Statistical Analysis Plan I6A-MC-CBBE (a)

A Phase II Study of the Combination of LY3023414 and Necitumumab after First-Line Chemotherapy for Metastatic Squamous Non-small Cell Carcinoma of the Lung

NCT02443337

Approval Date: 28 December 2015

SCRI DEVELOPMENT INNOVATIONS

Statistical Analysis Plan

LUN 288/I6A-MC-CBBE

A Phase II Study of the Combination of LY3023414 and Necitumumab after First-Line Chemotherapy for Metastatic Squamous Non-small Cell Carcinoma of the Lung

Sponsor:	Eli Lilly and Company Indianapolis, Indiana, 46285 USA
Study Drug:	LY3023414
SCRI Protocol Number:	LUN 288
Sponsor Protocol Number:	I6A-MC-CBBE
Prepared By:	**SCRI Development Innovations (Innovations)**

History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	Dec 30 2015	Original document

Statistical Analysis Plan Review and Approval

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07/18/2016
04:07 PM EDT

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Glossary

AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
BID	Twice a day
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response
CT	Computerized tomography
DCR	Disease control rate
DP	Drug product
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOI	End of infusion
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous
LDH	Lactate dehydrogenase
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progressive disease
PDx	Pharmacodynamic
PHI	Protected health information
PFS	Progression-free survival
PK	Pharmacokinetic
PO	By mouth
PR	Partial response
QD	Once a day
RR	Response rate

LIST OF ABBREVIATIONS (continued)

SAE	Serious adverse event
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SIMC	Safety Internal Monitoring Committee
ULN	Upper limit of normal

1 Introduction

This document describes the Statistical Analysis Plan for study, *A Phase II Study of the Combination of LY3023414 and Necitumumab after First-Line Chemotherapy for Metastatic Squamous Non-small Cell Carcinoma of the Lung sponsored by Eli Lilly Company.*

1.1 Objectives

Primary Objective

- To evaluate the 6-month disease control rate (DCR) in patients receiving the combination of LY3023414 and necitumumab after first-line platinum-based chemotherapy regimen for advanced or metastatic squamous non-small cell carcinoma of the lung.

Secondary Objectives

The secondary objectives of this study are to:

- To establish that the doses of LY3023414 and necitumumab being studied are safe and well-tolerated when administered in combination.
- To characterize exposure of necitumumab and LY3023414 when administered in combination.
- To evaluate additional measures of efficacy including overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) of the combination of LY3023414 and necitumumab after first-line platinum-based chemotherapy for advanced or metastatic squamous non-small cell carcinoma of the lung.

Exploratory Objectives

The exploratory objective of this study is:

- To potentially identify biomarkers (including but not limited to biomarkers of the EGFR and PI3K/mTOR pathways) associated with clinical efficacy and disease progression in this patient population.

1.2 Study Design

This is a Phase II single-arm, open-label, clinical study of the combination of LY3023414 (200 mg orally BID) and necitumumab (800 mg administered IV on Day 1 and 8 of each 21-day cycle) in patients with previously treated advanced or metastatic squamous non-small cell carcinoma of the lung.

Since the combination of LY3023414 and necitumumab will be given for the first time to humans, a safety lead-in will be conducted. After at least 6 patients (lead-in cohort) have been treated for a full cycle, a Safety Internal Monitoring Committee (SIMC) will conduct a review of the safety and available PK data to evaluate the

safety and PKs of the combination. If 2 (or more) of 6 patients in the lead-in cohort experience dose-limiting toxicities (DLTs) as defined in Section 5, 3 to 6 additional patients will be treated at a lower dose of study drug(s) following discussion of the safety data by the SIMC and assessed for DLTs. If there is a safety concern or PK interaction deemed to be clinically significant by the SIMC, the SIMC may recommend enrollment of approximately 6 additional patients to further evaluate the safety of the combination, or explore other doses of LY3023414 in combination with necitumumab. In the case of unacceptable and/or unmanageable toxicity of the combination at the intended dose level, the SIMC may decide to discontinue or modify the study (e.g. proceed with a lower dose level of study drug(s) tolerated in combination).

