Statistical Analysis Plan Version 3 I4X-JE-JFCM

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

NCT01763788

Approval Date: 07-Sep-2017

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

Necitumumab (IMC-11F8; LY3012211)
Gemcitabine (LY1880011)

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

Eli Lilly Japan K.K.
Kobe, Hyogo, Japan
Protocol I4X-JE-JFCM
Phase 1b/2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 01 March 2013
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 12 June 2017
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 07-Sep-2017 GMT

2. Table of Contents

Section **Page**

1. Statistical Analysis Plan: I4X-JE-JFCM: An Open-label, Multicenter, Phase 1b/2 Study to Evaluate Necitumumab in Combination with Gemcitabine and Cisplatin in the First-Line Treatment of Patients with Advanced (Stage IV) Squamous Non-Small Cell Lung Cancer (NSCLC) 1
2. Table of Contents 2
3. Revision History 6
4. Study Objectives 8
4.1. Primary Objective 8
4.2. Secondary Objectives 8
4.3. Exploratory Objectives 8
5. Study Design 9
5.1. Summary of Study Design 9
5.2. Determination of Sample Size 10
5.3. Method of Assignment to Treatment 10
6. A Priori Statistical Methods 12
6.1. General Considerations 12
6.2. Adjustments for Covariates 12
6.3. Handling of Dropouts or Missing Data 13
6.4. Multicenter Studies 13
6.5. Multiple Comparisons/Multiplicity 13
6.6. Use of an “Efficacy Subset” of Patients 13
6.7. Patient Disposition 13
6.8. Protocol Deviations 13
6.9. Patient Characteristics 13
6.10. Treatment Compliance 14
6.11. Concomitant Therapy 14
6.12. Efficacy Analyses 14
6.12.1. Primary Endpoint: Overall Survival 14
6.12.2. Secondary Efficacy Endpoints 15
6.12.3. Sensitivity Analyses 16
6.13. Post-discontinuation Therapy 16
6.14. Health Outcomes Analyses 16
6.15. Biomarker Analyses 17
6.16. Pharmacokinetic/Pharmacodynamic Methods 17

6.17. Safety Analyses 18
6.17.1. Extent of Exposure 18
6.17.2. Adverse Events 19
6.17.3. Deaths, Other Serious Adverse Events, Adverse Events of Special Interest, Consolidated Treatment-Emergent Adverse Events, and Other Notable Adverse Events 20
6.17.4. Clinical Laboratory Evaluation 22
6.17.5. Vital Signs and Other Physical Findings 22
6.17.6. Electrocardiograms 23
6.17.7. Immunogenicity of Necitumumab 23
6.18. Subgroup Analyses 23
6.19. Interim Analyses and Data Monitoring 24
6.19.1. Phase 1b Part 24
6.19.2. Interim Analysis for Data Monitoring Committee 24
6.19.3. Other Possible Interim Analysis 25
6.20. Data of Extension Phase 25
7. Unblinding Plan 26
8. References 27

Table of Contents

Table **Page**

Table 6.1. PFS Definition 15
Table 6.2. Sensitivity Analysis 16
Table 6.3. Dose Reductions for Necitumumab, Gemcitabine, and Cisplatin 19

Table of Contents

Figure **Page**

Figure JFCM. 1. Study design for Protocol I4X-JE-JFCM.....9

3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

SAP Version 2 was approved prior to the data base lock.

SAP Version 3 was approved prior to the data base lock.

Changes from Statistical Analysis Plan Version 1

1. Clarified the definition of Safety Population.
2. Removed the analyses for treated patients with necitumumab (Phase 1b part + Arm A in Phase 2 part) because it was considered unnecessary (it could be evaluated by separate analyses).
3. Removed language regarding Independent Radiography Review Committee (IRRC) because it was not established.
4. Removed Per Protocol Set analyses because the number of major protocol deviations which require PPS analysis was not occurred.
5. Removed some factors of interest list in “Adjustments for Covariates” because the number of patients who had the factor was not enough for appropriate evaluation.
6. Clarified the target patients for efficacy analyses in “Use of an “Efficacy Subset” of Patients”.
7. Added summary of analysis population in “Patient Disposition”.
8. Removed language regarding flow chart in “Patient Disposition” because it was considered unnecessary (the information was included in other summary).
9. Added summary of transfusions in “Concomitant Therapy”.
10. Clarified the category of survival rates in “Primary Endpoint: Overall Survival”.
11. Clarified the target patients (“for patients who receive necitumumab of the maintenance therapy”) in “Primary Endpoint: Overall Survival”.
12. Added disease control rate analyses in order to harmonize with JFCC study.
13. Added forest plots of the estimated HRs with 95% CIs for Lung Cancer Symptom Scale and subgroup analyses.
14. Removed the Mixed-Effect Model with Repeated Measures (MMRM) analysis from LCSS and EQ-5D analyses based on the revised the SAP of JFCC.
15. Added a listing of blood concentration in “Pharmacokinetic/Pharmacodynamic Methods”.

