Statistical Analysis Plan I4X-MC-JFCQ (V3)

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

NCT02451930

Approval Date: 14-Dec-2016

1. Statistical Analysis Plan: I4X-MC-JFCQ A Single-Arm, 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 (NSCLC)

Necitumumab (LY3012211), Pembrolizumab (MK3475)

This is a single-arm Phase 1b study with an expansion cohort in patients with Stage IV non-small cell lung cancer (NSCLC). The study consists of 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 for Part B (expansion cohort) and Part C (Japanese patients). 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.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Statistical Analysis Plan Version 1.0 electronically signed and approved by Lilly: 24 August 2015.
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 05 May 2016
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 14-Dec-2016 GMT

2. Table of Contents

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3. Revision History

Changes from Statistical Analysis Plan Version 1.0

1. Part C has been added according to the protocol JFCQ(a)
2. The timing of Primary analysis and final analysis for Parts A and B have been updated according to the protocol JFCQ(a)
3. Events of Clinical Interest (ECIs) have been updated according to the protocol JFCQ(a)
4. Interim efficacy analyses have been added according to the protocol JFCQ(a)
5. Various sections modified according to the new TAFFY standard TFL shells

Changes from Statistical Analysis Plan Version 2.0

1. The final analysis has been removed per protocol update
2. Interim efficacy analyses for squamous patients has been added

4. Study Objectives

4.1. 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 dose-limiting toxicity (DLT) during 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 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.

4.2. Secondary Objectives

The secondary objectives of the study are as follows:

Part A and 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 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 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), progression-free survival (PFS) by RECIST 1.1, and overall survival (OS)
- determining PK of necitumumab in the presence of pembrolizumab
- determining the immunogenicity of necitumumab in the presence of pembrolizumab

4.3. Exploratory Objectives

- to investigate biomarkers, including pharmacodynamics markers, related to necitumumab, pembrolizumab, EGFR, immune cells/function, and disease state, 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])

5. A Priori Statistical Methods

5.1. Determination of Sample Size

A total of approximately 78 patients for either Part A, Part B or 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. 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.

5.2. General Considerations

In Part A, data will be summarized by assigned necitumumab + pembrolizumab dose levels unless stated otherwise. Patients with squamous and nonsquamous NSCLC from Part A who received the recommended Phase II dose will also be analyzed together with Part B. They are:

- NSCLC squamous at the recommended Phase 2 dose: Part A patients with squamous NSCLC and treated at the recommended Phase 2 doses of necitumumab and pembrolizumab + Part B patients with squamous NSCLC
- NSCLC nonsquamous at the recommended Phase 2 dose: Part A patients with nonsquamous NSCLC and treated at the recommended Phase 2 doses of necitumumab and pembrolizumab + Part B patients with nonsquamous NSCLC

Part C patients will be summarized separately.

The following populations will be defined for this study:

- **All entered population:** anyone who signed the informed consent will be included in this population.
- **Safety population:** all patients who have received any amount of study drug [necitumumab, and/or pembrolizumab]

- **Evaluable population:** To be evaluable for the 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.

  An evaluable patient for Part B will include any patient enrolled in Part A with squamous and nonsquamous NSCLC and treated at the recommended Phase 2 doses of necitumumab and pembrolizumab, and patients who entered strictly to Part B.

Unless otherwise specified, for continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequency and percentages.

- **Age (years):** (Informed Consent Date - Date of Birth + 1)/365.25, if only year of birth is collected, see Section 5.3 for date imputation.
- **Missing Data:** All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or "carried forward."
- **Baseline Measurement:** Unless otherwise specified, the last non-missing measurement prior to the first dose of study drug will serve as the baseline measurement.
- **Study Day:** Study day is calculated as assessment date – first dose date + 1 day if the assessment is done on or after the first dose day. If the assessment is done prior to the first dose day, study day will be calculated as assessment date – first dose date. Date of first dose is defined as study day 1.
- **Duration:** Duration is calculated as:

  Duration (days): (End Date – Start Date + 1)

  Duration (weeks): (End Date – Start Date + 1)/7

  Duration (months): (End Date – Start Date + 1)/30.4375 (Days in months = (1/12)*average number of days in a year.)

  Duration (years): (End Date – Start Date + 1)/365.25 (Average days in a year = 365.25, reflecting the Julian Year of three years with 365 days each and one leap year of 366 days.)