The total number of evaluable patients needed from the lead-in and the post lead-in cohort is approximately 48, with a planned interim analysis after 24 patients have completed up to 6 months of follow-up. An interim analysis will be performed purely for the purpose of detecting any early efficacy signal, and not for the purpose of stopping recruitment. .

Cycles will be 21 days in length. Patients will be treated until disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1, or they develop an unacceptable toxicity requiring discontinuation of the drug, or patient/physician choice. Patients will be evaluated for response to treatment after every 2 cycles.

The evaluable patients to assess the 6-months PFS event free rate are the FAS population defined in section 2.2.

The evaluable patients to assess the DLT rate are those patients who had been stay on study medication for more than 21 days, or have discontinued treatment due to DLT(s).

1.3 Statistical Considerations

Sample Size Justification

CCI [redacted] CCI [redacted] Based upon a 1-sided type I error rate of 20% and power of 90% the total sample size required to test the null hypothesis is 48 evaluable patients. A planned interim analysis will take place when 24 patients are evaluable for the primary endpoint, including the initial 6 patients treated at that dose to establish the safety and pharmacokinetics of the combination. The O'Brien Fleming alpha spending function is 0.067 at the interim analysis and 0.131 at the final analysis. CCI [redacted] CCI [redacted] CCI [redacted] The sample size is calculated using EAST.

1.4 Timing Of Analysis

A Safety Internal Monitoring Committee (SIMC) will conduct a review of the safety and PK data after at least 6 patients (lead-in cohort) have been treated for a full cycle.

Interim efficacy analysis will take place when the first enrolled 24 treated, post lead-in patients have finished tumor assessment at month 6 or early terminated from the trial for any reason. In addition to the efficacy analysis, the interim analysis will also include disposition, demographics, baseline characteristics, safety summary, and study drug administration.

The final analysis will take place when all of the 48 patients have finished tumor assessment at month 6 or early terminated from the trial for any reason.

1.5 Responsibilities

The final statistical analysis for the study will be performed by SCRI Development Innovations. Pharmacokinetic parameter estimation and modelling will be performed by Eli Lilly and Company.

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1.6 Analysis Software

Analyses will be performed using SAS® version 9.3 or higher. PK parameter will be estimated WinNonlin® within Phoenix 6.3 or higher (Pharsight.a Certara ™ Company) and any software, approved and validated by Eli Lilly global PKPD organisation, to analyse the PK data using non-linear mixed effect modelling technics. A separate PK analysis plan is developed by Eli Lilly for the PK analysis.

2 Definition of Analysis Sets

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

2.1 *All Patients*

All patients who have signed the informed consent form (i.e. screening failures plus patients enrolled) will comprise the All Patients Set (ALL). The All Patients Set will be used to describe the patient disposition and all-cause deaths.

2.2 *Full Analysis Set (FAS)*

All enrolled patients who have received at least one dose of study medication will comprise the Full Analysis Set (FAS). This population will be used for the safety analysis and the primary analyses of the efficacy endpoints.

2.3 *Per Protocol Analysis Set (PPAS)*

All treated patients having no major protocol deviations will comprise the Per Protocol Analysis Set (PPAS). Those protocol deviations deemed to have an important impact on the analysis of study endpoints and leading to the exclusion of a patient will be listed in the Statistical Analysis Plan (SAP) prior to database lock. This analysis set will be used for sensitivity analyses of efficacy endpoints. The following are defined major protocol violations:

- *Administration of prohibited concomitant medication as described in the Study Protocol.*
- *Violation of inclusion or exclusion criteria which may affect the assessment of the safety and/or efficacy of the study drug.*

Prior to database lock, there will be a review of all reported protocol violations to determine the inclusion/exclusion of patients in each analysis set.

2.4 *Safety Analysis Set (SAF)*

All patients who have received at least one (full or partial) dose of study treatment will comprise the Safety Analysis Set (SAF). In this study, the Safety Analysis Set is same as the Full Analysis Set.

2.5 *Pharmacokinetics Analysis Set (PKAS)*

Pharmacokinetics Analysis Set (PKAS) includes patients who received LY3023414 200 mg orally twice daily (BID) and for whom the pharmacokineticist determines that there is sufficient data. The PKAS is used for all listings, tables and graphical summaries of the PK data.

2.6 Pharmacodynamic Analysis Set (PDAS)

Not Applicable.