16. Clarified the definition of dose modification, adjusted the categories of dose reduction and cycle start delay, and BSA (body surface area) in “Extent of Exposure” in order to harmonize with JFCC study.
17. Added analyses for gemcitabine in “Adverse Events” in order to evaluate safety profile in more detail for gemcitabine.
18. Clarified the definition of TEAE and AEs leading to delay/modification in “Adverse Events”.
19. Added summary of consolidated treatment-emergent adverse events and AEs of special interest in “Adverse Events” in order to evaluate safety profile in more detail based on same category as JFCC study.
20. Removed the analyses for thromboembolic-like and ILD-like AEs in “Adverse Events” because it was considered unnecessary (it could be evaluated by analyses for AEs of special interest).
21. Added listing for weight and ECOG performance status in “Vital Signs and Other Physical Findings” because it was not included in SAP version 1.
22. Clarified the factors of subgroups analyses in “Subgroup Analyses”.
23. Modified age subgroups in “Subgroup Analyses” to harmonize with JFCC study.
24. Several other changes were made for minor editorial update.

Changes from Statistical Analysis Plan Version 2

1. Corrected of category of "Other factors of interest" in “Adjustments for Covariates” to harmonize with the category of subgroups analyses.
2. Corrected the definition of combination therapy period and maintenance therapy period in “Extent of Exposure”.
3. Clarified the definition of combination therapy period and maintenance therapy period for adverse event in “Adverse Events”.
4. Clarified the definition of time point in “Clinical Laboratory Evaluation” and “Vital Signs and Other Physical Findings”.
5. Clarified the definition of QT Interval corrected using Fridericia's correction.
6. Modified the definition of QTcF category to harmonize with JFCI study.
7. Several other changes were made for minor editorial update.

4. Study Objectives

4.1. Primary Objective

The study is divided into two parts:

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

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

4.2. Secondary Objectives

The secondary objectives of the study are as follows:

Phase 1b part

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

Phase 2 part

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

4.3. Exploratory Objectives

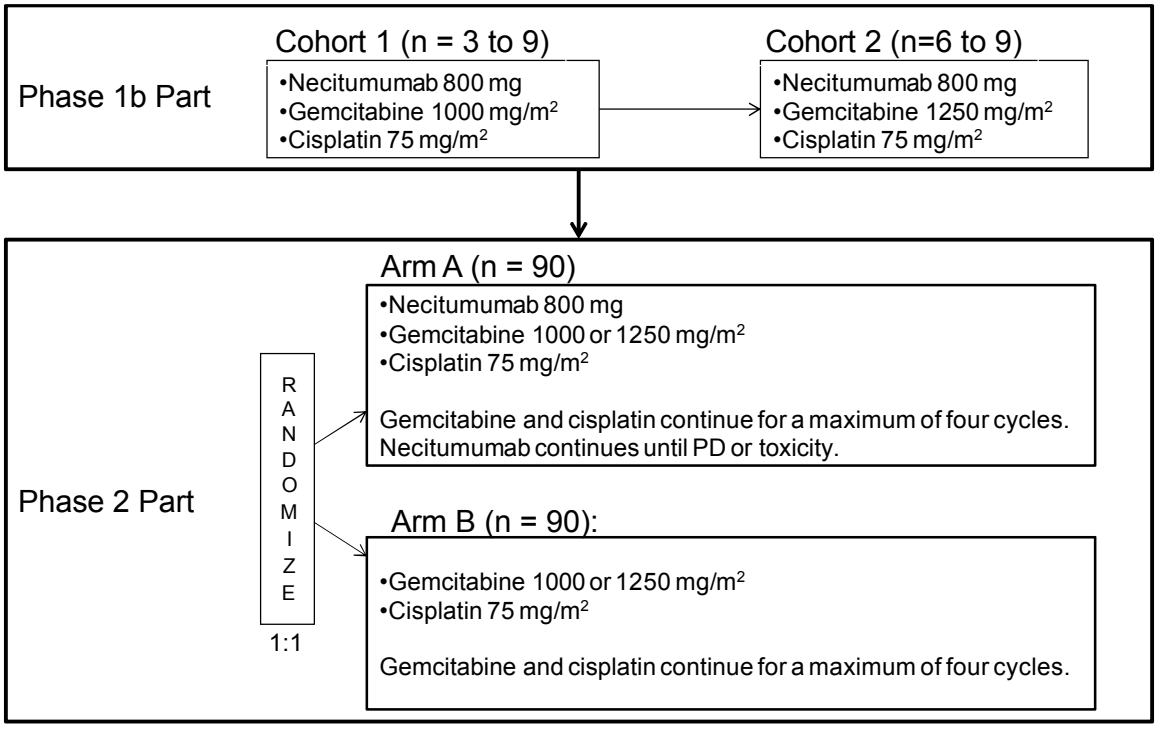
Only Phase 2 part: to explore biomarkers including HER2 and HER3 protein expression (IHC), KRAS and EGFR mutation status, fragment C gamma receptor (FCγR) polymorphisms, and/or additional biomarkers of interest related to the necitumumab, gemcitabine and cisplatin mechanism of action.

