Protocol I6A-MC-CBBE (b)

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: 16 December 2015

SCRI DEVELOPMENT INNOVATIONS

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

SCRI DEVELOPMENT INNOVATIONS, LLC (SCRI INNOVATIONS) STUDY NUMBER:	LUN 288
SPONSOR STUDY NUMBER:	I6A-MC-CBBE
STUDY DRUG:	LY3023414
SPONSOR:	Eli Lilly and Company Indianapolis, Indiana, 46285 USA
CONTRACT RESEARCH ORGANIZATION:	SCRI Innovations 3322 West End Avenue , Suite 900 Nashville, TN 37203 PPD
STUDY CHAIR:	PPD MD Sarah Cannon Research Institute 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI
SPONSOR CONTACT :	PPD MD, PhD Eli Lilly and Company Kolblgasse 8-10 A-1030 Vienna, Austria PPD
DATE FINAL:	27 February 2015

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	08 April 2015
AMENDMENT NUMBER:	2	**AMENDMENT DATE:**	23 November 2015

Protocol Approved by Lilly: 04 March 2015

Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 16-Dec-2015 GMT

SCRI DEVELOPMENT INNOVATIONS

Clinical Study Statement of Compliance

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

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Contract Research Organization (CRO) Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities as defined by the protocol, applicable Clinical Trial Agreements (CTA), and/or business contracts. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented with the Sponsor's review and approval prior to implementation.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted Sponsor responsibilities to the CRO and the Principal Investigator as defined by the protocol, applicable Clinical Trial Agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

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Clinical Study Signature Approval Page

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PPD MD	PPD	1 DEC 2015
Study Chair Sarah Cannon Research Institute	**Study Chair Signature**	**Date**
PPD MD, PhD		
Sponsor Representative Eli Lilly and Company	**Sponsor Representative Signature**	**Date**
PPD		
SCRI-Development Innovations, LLC Representative	**SCRI-Development Innovations, LLC Representative Signature**	**Date**
PPD MS		
Biostatistician SCRI Innovations	**Biostatistician Signature**	**Date**

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PPD MD

Study Chair Sarah Cannon Research Institute	**Study Chair Signature**	**Date**
PPD MD, PhD **Sponsor Representative** Eli Lilly and Company	PPD **Sponsor Representative Signature**	26-NOV-2015 **Date**
PPD **SCRI-Development Innovations, LLC Representative**	**SCRI-Development Innovations, LLC Representative Signature**	**Date**
PPD MS **Biostatistician** SCRI Innovations	**Biostatistician Signature**	**Date**

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PPD MD

Study Chair	**Study Chair Signature**	**Date**
Sarah Cannon Research Institute		

PPD MD, PhD

Sponsor Representative Eli Lilly and Company	**Sponsor Representative Signature**	**Date**

PPD	PPD	01 Dec 15
SCRI-Development Innovations, LLC Representative	**SCRI-Development Innovations, LLC Representative Signature**	**Date**

PPD MS

Biostatistician SCRI Innovations	**Biostatistician Signature**	**Date**

SCRI DEVELOPMENT INNOVATIONS

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PPD MD		
Study Chair	**Study Chair Signature**	**Date**
Sarah Cannon Research Institute		
PPD MD, PhD		
Sponsor Representative Eli Lilly and Company	**Sponsor Representative Signature**	**Date**
PPD		
SCRI-Development Innovations, LLC Representative	**SCRI-Development Innovations, LLC Representative Signature**	**Date**
PPD MS	PPD	12/6/2015
Biostatistician SCRI Innovations	**Biostatistician Signature**	**Date**

Clinical Study Principal Investigator Signature Form

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

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SPONSOR STUDY NUMBER:	I6A-MC-CBBE
DATE FINAL:	27 February 2015

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name	**Principal Investigator Signature**	**Date**

LUN 288 Clinical Study Summary of Changes

AMENDMENT NUMBER:	2	AMENDMENT DATE:	23 November 2015

Section 3.2 Exclusion Criteria and Synopsis

3. Patients who have received any other investigational agents, chemotherapy, biologic therapy, or radiation therapy ***(including whole brain radiation)*** within 28 days prior to Day 1 of Cycle 1. For investigational, chemotherapy, or biologic therapy, patients will be allowed on study if 5 half-lives or greater have elapsed since last dose of drug or 28 days, whichever is shorter. ***Treatment with limited radiation, including cyberknife, is allowed if completed ≥ 2 weeks prior to first study treatment, with approval of the medical monitor***.
4. History of brain metastases unless irradiated ~~≥ 2 weeks~~ prior to first study treatment and stable without requirement of corticosteroids.

16. ***The patient has a history of arterial thromboembolic event (ATE) or venous thromboembolic event (VTE) within 3 months prior to study enrollment. Patients with history of VTE beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin (LMWH).*** ~~History of arterial or venous embolism within 3 months prior to study enrollment. If the embolism occurred >3 and <6 months, the patient is eligible provided appropriate treatment according to institutional standard of care is ensured.~~

Section 5.1.1 Treatment Plan

Patients should take the morning and evening doses of LY3023414 approximately 12 hours apart (preferably within a 10- to 14-hour range). ~~LY3023414 will be taken in the morning and again 12 hours later in the evening.~~

Section 5.1.2 Necitumumab

All patients will receive 800 mg of necitumumab by IV over ~~a minimum of~~ 50 minutes on Days 1 and 8 of each 21-day cycle.

Section 5.4.1 Samples for ~~Pharmacogenetic~~ Biomarkers

~~In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3023414 and necitumumab. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.~~

AMENDMENT NUMBER:	2	AMENDMENT DATE:	23 November 2015

Section 5.4.1 Samples for ~~Pharmacogenetic~~ Biomarkers

Samples will be destroyed according to a process consistent with local regulation.

It is possible that biomarker data has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, this data may be requested from medical records for use in the research described in this section.

Section 5.6 Samples for Pharmacogenomic Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ethical review boards (ERBs) allow, a blood/saliva sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3023414 and necitumumab. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

Section 6.1.1 Hypersensitivity/Infusion Related Reactions

As a routine precaution ***each visit***, patients treated with necitumumab should be closely monitored for signs and symptoms indicative of a hypersensitivity/ IRR by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisolone equivalents, etc.) available.

Section 6.1.3 Hypomagnesemia

Hypomagnesemia has been reported with **necitumumab** ~~cetuximab~~ therapy and is considered to be a class effect with EGFR-targeting antibodies (as with panitumumab and cetuximab).

LUN 288 Clinical Study Summary of Changes

AMENDMENT NUMBER:	2	AMENDMENT DATE:	23 November 2015

Section 7.2 Baseline Study Assessments

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.

≤ 4 weeks prior to initiation of treatment

- CT/MRI of brain ***if a patient has known brain metastases or if clinically indicated.*** ~~only if the patient has a history of CNS metastasis~~

Section 7.3.1 Cycle 1– Day 1 and Appendix E

- ***PGx blood sample (if the sample is not collected Cycle 1 Day 1, it can be collected anytime during Cycle 1 or Cycle 2)***

Section 7.3.1 Cycle 1– Day 1 and Section 7.3.3 Cycle 2 and all Subsequent Cycles - Day 1

- Immunogenicity blood sample ± 15 minutes (pre-dose of LY3023414 and necitumumab [see Table 2 and Table 3]). ***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.***

Section 11.2.1 Adverse Event and Serious Adverse Event Reporting

Prior to Administration of Study Drug(s)

Although all AEs after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

~~During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent document. For patients who do not enroll in the study (that is, receive at least 1 dose of study drug), only AEs and SAEs related to protocol procedures are required to be collected.~~

LUN 288/I6A-MC-CBBE PROTOCOL SYNOPSIS

Title of Study:	A Phase II Study of the Combination of LY3023414 and Necitumumab after First-Line Chemotherapy for Advanced or Metastatic Squamous Non-small Cell Carcinoma of the Lung	
SCRI Innovations Study Number:	LUN 288	
Sponsor Number:	I6A-MC-CBBE	
Sponsor:	Eli Lilly and Company, Indianapolis, IN	
Study Duration:	The total duration of the study is planned to include 12 months enrolment, and approximately 6 months active treatment followed by about 2 years of survival follow up.	**Phase of Study:** II
Study Centers:	This study will be conducted at approximately 14 sites.	
Number of Patients:	Approximately 48 evaluable patients with histologically-confirmed advanced or metastatic squamous non-small cell lung cancers (NSCLC), with progressive disease after receiving a platinum-based chemotherapy regimen.	
Objectives:	**Primary Objective** The primary objective of this study is: • 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 Objective** 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.	

LUN 288/I6A-MC-CBBE PROTOCOL SYNOPSIS

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 3 or 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 6 months of follow-up. An interim analysis will be performed purely for the purpose of detecting an 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.
Study Drugs, Doses, and Modes of Administration:	Necitumumab 800 mg will be administered by IV on Day 1 and 8 of each cycle. LY3023414 200 mg will be administered orally (PO) twice a day (BID).

LUN 288/I6A-MC-CBBE PROTOCOL SYNOPSIS

Inclusion Criteria:	1. Histologically confirmed squamous advanced NSCLC (Stage IV). 2. Patients must have progressed on one prior line of platinum-based chemotherapy in the advanced or metastatic setting. (Immunotherapy, such as but not limited to PD-1/PDL-1 inhibitors, will not be considered a line of chemotherapy.) 3. Measurable disease as measured by RECIST criteria v 1.1 (Appendix F). 4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A). 5. Able to swallow the study drugs whole. 6. Resolution of side effects from prior treatment, including neuropathy, to CTCAE Grade 1 or baseline (with the exception of alopecia). 7. Adequate hematologic function defined as: • Absolute neutrophil count (ANC) ≥1500/μL • Platelets ≥100,000/μL • Hemoglobin ≥ 8 g/dL 8. Adequate liver function defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN). If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable. • Total bilirubin ≤1.5 x ULN (or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal limits in subjects with well documented Gilbert's Syndrome or a similar syndrome involving slow conjugation of bilirubin). 9. Adequate renal function defined as serum creatinine ≤ 1.5 mg/dL OR creatinine clearance ≥ 45 mL/min by Cockcroft-Gault formula for patients with serum creatinine > 1.5x ULN. 10. Adequate coagulation parameters, defined as International Normalization Ratio (INR) ≤ 2. Patients with history of blood clot may receive anticoagulation with low molecular weight heparin, central line prophylaxis-dose warfarin, or anti-factor Xa agents. 11. Women of childbearing potential must have a negative serum or urine pregnancy test performed ≤ 7 days prior to start of treatment. Women of childbearing potential or men with partners of childbearing potential must use effective birth control measures during treatment and during the 3 months following completion of study treatment. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately (Appendix D). 12. Life expectancy ≥ 3 months. 13. Age ≥ 18 years. 14. Willingness and ability to comply with study and follow-up procedures. 15. Ability to understand the nature of this study and give written informed consent.

Exclusion Criteria:	1. Patients who have received > 1 prior line of chemotherapy in the advanced or metastatic setting. (Immunotherapy, such as but not limited to PD-1/PDL-1 inhibitors, will not be considered a line of chemotherapy.) 2. Prior treatment with a PI3K/mTOR inhibitor, EGFR inhibitor, and/or necitumumab. 3. Patients who have received any other investigational agents, chemotherapy, biologic therapy, or radiation therapy (including whole brain radiation) within 28 days prior to Day 1 of Cycle 1. For investigational, chemotherapy, or biologic therapy, patients will be allowed on study if 5 half-lives or greater have elapsed since last dose of drug or 28 days, whichever is shorter. Treatment with limited radiation, including cyberknife, is allowed if completed ≥ 2 weeks prior to first study treatment, with approval of the medical monitor. 4. History of brain metastases unless irradiated prior to first study treatment and stable without requirement of corticosteroids. 5. Have serious pre-existing medical conditions, including major surgery within 30 days, (at the discretion of the investigator). 6. Have insulin-dependent diabetes mellitus. Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c < 7%. 7. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, Grade ≥ 2 diarrhea, and malabsorption syndrome). 8. Have a history of New York Heart Association (NYHA) Class ≥ 3 (Appendix B), Canadian Cardiovascular Society (CCS) Grade ≥ 3 (Appendix C), corrected QT (QTc) interval > 450 ms on screening electrocardiogram (ECG) per Fridericia's formula at several consecutive days of assessment, unstable angina, or myocardial infarction (MI) in 6 months prior to study drug administration. 9. Women who are pregnant or breast-feeding. 10. Clinically significant electrolyte imbalance ≥ Grade 2. 11. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin and oral Xa inhibitors are allowed. 12. Have initiated treatment with bisphosphonates or approved receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents (e.g. denosumab) ≤ 28 days prior to Day 1 of Cycle 1.