2.7 Biomarker Analysis Set (BMAS)

Not Applicable.

3 Efficacy Parameters / Endpoints

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the 6-month DCR, which is defined as the number of patients with PFS > 6 months (or 26 weeks (182 days), to accommodate the scheduled tumor assessment at week 24 be delayed by up to 2 weeks) divided by number of patients in FAS population.

3.1.2 Secondary Efficacy Endpoints

- Overall Response Rate (ORR)
- Disease Control Rate Based on Best Overall Response
- Progression–free survival (PFS)
- Overall survival (OS)

3.1.3 Exploratory Efficacy Endpoints

Exploratory analyses including, but not limited to, according to biomarker status of EGFR and PI3K/mTOR signalling alterations may be performed as deemed appropriate.

3.1.4 Other Efficacy Endpoints

Not Applicable

3.2 Definition of Endpoints

3.2.1 6-Month Disease Control Rate

Disease Progression Date:

The disease progression date for the primary endpoint will be derived from the time point overall assessment based on radiological tumor assessment.

Progression Free Survival based on Tumor Assessment

Progression-free survival (PFS) is defined as the time from first dose until the date of radiological tumor assessment based disease progression (PD) or death. PFS will be censored in the following senarios:

- If patient has neither PD nor death, the PFS will be censored at last radiological tumor assessment date.
- Patients who have started on any subsequent anti-cancer therapy without any documentation of progression will be censored on the date of previous radiological tumor assessment date.
- If patient had PD or Death occurred more than 85 days (2 tumor assessment intervals) after previous tumor radiological assessment, the PFS will be censored at last radiological tumor assessment date.
- If patient does not have post baseline tumor assessment nor death within 85 days after first dose date, the PFS will be censored at Day 1.
- If patient does not have valid baseline tumor assessment, the PFS will be censored at Day 1.

Progression Free Survival Sensitivity Analysis Endpoints

To evaluate the robustness of the 6-month DCR based on the radiological tumor assessment, the PFS defined by both radiological progression and clinical progression will be analyzed as sensitivity analysis for the primary endpoints.

Therefore, the PFS2 will be defined as the time from first dose until the date of tumor assessment based disease progression (PD), clinical disease progression or death. The date of clinical disease progression is the last dose date of study medication when the patient has the end of treatment checked with "due to progressive disease".

Except the event is defined differently from PFS, the same censoring of the PFS will be applied when deriving PFS2.

The 6-month DCR is defined as the number of patients with PFS > 6 months (182 days) divided by number of patientsin FSA population. Similiarly, the 6-month DCR2 will be defined based on PFS2.

3.2.2 Secondary Efficacy Endpoints

Tumor Respones and Response Rate

Timepoint Overall Tumor Response

Timepoint overall tumor response will be evaluated, using the RECIST 1.1 criteria, every 2 cycles until disease progression (as determined by the investigator). The categories are as follows:

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)
- Not Evaluable (NE)

The timepoint overall response at each assessment and the best overall response may be determined by Investigator and will be derived programmatically. Discrepancies will be queriedy, but Investigator assessment will be used for analytic purposes.

Overall Response Rate

Overall Response Rate (ORR) is the proportion of patients whose best overall response is Complete Response (CR) or Partial Response (PR). Analysis will be performed on FAS. Meanwhile, patients with measurable disease at baseline will be used in the separate analysis of ORR.

Best Overall Response is derived based on the time point response information on the CRF according to RECIST criteria:

- If a patient has at least two CR and the first and the last CR dates are more than 28 days apart, then the best overall response is defined as CR.
- If a patient has PR and another CR/PR with more than 28 days apart, then the best overall response for this patient is PR.
- For those patients who do not have confirmed CR or PR, if the patient's last tumor assessment record of CR/PR/SD is at least 42 days after date of first dose, then best overall response is defined as SD.
- For those patients who do not have SD defined as above, but they have PD, their best overall response is PD.
- Otherwise, best overall response is defined as NE.

The derivation above will be implemented using SAS to evaluate the accuracy of the best overall response in the CRF.

Based on patients' best overall response during the study, the following rates are calculated:

- Disease Control Rate (DCR) = Proportion of patients with a best overall response of CR, PR, or SD.

