FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting

July 9, 2015

BLA 125547/0
Necitumumab

Applicant: Eli Lilly & Co

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the necitumumab BLA with the Applicant's proposed indication to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

Glossary

ASBI	Average Symptom Burden Index
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BLA	Biologics License Application
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebral Vascular Accident
D	Day
DM	Diabetes Mellitus
DMC	Date Monitoring Committee
DOR	Duration of Response
DVT	Deep Venous Thrombosis
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiography
EGFR	Epidermal Growth Factor Receptor
EOS	End of Study
FDA	Food and Drug Administration
F/U	Follow-up
GC	Gemcitabine plus Cisplatin
HR	Hazard Ratio
HTN	Hypertension
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IND	Investigational New Drug
ITT	Intention-to-Treat
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
KRAS	Kistern rat Sarcoma
mAb	Monoclonal Antibody
MI	Myocardial Infarction
MedDRA	Medical Dictionary for Regulatory Activities
mDOR	Median Duration of Response
mOS	Median Overall Survival
mPFS	Median Progression-free-Survival
MRI	Magnetic Resonance Imaging
mTTP	median Time-to-Progression
N	Number of Subjects
N+GC	Necitumumab plus Gemcitabine and Cisplatin
N+PC	Necitumumab plus Pemetrexed and Cisplatin
NCI	National Cancer Institute
NOS	Not otherwise Specified
NSCLC	Non-Small Cell Lung Cancer
ODAC	Oncologic Drug Advisory Committee
ORR	Objective Response Rate
OS	Overall Survival
PC	Pemetrexed and Cisplatin
PD	Progressive Disease
PE	Pulmonary Emboli
PI	Package Insert
PP	Per Protocol
PR	Partial Response
PS	Performance Status
PRO	Patient Reported Outcome
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SD	Standard Deviation
TE	Thromboembolic Events
TTF	Time to Treatment Failure
ULN	Upper Limit of the Normal Range
U.S.	United States
VEGF	Vascular Endothelial Growth Factor

I. Executive Summary

Necitumumab is a recombinant human IgG1 monoclonal antibody (mAb) that binds to the extracellular domain of the human epidermal growth factor receptor (EGFR) and blocks interaction between EGFR and its ligands. Eli Lily is seeking initial approval of necitumumab in combination with gemcitabine and cisplatin for use in first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).

The efficacy for the proposed indication is based on the results of SQUIRE (I4X-IE-JFCC), a randomized, controlled, open-labeled, international study in 1093 patients with advanced squamous NSCLC who had not received prior chemotherapy for metastatic disease. Eligible patients were randomized 1:1 to receive either necitumumab with gemcitabine and cisplatin (N+GC, N=545) or gemcitabine and cisplatin (GC, N=548) alone. Randomization was stratified by ECOG (Eastern Cooperative Oncology Group) performance status and geographic region. The primary efficacy endpoint of the study is overall survival (OS). Key secondary endpoints are progression-free survival (PFS) and overall response rate (ORR). The addition of necitumumab to GC resulted in a 1.6 month improvement in OS which was statistically significant. The median OS was 11.5 months (95% CI 10.4, 12.6) in the N+GC arm compared to 9.9 months (95% CI 8.9, 11.1) in the GC arm [Hazard Ratio (HR)=0.84 (95% Confidence Interval (CI) 0.74; 0.96); logrank p=0.012)]. The median PFS was 5.7 months (95% CI 5.6, 6.0) in the N+GC arm compared to 5.5 months (95% CI 4.8; 5.6) in the control arm [HR=0.85 (95% CI 0.74, 0.98); logrank p=0.02)]. Overall response rate (ORR) was 31% vs. 29% (p=0.40) in the N+GC and GC arm, respectively.

Data from a second randomized, controlled study INSPIRE (I4X-IE-JFBB) of necitumumab in patients with advanced non-squamous NSCLC who had not received prior chemotherapy for metastatic disease was submitted to provide safety information. Eligible patients were randomized 1:1 to receive either necitumumab with pemetrexed and cisplatin (N+PC) or pemetrexed and cisplatin (PC) alone. The study was closed prematurely at the request of the data monitoring committee (DMC) due to an imbalance on the number of deaths attributed to potential thromboembolic events (TE) and deaths of all causes observed in the N+PC arm compared to the PC arm. At the time of the study closure, 633 patients out of 947 planned were enrolled. There was no difference in OS based on the available data (median OS 11.3 vs.11.5 months in the treatment and control arms, respectively, [HR=1.01, 95% CI 0.84; 1.21)].