5. Study Design

5.1. Summary of Study Design

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

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



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

Figure JFCM. 1. Study design for Protocol I4X-JE-JFCM.

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

Terms used to describe the study periods are defined below:

- **Baseline:** from the time of screening to first study treatment (or discontinuation, if no treatment is given)
- **Study Treatment Period:** time from treatment start to discontinuation from study treatment

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

5.2. Determination of Sample Size

Phase 1b part

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

Phase 2 part

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

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

5.3. Method of Assignment to Treatment

Phase 1b part:

Patients who meet all criteria for enrollment will be assigned to receive necitumumab 800 mg, gemcitabine 1000 or 1250 mg/m^2, and Cisplatin 75 mg/m^2 in this part. Upon confirmation of eligibility, the Sponsor will assign the treatment cohort (dose level) for each patient.

Phase 2 part:

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

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

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

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline (0 vs. 1)
- Gender (females vs. males)

6. A Priori Statistical Methods

6.1. General Considerations

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

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

The safety analyses will be conducted on the Safety Population, defined as all patients who are treated with any study drugs in Phase 1b part and Phase 2 part, and patients will be grouped as follows; Phase 1b part, Arm A and Arm B in Phase 2 part. Patients will be grouped according to treatment received.

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

Baseline is defined as the last measurement for a variable prior to the initial dose of any study drug.

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

The patient listings corresponding to all analyses/summaries for this study will be provided unless otherwise specified.

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

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

A description of the PK analyses will be described in a separate PK analysis plan. Biomarker analyses will be described in a separate translational research statistical analysis plan.

6.2. Adjustments for Covariates

The primary and secondary efficacy endpoints will also be analyzed adjusting for the variables used for randomization listed below.

- Randomization stratification factors:
  - ECOG PS (0 versus 1)
  - gender (females versus males)

As supportive analysis, the other factors of interest listed below might be considered in addition to randomization stratification factors. Cox proportional hazard model will be developed using stepwise selection to estimate the HR of treatment effect and the CI. The stepwise selection will use p-value of 0.2 for adding and dropping a variable;

- Other factors of interest:
  - age (< 70 vs. ≥ 70 years)

6.3. Handling of Dropouts or Missing Data

For the birth date, Lilly collects only the year of birth, and it will be imputed by assigning month and day with July 1st to calculate age.

Missing data will generally not be imputed, except for partial dates concerning pivotal efficacy or safety parameters.

6.4. Multicenter Studies

The Phase 2 part is a multicenter, randomized portion. Investigative center was not a stratification factor because the large number of investigative centers would breakdown the intended balance within each combined stratification level by the stratified randomization method. It will not be included as a covariate in any covariate-adjusted analysis because the large number of investigative centers in this study cannot be practically incorporated into such analysis.

6.5. Multiple Comparisons/Multiplicity

No multiplicity adjustments are applied for the Phase 2 part since it is exploratory and no statistical tests is planned (p values will be shown just for reference).

6.6. Use of an "Efficacy Subset" of Patients

All efficacy analyses will be conducted for the patients who are treated any study drugs.

6.7. Patient Disposition

Frequency distributions of patients entered into the study, enrolled in the study, FAS and Safety Population will be summarized.