- **Time-to-event:** The event or censoring time (days) is calculated as:
  Date of event/censoring – Date of first dose of study drug + 1

5.3. Handling of Dropouts or Missing Data

Dates missing the day or both the day and month of the year will adhere to the following conventions:

- The missing day of onset of an adverse event (AE) or start date of a concurrent therapy will be set to:

  - first day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment
  - the day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment
  - the date of informed consent, if the onset yyyy-mm is before the yyyy-mm of the first treatment.

- The missing day of resolution of an AE or end date of a concurrent therapy will be set to:
  - the last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.
- If the onset date of an AE or start date of a concurrent therapy is missing both the day and month, the onset date will be set to:
  - January 1 of the year of onset, if the onset year is after the year of the first study treatment
  - the date of the first treatment, if the onset year is the same as the year of the first study treatment
  - the date of informed consent, if the onset year is before the year of the first treatment
- If the resolution date of an AE or end date of a concurrent therapy is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date
- If date is completely missing, then no imputation will be done and the event will be considered as treatment emergent unless the end date rules out the possibility.

For initial diagnosis date, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, “Jul 1” will be used to replace the missing information.

5.4. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients never treated, still under treatment (that is, have not completed the End of Treatment [EOT] visit) at data cut-off date will be summarized. Patients discontinued from treatment will be presented by reason.

The number and percentage of patients with any important protocol violation will be summarized overall and by type of violation. The pre-defined important protocol violations are listed in below; in addition, any other protocol violations reviewed by CRP and deemed to be important protocol violations will be included in the summary.

- Patient failed to meet study inclusion/exclusion criteria
- Study treatment continued after progressive disease (PD) occurred
- Patient received concurrent prohibited therapy (Listing to identify Anatomical Therapeutic Chemical (ATC) codes is to be provided for medical review) while receiving study treatment.
- Necitumumab continued after Grade 3-4 infusion reaction occurred (as defined by dictionary term "Infusion related reaction")
- Post-baseline tumor assessments use different methods than baseline assessment
- Actual doses of study drug was more than 10% greater than protocol defined dose (800 mg for necitumumab, 200mg for Pembrolizumab), at any of dose administration
- Patient started next cycle less than 18 days later after Day 1 of the most recent treatment cycle
- Patient received more than 2 dose reductions of necitumumab

5.5. Patient Characteristics

5.5.1. Demographics and Baseline Characteristics

- Age (years)
- Age group (<65, ≥65-<70, ≥70 years)
- Race (In case of multiple races checked in the case report form [CRF] [for example, "White" and "Asian"], patients will be counted only once in the summary and will be presented as combined race [for example, "White/Asian"])
- Gender
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Tobacco consumption habits

Demographics and baseline characteristics will be summarized.

5.5.2. Disease Characteristics (Pre-treatment)

- Squamous or nonsquamous (including Adenocarcinoma lung or Large cell lung cancer) or Non-small cell lung cancer NOS
- Initial pathological diagnosis basis of determination: Histopathological or Cytological
- Histopathological Diagnosis Grade (at Initial Diagnosis or at Study Entry)

Prior therapies, including systemic therapy, radiotherapy and surgeries will be summarized by the number of patients with at least one of each type of treatment, as well by reason for regimen (e.g., palliative, curative, etc.). Additionally, the number of regimens of prior systemic therapy, and (where available) the reason for prior regimens will be summarized.

5.5.3. Medical History

Pre-existing conditions and medical history will be summarized by the number and percentage of patients reporting at least one diagnosis and by Medical Dictionary of Regulatory Activities (MedDRA) preferred term (PT).

5.5.4. Efficacy Analyses

The efficacy analyses will be performed for evaluable population.

5.5.5. Primary Efficacy Endpoint

The primary endpoint for Part B is ORR. The denominator of ORR includes all evaluable patients, and the numerator includes those patients counted in the denominator with a best overall tumor response of partial or complete response (PR or CR) per RECIST 1.1. Confirmation of objective response is required for this trial. To be assigned a best overall response status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In this circumstance, the best overall response can be interpreted as in Table JFCQ.5.1. In the case of stable disease (SD), measurements must have met the SD criteria at least once after first dose at a minimum interval of 6 weeks. Patients' responses after objective progression or start of new anticancer therapy are excluded from the determination of best response.

