above, it is more important to ensure predose sample is actually collected before the start of first infusion and postdose infusion samples are collected after infusion has actually completed. It is also equally important to record ACTUAL date and time of blood collection for PK/IK sample on the Requisition Form AFTER drawing the sample and to accurately record the ACTUAL infusions start and end dates and times on the eCRF to be able to use the data for analyses. Sample collection for PK/IK must be from the opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, the sample collection should be from a different site.

[f] Record ACTUAL date and time of blood collection for PK/IK sample on the Requisition Form AFTER drawing the sample. PK/IK sample should be taken within 15 minutes of one another.

Attachment 7. Protocol Amendment I4X-MC-JFCQ(d) Summary An Open-Label, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of the Combination of Necitumumab with Pembrolizumab in Patients with Stage IV Non-Small Cell Lung Cancer

Overview

Protocol I4X-MC-JFCQ, An Open-Label, Multicenter, Phase 1b Study with Expansion Cohorts to Evaluate Safety and Efficacy of the Combination of Necitumumab with Pembrolizumab in Patients with Stage IV Non-Small Cell Lung Cancer, has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

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

- A second dosage form is available for pembrolizumab. Details of the pembrolizumab solution for infusion (100 mg/vial) have been added to Section 2 (Synopsis) and Section 9.2 (Materials and Supplies).

Revised Protocol Sections

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

2. Synopsis

Test Product, Dosage, and Mode of Administration:

- Necitumumab is a sterile, preservative-free, intravenous infusion supplied in 50-mL vials containing 16 mg/mL (800 mg/50 mL) of product, and administered over 60 minutes at a dose of 600 mg or 800 mg on Days 1 and 8 of each 21-day cycle.
- Pembrolizumab drug product is available in 2 dosage forms intended for intravenous administration: ~~dosage form is~~ a lyophilized powder, 50 mg/vial, ready to be reconstituted with sterile water for injection prior to use, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only. Pembrolizumab is ~~and~~ administered over 30 minutes (-5 min/+ 10 min) at a dose of 200 mg on Day 1 of each 21-day cycle.

9.2 Materials and Supplies

Pembrolizumab drug product is available in 2 ~~-~~dosage forms: ~~is~~ a white to off-white lyophilized powder, 50 mg/vial, and a liquid, 100 mg/vial, both in Type I glass vials intended for single use only.

- Pembrolizumab ~~powder~~ Powder for ~~solution~~ Solution for ~~infusion~~Infusion, 50 mg/vial, is a lyophilized powder that is reconstituted with sterile water for injection prior to use. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (if necessary).
- Pembrolizumab Solution for Infusion 100 mg/vial is a liquid, manufactured fully formulated with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier.

Both ~~The~~ pembrolizumab product dosage forms are ~~is~~ stored under refrigerated conditions ~~(~~2°C to 8°C~~)~~ (36-46°F) and protected from light. Refer to pembrolizumab IB for detailed storage information.

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