Summary of the screen failure and reason will be provided.

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients treated as well as number and percentage of patients completing the study treatment. The disposition will be listed by patient.

The reason for study treatment discontinuation will be provided in summary tables for each of the whole treatment period and the combination therapy period. The reason for discontinuation of study and study treatment will be listed by patient.

6.8. Protocol Deviations

A summary of all important protocol deviation will be provided. Important protocol deviation is defined in a separate document, and the final list of important protocol deviations will be provided from study team as a part of source data from data management.

6.9. Patient Characteristics

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

Baseline disease characteristics will be summarized for histologic subtype, disease stage, TNM classification, baseline ECOG PS and screening smoking status.

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

6.10. Treatment Compliance

Necitumumab, gemcitabine and cisplatin will be intravenously administered only at the investigational sites. As a result, patient compliance will be ensured. If there are any cases deemed as not compliance, they will be reported as protocol deviations.

6.11. Concomitant Therapy

Concomitant medications used in study treatment period or the 30-day post discontinuation follow-up period will be used for the summary tables and all concomitant medication reported in the study will be listed.

The concomitant medications will be summarized in decreasing frequency of drug name. A separate summary of transfusions will be reported.

Steroids for skin toxicity with ATC code under the following codes will be summarized by drug name and cycle. In addition, steroids for systemic use will be summarized by category of titer.

- D07*: CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS
- H02*: CORTICOSTEROIDS FOR SYSTEMIC USE

Premedication for gemcitabine and cisplatin, each of gemcitabine and cisplatin will be summarized by drug name.

6.12. Efficacy Analyses

6.12.1. Primary Endpoint: Overall Survival

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

The analyses will be performed in FAS. The Kaplan-Meier (KM) method will be used to generate KM curves, the medians, quartiles and percentages of patients event-free every 3-month interval up to 12 months, and 24 months for each arm. The HR of Arm A to Arm B and the CI will be estimated using a stratified Cox regression model by the variables used for randomization (ECOG PS and gender), and a stratified log-rank test will be performed.

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

For patients who complete 4 cycles of chemotherapy drugs (gemcitabine and cisplatin) and receive necitumumab of the maintenance therapy in Arm A of Phase 2 part, KM curve and the summary statistics of OS and PFS from the start date of maintenance therapy will be provided.

6.12.2. Secondary Efficacy Endpoints

6.12.2.1. Progression Free Survival

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

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

Table 6.1. PFS Definition

Situation	Date of progression or censoring	Outcome
No baseline tumor assessment	Randomization	Censoring
No post-baseline tumor assessment	Randomization	Censoring
Progression documented	Earliest date of radiologic assessment showing new lesion or progression defined by increase in sum of measured lesions according to RECIST criteria	Progressed
No progression by the cut-off date	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started before documented progression	Date of last radiological assessment of measured lesions prior to the start of new anticancer treatment	Censored
Death before the first progression assessment or between adequate assessment visits	Date of Death	Progressed
Death or progression after two or more missesing visit	Date of last radiological assessment of measured lesions prior to missing visit	Censored

6.12.2.2. Objective Response Rate

The ORR is defined as the proportion of treated patients achieving a best response of PR or CR.

Phase 1b part

The ORR and CI will be calculated on the patients who are treated any study drugs.

Phase 2 part

For ORR, a CI of each arm will be calculated based on binominal distribution, and the difference of ORR between two arms and the CI will be estimated in FAS. The ORR will be compared between Arm A and Arm B using Fisher exact test.

6.12.2.3. Disease Control Rate

The DCR is defined as the proportion of treated patients achieving a best response of PR or CR or SD.

As for DCR, the same analysis as ones for ORR will be performed for Phase 1b part and Phase 2 part, respectively.

6.12.2.4. Time to Treatment Failure

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

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

6.12.3. Sensitivity Analyses

The sensitivity analyses for PFS, under the following conditions will be conducted:

Table 6.2. Sensitivity Analysis

Situation	Date of Event or Censoring	Outcome
With some post-baseline radiologic assessment but missing prior to lost to follow-up	Date of first missing radiographic assessment	Event
Starting new anticancer therapy prior to documented progression	Date of radiographic assessment with confirmed progression	Event

6.13. Post-discontinuation Therapy

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

6.14. Health Outcomes Analyses

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

- Patients with Baseline and Post-Baseline Data
- Patients with Only Baseline Data
- Patients with Only Post-Baseline Data
- Patients with no Baseline and Post-Baseline Data

6.14.1.1. Lung Cancer Symptom Scale

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

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

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

Analysis of each of the ASBI and total score will be conducted using Time to Worsening (TW) as measured from the date of randomization to the first date of a clinically meaningful worsening/change. For each patient who is not known to have had a worsening, or who is lost to follow-up, TW will be censored at the date of the patient's last LCSS assessment. The KM curves of TW for the index will be estimated using KM method and the HR and the CI will be estimated using an unstratified Cox regression model. A forest plot of the estimated HRs with 95% CIs will be provided.

