Statistical Analysis Plan Version 1 I4X-MC-JFCP

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

NCT02392507

Approval Date: 14-Aug-2015

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

Necitumumab (LY3012211; IMC-11F8)

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

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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3. Revision History

Not applicable.

4. Study Objectives

4.1. Primary Objective

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

4.2. Secondary Objectives

The secondary objectives of this study are:

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

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

5. A Priori Statistical Methods

5.1. Determination of Sample Size

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

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

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

5.2. General Considerations

The following populations will be defined for this study:

- **All enrolled population:** all patients who signed the informed consent will be included in this population.
- **Safety population:** all patients who have received any amount of study drug (necitumumab, *nab*-paclitaxel, and/or carboplatin)
- **Qualified population:** all enrolled patients who have received any amount of study drug (necitumumab, *nab*-paclitaxel, and/or carboplatin) and have had a complete radiographic assessment at baseline. A patient who is alive for at least 8 weeks after first dose and has had no postbaseline radiographic assessment will be disqualified.

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 3 years with 365 days each and 1 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; or
  - 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:
  - 01 January 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; or

  - 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:
  - 31 December of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.
- If the 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 all enrolled population, qualified population, and safety population.

Moreover, the number and percentage of patients never treated or 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 predefined important protocol violations are listed in below; in addition, any other protocol violations reviewed by the clinical research physician 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 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").
- Postbaseline tumor assessments use different methods than baseline assessment.
- Actual dose of study drug was more than 10% greater than protocol-defined dose (800 mg for necitumumab, 100 mg/m^2 for *nab*-paclitaxel) or more than 900 mg for carboplatin, at any of dose administration.
- Dose of *nab*-paclitaxel or carboplatin is escalated after previous dose reduction.

- Carboplatin continued after more than 4 cycles.
- 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 within any of necitumumab or *nab*-paclitaxel or carboplatin.

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 electronic case report form [eCRF] [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
- Eastern Cooperative Oncology Group (ECOG) performance status (PS)

Demographics and baseline characteristics will be summarized.

5.5.2. Disease Characteristics (Pre-treatment)

- Initial pathological diagnosis basis of determination: Histopathological or Cytological
- Duration of disease (defined as time from diagnosis date to first dose of study drug)
- Current disease stage

Previous anticancer treatment will be presented by type (radiotherapy, systemic therapy, or surgery).

5.5.3. Medical History

Preexisting conditions and medical history will be summarized by the number and percentage of patients reporting at least 1 diagnosis and by Medical Dictionary for Regulatory Activities (MedDRA™) preferred term (PT).

5.6. Efficacy Analyses

Efficacy analyses for ORR and DCR will be performed for qualified population; all other efficacy analyses (OS and PFS) will be analyzed for all treated patients (safety population).

5.6.1. Primary Efficacy Endpoint

The primary endpoint is ORR. The denominator of ORR includes all qualified 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 Response Evaluation Criteria in Solid Tumors (RECIST) Version 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 JFCP.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 ORR and its exact 95% CIs will be estimated.

Table JFCP.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.

5.6.2. Secondary Efficacy Endpoints

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

5.6.2.1. Overall Survival (OS)

Overall survival (OS) duration is measured from the date of first dose of study drug (necitumumab, nab®-paclitaxel and/or carboplatin) 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 cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date). Overall survival will be evaluated primarily in terms of the estimated 6-month survival.

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. sex (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 model, and then all factors are incorporated into the multivariate Cox proportional hazard model. This exploratory analysis may be performed on OS and PFS.

5.6.2.2. Progression-Free Survival (PFS)

Progression-free survival (PFS) 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 JFCP.5.2.

Table JFCP.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)

Abbreviations: PD = progressive disease; PFS = progression-free survival.

Notes:

(1) Symptomatic deteriorations (that is, 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+3 days window).

5.6.2.3. 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.

5.7. Analysis of Safety Data

5.7.1. Extent of Exposure

The body weight to be used for calculating each dose of nab-paclitaxel or carboplatin medications will be the last available measure of the patient on or prior to the first day of dosing, unless there is a weight loss ≥10% from baseline in which case dose will be adjusted. Calculated dose intensity will be rounded to the nearest integer. For the calculation of dose intensity, body surface area (BSA) at baseline will be used.