The primary analysis for ORR is a one-sided exact binomial test with the null hypothesis of 20% at a 10% significance level. For Part B evaluable patients, the p-value from this test will be presented. The ORR and its 95% confidence intervals (CIs) will be estimated.

Table JFCQ.5.1. Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time point	Overall Response Subsequent Time point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
NE	NE	NE

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

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

5.5.6. Secondary Efficacy Endpoints

For all time-to-event variables (OS, PFS and DOR), the Kaplan-Meier product limit method will be used to estimate the survival curve as well as survival rates at various time points (for example, 6-month and 1-year for OS, 3-month and 6-month for PFS). A 2-sided, 95% CI for medians will be computed by the Brookmeyer and Crowley method.

5.5.6.1. Overall Survival (OS)

Overall survival duration is measured from the date of first dose of study drug (necitumumab and/or pembrolizumab) to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cut-off date (contacts considered in the determination of last contact date include adverse event date, lesion assessment date, visit date, and last known alive date).

An exploratory analysis on the potential prognostic factors may be performed. The following potential prognostic factors may be considered:

1. histology (squamous versus nonsquamous)
2. age (<70 versus >=70)

3. number of sites of metastases (>2 versus <=2)
4. ECOG PS (0 versus >0)
5. gender (females versus males)
6. baseline sum of target lesions (as a continuous variable)
7. baseline hemoglobin (as a continuous variable)
8. baseline leukocytes (as a continuous variable)
9. baseline platelets (as a continuous variable)

Each factor is assessed through separate univariate Cox proportional hazard models, and then all factors are incorporated into the multivariate Cox proportional hazard model. This exploratory analysis may be performed on OS and PFS.

5.5.6.2. Progression-Free Survival (PFS)

Progression-free survival is defined as the time from the date of first dose of study drug until first observation of objective (radiographically documented) PD as defined by RECIST version 1.1 or death from any cause, whichever comes first. The censoring is taken in the following order

- If a patient does not have an adequate baseline radiological tumor assessment, then the PFS time will be censored at the date of first study drug, 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 adequate objective progression-free disease assessment date.

Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD or PD. If a tumor assessment was done on multiple days, the earliest date for that visit will be used if overall response is PD, and the last date will be used otherwise (censor).

Progression-free survival sensitivity analysis will be performed. The censoring rules for PFS sensitivity analysis are listed in Table JFCQ.5.2.

Table JFCQ.5.2. Rules for Determining Date of Progression or Censor for PFS Sensitivity Analysis

Situation	Event / Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of first dose (whichever is later)
unless		
No baseline radiological tumor assessment available	Censored	Date of first dose
No adequate post baseline radiological tumor assessment available and death reported after 2 scan intervals following first dose	Censored	Date of first dose
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of first dose (whichever is later)
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or first dose (whichever is later)	Censored	Date of last adequate radiological assessment or date of first dose (whichever is later)

Notes:
(1) Symptomatic deteriorations (i.e., symptomatic progressions, which are not radiologically confirmed) will not be considered as progressions
(2) 2 scan intervals = 90 days# for this trial
#: 2*(6 weeks+5 days window)

5.5.6.3. Disease Control Rate (DCR)

Disease control rate (DCR) will be analyzed, with the same denominator as defined in ORR. Among patients counted in the denominator, the numerator counts those with a confirmed best tumor response of SD, PR, or CR per RECIST 1.1. The DCR and its exact 95% CI will be estimated.

5.5.6.4. Duration of Response (DOR)

The DOR is defined only for responders (patients with a confirmed CR or PR). 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.

5.5.6.5. Exploratory Outcome and Methodology Based on irRECIST

The irORR, irDCR, irDOR, and irPFS assessment based on adapted RECIST 1.1 (irRECIST) will be used for exploratory analysis to account for the unique tumor response characteristics

seen with treatment of pembrolizumab. irRECIST will be applied as detailed in the study protocol, and the resulting data will be included in the clinical database.

Objective response rate (irORR) is defined as the proportion of evaluable patients achieving a best overall response of PR or CR per irRECIST. Particularly, the best overall response by irRECIST is closely related to confirmed response by RECIST. IrORR further captures responses after unconfirmed PD and it does not require confirmation. In addition, patients' responses after start of new anticancer therapy are excluded from the determination of best response. For example:

- If the best response by RECIST is CR, then the best response by irRECIST is CR.
- If the best response by RECIST is PR, SD, or PD, the best response by irRECIST is the best response over the initial assessment (prior to PD by RECIST) and the confirmation stage.