6.14.1.2. EQ-5D: Health State Utilities

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

Descriptive statistics for the index and VAS will be calculated. Frequency distributions, including measures of central tendency and variability (for example, means, medians, and standard deviations) will be calculated for individual items and for the index score.

6.15. Biomarker Analyses

Descriptive statistics for EGFR protein expression will be summarized for the Phase 1b part and the Phase 2 part of the study. All the translational research data analyses evaluating the relationship between biomarkers and efficacy variables will be performed by the Oncology Tailored Therapeutics Biomarker Statistics group at Eli Lilly. These analyses are described in a separate translational research statistical analysis plan.

6.16. Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic assessments will be summarized in the pharmacokinetic analysis plan described in the protocol. Exploratory pharmacokinetic analyses will be described in a separate PK/PD analysis plan.

A listing of blood concentration of necitumumab, gemcitabine, its deaminated metabolite 2',2'-difluorodeoxyuridine (dFdU), and total and free platinum from cisplatin will be provided.

6.17. Safety Analyses

6.17.1. Extent of Exposure

Dosing data of combined therapy (any of the study drugs) will be summarized by treatment group to include duration of treatment (weeks), number of patients treated by cycle, number of cycles of treatment per patient received.

For each of the study drugs (necitumumab, gemcitabine and cisplatin), dosing data will be summarized by treatment group to include duration of treatment (weeks), number of patients treated by cycle, number of cycles of treatment per patient received, number of infusion, cumulative dose, dose intensity and relative intensity, and number and percentage of patients with any dose reduction (reduction to first or second dose level), treatment interruption, cycle start delay(4 - 7 days or >7 days), dose omission, and dose increase. The similar analysis will be performed for dosing data in each of combination therapy period and maintenance therapy period. The definition of combination/maintenance therapy period defined here will be applied for all analyses/summaries unless otherwise specified.

Cumulative dose, duration of therapy, dose intensity (DI), cycle start delay and number of planned dose reductions of necitumumab, gemcitabine and cisplatin are defined according to the following formulas:

- Expected weekly dose (EWD) = (total dose per cycle) / 3 weeks
  - Necitumumab: EWD (mg/week) = 1600 / 3 = 533.3
  - Gemcitabine: EWD (mg/m^2/week) for 1250 mg dose level is 2500/3 = 833.3
  - Cisplatin: EWD (mg/m^2/week) = 75 / 3 = 25
- Total dose per patient (TD) (mg) per cycle = total amount of drug the patient received during cycle.

Study Treatment	Period	Variables
Gemcitabine / Cisplatin	Combination therapy	**Cumulative dose (CD) (mg/m^2)** = $(TD_{Cycle\ 1}/BSA_{Cycle\ 1}) + (TD_{Cycle\ 2}/BSA_{Cycle\ 2}) + (TD_{Cycle\ 3}/BSA_{Cycle\ 3}) + (TD_{Cycle\ n}/BSA_{Cycle\ n})$, where $BSA_{Cycle\ X}$ is BSA prior to Cycle X and Cycle n is last cycle of gemcitabine/cisplatin dose. **Duration of therapy (day)** = Cycle n Day 1 + 21 – Cycle 1 Day 1
Necitumumab *	Entire (combination + maintenance)	**Cumulative dose (CD) (mg)** = $TD_{Cycle\ 1} + TD_{Cycle\ 2} + TD_{Cycle\ 3} + TD_{Cycle\ N}$ **Duration (day)** = Day 1 of last cycle + 21 – Cycle 1 Day 1
	Combination therapy	**Cumulative dose (CD) (mg)** = $TD_{Cycle\ 1} + TD_{Cycle\ 2} + TD_{Cycle\ 3} + TD_{Cycle\ n}$, where Cycle n is last cycle of gemcitabine/cisplatin dose. **Duration of therapy (day)** = Cycle n Day 1 of last cycle + 21 – Cycle 1 Day 1