Overall Survival (OS)

Overall Survival (OS) is the time from date of first dose to death due to any cause. If a patient has not died, overall survival is censored at the last known alive date. The last known alive date is the maximum of last dose date, the treatment discontinuation date, the study discontinuation date, and last known alive date.

3.2.3 Pharmacokinetic Parameters

Pharmacokenitics parameters will be defined in separate SAP authored by Eli Lilly and Conmpany.

3.2.4 Exploratory Endpoints

The biomarker status of EGFR and PI3K/mTOR signalling alterations will be obtained. PFS analysis and Overall Survival Analysis will be performed by such subgroups.

3.3 General Rules in Deriving Time To Event Variables

The general rule for time to event analysis is described below:

Time To Event = Date of event with interest (with event) – Start Date + 1 day, if there is an event.
Time To Event = Last Date of event with interest (no event) – Start Date + 1 day, if there is no event.

If dates of event of interests are not available, the date of first dose will be used as event date (ie censored on day 1).

Start Date

Date of first dose is the start date to calculate the event.

Event Dates

For Overall Survival (OS), Progression-Free Survival (PFS) and Time To Progression (TTP), multiple dates will be used to derive the event dates for these endpoints, with the following rules:

- Events always take precedence to Censoring
- If multiple event dates are applicable, the earliest date will be used.
- If multiple censoring dates are applicable, the last date available will be used.

Cut-off Date

Any Event of interest after cut-off date will not be considered in the primary analyses. If the first event of interest is after cut-off date, the time to event variable will be censored to the previous date associated with the event of interest date. Follow-up evaluations of time to event measures may be conducted at a later date and appended to the CSR as appropriate.

3.4 Handling of Missing Efficacy Data

No imputation will be done for efficacy derived data.

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4 Safety Parameters / Endpoints

4.1 Adverse Events

Adverse events will be coded using MedDRA version 18.0 or higher. Particular preferred terms will be summarized in consolidation when appropriate, e.g. anaemia, haematocrit decreased, haemoglobin decreased, hypochromic anaemia and red blood cell count decreased will be summaried as anemia.

Treatment-emergent adverse event is defined as the adverse event that has started or worsened after the start of the first dose of study treatment up to 30 days after discontinuation of study drug. Adverse events will be graded using the NCI-CTCAE version <4.03> where applicable, or using the 5-point severity scale:

NCI-CTCAE Grade	Severity scale
1	Mild
2	Moderate
3	Severe
4	Life-Threatening
5	Death

In grading the adverse events the worst grade observed is to be reported.

4.2 Laboratory Parameters

Laboratory toxicity grading will be derived from the laboratory values using NCI-CTCAE version <4.03>.

4.3 Other Variables

The duration of exposure
For each subject, the Length of Time on treatment will be calculated in days, using the following formula:

('Date last dose of study drug'# - 'Date first dose*) + 1

Total Dose Consumed
For each subject, the total dose on treatment will be calculated.

Dose Intensity

Dose Intensity on Study Days will be calculated as:

[Total Dose Consumed]

[Last Dose Date-First Dose Date+1]

Dose Intensity on Dosing Days will be calculated as:

[Total Dose Consumed]

[Sum of all Dosing Intervals]

Compliance

Compliance will be calculated as:

[Total Dose Consumed]
--- *100%
[Total Planned Dose]

Total planned dose should take into consideration any dose adjustment(s) before treatment discontinuation.

Prior and concomitant medication

Prior medication is defined as medication with a stop date before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

4.4 Handling of Missing Safety Data

If a patient's birthdate is a partial date with month available, the 15th of the month will be used to calculate the age. If a patient's birthdate is a partial date with only year available, the July 1st will be used to calculate the age.

When defining treatment emergent adverse event, if the adverse event onset date is missing in day, the last date of the month will be used. Therefore, any adverse event with onset in the same month of the first dose, is considered as treatment emergent.

If the adverse event onset date is missing in both day and month, the last date of the year will be used.

For any concomitant medication, if the first use date is prior to the first dose of study medication, then the medication is defined as prior medication. If the first use of concomitant medication is missing in day, the last date of the month will be used. Therefore, any concomitant medication with first use in the same month of the first dose, is considered as the concomitant medication. If the first use date of concomitant medication is missing in both day and month, the last date of the year will be used.