Exclusion Criteria, contd.:	13. Concurrent serious infection requiring parenteral antibiotic therapy. 14. Have a second primary malignancy that in the judgment of the investigator and Medical Monitor may affect the interpretation of results. 15. Have clinical evidence of concomitant infectious conditions including early signs of ongoing or active infection, tuberculosis or known infection with the human immunodeficiency virus (HIV) or hepatitis (HAV, HBV or HCV). Special attention should be paid to early signs of pulmonary infections in patients with large cavitary lesions. 16. The patient has a history of arterial thromboembolic event (ATE) or venous thromboembolic event (VTE) within 3 months prior to study enrollment. Patients with history of VTE beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin (LMWH). 17. Patients with known inherited thrombophilia (such as Factor V Leiden, Prothrombin 20210 mutation, protein C, protein S or antithrombin 3 deficiency; no screening required). 18. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
Correlative Testing:	Blood and tumor samples will be collected and may be evaluated for biomarkers including but not limited to the PI3K/mTOR and EGFR pathways.
Statistical Methodology:	This is a Phase II open-label, non-randomized 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. 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 spending function is 0.067 at the interim analysis and 0.131 at the final analysis. CCI [redacted]

LUN 288/I6A-MC-CBBE CONTACT INFORMATION

CRO Contact Information:	SCRI Innovations 3322 West End Avenue, Suite 900 Nashville, TN 37203 PPD
Study Chair:	PPD, MD Sarah Cannon Research Institute 3322 West End Avenue, Suite 900 Nashville, TN 37203 PPD
Medical Monitor:	PPD M.D. SCRI Innovations 3322 West End Avenue, Suite 900 Nashville, TN 37203 PPD
Sponsor Contact Information:	PPD MD, PhD Eli Lilly and Company Kolblgasse 8-10 A-1030 Vienna, Austria PPD
Sponsor Safety Dept. Fax #:	PPD
Regulatory Phone # / Fax #: **Regulatory Email:**	PPD

LIST OF ABBREVIATIONS

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

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1. INTRODUCTION

1.1 Background

Lung cancer is the second most common cancer in both men and women, after skin cancer. It is estimated that lung cancer accounts for about 13% of all new cancers, and about 27% of all cancer deaths. Each year more people die from lung cancer than from prostate, colon, and breast cancers combined. Patients with advanced or metastatic non-small cell lung cancer (NSCLC) continue to have a poor prognosis with standard treatments (Rooney et al. 2013). Squamous cell carcinoma is often linked to a history of smoking and comprises 25% to 30% of all lung cancers (American Cancer Society 2014).

1.2 Treatment for Non-Small Cell Lung Cancer

Platinum-containing chemotherapy for first-line treatment alone or in combination with other cytotoxic drugs is standard treatment (American Society of Clinical Oncology Guidelines 2014). Specifically for squamous cell lung cancers, first-line therapy options include platinum-taxane combinations and platinum-gemcitabine combinations, as pemetrexed has little efficacy for squamous cell lung cancers (Scagliotti et al. 2008, Syrigos et al. 2010). First-line combination chemotherapy is typically limited to 4 to 6 cycles of active therapy, followed by single agent maintenance therapy per National Comprehensive Cancer Network guidelines; however, a definitive standard of care has not been defined. Upon progression, second-line chemotherapy options have produced response rates in the 10% range, progression-free survival (PFS)/time to progression (TTP) in the 3-month range, and overall survival (OS) in the 7-month range (Dancey et al. 2004). Docetaxel, an FDA-approved taxane for the treatment of second-line advanced or metastatic NSCLC, has a response rate of 10.8% with 100 mg/m^2 and 6.7% with 75 mg/m^2 dosing, respectively, demonstrating a benefit to patients with disease that has relapsed or progressed after first line treatment (Shepherd et al. 2000, Fossella et al. 2000).

Molecularly targeted therapies, where treatment is based on mutations seen in individual patient tumors, have increased the survival benefit for subsets of NSCLC patient populations (Kris et al. 2014). Specifically, therapies targeting EGFR mutations and ALK translocations have shown benefit, as evidenced by the approvals of erlotinib (Mok et al. 2009, Mitsudomi et al. 2010, Maemondo et al. 2010, Rosell et al. 2012) and crizotinib (Kwak et al. 2010, Shaw et al. 2011, Camidge et al. 2012, Shaw et al. 2013). Therapies which target mutations in the MAPK and PI3K pathway are also showing promise, but have not yet shown definitive efficacy in randomized trials. However, significant molecularly targeted breakthroughs for patients with squamous cell lung cancers have not been achieved, in part, due to the low rates of EGFR mutation and ALK translocation in squamous cell lung cancers (Gold et al. 2012).

The PI3K/AKT signaling pathway is central to NSCLC growth and survival (Sacco et al. 2014). Approximately 6.5% of squamous cell lung cancer patients have PI3K mutations. An additional 33% have PI3K copy number gain. In addition, as high as 70% of squamous cell lung cancers have shown loss of PTEN, with PTEN mutation occurring in 10% (Kim et al. 2013). The PI3K pathway is therefore a promising target for treatment (Yamamoto et al. 2008, Herzog et al. 2013).

The REVEL trial (Lilly Study I4T-MC-JVBA), a randomized Phase III study of ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV NSCLC after disease progression on platinum-based therapy showed an increase in PFS and disease control rate (DCR) with the combination of ramucirumab and docetaxel over docetaxel alone. Ramucirumab is a human IgG1 monoclonal antibody that inhibits VEGFR-2. The combination therapy in this trial resulted in an overall DCR of 64% and median PFS of 4.5 months. These findings were largely consistent across the subgroups of squamous and non-squamous lung cancers (Garon et al. 2014). CCI [redacted]

1.3 LY3023414

LY3023414 is an orally available, small molecule dual kinase inhibitor of class I PI3K isoforms and mTOR with good solubility across a wide pH range. *In vitro* kinase studies have shown that LY3023414 binds to the adenosine triphosphate (ATP) active site of PI3K to competitively inhibit phosphorylation of PIP2 at low nanomolar concentrations. In nonclinical studies, LY3023414 has demonstrated potent *in vivo* target inhibition that was linked to potent antitumor efficacy. The nonclinical toxicology profile of LY3023414 has enabled a safe clinical starting dose, and a benefit-risk profile acceptable for cancer treatment, with toxicities observed in animal species that are manageable, readily monitored, and likely reversible. The Phase I first-in-human study is currently underway and is showing this drug to be well-tolerated with preliminary signs of clinical activity (see Investigator's Brochure [IB] and Section 1.3.3).

1.3.1 Nonclinical Toxicology and Safety Pharmacology

1.3.1.1 Nonclinical Toxicology

LY3023414 was evaluated in nonclinical toxicology studies up to 1 month in duration using daily oral dosing in rats and dogs to characterize the toxicity. Based on results from nonclinical studies in the rat and the dog, toxicities patients may experience include (but are not limited to) gastrointestinal toxicity, bone marrow and lymphoid organ toxicity (decreases in lymp hocytes), sores/scabbing of the skin, and adrenal toxicity. These toxicity effects are anticipated to be reversible. Pharmacologic effects of PI3K/mTOR inhibition related to glucose metabolism have also been observed, including hyperinsulinemia, hyperglycemia, and QT interval prolongation in nonclinical studies. In a rat embryo-fetal developmental pilot study of LY3023414, embryo-fetal lethality was seen along with an increase in fetal and litter incidence of external, visceral, and skeletal malformations.

For additional details on nonclinical toxicology data, see Section 5.2.1 of the IB.

1.3.1.2 Nonclinical Efficacy Pharmacology Summary

LY3023414 is a potent selective inhibitor of the class I PI3K isoforms, mTOR and DNA-PK, with selectivity in kinase enzyme assays as an ATP competitive inhibitor of PI3Kα (inhibition binding constant [Ki] of CCI [redacted]). LY3023414 demonstrated inhibitory activity against PI3K/mTOR pathway targets *in vitro* and *in vivo* as measured by phosphoprotein levels from cultured cells and tumor xenografts. LY3023414 showed antiproliferative and cell-cycle arresting effects in cultured cancer cells, and anti-angiogenesis activity via inhibition of *in vitro*

vascular cord formation. LY3023414 has excellent solubility and oral bioavailability across a wide pH range, allowing for simple suspension formulations to be used for oral administration in nude mice. In xenograft tumor models, LY3023414 demonstrated dose-and time-dependent target inhibition, as well as antitumor efficacy in a wide range of tumor models (including renal cancer and NSCLC). The mouse pharmacokinetic (PK)/pharmacodynamics (PDx) model indicates a direct inhibition of downstream target phosphoproteins (such as, phospho-AKT [pAKT], phospho -0S6K [p70S6K]). LY3023414 has potential for combination with standard of care agents to produce synergistic effects in cell culture and *in vivo* xenograft models.

1.3.2 Nonclinical Pharmacokinetics/Pharmacodynamics

Bioavailability of LY3023414 was CCI in dogs, and the clearance was less than hepatic blood flow. No accumulation of LY3023414 was noted following repeated dosing to rats and dogs. Also, no consistent gender differences in toxicokinetic parameters were observed in rats or dogs throughout a 1-month study. *In vivo* metabolism data showed that LY3023414 is metabolized predominantly via oxidation in rats and via oxidation and glucuronidation in dogs. In both species, LY3023414 was the largest circulating entity in plasma. Overall, clearance of LY3023414 in rats was primarily via metabolism while clearance in dogs involved metabolism as well as elimination via feces and urine. Fecal excretion was the major route of elimination for LY3023414-related radioactivity in both species.

1.3.3 Clinical Experience with LY3023414

One Phase I study I6A-MC-CBBA (Study CBBA) of LY3023414 is ongoing. Study CBBA is a multicenter, nonrandomized, open-label, First-in-Human dose escalation study followed by cohort expansion of oral LY3023414 in patients with advanced and/or metastatic cancer. Study CBBA was designed to evaluate the safety and tolerability of LY3023414 administered orally over 21 days (one cycle).

As of 26 September 2014, a total of 47 patients have received LY3023414 in the first-human-dose Study CBBA. Of these patients, a total of 40 patients (83%) experienced at least 1 possibly study drug-related, treatment-emergent adverse event (TEAE). The most common possibly LY3023414-related AEs reported in at least 10% of patients included nausea (37.5%), fatigue (31.3%), vomiting (27.1%), diarrhea (16.7%), decreased appetite (14.6%), anemia (14.6%), stomatitis (12.5%), and asthenia (10.4%). Most of these events were graded as mild or moderate by the investigators.

Dose-limiting toxicities (DLTs) for LY3023414 daily (QD) dosing have been reported at 450 mg LY3023414 in 3 out of 3 patients, including 1 case each of thrombocytopenia (Grade 4), hypotension (Grade 3), and hyperkalemia (Grade 3). Therefore, a dose of 325 mg LY3023414 was defined as the maximum tolerated dose (MTD) for QD dosing. For twice daily (BID) dosing, DLTs were observed in 3 out of 4 patients at the 250 mg BID LY3023414 dose in the form of hypophosphatemia (Grade 4), fatigue, and mucositis (Grade 3; all n = 1). At the next lower dose level of 200 mg BID in the dose escalation phase, 1 out of 6 patients experienced a DLT in the form of nausea (Grade 2; n = 1). Therefore, a dose of 200 mg LY3023414 was defined as the MTD for BID dosing.