The safety profile of necitumumab is in general consistent with the adverse events (AEs) observed with anti-EGFR antibody class products. In the SQUIRE trial, significant grade ≥ 3 necitumumab related AEs are hypomagnesemia (9%), skin rash (7%) and hypersensitivity/infusion reaction (0.4%) Fatal cardiopulmonary arrest and/or sudden death were observed in 2.2 % of the patients in the N+GC arm compared to 0.5 % in the control arm. The incidences of thromboembolic events were higher in the necitumumab-containing arms in both SQUIRE and INSPIRE trials. The incidence of grade ≥ 3 TEs were 9% vs. 5% in the SQUIRE trial and 11% vs. 6% in the INSPIRE trial. The most common venous TE events, some fatal, were pulmonary emboli (PE) and deep vein thrombosis (DVT) while the most common arterial TEs were myocardial infarction (MI) and cerebrovascular accidents (CVA).

The key issue for this application is the balance of benefit versus risk. SQUIRE and INSPIRE are two well designed, add-on trials in two distinct histologies in metastatic NSCLC (squamous and non-squamous). The addition of necitumumab to GC resulted in a statistically significant 1.6 month median OS and a 0.2 month median PFS improvement compared to GC alone in patients with squamous NSCLC histology. This activity was not replicated in the nonsquamous NSCLC trial with pemetrexed and cisplatin as the backbone chemotherapy. Although the safety profile of necitumumab is noted to be similar to what is known for other anti-EGFR mAbs, the increased number of TE events in this already high risk population[1-4] is of concern.

The Division of Oncology Products 2 seeks the advice of the ODAC regarding the pending BLA for necitumumab on the following issues:

1. Do the efficacy and safety results of SQUIRE in squamous cell NSCLC support a positive benefit: risk assessment of necitumumab in combination with gemcitabine/cisplatin in the proposed population?

2. Do the INSPIRE trial results in the nonsquamous NSCLC population impact the benefit: risk assessment of necitumumab for squamous NSCLC?

II Background

Lung Cancer

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide[5] and the leading cause of cancer related deaths in the US[6]. The two major histological subtypes of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for nearly 85% of all cases of lung cancer. NSCLC is further classified into squamous and non-squamous cell carcinoma, the latter comprised of adenocarcinoma and large cell carcinoma histology.

Squamous cell carcinoma comprises 30-35% of all lung cancers and is often associated with heavy tobacco use. Squamous tumors are typically centrally located, arising from and extending into a bronchus. Larger tumors tend to present with central necrosis and cavitation. The majority of patients with squamous NSCLC present with locally advanced or metastatic disease at the time of diagnosis, which is incurable with currently available therapeutic options. The 5-year survival for this population is less than 5%.

Approved Therapies for NSCLC

The current standard systemic first-line treatment for patients with advanced, metastatic squamous NSCLC is cytotoxic chemotherapy with cisplatin or carboplatin-based doublets. Platinum combination with vinorelbine, paclitaxel, docetaxel, or gemcitabine yields similar improvements in survival. In historic front-line platinum based chemotherapy trials, the ORR range from 12 to 37%, median PFS range from 4 to 7 months, median OS range from 8 to 13 months, and a 1- year survival rate of approximately 33% [7].

In recent years, identification of driver mutations in the kinase domain of the EGFR gene and alterations of Anaplastic Lymphoma Kinase (ALK) gene[8] in lung cancer has led to the development and approval of several molecularly targeted agents to improve the outcome of subsets of patients with non-squamous NSCLC. EGFR tyrosine kinase inhibitors such as erlotinib and afatinib and ALK inhibitors such as crizotinib are now available for use in first-line treatment of patients with tumors that harbor these mutations.