Missing relationship to study medication of any adverse event, if the adverse event onset date is after the first dose of study medication, the relationship will be considered as probably related.

5 Statistical Methods

5.1 Study Day in Data Display

- Date of first dose date will be used in all analysis

5.2 General Consideration

For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation, median, minimum and maximum. In addition, for continuous PK parameters, the coefficient of variation will be calculated and for Cmax and AUC the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of patients with no missing data, i.e. will add up to 100%.

All statistical comparisons will be made using two sided tests at the alpha=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using SAS Version 9.2 or higher. Specifications for table, graphs, and data listing formats can be found in the TLG specifications for this study.

The lead-in cohort is considered part of the fourty eight patients in this study. The patient in lead-in cohort will be analysed in the same same group of patients as the rest of patient population.

5.3 Study Population

5.3.1 Disposition of Patients

The following patient data will be summarized:

- Number and percentage of patients enrolled, and treated;
- Number and percentage of patients in each patient population, FAS, PKAS, and Safety Population;
- Number and percentage of patients who prematurely discontinued from investigational period, by reason for discontinuation. Reasons for study treatment discontinuation will be summarized by the following categories: disease progression, adverse event (AE), lost follow up, Non-compliance with study medication, pregnancy, protocol violation, and subject withdrawn consent.

5.3.2 Protocol Violations

The number of protocol deviations/unevaluable criteria and the number of patients with at least one protocol deviation or unevaluable subjects will be summarized by each treatment group and overall for the FAS. The protocol deviation/unevaluable criteria types will also be summarized, which may include any of the following: Not Done, Outside of Window, Excluded Prior Therapy, Excluded Concomitant Medication, Value Out of Range, Same Method Not Used, Incorrect Dose Level, Dose Not Held, Dose Not Reduced, Incorrect Drug Dispensed, Incorrectly Stratified, and Other.

Major protocol violations/unevaluable criteria as defined in section 2.4 will also be summarized by violation type/unevaluable criterion and treatment group for the FAS.

5.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics;

Descriptive statistics for age, sex, weight, height and Time from initial diagnosis at study entry will be presented. Age will be calculated as the integer part of (Date of first dose – Date of Birth + 1)/365.25. Age will also be categorized using the categories < 65 and ≥ 65 and will be presented using frequencies and percentages. Frequency tabulations for sex, race and Cigarette Smoking History will be presented.

The patient cancer diagnosis characteristics such as metastics status, months from first diagnosis, months from locally advanced or metastatics will be summarized. The cancer histology, metastatics sites, and prior disease related therapies and their outcome will also be summarized.

5.3.4 Prior and Concomittant Medications

Previous medications are coded with WHO-DRL, and will be summarized by ATC class (4th level, chemical subgroup) and coded term by treatment group for the SAF.

All medications received during the treatment period (i.e. overlapping with the administration of study medication including necitumumabnecitumumab) other than study drug will be considered concomitant medications. As with previous medication, concomitant medication will be summarized for each treatment group by ATC class (level 2 and 4) and WHO-DRL reference for the SAF. Patients taking the same medication multiple times will be counted once per medication and investigational period. Patients who received concomitant medications will be listed as well.

5.4 Efficacy Analysis

5.4.1 Analysis of Primary Variable

The primary endpoint, 6-month DCR, defined as the number of patients with PFS > 6 months (182 days) divided by number of patients in FAS population. The number will be presented as the point estimate with its associated ~~95%~~ 80% two sided Clopper-Pearson confidence interval (CI).
Similiarly, the 6-month DCR defined based on PFS2 will be analyzed in the same manner.

5.4.2 Analysis of Secondary Efficacy Variables

The ORR and DCR defined based on best overall response will be summarized along with the 80% Clopper Pearson CI.

Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI will be provided for PFS, PFS2(based on clinical progression) and OS. Survival rates at 3 months, 6 months, 9 months and 12 months will also be provided based on Kaplan-Meier curves for PFS, PFS2 and OS.

Categorical summary of change in ECOG will be summarized.

5.4.3 Subgroup Analysis

Subgroups will be defined by the ECOG status, age group, and smoking history.