	Maintenance therapy	<Only for patients who receive any dose of the maintenance therapy> **Cumulative dose (CD) (mg)** = $TD_{Cycle\ (n+1)} + TD_{Cycle\ (n+2)} + \ldots + TD_{Cycle\ N}$, where Cycle n is last cycle of gemcitabine/cisplatin dose. **Duration (day)** = Day 1 of last cycle in maintenance therapy period + 21 – Cycle (n+1) Day 1

- BSA (m^2) = $0.007184*Height^{0.725}*Weight^{0.425}$
- Dose intensity (Calculated weekly dose (CWD)) = CD / (Duration / 7))
- Relative Dose Intensity (%) = CWD/EWD*100%
- Cycle start delay (days): Start of cycle n is considered delayed if [Date of cycle (n) day 1 – date of cycle (n-1) day 1] ≥25 (i.e. 4 days delay). In case of no administration at cycle n-1, the start of cycle n will be compared to the start of the previous cycle with any administration (e.g. cycle n-2).
- Number of planned dose reductions = Total number of reduction steps comparing the intended dose level before each infusion (as entered in the eCRF) to the protocol planned dose level as referenced in below table.

Table 6.3. Dose Reductions for Necitumumab, Gemcitabine, and Cisplatin

Dose Level	Necitumumab	Gemcitabine		Cisplatin
Starting Dose	800 mg	1000 mg/m^2	1250 mg/m^2	75 mg/m^2
First Dose Reduction	600 mg	75% / 750 mg/m^2	75% / 950 mg/m^2	75% / 56 mg/m^2
Second Dose Reduction	400 mg	50% / 500 mg/m^2	50% / 625 mg/m^2	50% / 38 mg/m^2

6.17.2. Adverse Events

All adverse events which observed after the first dose of the study treatment and until the 30-day post-discontinuation follow-up period will be included in the summary tables. Adverse events will be summarized by MedDRA preferred term (PT), unless otherwise stated.

For causality of study treatment, the following status will be considered;

- regardless of causality
- related to any study drugs; necitumumab, gemcitabine or cisplatin
- related to necitumumab
- related to gemcitabine

Any adverse events reported in the study will be included in patient listings.

6.17.2.1. Dose Limiting Toxicity in Phase 1b Part

In Phase 1b Part, DLTs will be summarized by DLT criteria for all patients in DLT evaluation set. Patient listings will be produced.

6.17.2.2. Treatment-emergent Adverse Event

Treatment-emergent adverse events (TEAEs) are defined as adverse events that meet either of the following criteria:

- Onset date occurred any time during or after the administration of the first dose of study treatment or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment); or
- The event occurred prior to the date of first dose and worsened while on therapy or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment).

If an event occurred on the day of the first treatment and the event time is missing, the event is regarded to be occurred after the administration of study drug.

For the summary tables per MedDRA term, the MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each MedDRA LLT during screening will be used as baseline, and the maximum severity during the study treatment (including 30-day post-discontinuation follow-up period) will be included as post-baseline for the analysis.

TEAEs will be summarized with the incidence and percentage of patients with at least one occurrence of a PT by causality status for each of the whole treatment period, the combination therapy period and maintenance therapy period. For arm B, all TEAEs are assigned to the combination therapy period. For arm A, all TEAEs that occur within 30 days after the last dose of gemcitabine or cisplatin, are assigned to the combination therapy period; all TEAEs that occur later are assigned to the maintenance therapy period. The summaries including the incidence of MedDRA SOC and PT, and maximum grade will be provided.

6.17.3. Deaths, Other Serious Adverse Events, Adverse Events of Special Interest, Consolidated Treatment-Emergent Adverse Events, and Other Notable Adverse Events

An overall summary of adverse events will be provided by categorizing the following events; TEAE, TEAE at grade 3/4/5, serious adverse event (SAE), AE leading to discontinuation and death.

AEs leading to deaths, SAEs, AEs leading to study treatment discontinuation, AEs leading to delay/modification (dose delayed or treatment interrupted) of study treatment will be summarized for any events regardless of relation to study drugs. AEs leading to deaths will also be summarized for any events related to study drug (related to any study drugs, related to necitumumab, and related to gemcitabine).

6.17.3.1. Death

Deaths will be summarized by cause of death in the following group;

- All deaths reported during the study

- Deaths that occur after the administration of the first dose and within 30 days of last dose of study treatment

All deaths reported during the study will be listed by patient.