5.7.1.1. Necitumumab

- Number of infusions
- 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) ÷ (800 mg *2 / 3 weeks)
- Relative dose intensity (%) by cycle, for Cycles 1 and 2 (for Cycle 2 relative dose intensity, only patients who entered Cycle 2 will be considered)
- Number of dose reductions = Total number of reduction steps comparing the planned dose level before each infusion (as entered in the eCRF) to the protocol planned dose level as referenced in Table JFCP.5.3
- Dose delay as recorded on the eCRF

In addition to the overall necitumumab exposure summary, a separate exposure of necitumumab in the maintenance period will be summarized. Dose in the maintenance period is defined as any dose administered at the cycles after the cycle where last dose of carboplatin was administered. For example, if the last dose of carboplatin was administered at Cycle 4, then Cycle 5 and beyond is the maintenance period.

5.7.1.2. *Nab*-Paclitaxel

- Number of infusions
- 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)+7]÷7 if last dose is in the chemotherapy period
  = [(Date of last dose – date of first dose)+14]÷7 if last dose is in the maintenance period
- Cumulative dose (mg) = Sum of all doses administered
- Dose intensity (mg/m^2/week) in the chemotherapy period = (Cumulative dose in the chemotherapy period / Baseline BSA) ÷ (Duration of treatment in the chemotherapy period)
- Dose intensity (mg/m^2/week) in the maintenance period = (Cumulative dose in the maintenance period / Baseline BSA) ÷ (Duration of treatment in the maintenance period)
- Relative dose intensity in the chemotherapy period (%) = Dose intensity in the chemotherapy period (mg/m^2/week) ÷ (100 mg /m^2 / week)

- Relative dose intensity in the maintenance period (%) = Dose intensity in the maintenance period (mg/m^2/week) ÷ (100*2 / 3 mg /m^2 / week)
- Relative dose intensity (%) by cycle, for Cycles 1 and 2 (for Cycle 2 relative dose intensity, only patients who entered Cycle 2 will be considered)
- Number of 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 Table JFCP.5.3
- Dose delay as recorded on the eCRF

  In addition to the overall nab-paclitaxel exposure summary, a separate exposure of nab-paclitaxel in the maintenance period will be summarized.

Note: Chemotherapy period in this document =induction period in the protocol.

5.7.1.3. Carboplatin

- Number of infusions
- 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/mL/min/week) = (Cumulative dose level in area under the concentration-time curve [AUC]) ÷ (Duration of treatment) where the dose level in AUC is calculated as: AUC (mg•min/mL)= Dose in mg/ (min(glomerular filtration rate [GFR],125) + 25) where GFR(mL/min) is either collected as 'measured' GFR on the eCRF or (if 'measured' GFR is not available,) the creatinine clearance (**CrCl)** ((mL/min) calculated from the CrCl formula in Protocol Attachment 5.
- Relative dose intensity (%) = Dose intensity (mg/mL/min/week) ÷ (2 mg/mL/min/ week)
- Relative dose intensity (%) by cycle, for Cycles 1 and 2 (for Cycle 2 relative dose intensity, only patients who entered Cycle 2 will be considered)
- Number of 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 Table JFCP.5.3
- Dose delay as recorded on the eCRF

Table JFCP.5.3. Dose Reductions for Necitumumab, Nab-Paclitaxel, and Carboplatin

Dose Level	Necitumumab	Nab-Paclitaxel	Carboplatin
Starting Dose	800 mg	100 mg/m^2	AUC 6
First Dose Reduction	600 mg	75 mg/m^2	AUC 4.5
Second Dose Reduction	400 mg	50 mg/m^2	AUC 3.5

Abbreviations: AUC = area under the concentration-time curve; CRF = case report form.

Note: Actual dose levels entered in the CRF will be rounded to the nearest dose level listed in this table (for example, 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).

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%, and ≥110%).

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

Patients who did not receive any amount of a given treatment will be assigned a value of 0 for exposure to that treatment (that is, number of infusions, duration of treatment, cumulative dose, dose intensity, and relative dose intensity). Cumulative dose, dose intensity, and relative dose intensity will remain missing if they cannot be derived due to missing weight or BSA.