At doses up to and including the MTD for QD and BID dosing (n = 31 patients, dose escalation phase), no study drug related Grade 4 AEs have been reported. Six possibly related Grade 3 AEs have been observed in those patients, including 1 case each of fatigue, hyperglycemia, hypokalemia, neutropenia, hypomagnesemia, and anemia (anemia occurred in a patient entering the study with Grade 2 anemia). LY3023414 200 mg BID was confirmed as the MTD based on the safety data on 9 additional patients (part B1 of Study CBBA). As of 26 September 2014, a total of 15 patients have received LY3023414 200 mg BID.

Initial clinical LY3023414 PK data showed that LY3023414 maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{∞}) increased approximately dose-proportionally from 20 to 325 mg QD (that is within the QD dose range determined to be safe). However, the C_{max} and AUC_{∞} increase was greater than dose proportional at 450 mg QD (i.e., that is at the dose exceeding the MTD). LY3023414 PK data following repeated BID dosing (dose range of 150 to 250 mg BID) were consistent with PK data following 20 to 325 mg QD. LY3023414 mean apparent clearance (CL/F) and mean apparent volume of distribution (Vz/F) were calculated to be 85 L/hr (CV% 56.8%) and 237 L (CV% 53.9%), respectively, across the 20 to 325-mg dose range based on Day 1 data. This clearance and volume lead to mean half-life ($t_{1/2}$) of 1.93 hours (coefficient of variation CV% = 42.9%; n = 38 for all doses combined within a dose-proportionality range of 20 mg to 325 mg).

The relative contribution of microsomal CYP-mediated clearance of LY3023414 was studied *in vitro* using human liver microsomes. Based on a substrate depletion approach, CYP 3A and CYP1A2 are responsible for 82% and 18% of hepatic CYP-mediated clearance of LY3023414, respectively. No *in vivo* data are yet available.

The recent data from study CBBA indicate that LY3023414 is a weak inhibitor of CYP3A4. Concomitant administration of LY3023414 and midazolam lead to increase in midazolam exposure (fold increase: mean 1.459 [CV 30.5 %] [90% CI 1.21 – 1.76]). Hence LY3023414 may lead to increase in exposure of drugs predominantly cleared by CYP3A4.

Biomarker assessment demonstrated target inhibition as measured by p4EBP1 inhibition in peripheral blood mononuclear cells (PBMC) at LY3023414 dose levels greater or equal to 150 mg QD in a dose related manner. With respect to anti-tumor activity, clinical benefit was observed in patients treated on both schedules of LY3023414, including 1 patient with a confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer et al. 2009) and 10 additional patients (26.3%) who demonstrated a decrease in their tumor target lesion as best response to LY3023414 monotherapy in the dose-escalation part of Study CBBA (see Section 6.2.2 of the IB).

Based on the safety and tolerability, PK, target inhibition, and preliminary activity data outlined above, the recommended dose for LY3023414 is 200 mg by mouth (PO) BID.

Additional data are available in the latest LY3023414 Investigator's Brochure (IB).

1.4 Necitumumab

Necitumumab is a recombinant human monoclonal antibody (mAb) of the immunoglobin G, subclass 1, which blocks the ligand binding site of the epidermal growth factor receptor (EGFR). Necitumumab has shown *in vivo* antitumor activity against a variety of human xenograft tumors,

including NSCLC. Preclinical studies were conducted using mice with lung cancer xenografts (NCI-H1975 and NCI-H292) administered necitumumab as monotherapy. In these studies, administration of necitumumab inhibited the growth of both xenograft models; antitumor activity was statistically significant for both models at all dose levels.

The necitumumab Phase I program included 2 single-agent dose-escalation Phase I trials in Western (I4T-IE-JFCE [JFCE]) and Japanese (I4T-IE-JFCA [JFCA]) patients with advanced solid tumors or for which no standard therapy was available.

Study JFCE included 60 patients and investigated necitumumab intravenous (IV) once a week (Arm A, n=29) or once every 2 weeks (Arm B, n=31) at sequential absolute dose levels from 100 mg to 1000 mg. Safety data from Study CP11-0401JFCE demonstrated that the maximum tolerated dose (MTD) of necitumumab is 800 mg once weekly or once every 2 weeks (Kuenen et al. 2010). The major dose limiting toxicity (DLT) was Grade 3 headache. The most common drug-related AEs were typical for this class of agents and consisted of skin reactions, headache, nausea/vomiting, and fatigue (mostly of Grades 1 and 2) (for details, see Section 6.2.1.1 of necitumumab IB). In Study JFCA, 15 patients were enrolled and treated (Cohort 1: 600 mg necitumumab on Days 1 and 8 of a 3-week cycle, n = 3; Cohort 2: 800 mg every 2 weeks, n = 6; and Cohort 3: 800 mg on Days 1 and 8 of a 3-week cycle, n = 6).

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

Based on both Phase I trials, the recommended necitumumab dosing schedule is 800 mg once every week, once every 2 weeks, or on Days 1 and 8 of a 3-week cycle.

The pivotal, randomized Phase III trial SQUIRE (I4T-IE-JFCC) compared gemcitabine/cisplatin plus necitumumab (GC+N) versus gemcitabine/cisplatin (GC) as first-line therapy in 1093 patients with Stage IV squamous NSCLC (Thatcher et al. 2014). The study met its primary objective, demonstrating a statistically significant improvement in overall survival (OS) in the GC+N Arm compared with the GC Arm (hazard ratio [HR] = 0.84; p=0.012). This was supported by a statistically significant improvement in progression-free survival (PFS; HR = 0.85; p=0.02). Several prespecified subgroup analyses for OS and PFS showed a consistent treatment effect in favor of GC+N. Post-progression anticancer therapy was similar (47% vs. 45%).

Additional data are available in the latest necitumumab Investigator's Brochure (IB)

1.5 Rationale for the Study

Preclinical data has suggested that the PI3K pathway plays a role in the antitumor efficacy of EGFR antibodies. In NSCLC models, acquired cetuximab resistance is mediated by increased PTEN instability (Kim et al. 2010). In head and neck squamous cell carcinoma (HNSCC) models, resistance to cetuximab may be bypassed by inhibition of AKT (Rebucci et al. 2011). In patients with colorectal cancer, resistance to cetuximab is increased in patients with PI3K

mutations and aberrations in PTEN (Sood et al. 2012). In addition, internal preclinical data from Lilly shows that in squamous patient-derived xenograft models, the combination of necitumumab and LY3023414 resulted in improved anti-tumor activity relative to monotherapy with necitumumab or LY3023414 alone.

Based on the need for better treatment options after first-line therapy for patients with squamous cell lung cancer, the benefit recently seen with necitumumab, the preclinical synergy of LY3023414 and necitumumab, and the favorable safety profile of LY3023414 and necitumumab, a combination trial of necitumumab plus LY3023414 in patients with advanced or metastatic squamous NSCLC which has relapsed or progressed after first-line treatment with a platinum-containing regimen is proposed to explore whether the 6-month DCR with this combination will confer a greater benefit than what has been observed for patients with squamous histology in the REVEL study (Lilly Study I4T-MC-JVBA).

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To evaluate the 6-month 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.

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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.

2.3 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.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the research study:

1. Histologically confirmed squamous advanced NSCLC (Stage IV).
2. Patients must have progressed on one prior line of platinum-based chemotherapy in the advanced or metastatic setting. (Immunotherapy, such as but not limited to PD-1/PDL-1 inhibitors, will not be considered a line of chemotherapy.)
3. Measurable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria v 1.1 (Appendix F).
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
5. Able to swallow the study drugs whole.
6. Resolution of side effects from prior treatment, including neuropathy, to CTCAE Grade 1 or baseline (with the exception of alopecia).
7. Adequate hematologic function defined as:
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Platelets ≥100,000/μL
   - Hemoglobin ≥ 8 g/dL
8. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN). If the liver has tumor involvement, AST and ALT equaling ≤ 5 times ULN are acceptable.
   - Total bilirubin ≤ 1.5 x ULN (or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal limits in subjects with well documented Gilbert's Syndrome or a similar syndrome involving slow conjugation of bilirubin).
9. Adequate renal function defined as serum creatinine ≤ 1.5 mg/dL OR creatinine clearance ≥ 45 mL/min by Cockcroft-Gault formula for patients with serum creatinine > 1.5x ULN.
10. Adequate coagulation parameters, defined as International Normalization Ratio (INR) ≤ 2. Patients with history of blood clot may receive anticoagulation with low molecular weight heparin, central line prophylaxis-dose warfarin, or anti-factor Xa agents.
11. Women of childbearing potential must have a negative serum or urine pregnancy test performed ≤ 7 days prior to start of treatment. Women of childbearing potential or men with partners of childbearing potential must use effective birth control measures during treatment and during the 3 months following completion of study treatment. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately (Appendix D).

12. Life expectancy ≥ 3 months.
13. Age ≥18 years.
14. Willingness and ability to comply with study and follow-up procedures.
15. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients who have received > 1 prior line of chemotherapy in the advanced or metastatic setting. (Immunotherapy, such as but not limited to PD-1/PDL-1 inhibitors, will not be considered a line of chemotherapy.)
2. Prior treatment with a PI3K/mTOR inhibitor, EGFR inhibitor, and/or necitumumab.
3. Patients who have received any other investigational agents, chemotherapy, biologic therapy, or radiation therapy (including whole brain radiation) within 28 days prior to Day 1 of Cycle 1. For investigational, chemotherapy, or biologic therapy, patients will be allowed on study if 5 half-lives or greater have elapsed since last dose of drug or 28 days, whichever is shorter. Treatment with limited radiation, including cyberknife, is allowed if completed ≥ 2 weeks prior to first study treatment, with approval of the medical monitor.
4. History of brain metastases unless irradiated prior to first study treatment and stable without requirement of corticosteroids.
5. Have serious pre-existing medical conditions, including major surgery within 30 days, (at the discretion of the investigator).
6. Have insulin-dependent diabetes mellitus. Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c < 7%.
7. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, Grade ≥ 2 diarrhea, and malabsorption syndrome).
8. Have a history of New York Heart Association (NYHA) Class ≥ 3 (Appendix B), Canadian Cardiovascular Society (CCS) Grade ≥ 3 (Appendix C), corrected QT (QTc) interval > 450 ms on screening electrocardiogram (ECG) per Fridericia's formula at several consecutive days of assessment, unstable angina, or myocardial infarction (MI) in 6 months prior to study drug administration.
9. Women who are pregnant or breast-feeding.
10. Clinically significant electrolyte imbalance ≥ Grade 2.
11. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin and oral Xa inhibitors are allowed.

12. Have initiated treatment with bisphosphonates or approved receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents (e.g. denosumab) ≤ 28 days prior to Day 1 of Cycle 1.
13. Concurrent serious infection requiring parenteral antibiotic therapy.
14. Have a second primary malignancy that in the judgment of the investigator and Medical Monitor may affect the interpretation of results.
15. Have clinical evidence of concomitant infectious conditions including early signs of ongoing or active infection, tuberculosis or known infection with the human immunodeficiency virus (HIV) or hepatitis (HAV, HBV or HCV). Special attention should be paid to early signs of pulmonary infections in patients with large cavitary lesions.
16. The patient has a history of arterial thromboembolic event (ATE) or venous thromboembolic event (VTE) within 3 months prior to study enrollment. Patients with history of VTE beyond 3 months prior to study enrollment can be enrolled if they are appropriately treated with low molecular weight heparin (LMWH).
17. Patients with known inherited thrombophilia (such as Factor V Leiden, Prothrombin 20210 mutation, protein C, protein S or antithrombin 3 deficiency; no screening required).
18. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable AE thought to be related to study drug(s) (e.g. infusion related reactions ≥ Grade 3 to necitumumab)
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Inability of the patient to comply with study requirements or lost to follow -up
- Patient requests to discontinue treatment
- Patient withdraws consent
- Investigator or Sponsor team, for any ethical, medical, or scientific reason, while considering the rights, safety, and well-being of the patient(s), stops the study treatment.
- Any patient requiring an AE-related dose delay of more than 21 days due to a study drug related AE must be discontinued from the study treatment, unless discussed with the Medical Monitor.

Refer to Section 7.6 for Follow-Up information.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Institutional Review Board (IRB) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patient registration will be performed by SCRI Innovations and will be outlined in the Study Reference Manual.

5. 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.