Overall, the best response by irRECIST should be the same or better than the best response by RECIST criteria.

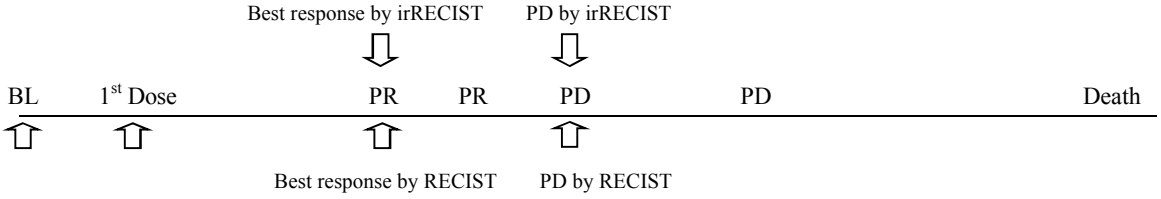
IrPFS: The date from the treatment started date to the time of PD assessed by irRECIST or death from any cause, whichever comes first.

- If the initial PD is confirmed, then the date of immune-related (ir)PD is the initial PD date by RECIST.
- If the initial PD is unconfirmed, then the date of irPD is the date of second non-consecutive PD.

Duration of response by irRECIST: The duration of response is defined from the date of first documented irCR or irPR (responder) to the date of irPD or the date of death due to any cause, whichever is earlier.

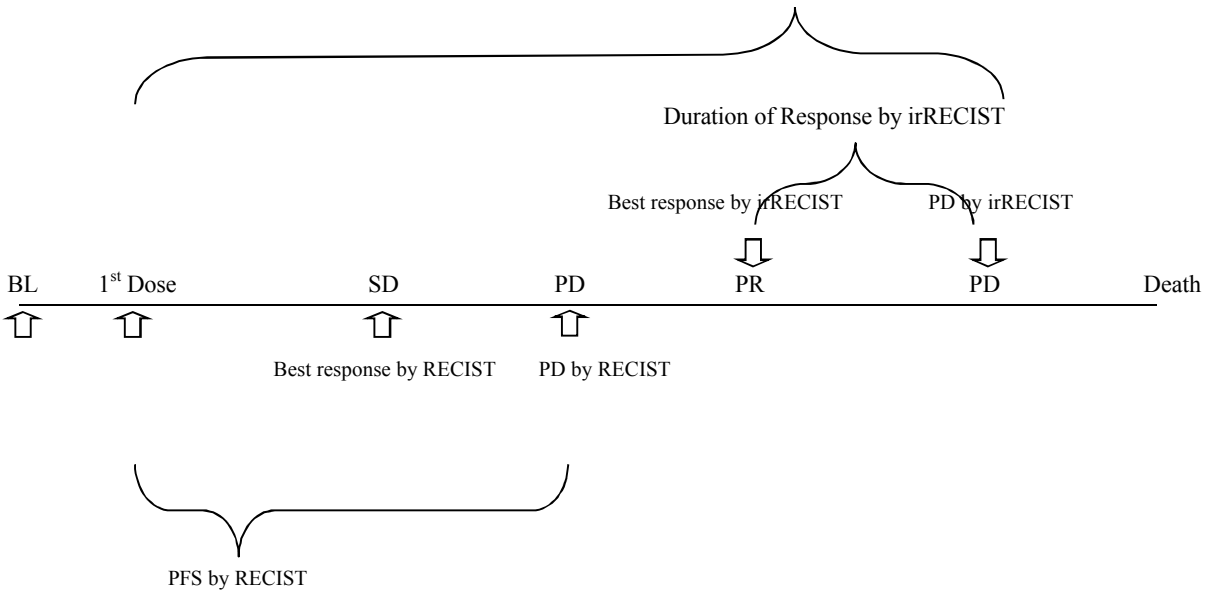
Graphic Example:

Scenario 1: The initial PD is confirmed at the next scan (consecutive PD). The efficacy variables by irRECIST and RECIST are the same.



Scenario 2: The initial PD is not confirmed at the next scan (non-consecutive PD). The efficacy variables by irRECIST and RECIST may be different.