Primary analyses will be conducted for patient subgroups as defined by the stratification factors and other patient characteristics. A Cox proportional hazard model will be used to estimate hazard ratio and to create a 95% confidence interval for the hazard ratio in each subgroup.

5.4.4 Analysis of Other Variables

Exploratory analysis will be conducted for key efficacy endpoints in subgroups in addition to the patient baseline characteristics. Variables that may be considered include, but are not limited to age, disease history, and previous treatment history. Both univariate and multivariate analysis by the Cox proportional hazard model will be used to examine the association between the key efficacy endpoint and prognostics factor. The logistic regression analysis may be performed to examine the association between the stratification factors, baseline variables and response rates.

5.5 Safety Analysis

All safety analyses will be performed on the SAF.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that begin or worsen in severity on or after the date of the first dose of study drug and within 30 days of the date of the last dose of study drug. If date of last dose of study drug is missing but first dose date is non-missing, AEs that begin after the first dose of study drug will be considered as TEAEs.

5.5.1 **Adverse Events**

The coding dictionary for this study will be MedDRA Version 18.0 or higher. It will be used to summarize AEs by system organ class (SOC) and/or preferred term (PT).

Toxicity grade is defined according to the version 4.03 or later of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

The number and percentage of patients with TEAEs, as classified by SOC and PT, will be summarized for each treatment group. Similar summaries will also be provided for drug related TEAEs, treatment-emergent SAEs, drug related serious TEAEs and TEAEs that lead to study drug discontinuation or death. The TEAE leading to death is defined by the CTCAE grade=5. A drug-related TEAE is defined as any TEAE related to study medication as assessed by the investigator, or with missing assessment of the causality relationship.

TEAEs will also be summarized by severity in CTCAE grade. If an adverse event changes in severity, then the adverse event will be counted only once with the worst severity.

All AEs and SAEs occurring throughout the conduct of the study, including all-cause deaths, will be summarized in listings. Treatment-emergent SAEs will be summarized by MedDRA SOC and PT.

Tables will include the following details:

- Number and percentage of patients with TEAEs
- Number and percentage of patients withdrug related TEAEs
- Number and percentage of patients with treatment-emergent SAEs
- Number and percentage of patients with drug related treatment-emergent SAEs
- Number and percentage of patients with TEAEs by maximum CTCAE grade
- Number of TEAEs leading to permanent discontinuation of study drug.
- Number of drug related TEAE leading to permanent discontinuation of study drug.
- Number of deaths.

5.5.2 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration.

The following clinical laboratory variables will be summarized:

- Hematology – red blood cells, full blood count with hemoglobin, hematocrit, platelets, leukocytes, neutrophils, lymphocytes, mid cell fraction, prothrombin time (PT) and INR.
- Biochemistry – blood glucose, HbA1c, electrolytes (Ca, Cl, Mg, Na, and K), phosphorus, BUN, creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, AST, ALT, total protein, albumin.
- Urine Analysis.

Means, standard deviation, minimum, maximum and median for numeric results will be summarized at each visit by treatment group.

Biochemistry and hematology lab tests will be graded according to NCI CTCAE v4.03 or later where applicable. Shift from baseline to the worst grade on study by CTCAE grades will be presented. Shifts from baseline to worst value on study will be presented for categorical or ordinal lab parameters. Incidence of patients with laboratory values outside laboratory supplied normal range will also be presented.

Microscopic urinalysis and adrenal hormones results will be summarized by categoricals and will also presented in the listing only.

The potential for drug-induced liver injury (DILI) will be evaluated via liver function tests as outline in the FDA guidance on DILI. Summary tables will be presented for the following:

- Shifts from baseline to maximum post baseline value as a function of the upper limit of normal (ULN) as follows:
  - AST, ALT and either ALT or AST >= (3xULN, 5xULN, 10xULN, 20xULN, exclusively)
  - Total bilirun >= (1.5xULN and 2xULN, exclusively)
  - ALP >= 1.5xULN.
- The incidence of subject's meeting the criteria for Hy's Law defined as elevations in ALT and/or AST of >= 3xULN with accompanying elevations in total bilirubin of >= 2xULN.

5.5.3 Vital Sign

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs and change from baseline for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate and weight) will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, change from baseline at end of treatment will be summarized.