Safety Lead-In Cohort

Since the combination of LY3023414 and necitumumab will be given for the first time to humans, a safety lead-in cohort will be conducted. After at least 6 patients have been treated for a full cycle in the lead-in cohort, 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 3 or 2 (or more) of 6 patients in the lead-in cohort experience DLTs as defined in Section 5, 3 to 6 additional patients will be treated at the next 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). All outcomes from these safety reviews will be communicated in a timely manner to the participating investigators so that they may notify their IRBs. No amendment will be needed to proceed with a lower dose level of study drug(s).

The SIMC will, at a minimum, be composed of a Sponsor-Assigned Clinical Research Physician, Study Chair, Medical Monitor, Sponsor-Assigned Safety Scientist, and Biostatistician.

A toxicity will be considered dose-limiting, if it occurs within the first cycle of treatment (21 days) to lead-in patients and is deemed at least possibly related to study drug.

Dose-limiting toxicities will be defined as any of the following AEs:

- Grade 4 thrombocytopenia; Grade 4 neutropenia ≥ 7 days; Grade ≥ 3 febrile neutropenia; and Grade ≥ 3 thrombocytopenia with Grade ≥ 2 hemorrhage
- Grade ≥ 3 non-hematologic toxicity despite maximal medical management with the exception of:
    - Diarrhea, nausea, or vomiting that resolves to ≤ Grade 2 within 48 hours
    - Skin toxicity that resolves to ≤ Grade 2 within 7 days
    - ALT/AST elevation that resolves to ≤ Grade 2 within 7 days
    - Hypomagnesemia that resolves to ≤ Grade 2 within 7 days
    - Grade 3 mucositis that resolves to ≤ Grade 2 within 7 days. Grade 4 mucositis of any duration will be considered a DLT.
    - Grade 3 fasting hyperglycemia that resolves to ≤ Grade 2 within 7 days. Grade 4 hyperglycemia of any duration that results in intensive care unit admission will be considered a DLT.
    - Grade 3 fatigue that resolves to ≤ Grade 2 within 5 days.
    - Grade 3 hypertension controlled with medical therapy.
    - Any lab abnormalities that are not clinically significant and resolve in 72 hours.
    - Infusion reactions attributed only to necitumumab
- Hy's law: Hepatocellular injury defined as ALT (or AST) > 3x ULN and total bilirubin > 2x ULN with no significant cholestasis (ALP< 2 x ULN) and no other cause which explains the abnormality in liver tests.
- Grade >2 skin toxicities despite best supportive care
- Unresolved AE that leads to treatment delay of ≥ 14 days
- Any other clinically significant study drug related AE which does not respond to supportive care, or is judged to be an unacceptable and/or unmanageable by the investigator in collaboration with the Medical Monitor.

Determination of Dose-Limiting Toxicities

The patient population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 75% of study drug regimen (LY3023414 and necitumumab) and is observed for at least 21 days following the first dose of study drugs. Any patients enrolled in the lead-in cohort that do not meet the dosing criteria defined above in order to be considered complete will be replaced.

Post Lead-In Cohort

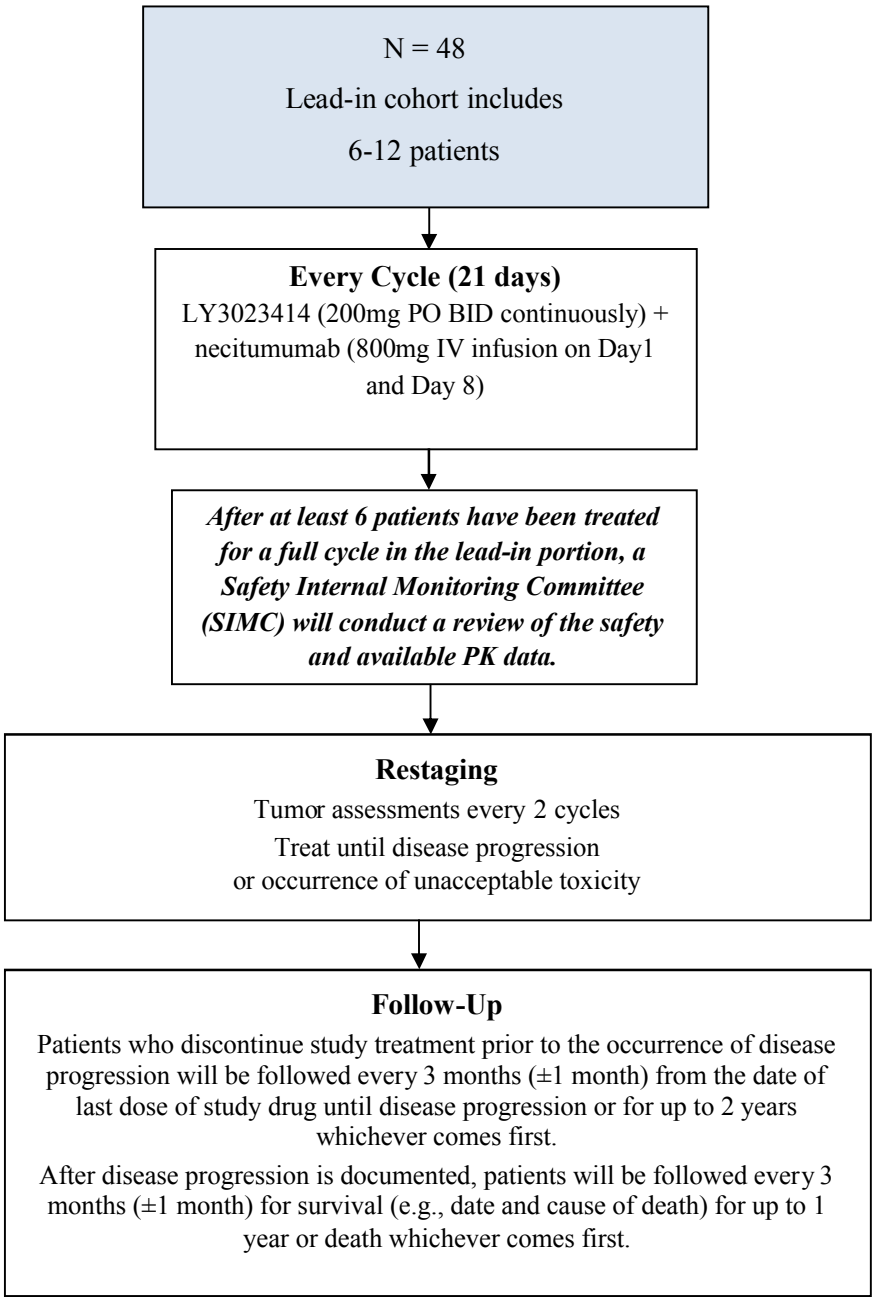
Following the confirmation of safety for the combination of LY3023414 and necitumumab by the SIMC, the study will continue to enroll up to a total of approximately 48 evaluable patients, with a planned interim analysis after 24 patients have completed 6 months of follow-up. The interim analysis will be performed purely for the purpose of detecting an 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 RECIST v1.1, or any other discontinuation criteria outlined in Section 3.3 as applicable. Patients will be evaluated for response to treatment after every 2 cycles.

As further clinical data become available, this clinical trial may be amended to include the addition of other agents to the combination of necitumumab and/or LY3023414.

The Study Schema is presented in Figure 1.

Figure 1 Study Schema



5.1 Treatment Plan

5.1.1 LY3023414

LY3023414 will be self-administered by the patient PO BID on continuous daily dosing.

Patients should take the morning and evening doses of LY3023414 approximately 12 hours apart (preferably within a 10- to 14-hour range). Patients should not consume food for approximately 1 hour before taking the dose of LY3023414 and should remain in a fasted stated for 1 hour post-necitumumab infusion. LY3023414 should be taken with a glass of water at approximately the same time each day. Patients should swallow the capsules as a whole and should not chew or crush them.

If the patient misses a dose of LY3023414, the patient should take the dose as soon as possible, but not less than 6 hours before the next dose is due for twice daily dosing. If the next dose is due in less than 6 hours, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking LY3023414, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of LY3023414. If vomiting persists the patient should contact the investigator.

LY3023414 compliance will be assessed by pill counts on Day 1 of each cycle. The research staff will count and document the amount of LY3023414 taken and returned by the patient.

5.1.2 Necitumumab

All patients will receive 800 mg of necitumumab by IV over 50 minutes on Days 1 and 8 of each 21-day cycle. The infusion of necitumumab should start shortly (within 15 min) after the oral administration of LY3023414 on days that PKs are being collected. Patients should remain in a fasted stated for 1 hour post-necitumumab infusion.

5.1.2.1 Premedication for Necitumumab after Cycle 1

Routine premedication prior to the administration of necitumumab is not mandatory, except in patients who have experienced a hypersensitivity/infusion-related reaction (IRR) to necitumumab.

Patients who have experienced any prior Grade 1-2 hypersensitivity/IRR during the infusion of necitumumab should receive premedication with an antihistamine prior to all subsequent infusions. After the second occurrence of a Grade 1-2 hypersensitivity/IRR, a corticosteroid and an antipyretic (e.g., acetaminophen) should be added to the premedication regimen. Additional premedication may be administered at the discretion of the investigator. For dose reductions and more information see Section 6.1.1.

Treatment with skin moisturizers, topical steroids, oral doxycycline, or sunscreen may be administered as clinically appropriate to patients receiving necitumumab (Mitchell et al. 2008). For additional information regarding reactive management of skin toxicity, see Section 6.1.2 for more information.

As with all concomitant medications/procedures, any actions taken to ameliorate skin toxicity with preemptive medications or procedures will be documented in the concomi tant medication module of the eCRF.

5.2 Treatment Duration

The end of the study treatment is defined as the date of the last dose of the last patient receiving study medication.

Patients will be evaluated for toxicity at the start of each cycle. Every 2 cycles, restaging will occur with imaging, laboratory chemistries, and tumor markers as defined in Appendix E (Schedule of Assessments).

Patients will be allowed to continue on therapy as long as they do not meet the discontinuation criteria listed in Section 3.3, and are considered, by the investigator, to still be receiving clinical benefit (patients may continue on therapy after progression criteria have been met only if they are considered to be receiving clinical benefit after consulting with the study Medical Monitor and depending upon availability of study drug).

5.3 Concomitant Medications

Medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 5.3.2. At each visit, patients will be asked about any new medications they are taking or have taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics is allowed according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines
- Anticoagulation with couma din-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Should a thrombotic event occur while the patient is receiving treatment the patient may continue, but low molecular weight heparin (LMWH) will be the preferred treatment.
- Patients who develop hyperglycemia during the study should be treated according to the American Diabetes Association guidelines. It is recommended to start treatment with metformin if hyperglycemia occurs.

See Section 5.1.2.1 for additional medications allowed.

Palliative radiation treatment may be allowed after discussion and approval by Medical Monitor.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.

5.3.3 Concomitant Medications to be avoided

LY3023414 is a weak inhibitor of CYP3A4 based on *in vivo* data generated during the DDI arm of clinical study CBBA (exposure of probe substrate midazolam increased but the increase was less than 2-fold). Therefore drugs that are either sensitive substrates of CYP3A4 or CYP3A4 substrates with a narrow therapeutic range should be administered with caution in combination with LY3023414.

In vitro data showed that the major cytochrome P450 involved in the clearance of LY3023414 was identified as CYP3A (~80%) and approximately 20% of LY3023414 is metabolized by CYP1A2.

Therefore, it is recommended to:

- Avoid, if possible, strong inhibitors of CYP3A4 and strong and moderate inducers of CYP3A4 (Appendix I).
- Avoid drugs causing QTc interval prolongations (Appendix G, Appendix H).
- Avoid smoking and record smoking history for all patients.
- Avoid grapefruit, Seville oranges, or Star fruit.
- Avoid herbal preparations/medications throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

5.4 Correlative Studies

Biological samples (i.e., blood and fresh or archival tissue samples, primary or metastatic lesions) will be requested and may be analyzed to identify potential biomarkers predictive of clinical efficacy of the study drugs and disease progression in this patient population. The time points for the collection of samples for correlative testing are specified in Appendix E.