5.7.1.4. Combination Therapy

A patient is considered in combination therapy starting from the first dose of any of the study drugs until the last dose of any of the study drug. The following items will be summarized for the combination therapy:

- Number of cycles received by patient: if a patient received at least 1 dose of any compound during a cycle, then the patient is considered having received the cycle; if a patient was treated at, for example, Cycle 1 and Cycle 3 only, then the total number of cycles received for this patient is 2.
- Number of patients treated by cycle: if a patient received at least 1 dose of any compound during a cycle, then the patient is considered having received the cycle; if a patient was treated at, for example, Cycle 1 and Cycle 3 only, then this patient will be counted in the Cycle 1 and Cycle 3 summaries.

5.7.2. Adverse Events

Adverse events will be summarized by MedDRA System Organ Class (SOC) and 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.

AE in the chemotherapy phase: if a TEAE start date is ≤30 + date of last dose of chemotherapy, then the TEAE is in the chemotherapy phase;

AE in the maintenance phase: if TEAE start date is > 30 + date of last dose of chemotherapy, then the TEAE is in the maintenance phase.

Please note that for patients who did not enter the maintenance period, all of their TEAEs are considered as in the chemotherapy phase, regardless of before or after 30 + date of last dose of chemotherapy.

5.7.2.1. Overall Summary of Adverse Events

An overall and by study phase (chemotherapy phase and maintenance phase) summary of AEs will be provided to summarize the following categories using frequency counts and percentages:

- patients with at least one TEAE, SAE, CTCAE Grade 3 or 4 TEAE
- patients with AEs that led to death (all, on study therapy, or up to 30 days after treatment discontinuation)
- Subjects who discontinued study treatment due to AE
- Subjects who discontinued study treatment due to SAE

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

5.7.2.2. 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; # repeat for by study phase):

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

A patient listing of all AEs will be provided.

5.7.2.3. 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 incidence of treatment-emergent AESI will be summarized by AESI category and PT, overall and by study phase.

5.7.2.3.1. 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 AEs will be generated.

In order to further assess the thromboembolic AEs 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).

5.7.2.4. 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 incidence of treatment-emergent consolidated AEs will be summarized by consolidated category and PT, overall and by study phase.

5.7.3. 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, overall and by study phase, 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

- Adverse events leading to study treatment dose modification by SOC and PT

5.7.4. Weight, Performance Status, and Vital Signs

5.7.4.1. Weight and ECOG Performance Status

Weight at baseline will be presented using summary statistics. Changes from baseline to on-treatment weight assessments will be presented by time point by considering the frequency of patients with changes falling in the following categories: <-10% (loss), ≥-10% -0, ≥0 - <10%, and ≥10% (gain).

The ECOG PS results will be summarized using frequency distributions for each scheduled visit, including also the best postbaseline value.

5.7.4.2. Vital Signs

Vital sign shift from baseline will be presented by scheduled visit and overall, with frequency distribution according to the following categories:

- temperature (<36, 36 - <38.5, ≥38.5°C)
- respiration rate (<20, 20 - <30, ≥30 bpm)
- arterial pulse (<60, 60 - <120, ≥120 bpm)
- systolic blood pressure (<140, 140 - <160, ≥160 mmHg) diastolic blood pressure (<90, 90 - <100, ≥100 mmHg)

5.7.5. 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.

5.7.6. Electrocardiogram

Electrocardiogram change from baseline (yes or no) will be summarized using frequency distributions by scheduled visit and overall.

5.8. Other Analyses

5.8.1. Pharmacokinetic (PK) Analyses

Pharmacokinetic (PK) analyses will be performed by Lilly PK according to a separate PK analysis plan.

5.8.2. Immunogenicity Analyses

The number and percentage of patients with positive anti-necitumumab response will be summarized. Additional efficacy and/or safety analyses may be performed in the subgroup of patients with positive anti-necitumumab responses if appropriate.

5.8.3. Concomitant Therapy and Post-Study Anticancer 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.

5.9. Hospitalizations

Patient hospitalizations during the study treatment or within 30 days of the last dose of study drug will be summarized, overall and by study phase.

5.10. Interim Analyses

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

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

6. References

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