5.5.4 Physical Examination Findings

Physical examination findings will be provided in a listing.

5.5.5 Electrocardiograms (ECGs)

The baseline visit is the last measurement taken prior to initial study drug administration.

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results for the 12 lead ECG will be tabulated by treatment group at each treatment visit. A 2 x 2 shift table showing investigator's assessment of changes in normal, abnormal, and abnormal and clinically significant results during the study will be displayed. Abnormal and clinically significant results will be documented as AE.

5.5.6 Exposure

Patients will be taking necitumumab 800 mg IV in combination with LY3023414 200 mg orally BID.

Extent of Exposure

Duration of exposure will be summarized in two ways.

Descriptive statistics will be presented for duration of exposure in months by treatment group for the SAF.

Exposure time will be categorized according to the following categories by treatment group:

- <=1 Cycle completed
- 2 Cycle completed
- 3 Cycle completed
- 4 Cycle completed
- Etc

Counts and percentages of subjects in each of these categories will be summarized for each treatment group for the SAF.

Treatment Compliance

Overall compliance with the dosing schedule will be examined by evaludation of dosing administration data in the SAF whose total study drug count and first and last days of treatment are known. Descriptive statistics will be presented by treatment group for cumulative dose, duration of exposure, dose intensity and relative dose intensity.

Treatment Modifications

Treatment modifications will be summarized by each treatment group and overall for the SAF. The number of subjects with dose interruptions and /or dose reductions will be summarized by treatment periods using frequency counts and percentages.

5.6 Prior/Concurrent Medications and Concomitant Medications

All medications will be coded using the WHO-Drug Dictionary <MAR. 2015>. The number of patients receiving each class of concomitant medication will be summarized by treatment group by ATC level X and preferred term. Medications stopped prior to initiation of study drug and/or started after discontinuation of study drug will be summarized in listings.

5.7 Pharmacokinetic Analysis

Pharmacokinetic analyses will be proposed in separated SAP authored by Eli Lilly and Company.

5.8 Pharmacodynamic Analyses

Not Applicable.

5.9 Quality of Life Analyses

Not Applicable.

5.10 Pharmacoeconomics Analyses

Not Applicable.

5.11 Interim Analyses

Interim Analysis

All interim analyses will be conducted. Production of tables and listings will be performed by current study team. For more details consult the DMC Charter.

6 References

Brookmeyer, R. and Crowley, J. (1982): A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.

SAS Institute Inc. (2001): The SAS System, Version 8.2. Cary, NC. SAS Institute Inc.

FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). U.S. Department of Health and Human Service, FDA. Rockvill, MD.

7 Appendices

7.1 Appendix 1: Schedule of Assessments

Assessments	Screening	Study Treatment				Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5, 7, etc.)	Off-Treatment	Follow-Up	
		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)			End of Study Treatment[p] (+3 days)	Off Treatment Prior to Progression[q] (±1 month)	Survival[r] (±1 month)
	Baseline[a]	D1	D8	D1	D8				
TESTS AND OBSERVATIONS									
Informed consent	X								
Medical history	X								
Physical exam[b]	X	X		X			X	X	
Vital Signs[c]	X	X	X	X	X		X	X	
ECOG PS	X	X	X	X	X		X	X	
12-lead ECG[d]	X	X		X[d]			X		
Adverse event evaluation		X	X	X	X		X		
Concomitant medication review	X	X	X	X	X		X		
Study drug compliance			X	X			X		
Survival status									X
STUDY TREATMENT									
LY3023414 PO BID (continuous dosing)[k]		X	X	X	X				
Necitumumab IV[k]		X	X	X	X				
LABORATORY EVALUATIONS									
CBC, 3-part differential, and platelets	X	X	X	X	X[s]		X		
Fasting CMP[e], phosphorus, magnesium and LDH	X	X	X	X			X		
PT/INR[f]	X	X[f]		X[f]					
Serum or urine pregnancy test[g]	X[g]	X[g]							
Urine dipstick	X	X	X	X			X		
Biomarker blood sample[h]	X[h]	X[h]		X[h]			X		
HbA_{1c} blood sample[i]	X			X[i]			X[i]		
PK blood sample[j,k]		X[j,k]	X[j,k]	X[j,k]	X[j,k]		X[j]		
Immunogenicity blood sample[l]		X[l]		X[l]			X[l]		