Tumor biopsy specimens from the primary site or from metastatic lesions from all patients will be collected. Tumor and blood specimens may be tested for biomarkers including, but not limited to, CCI [redacted]. The status of these biomarkers may be analyzed in an attempt to correlate to the clinical patient outcome (e.g. 6-month DCR, ORR and PFS). Blood samples drawn from the patients at baseline, Day 1 of Cycle 1 and Cycle 3, and every 2 cycles thereafter, and at the End of

Treatment visit may be assessed to explore potential gene signature(s) for clinical benefit to study treatment, such as *PI3K/mTOR* and *EGFR*.

Information regarding shipment, handling, and length of retention time, etc. of tissue and blood will be provided in the Laboratory Manual.

5.4.1 Samples for Biomarkers

Collection of samples for biomarker research is also part of this study. Blood and tissue samples will be collected.

Samples for biomarker research to be collected from all patients in this study are in Table 1.

Table 1 Biomarker Sample Collection Times

Sample	Baseline	C1D1 pre-dose	C3D1 pre-dose	CX*D1 pre-dose	End of Treatment
Biomarker Blood	✓	✓	✓	✓	✓
Tumor Tissue**	✓				

* Day 1 of every 2 cycles (C5D1, C7D1, etc.)

** Archival or fresh, primary or metastatic lesions

If a patient has available archived tumor tissue, no pretreatment biopsy is required. If archived tissue is not available, a fresh tumor biopsy should be obtained after all other study entry criteria have been confirmed, unless in exceptional cases the Medical Monitor and Investigator agree and document that the patient may be enrolled without pretreatment tumor tissue.

For patients in the study, a small amount of preserved tumor tissue previously (for example, at diagnosis) taken to evaluate the patient's disease will be required for biomarker research. Pretreatment formalin-fixed paraffin-embedded tumor tissue should be in a block, or unstained slides. Any block submitted will be returned to the site after sectioning; slides will not be returned.

A tissue biopsy may be taken to provide the required tissue. Details for the handling and shipping of the tumor tissue will be provided by the Sponsor in a separate document. The tissue samples will be obtained using appropriate method. However, cytological or fine-needle aspiration specimens are not acceptable. Due diligence should be used to ensure that tumor specimen (not normal adjacent or tumor margins) is provided. Pathology reports accompanying the tissue may also be requested. Each sample will be labeled with the patient number and will be stored for up to 15 years after the last patient visit at a facility selected by the Sponsor.

Samples may be tested to identify biomarkers predictive of clinical efficacy and disease progression as well as to CCI [redacted] CCI

Samples will be stored and analysis may be performed on biomarker variants thought to play a role in CCI [redacted]

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the Sponsor to respond to regulatory requests related to the LY3023414 and necitumumab.

Samples will be destroyed according to a process consistent with local regulation.

It is possible that biomarker data has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, this data may be requested from medical records for use in the research described in this section.

5.5 Pharmacokinetic Assessments

Information about LY3023414 PK is available in Section 1.3.3 and in the LY3023414 IB. Information about necitumumab PK is available in the necitumumab IB.

CCI [redacted] LY3023414 PK will be investigated at steady state in this study CBBE on Day 8 of Cycle 1 and 3 and Day 1 of Cycle 1, 2, and 6. A limited PK sampling will be implemented in this study as illustrated in Table 2 and Table 3. This sampling scheme aimed at capturing LY3023414 pre-dose and C_{max} (LY3023414 concentrations reach a maximum value at approximately 1 to 2 hours post-dose). The mean half-life ($t_{½}$) of LY3023414 is approximately 2 hours (range 1 to 5 hours). Given all this information, the proposed sampling scheme in Table 2 and Table 3 is adequate to estimate LY3023414 PK using non-linear mixed effect modelling technique.

Necitumumab pharmacokinetics have been investigated across a range of studies in cancer patients, and a population PK analysis indicate target mediated drug distribution and a half-life of approximately 2 weeks, in accordance with other IgG type mAbs. Based on the long half-life of the drug and the availability of a population PK model, the proposed sampling scheme in Table 2 and Table 3 is adequate to estimate necitumumab PK using non-linear mixed effects modelling techniques.

5.5.1 Bio-Analytical Assays for Drug Concentration Measurements Pharmacokinetics Samples

LY3023414 concentration will be characterized in whole blood (per the schedule presented in Table 2 and Table 3). Venous blood will be drawn at each time point using a micro sampling technique (dried blood spot [DBS] sampling) for quantifying LY3023414 concentration. In the lead-in cohort (i.e. in the initial cohort of 6 and up to 12 patients), classical plasma samples will also be drawn to compare LY3023414 plasma concentrations and DBS concentrations. Detailed instructions and supplies for the collection, handling, and shipping of blood and plasma samples will be provided by the laboratory manual. LY3023414 will be assayed using a validated DBS or plasma liquid chromatography (LC)-mass spectrometry (MS)/MS method.

Necitumumab concentrations will be characterized in serum per the schedule presented in Table 2 and Table 3 Section 5.5 using a validated enzyme-linked immunosorbent assay (ELISA).

A maximum of 5 samples may be collected at additional time points during the study in addition to the planned sampling schedule if warranted and agreed upon between both the Investigator and Study team.

Bioanalytical samples collected to measure LY3023414 and necitumumab concentrations will be retained for a maximum of 1 year following last patient visit for the study.

Samples will be destroyed according to a process consistent with local regulation.

5.5.2 Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against necitumumab. Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of necitumumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of necitumumab. Immunogenicity samples will be collected according to the schedule in Table 2 and Table 3.

When any immunogenicity sample is drawn, a sample for drug concentration measurement (PK) should also be drawn and analyzed to allow interpretation of immune response.

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

Table 2 Pharmacokinetic and Immunogenicity Sample Collection Times for Assessment of LY3023414 and Necitumumab Concentration – Lead-In Patients

Study Visit	Collection Time (± 15 minutes)	LY3023414 PK-DBS/Plasma Sample	Necitumumab PK Serum Sample	Necitumumab Immunogenicity Sample[e]
Cycle 1 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	X
Cycle 1 Day 8	Pre-dose of LY3023414 and necitumumab[a]	X	X	
Cycle 1 Day 8	At the end of infusion (EOI) of necitumumab[b]	X	X	
Cycle 1 Day 8	1 hour post EOI[c,d]	X	X	
Cycle 2 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	X
Cycle 3 Day 8	Pre-dose of LY3023414 and necitumumab[a]	X	X	
Cycle 3 Day 8	At the EOI of necitumumab[b]	X	X	
Cycle 3 Day 8	1 hour post EOI[c,d]	X	X	
Cycle 4 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	X
Cycle 6 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	
End of Treatment	~ 30 days post last dose	X	X	X

a: The infusion of necitumumab should start shortly (within 15 min) after the oral administration of LY3023414.

b: This end of necitumumab infusion time point corresponds to approximately 1hour post LY3023414 dose.

c: This time point, 1 hour post end of necitumumab infusion, corresponds to approximately 2 hours post LY3023414 dose.

d: 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.

e: 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.

Table 3 Pharmacokinetic and Immunogenicity Sample Collection Times for Assessment of LY3023414 and Necitumumab Concentration – Post Lead-In Patients

Study Visit	Collection Time (± 15 minutes)	LY3023414 PK-DBS Sample	Necitumumab PK Serum Sample	Necitumumab Immunogenicity Sample[e]
Cycle 1 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	X
Cycle 1 Day 8	Pre-dose of LY3023414 and necitumumab[a]	X	X	
Cycle 1 Day 8	At the end of infusion (EOI) of necitumumab[b]	X	X	
Cycle 1 Day 8	1 hour post EOI[c,d]	X	X	
Cycle 2 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	X
Cycle 3 Day 8	Pre-dose of LY3023414 and necitumumab[a]	X	X	
Cycle 3 Day 8	At the EOI of necitumumab[b]	X	X	
Cycle 3 Day 8	1 hour post EOI[c,d]	X	X	
Cycle 4 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	X
Cycle 6 Day 1	Pre-dose of LY3023414 and necitumumab[a,d]	X	X	
End of Treatment	~ 30 days post last dose	X	X	X

a: The infusion of necitumumab should start shortly (within 15 min) after the oral administration of LY3023414.

b: This end of necitumumab infusion time point corresponds to approximately 1 hour post LY3023414 dose.

c: This time point, 1 hour post end of necitumumab infusion, corresponds to approximately 2 hours post LY3023414 dose.

d: 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.

e: 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.

On the days when PK samples are collected, patients will not take the morning LY3023414 dose and will not receive their necitumumab infusion until after the pre-dose specimen is obtained.

On the PK days the date and time and amount of the LY3023414 doses associated with the LY3023414 PK samples must be recorded in the eCRF.

The date and time of samples collection will be recorded on the requisition form.

Information regarding shipment, handling, and length of retention time, etc. of PK samples will be provided in the Laboratory Manual.

5.6 Samples for Pharmacogenomic Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ethical review boards (ERBs) allow, a blood/saliva sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3023414 and necitumumab. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

6. DOSE MODIFICATIONS

If an AE occurs, the AE will be graded utilizing the NCI CTCAE v 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), and appropriate supportive care treatment will be administered as needed to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Doses of LY3023414 and necitumumab will be modified based on hematologic and non-hematologic toxicity. If dose reductions are necessary, they will be permanent for the remainder of the treatment except as noted below in Table 6 for necitumumab due to Grade 3 skin reaction.

Doses of necitumumab and LY3023414 may be adjusted according to Table 4. If the responsible study drug can be identified, it may be omitted or reduced according to the dose modification table and the patient may continue with the other study drug, as appropriate. For toxicities possibly caused by both drugs, both drugs may be omitted or the dose levels of both may be

reduced. If the patient is receiving the lowest allowable dose and experiences an AE requiring a dose reduction, the offending study drug should be discontinued. If the offending study drug is discontinued, the patient may continue single-agent treatment.

If any AE occurs, it should resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment taking into consideration the recommendations below.

If a patient experiences a Grade 3 drug related AE or an intolerable Grade 2 AE (with the exception of skin toxicity, see Table 6), omit dosing of the offending study drug(s) until symptoms improve to ≤ Grade 1 or baseline, then resume at a reduced dose of the offending study drug(s) according to Table 4. Permanently discontinue study drugs for Grade 4 AEs. Grade 3 or 4 laboratory changes that are not clinically significant and which can be corrected within 48 hours may not require dose modification.

Re-escalation of study drug(s) may be considered if clinically warranted, following discussion and approval by the Medical Monitor. Re-challenge of patients with dose-reduced study drug(s) following recovery from Grade 4 AEs may be considered on a case-by-case basis in consultation with the Medical Monitor.

For specific necitumumab modifications, see section 6.1.

Any patient requiring an AE-related dose delay of more than 21 days after Cycle 1 from the intended day of the next scheduled dose due to a study drug related AE should be discontinued from the study, unless discussed with the Medical Monitor.

Dose omissions within a cycle do not alter the start of the next scheduled cycle. Missed doses of necitumumab or LY3023414 will not be made up.

A maximum of two dose reductions per drug are allowed in this study. If more than two dose reductions of study drug(s) are necessary for a patient, the responsible agent will be discontinued.

Table 4 Dose Level Modifications

Dose Level	LY3023414*	Necitumumab*
Starting Dose	200 mg PO BID	800 mg IV
Dose Level -1	150 mg PO BID	600 mg IV
Dose Level -2	100 mg PO BID	400 mg IV

*If the responsible study drug can be identified, it may be omitted or reduced according to the dose modification table and the patient may continue with the other study drug, as appropriate.

6.1 Necitumumab Non-Hematologic Toxicities

Dose modifications for non-hematologic toxicities due to necitumumab are summarized below in Table 5 and Table 6.

6.1.1 Hypersensitivity/Infusion-Related Reactions

As with other monoclonal antibodies, hypersensitivity/IRRs may occur during or following necitumumab administration. As a routine precaution each visit, patients treated with

necitumumab should be closely monitored for signs and symptoms indicative of a hypersensitivity/IRR by the medical staff from the start of the infusion until at least 1 hour after the end of the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisolone equivalents, etc.) available.