6.17.3.2. Serious Adverse Event

Treatment-emergent SAEs will be summarized with the incidence and percentage of patients with at least one occurrence of a PT by causality status (regardless of causality, related to any study drugs, related to necitumumab, and related to gemcitabine). The summaries including the incidence of MedDRA SOC and PT, and maximum grade will be provided.

All SAEs will be listed by patient.

6.17.3.3. Consolidated Treatment-Emergent Adverse Events

All consolidated TEAEs are compound level consolidated TEAEs. The process for identifying MedDRA PTs included in each category will be provided in a separate document. Categories of consolidated TEAEs may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be reported in the CSR.

All consolidated TEAEs will be summarized for any events regardless of relation to study drugs as well as events related to any study drugs by PT and maximum grade.

6.17.3.4. Adverse Events of Special Interest

AEs of special interest (AESIs) include arterial thromboembolic events (ATE), conjunctivitis, hypersensitivity/infusion related reaction (IRR), hypomagnesemia, interstitial lung disease (pneumonitis), skin reactions, and venous thromboembolic events (VTE).

All AESIs are compound level AESIs. The process for identifying MedDRA PTs included in each category will be provided in a separate document. Categories of AESI may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be reported in the CSR.

All AESIs will be summarized for each of the whole treatment period and combination therapy period. The summaries including the incidence of any events regardless of relation to study drugs as well as events related to any study drugs by PT will be provided. As for grade ≥ 3 AESIs, the same analysis will be performed.

The following items also will be summarized for all AESIs except for IRR (ATE, conjunctivitis, hypomagnesemia, interstitial lung disease (pneumonitis), skin reactions, VTE), Rash of consolidated TEAE, and five PTs (“dry skin”, “pruritus”, “paronychia”, “dermatitis acneiform”, and “acne”);

- time to first occurrence: (the first occurrence date) – (Cycle 1 Day 1)
- the incidence and percentage of patients with multiple events
- duration: (the date of recovered/resolved) – (start date of the event),

  applicable only for events which were recovered/resolved

- outcome

As for grade ≥3 AESIs, the same analysis will be performed for the events whose grade is 3 or above. The duration is defined as the time from the start date of grade is 3 or above to the end date of the TEAE which grade is 3 (i.e, until the TEAE is recovered to grade < 3).

The frequency of first occurrence with grade by cycle (Cycle 1, Cycle 2, Cycle 3, Cycle 4 or more) for IRR will be shown by bar chart.

6.17.3.5. Other Notable Adverse Events

The following events will be summarized by maximum grade and listed by patient.

- AEs leading to discontinuation of any study drugs
- AEs leading to discontinuation of necitumumab
- AEs leading to discontinuation of gemcitabine
- AEs leading to discontinuation of any chemotherapy drugs
- AEs leading to delay/modification of any study drugs
- AEs leading to delay/modification of necitumumab
- AEs leading to delay/modification of gemcitabine
- AEs leading to delay/modification of any chemotherapy drugs

They may be modified as the understanding of the safety profile of the investigational drug increases, and final list of the events for each category will be reported in the study report.

6.17.4. Clinical Laboratory Evaluation

Abnormal values will be graded according to NCI-CTCAE version 4.0.

Shift table of maximum grade for the measurements after the first dose of the study treatment up to the 30-day safety follow-up visit versus baseline grade will be produced by the items, including the total for maximum grade 3 and 4.

Box whisker plots will be provided for each day 1 of cycle up to 12 cycles for phase 1b pert and Arm A of phase 2 part and 4 cycles for Arm B of phase 2 pert, and follow-up visit, where the time point of day 1 of each cycle will be derived by last test value within 3 days prior to day 1 dose of any study drug, and follow-up visit will be derived by last test value at or after treatment discontinuation.

6.17.5. Vital Signs and Other Physical Findings

Vital sign measurements will be summarized at scheduled time point (pre- and post- infusion of necitumumab and chemotherapy, follow-up visit) using descriptive statistics and the frequency and percentage of the patients with each category, where follow-up visit will be derived by last test value at or after treatment discontinuation.

- Temperature (ºC); < 36, 36- <38.5, >=38.5.

- Pulse rate (bpm); <60, 60- <120, >=120.
- Respiration rate (/min); <20, 20- <30, >=30.
- Systolic blood pressure (mmHg); <140, 140- <160, >=160.
- Diastolic blood pressure (mmHg); <90, 90- <100, >=100.