Appendix E: Schedule of Assessments

a The physical examination, vital signs, ECOG PS, CBC including differential and platelets, fasting CMP, urine dipstick, PT/INR, biomarker blood sample, and HbA1c blood sample should be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours prior to the initiation of treatment they do not have to be repeated. The ICF, medical history, concomitant medications review, 12-lead ECG, scans to document evaluable disease (i.e., tumor measurement) and archived or fresh tumor tissue should be collected ≤ 4 weeks prior to initiation of treatment.

b Physical examination will include measurements of height and weight at the baseline visit. Physical examinations (PE) done at all other times during the study will include only weight.

c Vital signs include resting heart rate, blood pressure, oral temperature

d ECG performed locally at baseline, pre-dose on Cycles 1 -4, and at the End of Treatment visit. Repeat if clinically indicated.

e Fasting CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, albumin, phosphorus, magnesium and LDH.

f PT/INR will only need to be repeated if abnormal at baseline or if clinically indicated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have their coagulation test performed on a weekly basis.

g Pregnancy tests will only be performed in women of childbearing potential ≤ 72 hours prior to first dose of study treatment.

h Biomarker blood samples will be taken at baseline and pre-dose on Day 1 of Cycles 1 and 3, and every 2 cycles thereafter, and at the End of Treatment visit.

i HbA_{1c} blood sample will be taken at baseline, on Day 1 of Cycle 4 and every 3 cycles thereafter, and at the End of Treatment visit..

j PK blood samples will have a window of ± 15 minutes. PK blood samples on Cycle 1 and Cycle 3 Day 8 are pre-dose of LY3023414 and necitumumab, at EOI, and 1 hour post EOI.. PK blood samples for Cycles 2, 4, and 6 Day 1 are pre-dose of LY3023414 and necitumumab . A PK sample will be taken at the End of Treatment visit.

Appendix E: Schedule of Assessments

k On PK days, pre-dose measurements and dose administration will be done in a fasted state. Patients should remain in a fasted stated for 1 hour post-necitumumab infusion.

l Immunogenicity blood samples will have a window of ± 15 minutes. Immunogenicity blood samples on Cycles 1, 2, and 4 Day 1 are pre-dose of LY3023414 and necitumumab (see Table 2 and Table 3). An immunogenicity sample will be taken at the End of Treatment visit. In the event of an IRR, sampling as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

m Confirm availability of pretreatment tumor tissue (see Protocol Section **Error! Reference source not found.**). If archived tissue is not available, a fresh tumor biopsy should be obtained after all other study entry criteria have been confirmed, unless the Sponsor and Investigator document that the patient may be enrolled without pretreatment tumor tissue.

n CT scans of the chest, abdomen and pelvis ≤4 weeks prior to initiation of treatment. CT scans should be taken prior to Cycle 3 and after every 2 cycles of treatment thereafter, and at the End of Study visit (if scans were not taken in the previous 8 weeks).

o CT/MRI of the brain at baseline if a patient has known brain metastases or if clinically indicated. If abnormal at baseline, repeat prior to Cycle 3 and after every 2 cycles of treatment thereafter, and at the End of Study visit (if scans were not taken in the previous 8 weeks).

p After patients complete therapy or are discontinued from treatment they will visit the study center within 30 days (+3) after finishing treatment for end of treatment assessments. Patients must be followed for AEs for 30 calendar days after the last dose of study drug. For ongoing AEs and serious adverse events (SAEs) see Protocol Section **Error! Reference source not found.**.

q Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression or for up to 2 years whichever comes first.

r After disease progression is documented, patients will be followed every 3 months (±1 month) for survival (e.g., date and cause of death) for up to 2 years or death whichever comes first. Patients may be contacted during outpatient visits or by telephone.

s Cycle 3 only.

t If the PGx blood sample is not collected Cycle 1 Day 1, it can be collected anytime during Cycle 1 or Cycle 2

7.2 Appendix 2: Tables, Figures and Listings Shells

7.3 Appendix 3: In-Text Tables and Figures Specifications

7.4 Appendix 4: Derived Variables and Datasets Specifications