Hypersensitivity/IRRs are defined according to the NCI-CTCAE Version 4.03 definition of allergic reaction / hypersensitivity, as follows:

- Grade 1: transient flushing or rash, drug fever < 38°C
- Grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥ 38°C
- Grade 3: symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema, hypotension
- Grade 4: anaphylaxis (a life-threatening event characterized by the rapid onset [often within minutes] of airway obstruction [bronchospasm, stridor, hoarseness], urticaria, and/or hypotension)

Consistent with usual medical practice, selected parenteral medications may be utilized as detailed below (Table 5). Additional treatments, chosen according to clinical symptoms and institutional standard of care, may be utilized at investigator discretion.

Table 5 Infusion-Related Reactions – Management Recommendations

Toxicity	First Occurrence	Second Occurrence
Grade 1	• Decrease infusion rate by 50% for the duration of the infusion, and monitor patient for worsening of condition[a]. • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.	• Decrease infusion rate by 50% for the duration of the infusion, and monitor patient for worsening of condition[a]. • Administer dexamethasone 10 mg IV (or equivalent). • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally (or equivalent), and dexamethasone 10 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.
Grade 2	• Stop the infusion, and resume the infusion when the infusion reaction has resolved to ≤ Grade 1; decrease infusion rate by 50% when the infusion resumes[a]. • Monitor patient for worsening of condition. • If necessary, administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.	• Stop the infusion, and resume the infusion when the infusion reaction has resolved to ≤ Grade 1; decrease infusion rate by 50% when the infusion resumes[a]. • Administer dexamethasone 10 mg IV (or equivalent). • Monitor patient for worsening of condition. • If necessary, administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally (or equivalent), and dexamethasone 10 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

[a] Once the infusion rate has been reduced for a Grade 1-2 reaction, it is recommended that the lower rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

Table 5 Infusion-Related Reactions – Management Recommendations (continued)

Toxicity	First Occurrence	Second Occurrence
Grade 3-4	• Stop the infusion and disconnect the infusion tubing from the patient. • Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 10 mg IV (or equivalent), bronchodilators for bronchospasm, epinephrine, and other medications / treatments as medically indicated. • Hospital admission may be indicated. • **Permanently discontinue necitumumab.**	• N/A

If a patient should have a hypersensitivity/IRR to necitumumab, all attempts should be made to obtain a blood sample for assessment of anti-necitumumab antibody and necitumumab concentration as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event.

In addition, these same samples may be assessed for PDx markers to provide information on the nature of the infusion reaction.

6.1.2 Skin Reactions

If a patient experiences a Grade 1-2 acne-like rash, necitumumab treatment should continue without dose modification or delay. Reactive treatment recommendations for skin reaction, based on the Canadian recommendations presented by Melosky et al. 2009 are summarized in Table 6.

Table 6 Skin Reactions – Management Recommendations

Toxicity	Management Recommendations
Grade 1	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity.
Grade 2	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • If clinically appropriate in the opinion of the investigator, administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity.

Table 6 Skin Reactions – Management Recommendations (continued)

Toxicity	Management Recommendations
Grade 3	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity. • Necitumumab administration will be temporarily withheld until symptoms resolve to Grade ≤ 2, but not for longer than a maximum of 6 weeks following Day 1 of the most recent treatment cycle. • Following improvement to Grade ≤ 2, necitumumab may be readministered, with a dose reduction of 50% (400 mg). This dose may be increased to 75% of the original dose (600 mg) after a minimum of one treatment cycle (3 weeks), if symptoms do not recur. If symptoms do not recur for another treatment cycle, the dose may be re-escalated to the full recommended dose (800 mg). • If reactions do not resolve to Grade ≤ 2 after 6 weeks (that is, after withholding 2 consecutive doses of necitumumab), or if reactions recur or become intolerable at 50% of the original dose, necitumumab treatment should be permanently discontinued. • Patients who experience Grade 3 skin induration/fibrosis will be immediately discontinued from necitumumab.
Grade 4	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • Administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continuing for as long as rash is symptomatic. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity. • Necitumumab administration must be immediately and permanently discontinued.

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

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

6.1.3 Hypomagnesemia

Hypomagnesemia has been reported with necitumumab therapy and is considered to be a class effect with EGFR-targeting antibodies (as with panitumumab and cetuximab). Hypomagnesemia is reversible following discontinuation of EGFR antibody therapy. Treatment of any hypomagnesemia should be as clinically indicated according to institutional standard of care, and necitumumab therapy should be continued unless the investigator has any related safety concern.

6.1.4 Thromboembolic Events

In a randomized Phase III study (INSPIRE) for the combination of necitumumab with pemetrexed and cisplatin in non-squamous NSCLC, an increased rate of serious thromboembolic events, including fatal events, as compared to the treatment with pemetrexed and cisplatin alone has been observed. In the Phase III study SQUIRE, a higher rate of thromboembolic events (e.g., pulmonary embolism, venous thrombosis, cerebral ischemia, peripheral ischemia, myocardial infarction) was observed in patients treated with the combination of necitumumab, gemcitabine, and cisplatin as compared to patients treated with gemcitabine and cisplatin alone. No relevant imbalance was observed with regard to fatal thromboembolic events.

However, no safety signal with regard to thromboembolic or potential thromboembolic events, including fatal events, has been identified for necitumumab in completed clinical trials when administered as monotherapy or in combination with mFOLFOX-6 chemotherapy.

Treatment of any thromboembolic events occurring during necitumumab treatment should be as clinically indicated according to institutional standard of care, and the continuation of necitumumab therapy in these cases should be decided by the investigator after thorough risk-benefit assessment for the individual patient.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix E.

7.2 Baseline Study Assessments

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 following information will be collected and procedures will be performed for each patient at screening:

≤ 4 weeks prior to initiation of treatment

- Written informed consent prior to any other study-related
- Medical history
- 12-lead ECG performed locally (repeat if clinically indicated)
- Concomitant medication review
- CT scan of chest
- CT scan of the abdomen and pelvis
- CT/MRI of the brain if a patient has known brain metastases or if clinically indicated
- Confirm availability of pretreatment tumor tissue (see Section 5.4). 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.

≤ 7 days prior to initiation of treatment

- Physical examination, measurements of height (first visit), weight
- Vital signs (resting heart rate, blood pressure [BP], and oral temperature)
- ECOG performance status (Appendix A)
- Complete blood count (CBC) with 3-part differential and platelets
- Fasting comprehensive metabolic profile (CMP) to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin, phosphorus, magnesium, and lactate dehydrogenase (LDH).
- PT/INR (repeat if clinically indicated)
- HbA1c
- Serum or urine pregnancy test (must be performed within 72 hours prior to the initiation of treatment)
- Urine dipstick
- Blood sample for biomarker analysis

7.3 Study Treatment Assessments

7.3.1 Cycle 1 – Day 1

- Physical examination including measurement of weight
- Vital signs (unless collected within the previous 72 hours)
- ECOG PS (unless collected within the previous 72 hours [see Appendix A])
- 12-lead ECG pre-dose

- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets (unless collected within the previous 72 hours)
- Fasting CMP, phosphorus, magnesium and LDH (unless collected within the previous 72 hours)
- PT/INR (repeat only if abnormal at baseline or if clinically indicated)
- Serum or urine pregnancy test (unless collected within 72 hours prior to the initiation of treatment)
- Urine dipstick (unless collected within the previous 72 hours)
- Biomarker blood sample (pre-dose)
- PK blood sample ± 15 minutes (pre-dose of LY3023414 and necitumumab[see Table 2 and Table 3])
- Immunogenicity blood sample ± 15 minutes (pre-dose of LY3023414 and necitumumab [see Table 2 and Table 3]). 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.
- PGx blood sample (if the sample is not collected Cycle 1 Day 1, it can be collected anytime during Cycle 1 or Cycle 2)
- Dispense LY3023414. On PK days, pre-dose measurements and dose administration will be done in a fasted state.
- Necitumumab IV administration. Patients should remain in a fasted stated for 1 hour post-necitumumab infusion.

7.3.2 Cycle 1 – Day 8

- Vital signs
- ECOG PS (see Appendix A)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- Fasting CMP, phosphorus, magnesium and LDH
- Urine dipstick
- PK blood sample ± 15 minutes – (pre-dose of LY3023414 and necitumumab, at EOI, and 1 hour post EOI [see Table 2 and Table 3])

- Dispense LY3023414. On PK days, pre-dose measurements and dose administration will be done in a fasted state.
- Necitumumab IV administration. Patients should remain in a fasted stated for 1 hour post-necitumumab infusion.

7.3.3 Cycle 2 and all Subsequent Cycles – Day 1 (±72 hours)

- Physical examination including measurement of weight
- Vital signs
- ECOG PS (see Appendix A)
- 12-lead ECG pre-dose (Cycles 2, 3, and 4 only)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- Fasting CMP, phosphorus, magnesium and LDH
- PT/INR (repeat only if abnormal at baseline or if clinically indicated)
- HbA_{1c} (starting with Cycle 4 Day 1 and every 3 cycles thereafter)
- Urine dipstick
- Biomarker blood sample (pre-dose of Day 1 Cycle 3 and Day 1 of every 2 cycles thereafter)
- PK blood sample ± 15 minutes – (pre-dose of LY3023414 and necitumumab, **Cycles 2, 4, and 6 only** [see Table 2 and Table 3])
- Immunogenicity blood sample ± 15 minutes (pre-dose of LY3023414 and necitumumab, **Cycle 2 Day 1 and Cycle 4 Day 1 only** [see Table 2 and Table 3]). 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.
- Dispense LY3023414. On PK days, pre-dose measurements and dose administration will be done in a fasted state.
- Necitumumab IV administration. Patients should remain in a fasted stated for 1 hour post-necitumumab infusion.

7.3.4 Cycle 2 and all Subsequent Cycles – Day 8

- Vital signs
- ECOG PS (see Appendix A)
- AE assessment

- Concomitant medication review
- CBC, including 3-part differential, platelets, and hematocrit (**Cycle 3 Day 8 only**)
- PK blood sample ± 15 minutes – (pre-dose of LY3023414 and necitumumab, at EOI, and 1 hour post EOI, **Cycle 3 only** [see Table 2 and Table 3])
- Dispense LY3023414. On PK days, pre-dose measurements and dose administration will be done in a fasted state.
- Necitumumab IV administration. Patients should remain in a fasted stated for 1 hour post-necitumumab infusion.

7.4 Response Assessment Prior to Cycle 3 and After Every 2 Cycles

Patients will be evaluated radiographically for response to treatment prior to Cycle 3 and after every 2 cycles of treatment (i.e. Cycle 5, Cycle 7, etc.). The following assessments will be performed:

- CT scans of chest
- CT of the abdomen and pelvis
- CT/MRI of the brain only if abnormal at baseline

Patients with progressive disease (PD) or unacceptable toxicity should be discontinued from the study; patients with stable disease (SD) or response to therapy will continue treatment.

7.5 End of Treatment Visit

The follow-up evaluations required after treatment ends due to completion of the planned study treatment period, disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician are specified in Appendix E.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfil the end of treatment visit.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days (+ 3 days) after the last dose of study drug. The following assessments will be performed:

- Physical examination including measurement of weight
- Vital signs
- ECOG PS (see Appendix A)
- 12-lead ECG
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets

- Fasting CMP, phosphorus, magnesium and LDH
- HbA1c
- Urine dipstick
- Blood sample for biomarker analysis
- PK blood sample
- Immunogenicity blood sample
- CT scan chest (does not have to be repeated if done within 8 weeks of End of Study Treatment visit)
- CT of the abdomen and pelvis (does not have to be repeated if done within 8 weeks of End of Study Treatment visit)
- CT/MRI of the brain only if abnormal at baseline (does not have to be repeated if done within 8 weeks of End of Study Treatment visit)

7.6 Follow-up

7.6.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

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. For ongoing AEs and serious adverse events (SAEs) see Section 11.2.1. Assessments at these visits will be performed as described in Appendix E.

7.6.2 Survival Follow-Up

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.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 LY3023414

Investigational Product	Dosage Form and Strength	Manufacturer
LY3023414	25 mg, 100 mg, and 200 mg capsules	Eli Lilly and Company

8.1.1 Labeling, Packaging, and Supply

LY3023414 will be supplied as capsules by Eli Lilly and Company.