Vital sign data will be listed by patient.

Weight and ECOG PS will also be listed.

6.17.6. Electrocardiograms

In Phase 1b part, QT analyses will be performed with Bazett and Fridericia correction (QTcB and QTcF, respectively). The number of patients with post-baseline measurements which fulfill the following criteria will be calculated by cohort. All measurements of QTc measured after the first dose of the study treatment will be used.

- QTc values; >450 <=480, >480 <=500, and >500 msec
- The changes from baseline in QTc; >30 <=60 and >60 msec

QTcF based on each read is calculated as follows:

- $QTcF = QT / RR^{1/3}$

  where RR (msec) = 60000 (msec) / Heart Rate.

In Phase 2 part, the number of patients with assessment results of abnormal at post-baseline will be calculated.

ECG data will be listed by patient.

6.17.7. Immunogenicity of Necitumumab

For patients who have received at least one dose of necitumumab, the number of patients having antibody of necitumumab will be calculated for each time point. The number of patients with antibody of necitumumab at post-baseline out of the patients with no anti-necitumumab antibody at baseline might be calculated if appropriate.

Immunogenicity data will be listed by patient.

6.18. Subgroup Analyses

For OS, PFS and ORR, treatment effect will be estimated for each of the subgroups for the following factors:

- ECOG PS (0 vs. 1)
- age (< 65 vs. ≥ 65 years)
- age (< 70 vs. ≥ 70 years)

A forest plot of the estimated HRs with 95% CIs will be provided.

Adverse Events will also be summarized for each of the following subgroups:

- age (< 65 vs. ≥ 65 years)
- age (< 70 vs. ≥ 70 years)
- gender (male vs. female)
- ECOG PS (0 vs. 1)

6.19. Interim Analyses and Data Monitoring

6.19.1. Phase 1b Part

In Phase 1b part, the interim analysis will be performed after completing DLT evaluation period, and patient characteristics, clinical laboratory values, DLTs, and AEs occurring in Cycle 1 might be summarized by cohort.

6.19.2. Interim Analysis for Data Monitoring Committee

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

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

The IDMC will review the following data per treatment arm at closed session. A complete description of data handling rules and planned statistical analyses for IDMC is detailed in a separate document, IDMC analysis plan.

- Disposition
- Demographic and baseline characteristics
- Study drug exposure
- Treatment emergent adverse events
- Deaths
- Serious adverse events (including SAE reports if needed)
- Concomitant medication
- Historical/pre-existing conditions
- Laboratory parameters
- Vital sign
- Transfusion and G-CSF (granulocyte-colony stimulating factor)

6.19.3. Other Possible Interim Analysis

The Sponsor might consider the interim analysis to discuss complete clinical data package with Pharmaceutical and Medical Devices Agency (PMDA), considering the results in the global Phase 3 study (Study CP11-0806) which will be available during this study.

In this case, the safety and efficacy data collected at the time will be analyzed.

6.20. Data of Extension Phase

During the study extension phase, the following information will be collected. The listings for the data in the extension phase will be provided after all patients discontinue study treatment of the extension phase.

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

7. Unblinding Plan

The Phase 2 part is randomized, open-label design. Each patient will be aware of his or her own assigned treatment group of the Phase 2 part. At each investigative site, all staff involved in treating and caring for study patients will have full knowledge of treatment assignments for the patients under their care. Data will not be shared between investigators before completion of the study, maintaining the blind on aggregated data across sites.

In this study, treatment data will be included in the data capture system. To minimize the potential biases that could arise as a result of the study team knowledge of the summary data separated into treatment groups of the Phase 2 part, the study team (including the study statistician) will not be allowed to access the datasets and the test outputs until the database lock for the primary endpoint, OS. The stat analyst at the sponsor and programming staffs at the vendor will have access to unblinded data and the test outputs. When the study team reviews the test outputs during the study, the summary data for the Phase 2 part will be calculated using the treatment assignment scrambled. At the final review of test outputs just before the database lock, the summary data based on actual treatment assignment will be provided, except the efficacy data such as OS.

8. References

Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095-1108.

Ikeda S, Ikegami N. Preference-based measure (focus on EQ-5D). Handbook of QOL evaluation [in Japanese]. Tokyo: *Igaku-Shoin*; 2002:45–49

Leo Document ID = b8b74b18-ffec-46e2-b016-392d088496eb

Approver: PPD
Approval Date & Time: 07-Sep-2017 00:58:30 GMT
Signature meaning: Approved