PFS by irRECIST



5.6. Analysis of Safety Data

5.6.1. Extent of Exposure

5.6.1.1. Necitumumab

- Number of cycles received by patient
- Number of patients treated by cycle
- Duration of treatment (in weeks) = [(Date of last dose – date of first dose)+14]÷7
- Cumulative dose (mg) = Sum of all doses administered
- Dose intensity (mg/week) = (Cumulative dose) ÷ (Duration of treatment)
- Relative dose intensity (%) = Dose intensity (mg/week) ÷ (600 or 800 mg *2 / 3 weeks)
- Number of dose reductions = Total number of reduction steps comparing the planned dose level before each infusion (as entered in the CRF) to the protocol planned dose level as referenced in the table in below.
- Dose delay as recorded on the CRF.

Table JFCQ.5.3. Dose Reductions for Necitumumab

Dose Level	Necitumumab
Starting Dose	800 mg
First Dose Reduction	600 mg
Second Dose Reduction	400 mg

Note: Actual dose levels entered in the CRF will be rounded to the nearest dose level listed in this table (e.g., any necitumumab dose level ≥700 mg will be rounded to 800 mg for the purpose of the dose reduction calculation; any necitumumab dose level <400 mg will be rounded to 400 mg).

5.6.1.2. Pembrolizumab

- Number of cycles received by patient
- Number of patients treated by cycle
- Duration of treatment (in weeks) = [(Date of last dose – date of first dose)+21]÷7
- Cumulative dose (mg) = Sum of all doses administered
- Dose intensity (mg/week) = (Cumulative dose) ÷ (Duration of treatment)
- Relative dose intensity (%) = Dose intensity (mg/week) ÷ (200 mg / 3 weeks)
- Dose delay as recorded on the CRF.

The relative dose intensity will be additionally presented categorized (that is, number and percentage of patients with relative dose intensity of <60%, ≥60-<80%, ≥80-<90%, ≥90-<110%, ≥110%).

Moreover, the number and percentage of patients with any dose delay, with any dose reduction (reduction to first or second dose level) will be presented as well as the number (%) of patients with infusion interrupted.

5.6.2. Adverse Events

Adverse events will be summarized by MedDRA™ System Organ Class (SOC) and preferred term (PT), classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a PT will be included, according to the most severe National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 grade.

If more than one AE is recorded for a patient within any PT the patient will only be counted once on the most severe grade. Missing classifications concerning study treatment relationship will be considered as related to study treatment.

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 serious AEs (SAEs) reported beyond 30 days after the last dose of study treatment.

5.6.2.1. Overall Summary of Adverse Events

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages:

- patients with at least one TEAE, SAE,
- deaths
- subjects who discontinued study treatment due to AE
- TEAE related to study treatment

5.6.2.2. Treatment-Emergent Adverse Events (TEAEs)

The following summaries of TEAEs will be provided (*repeat for events deemed by the investigator to be possibly related to study medication):

- by PT*
- by SOC and PT, and by maximum CTCAE grade *

A patient listing of all AEs will be provided.

5.6.2.3. Adverse Event of Special Interest

Adverse events of special interest (AESI) include events related to arterial thromboembolism (ATE), venous thromboembolism (VTE), skin reactions (rash will be identified separately), conjunctivitis, hypersensitivity/infusion related reaction (IRR), hypomagnesemia, and interstitial lung disease (pneumonitis). Each AESI is defined by a set of MedDRA PTs and the PT lists were identified by the medical and safety physician for the compound based on the (blinded) review of all PTs (without looking at the number of patients/events for that PT) reported. The final list of AESI categories will be reported in the CSR.

The incidence of treatment-emergent AESI will be summarized by AESI category and PT.

5.6.2.3.1. Thromboembolic Adverse Events

Thromboembolic AEs according to the AESI criteria outlined above are classified as arterial thromboembolic AE and venous thromboembolic AE. Treatment emergent thromboembolic SAEs will be tabulated by overall, arterial thromboembolic AE and venous thromboembolic AE. A listing of all treatment emergent thromboembolic adverse events will be generated.

In order to further assess the thromboembolic adverse events observed in the study, an additional analysis examining possible risk factors for such events will be performed. Identification of these risk factors will be based on a literature search (Scappaticci et al. 2007; Khorana et al. 2008; Choueiri et al. 2010; Hurwitz et al. 2011; Petrelli et al. 2012; Lyman et al. 2013).