At each visit, patients will be dispensed sufficient supplies until the next visit. Study drug compliance will be assessed at each patient visit. The research staff will count and document the amount of LY3023414 taken and returned by the patient.

The immediate packaging will contain a statement that administration is limited to investigational use only.

LY3023414 must be kept in a secure place under appropriate storage conditions. Storage conditions for LY3023414 are included on the investigational product label.

The Sponsor or its representatives must be granted access on reasonable request to check LY3023414 storage, dispensing procedures, and accountability records.

If another formulation of LY3023414 becomes available at a later point in time (e.g. tablets), that might be used instead of capsules for this study.

8.1.2 Precautions and Risks Associated with LY3023414

Due to the early stage of development, clinical experience with LY3023414 is limited.

Nonclinical toxicology studies identified the GI tract as one of the primary target organs for toxicity of LY3023414. In the ongoing Study CBBA, nausea, vomiting and diarrhea, mostly mild-to-moderate in severity, have been reported among the most frequent AEs considered to be possibly related to LY3023414. Patients administered LY3023414 should be monitored for GI toxicities and receive supportive treatment as clinically appropriate. In the ongoing Study CBBA, fatigue, mostly mild-to-moderate in severity, has also been reported among the most frequent AEs considered to be possibly related to LY3023414.

Hyperglycemia

Nonclinical studies in rats and dogs showed transient, dose-responsive increases in glucose. Effects on glucose metabolism are an expected pharmacological effect based on the role that PI3K and mTOR pathways play in glucose metabolism. Dose-related, transient increases in glucose (Grade 1-3) and C-peptide levels were noted in patients administered LY3023414 as monotherapy. Patients who develop elevated glucose should be treated according to the institutional standard of care.

QT Interval Prolongation

Nonclinical studies in rats and dogs showed transient, dose-responsive increases in glucose coinciding with QT interval prolongation. Inhibition of PI3K/mTOR interferes with the metabolic actions of insulin, including glucose transport and glycogen synthesis, resulting in increased blood glucose and compensatory release of insulin (and C-peptide) from pancreatic cells. These changes in glucose metabolism might contribute to secondary QT interval prolongation. No clinically relevant QT interval prolongations were identified in patients administered LY3023414 as monotherapy. Patients should be monitored for potential secondary prolongation of corrected QT (QTc) intervals by ECG. Patients should avoid taking concomitant medications that are known to induce QTc prolongations as outlined in the protocol (Appendix H).

Please refer to the investigator brochure (IB) for a more thorough discussion.

8.2 Necitumumab

Investigational Product	Dosage Form and Strength	Manufacturer
Necitumumab	800 mg/50 mL	Eli Lilly and Company

8.2.1 Labeling, Packaging, and Supply

Necitumumab will also be supplied by Eli Lilly and Company.

All study medications must be kept in a secure place under the storage conditions specified on the label. The expiration date on the label must not be exceeded.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.2.2 Preparation and Administration of Necitumumab

Necitumumab drug product (DP) is compatible with infusion containers composed of polyolefin, polyvinyl chloride (PVC), ethylene vinyl acetate and evacuated glass (United States Pharmacopeia Type II or local equivalent). An infusion bag composed of polyolefin, polypropylene, and polyethylene prefilled with 0.9% Sodium Chloride Injection, such as AVIVA, may also be used.

The following infusion sets have been found to be compatible for necitumumab DP infusion:

- A polyethylene-lined PVC infusion set with a 0.22-µm downstream high-pressure, protein-sparing in-line filter made of polyethersulfone of 10-cm2 surface area
- A PVC (with DEHP) infusion set with a 0.2-µm protein-sparing filter made of polyethersulfone of 4.2-cm2 surface area
- A polyethylene-lined PVC infusion set with a 0.2-µm protein-sparing in-line filter made of polyethersulfone of 10-cm2 surface area
- A polyurethane infusion set with a 0.2-µm protein-sparing in-line filter made of polyethersulfone of 10-cm^2 surface area
- A polybutadiene tubing with a 0.2-µm protein-sparing in-line filter made of polysulfoneof 9-cm2 surface area

a) To administer using pre-filled I.V. infusion containers:

Calculate the respective dose and remove the corresponding volume of 0.9% normal saline from the prefilled 250 mL container of the correct composition. Aseptically transfer the calculated dose of necitumumab DP to the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix.

b) To administer using empty I.V. infusion containers:
Aseptically transfer the calculated dose of necitumumab DP into an empty I.V. container of the correct composition and add a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to bring the total volume to 250 mL. Gently invert the container to mix.

Only 0.9% normal saline should be used for dilution and post-infusion flushing of infusion line. Addition of 0.9% normal saline is not required for dose volumes exceeding 250 mL. Post-infusion, the infusion line must be flushed with equal to or greater than the hold-up volume of the infusion line to ensure delivery of the calculated dose. Necitumumab should be administered as an intravenous infusion over 50 minutes. The infusion rate must never exceed 25 mg/minute and consequently necitumumab infusion duration is about 1 hour. Different lot numbers of necitumumab must not be mixed in a single infusion. The lot number is printed on the container label.

8.2.3 Precautions and Risks Associated with Necitumumab

Common risks associated with necitumumab administration are:

- Hypersensitivity/ IRRs
- Skin reactions
- Thromboembolic events

Please refer to the necitumumab IB for detailed information on the risks associated with the use of necitumumab.

8.3 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused LY3023414 and necitumumab at the site.

All LY3023414 and necitumumab inventories must be made available for inspection by the monitor, Sponsor, or representatives of the aforementioned and regulatory agency inspectors upon request.

At the end of the study, all approved Drug Accountability Record Form (s) for LY3023414 and necitumumab will be completed by the site and sent to the SCRI Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Disposal of any study drug may occur according to your current drug destruction SOP, after review and approval of the SOP by SCRI Innovations.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the RECIST v 1.1 (see Appendix F). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical 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.

The primary, secondary and exploratory objectives are found in Section 2.

10.2 Sample Size Considerations

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]
The sample size is calculated using EAST.

10.3 Analysis Population

The following analysis populations will be used:

- 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.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. A SAP outlining methods for analysis and data display will be developed and approved prior to database lock. Any deviation(s) from the approved plan or ad-hoc evaluations or analyses will be properly documented in the clinical study report.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the FAS.

RECIST v 1.1 will be used to assess tumor response. Tumors will be assessed at screening, after every 3 cycles, and at follow-up visits. Reassessment of tumors will be done by the same methods used to establish baseline tumor measurements. All responding patients (CR and PR) must have their response confirmed no less than 4 weeks after the first documentation of response. For SD, follow-up measurements must meet the SD criteria at least 9 weeks after study entry.

10.4.2.1 Primary Endpoint

6-Month Disease Control Rate

The 6-month DCR is defined as the number of patients with PFS > 6 months (or 26 weeks, to accommodate the scheduled tumor assessment at week 24 be delayed by up to 2 weeks) divided by number of patients with baseline tumor assessment.

The primary endpoint, 6-month DCR, will be presented as the point estimate with its associated 95% Clopper-Pearson confidence interval (CI).

10.4.2.2 Secondary Endpoints

Overall Response Rate (ORR)

The ORR based on each patient's best objective response will be determined for all patients evaluable via the RECIST v 1.1 criteria. The ORR (%) will be calculated as the number of patients with best objective response of CR or PR divided by the number of patients with measurable disease at baseline. The best objective response for a given patient will be based on objective responses determined from data obtained up to: progression, the last evaluable assessment in the absence of progression, or initiation of subsequent anticancer therapy. Patients for whom an objective response cannot be determined or for who the best objective response is NE will be considered non-responders. The ORR will be summarized along with the 95% Clopper Pearson CI.

Disease Control Rate

DCR is defined as number of patients with CR, PR, or SD as the best objective response divided by number of patients with baseline tumor assessment.

Progression–free survival (PFS)

PFS is defined as the time from enrollment until the date of disease progression per RECIST or death by any cause. Patients who have not progressed or died at the time of assessment will be censored at the time of the last date of tumor assessment. Patients who are enrolled but do not receive treatment and patients who have no evaluable visits will be censored on day 1. Patients who received new anti-cancer therapy before disease progression or death will be censored to the last tumor assessment date prior to the new anti-cancer therapy. PFS will also be analyzed by including the clinical progression date as sensitivity analysis. Detailed derivation rules will be specified in the SAP.

Overall survival (OS)

OS is defined as the time from enrollment until the date of death by any cause. Patients who lost follow up or did not die at the time of assessment will be censored at the time of the last known alive date. Detailed derivation rules will be specified in the Statistical Analysis Plan.

10.4.2.3 Exploratory 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.

10.4.2.4 Subgroup Analyses

For exploratory purposes, efficacy sub-group analyses may also be performed if applicable, using the FAS. The details of these analyses and selection of the prognostic factors and/or baseline characteristics will be specified in the SAP.

For ORR, the estimates and the associated 95% CI (based on the Clopper-Pearson method) in each sub-group will be calculated.

For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI will be provided.

10.4.3 Safety Analysis

The NCI CTCAE v 4.03 will be used to grade all AEs (severity grade). A copy of the CTCAE scoring system may be downloaded from:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Duration and treatment of toxicities will be recorded. The safety measures will be assessed on an ongoing basis. The safety variables will be assessed by body system. Any AEs that are considered probably or possibly study drug-related will be monitored until resolution or stabilization.

Toxicity profile data will include AEs and laboratory parameters. Safety data will be tabulated for all patients. Adverse terms recorded on the eCRFs will be standardized using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment -emergent AEs (TEAEs) defined as events that start or worsen after the first dose of study treatment, will be summarized and tabulated in accordance with system organ class (SOC) and preferred term by overall incidence, severity, and relationship to study treatment. The tabulation of laboratory parameters will indicate the normal range of each parameter. Each value will be classified according to CTCAE v 4.03 where applicable.

Other safety endpoints, including laboratory results, vital signs and ECG findings, will be summarized for all patients in the Safety Analysis Set.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized.

10.4.4 Pharmacokinetics

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug(s) and have had sufficient post-dose samples collected to allow estimation of PK parameters. Blood (all patients) and plasma (initial lead-in cohort only, 6 to 12 patients) concentrations of LY3023414 and serum concentration for necitumumab will be used to calculate LY3023414 and necitumumab PK parameters, respectively. Based on the limited sampling scheme the primary LY3023414 and necitumumab PK parameters will be Cmax and Cmin of LY3023414 and necitumumab following multiple doses.

Pharmacokinetic parameters will be listed by individual patient and summarized by descriptive statistics (means, medians, ranges, standard deviations and coefficient of variation and, as appropriate, by dose levels.

Other parameters, such as $t_{1/2,}$ CLss/F, and Vss/F may be reported through analysis of the data using nonlinear mixed effect modeling (NLME) techniques. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Further details on the PK analysis will be documented in a separate PK analysis plan.

10.5 Analysis Time Point

10.5.1 Final Analysis

The final analysis of the study will occur when all patients have either finished month 6 tumor assessment or discontinued from the study medication.

10.5.2 Planned Interim Analysis

Interim analysis will be conducted when a total of 24 patients have had month 6 tumor assessment. A 6-month DCR rate of 44% will be used as the boundary to access the efficacy during the interim analysis. A 6-month DCR rate of 36% will be used as the boundary to assess the efficacy of LY3023414 and necitumumab in the final analysis.

The results from the interim analyses will be examined by a committee that will be established prior to the inclusion of the first patient in the trial. The committee will consist of at least a Lilly medical director, a Lilly clinical research physician/clinical research scientist, and a Lilly statistician and will make recommendations about the trial. The outcome of the interim analyses will be documented, and a written letter will be submitted to the IRB(s) and the investigators for documentation purposes. Enrollment will continue while the interim analysis is being performed.

10.5.3 Safety Review

After at least 6 patients in the lead-in cohort have been treated for a full cycle, a SIMC will review the safety and PK data. If 2 (or more) of 3 or 2 (or more) of 6 patients in the lead-in cohort experience 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 seen deemed to be clinically significant by the SIMC, the SIMC may recommend enrolling approximately 6 additional patients to further evaluate the safety of the combination, or explore other dose combinations to assure safety at a maximal exposure of study drug. 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). Any outcome of these safety reviews will be communicated in a timely manner to the participating investigators so that they may notify their IRBs. No amendment will be needed to proceed with a lower dose level of study drug(s).

Safety will be monitored as defined by the medical monitoring plan. The safety profile will be reviewed by the Medical Monitor and Sponsor Designees.

The SIMC will, at a minimum, be composed of a Sponsor-Assigned Clinical Research Physician, Study Chair, Medical Monitor, Sponsor-Assigned Safety Scientist, and Biostatistician.

The criteria for assessing safety in these patients are found in Section 5.

11. SAFETY REPORTING AND ANALYSES

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

The investigator remains responsible for following, through an appropriate health care option, all AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

Investigators or their designees must document their review of each laboratory report.

11.1 Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, ECGs, vital sign measurements, and so on, that occur should also be reported to Lilly or its designee as an AE using the same guidelines and schedules as those for AEs. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and Sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE Version 4.03.

The CTCAE Version 4.03 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the CTCAE Version 4.03 criteria, the investigator will be responsible for selecting the appropriate SOC and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

Minor updates to the CTCAE Version 4.03 from the NCI will not necessitate a protocol amendment, and the use of updated CTCAE Version 4.0 will not be considered a protocol violation.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the Sponsor or designee to corresponding terminology within MedDRA.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

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

The investigator decides whether he or she interprets the observed safety signals as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies.

To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Does not know:** the investigator cannot determine.

- **Not related**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "probably related," "possibly related," or "does not know" AEs and SAEs will be defined as related to study drug.

11.2 Serious Adverse Events

Previously planned (that is, prior to signing the informed consent form [ICF]) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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

An SAE is any AE during this study that results in 1 of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

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

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

If an investigator becomes aware of SAEs occurring after the patient's participation in the study has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the Sponsor, and the SAEs will be entered in the Lilly Safety System.

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

11.2.1 Adverse Event and Serious Adverse Event Reporting

Prior to Administration of Study Drug(s)
Although all AEs after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

On Study
All AEs and SAEs, regardless of relatedness to study drug, or protocol procedures, occurring while the patient is receiving study drug(s) must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug(s) to when he/she receives the last dose of study drug(s).

Follow-Up Visit
All AEs and SAEs, regardless of relatedness to study drug, or protocol procedures, occurring during the Follow-Up Visit must be reported to Lilly or its designee. The Follow-Up Visit starts the day after the last dose of study drug. At the end of the Follow-Up Visit, the patient will be required to have specific safety assessments according to the Study Schedule (Appendix E). The timing of these safety assessments is 30 days ± 3 days after the last dose of study drug.

Following the safety assessments, which mark the end of the Follow-Up Visit, the patient will be discontinued from the study. If there is an ongoing AE or SAE that is possibly related to study drug the investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

After the Follow-Up Visit, only new AEs or SAEs that are considered possibly related to study drug or protocol procedures should be reported to Lilly or their designee.

To report an SAE, the Lilly SAE Report Form should be completed with the necessary information.

The SAE report should be sent to Lilly via fax using the following contact information (during both business and non-business hours):

Lilly Safety Department

Safety Dept. Fax #: PPD

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Lilly as soon as it is available; these reports should be submitted using the Lilly SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the Study Reference Manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Complaint Handling

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

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

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

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

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

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, GCP/ICH and, when appropriate, regulatory guidelines.

12.2 Audits and Inspections

The investigator will permit study-related quality audits and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for review of applicable study-related facilities. The investigator will ensure that the auditor or inspector or any other compliance or QA reviewer is given access to all study-related documents and study-related facilities.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB, the Sponsor or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for LY3023414 and necitumumab will be prepared by the Sponsor or its representative as required, for distribution to the investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the relevant regulatory authorities, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been

obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF database system. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the Sponsor or the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, the Sponsor and/or SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided and retained.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representative. All amendments require review and approval of the Sponsor and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the relevant regulatory authorities by the Sponsor as applicable, and IRB approved obtained specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and if necessary other relevant regulatory authorities approval may include but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a Study Chair

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin in the United States (US) certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

SCRI Innovations
3322 West End Avenue, Suite 900
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB -approved consent form containing permission for audit by representatives of SCRI Innovations, the Sponsor, the IRB, and the FDA
- Financial disclosure forms for all investigators listed on Form FDA 1572 (if applicable, i.e., for covered trials)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts,

laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs on a compact disc, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified that the investigation has been discontinued.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs and medical records), all original, signed ICFs, and copies of all eCRFs, records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor or its representatives will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study. If study files are maintained by a representative of the Sponsor, the study files will be transferred to the Sponsor at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study may be published and/or presented as per the Sponsor's disclosure process.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements

described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disc losed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any SCRI Innovations Confidential Informa tion from all publications.

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16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Canadian Cardiovascular Society (CCS) Angina Grading Scale

The following table presents the CCS classification of cardiac disease.

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

References: Campeau Lucien. Grading of angina pectoris. Circulation 1976;54:5223
Available on the Canadian Cardiovascular Society Website at www.ccs.ca

Appendix D: Guidelines for Women of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 6 months after stopping treatment. Women must not breast-feed for 4 months after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS).

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 6 months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the SCRI-Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to **the Sponsor**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug(s) in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are > 45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value > 40 mIU/mL and an estradiol value < 40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH > 40 mIU/mL and estradiol < 40 pg/mL prior to initiation of hormone-replacement therapy.

SCRI DEVELOPMENT℠ INNOVATIONS

Appendix E: Schedule of Assessments

Assessments	Screening	Study Treatment					Off-Treatment	Follow-Up	
		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)		Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5, 7, etc.)	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

Assessments	Screening	Study Treatment					Off-Treatment	Follow-Up	
		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)		Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5, 7, etc.)	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				
LABORATORY EVALUATIONS									
PGx blood sample[t]		X							
Archived or fresh tumor tissue[m]	X[m]								
STAGING									
CT scan of chest, abdomen and pelvis[n]	X[n]					X[n]	X[n]	X[n]	
CT/MRI of the brain[o]	X[o]					X[o]	X[o]	X[o]	

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 (see Table 2 and Table 3). PK blood samples for Cycles 2, 4, and 6 Day 1 are pre-dose of LY3023414 and necitumumab (see Table 2 and Table 3). A PK sample will be taken at the End of Treatment visit.

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.

Appendix E: Schedule of Assessments

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 Section 5.4). 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 Section 11.2.1.

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

Appendix F: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Patients with Measurable Disease

Patients with measurable disease will be evaluated for response using the RECIST v 1.1 (Eisenhauer et al. 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.

Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Appendix F: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

As detailed above, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for trials in which response rate is the primary endpoint, but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

Appendix F: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Appendix G: Drugs That Prolong QT Interval and/or Induce Torsades de Pointes

All QT-prolonging drugs listed below should be avoided for all patients from screening through permanent discontinuation of study treatment.

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males,TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	This drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	This drug is a sensitive 3A4 sibstrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	This drug is a sensitive 3A4 substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.		

Appendix H: List of QT Prolonging Drugs to be Used with Caution

Below is a list of drugs with a known risk for Torsades de Pointes (TdP).

Drug	QT risk	Comment
Alfuzosin	possible risk for TdP	
Amantadine	possible risk for TdP	
Amitriptyline	conditional risk for TdP	
Azithromycin	possible risk for TdP	
Chloral hydrate	possible risk for TdP	
Citalopram	conditional risk for TdP	
Clomipramine	conditional risk for TdP	
Clozapine	possible risk for TdP	
Desipramine	conditional risk for TdP	
Diphenhydramine	conditional risk for TdP	
Dolasetron	possible risk for TdP	
Doxepin	conditional risk for TdP	
Dronedarone	possible risk for TdP	
Felbamate	possible risk for TdP	
Flecainide	possible risk for TdP	
Fluoxetine	conditional risk for TdP	
Foscarnet	possible risk for TdP	
Fosphenytoin	possible risk for TdP	
Galantamine	conditional risk for TdP	
Gatifloxacin	possible risk for TdP	
Gemifloxacin	possible risk for TdP	
Granisetron	possible risk for TdP	
Imipramine	conditional risk for TdP	
Indapamide	possible risk for TdP	
Isradipine	possible risk for TdP	
Levofloxacin	possible risk for TdP	
Lithium	possible risk for TdP	
Mexiletine	conditional risk for TdP	
Moexipril/HCTZ	possible risk for TdP	
Moxifloxacin	possible risk for TdP	
Nicardipine	possible risk for TdP	
Nortriptyline	conditional risk for TdP	
Octreotide	possible risk for TdP	
Ofloxacin	possible risk for TdP	

Appendix H: List of QT Prolonging Drugs to be Used with Caution (continued)

Drug	QT risk	Comment
Ondansetron	possible risk for TdP	
Oxytocin	possible risk for TdP	
Paliperidone	possible risk for TdP	
Paroxetine	conditional risk for TdP	
Perflutren lipid microspheres	possible risk for TdP	
Protriptyline	conditional risk for TdP	
Ranolazine	possible risk for TdP	
Risperidone	possible risk for TdP	
Roxithromycin*	possible risk for TdP	*not available in the United States
Sertindole	possible risk for TdP	
Sertraline	conditional risk for TdP	
Solifenacin	conditional risk for TdP	
Tizanidine	possible risk for TdP	
Trazodone	conditional risk for TdP	
Trimethoprim-Sulfa	conditional risk for TdP	
Trimipramine	conditional risk for TdP	
Venlafaxine	possible risk for TdP	
Ziprasidone	possible risk for TdP	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Appendix I: Common CYP1A2 Inducers, Substrates for CYP3A4, CYP3A Inducers and Inhibitors, and P-gp/CYP3A Dual Inhibitors

The following list describes medications and foods which are common inhibitors, inducers and substrates of CYP2C9 and CYP2C19, substrates of CYP34A, inducers of CYP2C8, inducers and inhibitors of CYP3A, and dual inhibitors of PgP and CYP3A.

This list should not be considered all-inclusive.

<table>
<tr><th colspan="2">CYP1A2 Inducers</th></tr>
<tr><td>Moderate Inducers
50-80% decrease in AUC:
montelukast
phenytoin</td><td>Weak Inducers
20-50% decrease in AUC:
moricizine
omeprazole
phenobarbital</td></tr>
<tr><th>CYP3A4 Substrates with Narrow Therapeutic Range</th><th>CYP3A4 Substrates (Oral Administration)</th></tr>
<tr><td>Alfentanil
Astemizole
Cisapride
Cyclosporine
Dihydroergotamine
Ergotamine
Fentanyl
Pimozide
Quinidine
Sirolimus
Tacrolimus
Terfenadine</td><td>Midazolam
Buspirone</td></tr>
<tr><th colspan="2">CYP3A/P-gp Dual Inhibitors</th></tr>
<tr><td colspan="2">Strong:
Clarithromycin
Conivaptan
Diltiazem
Dronedarone
Indinavir/ritonavir
Itraconazole
Ketoconazole
Lopinavir/ritonavir
Ritonavir
Moderate:
Diltiazem
Dronedarone
Erythromycin
Verapamil</td></tr>
</table>

Appendix I: Common CYP1A2 Inducers, Substrates for CYP3A4, CYP3A Inducers and Inhibitors, and P-gp/CYP3A Dual Inhibitors (continued)

CYP3A Inducers	CYP3A Inhibitors
Strong: • Avasimibe • Carbamazepine • Phenytoin • Rifampin (rifampicin) • St. John's wort (hypericum perforatum)	Strong: • Boceprevir • Clarithromycin • Conivaptan • Grapefruit juice • Indinavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telaprevir • Telithromycin • Voriconazole Moderate: • Amprenavir • Aprepitant • Atazanavir • Ciprofloxacin • Cyclosporine • Darunavir/ritonavir • Diltiazem • Erythromycin • Fluconazole • Fosamprenavir • Grapefruit juice (citrus parasidi fruit juice) • Imatinib • Verapamil

Source: FDA's Drug Development and Drug Interactions: Table of Substrates, Inhibitors and the University of Washington's Drug Interaction Database.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

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