5.6.2.4. Events of Clinical Interest (ECIs) - 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.

The treatment emergent ECIs will be summarized and listed separately.

5.6.2.5. Consolidated Adverse Event

Consolidated AE categories include Anemia, Fatigue, Hypercalcaemia, Hyperkalaemia, Hypermagnesaemia, Hypernatraemia, Hyperphosphataemia, Hypocalcaemia, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Hypophosphataemia, Leukopenia, Neutropenia and Thrombocytopenia. Each category contains PTs identified as clinically identical or synonymous and PT lists were identified by the medical and safety physician for the compound based on the (blinded) review of all PTs (without looking at the number of patients/events for that PT) reported. The final list of consolidated AE categories will be reported in the CSR.

The incidence of treatment-emergent consolidated AEs will be summarized by consolidated category and PT.

5.6.3. Deaths, SAEs, and Other Significant AEs

Reasons for deaths (study disease, AE [any AE, study treatment related AE], etc.) will be summarized separately for 1) all deaths, 2) death on therapy, 3) deaths within 30 days discontinuation of study therapy, 4) deaths on therapy or within 30 days of discontinuation of study therapy and 5) deaths after 30 days of discontinuation of study therapy.

Serious adverse events will be summarized by SOC and PT, by maximum CTCAE grade and by SOC and PT, and repeated for events deemed by the investigator to be possibly related to study medication. A listing of SAEs will be produced.

In addition, the following analyses will be performed:

- Listing of AEs leading to death
- Listing of AEs leading to study treatment discontinuations
- AEs leading to study treatment dose modification by SOC and PT

Dose-limiting toxicity (DLT) will be listed for Part A only.

5.6.4. Weight, Performance Status, and Vital Signs

5.6.4.1. Weight and ECOG Performance Status

Weight observed value and change from baseline will be presented by scheduled visit.

The ECOG Performance Status results will be summarized using frequency distributions for each scheduled visit, including also the best post-baseline value.

5.6.4.2. Vital Signs

Vital sign observed value and change from baseline will be presented by scheduled visit.

5.6.5. Laboratory Evaluations

Laboratory results will be converted to standard (SI) units, as referenced in the NCI-CTCAE v.4.0. Laboratory results not corresponding to a NCI-CTCAE v.4.0 term will not be graded.

Shift tables showing the change from baseline to the worst CTCAE toxicity grade (first dose up to 30 days after the last dose of study treatment) will be presented.

Laboratory results will also be presented in a data listing to include a flag for values outside of the laboratory normal range. A listing of patients who had laboratory toxicities of CTCAE grade 3 or greater will be presented.

5.6.6. Electrocardiogram

Electrocardiogram (ECG) will be listed.

5.7. Other Analyses

5.7.1. Pharmacokinetic (PK) Analyses

Pharmacokinetic (PK) analyses will be performed by Lilly PK and not included in this statistical analysis plan.

5.7.2. 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.

5.7.3. Concomitant Therapy and Post-Study Anti-Cancer Treatments

Prior and Concomitant therapy will be summarized separately by frequency tables.

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

Transfusions during the study treatment or within 30 days of the last dose of study drug will be summarized.

5.8. Hospitalizations

Patient hospitalizations during the study treatment or within 30 days of the last dose of study drug will be summarized.

5.9. 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.

In addition, exploratory subgroup analyses by tumor PD-1 expression at baseline may be performed.

Individual changes in the tumor burden over time may be presented graphically (for example, Waterfall plots and spider plots) within selected subgroups.

5.10. Biomarker Analyses

Plans for the exploratory biomarker analyses will be described separately.

5.11. 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 safety interim analysis.

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

Interim safety analysis will be performed by Spotfire. Patient disposition, AE, lab and other data if needed will be reviewed at the interim.

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. The interim efficacy analysis for nonsquamous patients may be performed at approx. 4 months (to evaluate the preliminary ORR result) and approx. 6 months (to evaluate the PFS and ORR) after at least 27 nonsquamous patients (in cohort 2 and part B) have been enrolled.

An interim efficacy analysis for the squamous patients may be performed to evaluate the preliminary results for ORR approximately 4 months after the last squamous patient in Part B has been enrolled.

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Leo Document ID = 8fcc202d-7c25-4852-904a-2ef9cf580b8e

Approver: PPD
Approval Date & Time: 14-Dec-2016 14:42:24 GMT
Signature meaning: Approved