In contrast to non-squamous NSCLC, the treatment landscape for first-line treatment of squamous NSCLC has not appreciably changed in recent decades. Paclitaxel, gemcitabine, docetaxel and vinorelbine were approved 10 to 20 years ago for use in NSCLC regardless of histology as add-on agents to platinum. The last agent approved for a 1st –line indication was nab-paclitaxel, an albumin-bound form of paclitaxel in 2012 (in combination with carboplatin), under the 505b2 pathway. Two agents approved for use in non-squamous histology, bevacizumab and pemetrexed, are not available for treatment of patients with squamous histology due to safety concerns for bevacizumab and lack of efficacy for pemetrexed.

Treatment options for patients with squamous NSCLC who progress after platinum based therapy include single agent docetaxel and erlotinib and two recently approved agents: ramucirumab (approved December 2014) and nivolumab (approved March 2015). Ramucirumab is a human vascular endothelial growth factor receptor 2 antagonist approved for use in combination with docetaxel. Approval was based on a 1.4 month improvement in OS [HR 0.86 (95% CI 0.75, 0.98) p = 0.024] in a 1253 patient trial comparing docetaxel plus ramucirumab to docetaxel plus placebo. Nivolumab is an IgG4 kappa anti-PD-1 mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Approval for 2nd line squamous NSCLC was supported by a 272 patient trial comparing nivolumab to docetaxel that demonstrated a 3.2 month improvement in OS [HR 0.59 (0.44, 0.79) p=0.00025]. Currently, there is no clinical data to support the use of ramucirumab or nivolumab in the first-line setting.

The following table lists the products currently available for the treatment of advanced or metastatic squamous NSCLC, their indication, and the efficacy data supporting their approval.

Table 1 Approved Therapies for Squamous NSCLC

FOR FIRST-LINE TREATMENT		
FDA Approval Date	**Product Indication**	**Studies and Approval Endpoints**
JUN-1998	**PACLITAXEL** In combination with cisplatin, for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy	Paclitaxel + cisplatin vs etoposide • Median OS (mOS): 10.0 vs 7.4 months p=0.08 • **Median TTP (mTTP): 4.9 vs 2.7 months p=0.004** • ORR: 35% vs 12% p<0.001
AUG-1998	**GEMCITABINE** In combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced Stage IIIA or IIIB, or metastatic (Stage IV) NSCLC	1. Gemcitabine + cisplatin vs cisplatin • **mOS: 9.0 (8.2-11.0) vs 7.6 (6.6-8.8) months p=0.008** • mTTP: 5.2 (4.2-5.7) vs 3.7 (3.0-4.3) months p=0.009 • ORR: 26% vs 10%; p<0.001 2. Gemcitabine + cisplatin vs etoposide + cisplatin • mOS: 8.7 vs 7.0 months p=0.18 • **mTTP:** 5.0 vs 4.1 months p=0.015 • ORR: 33% vs 14% p=0.01
DEC -1994 **OCT- 2001**	**VINORELBINE** In combination with cisplatin or as single agent, for the first-line treatment of ambulatory patients with unresectable, advanced NSCLC	1. Vinorelbine + cisplatin vs cisplatin • **mOS: 7.8 (6.9-9.6) vs 6.2 (5.4-7.7) months p=0.01** • ORR: 19% vs 8%; p< 0.001 2. Vinorelbine + cisplatin vs vindesine + cisplatin • Median OS: 9.2 (7.4-11.1) vs 7.4 (6.1-9.1) months p=0.087 • ORR: 28% (22-35) vs 19% (14-25) p=0.03 3. Vinorelbine vs. 5-FU • mOS 30 wks vs. 22 wks; p =0.06 • ORR 11.1% vs. 3.5%
NOV- 2002	**DOCETAXEL** In combination with cisplatin, unresectable, locally advanced or metastatic untreated NSCLC	Docetaxel + cisplatin vs vinorelbine + cisplatin • m OS: 10.9 vs 10.0 months; HR: 0.88 (0.74-1.06) p=0.122 • mTTP: 21.4 (19.3-24.6) vs 22.1 (18.1-25.6) weeks; p=NS • ORR: 31.6% (26.5-36.8) vs 24.4% (19.8- 29.2) p=NS
OCT-2012	**NAB-PACLITAXEL (505b2 pathway)** In combination with carboplatin, for the first-line treatment of locally advanced or metastatic NSCLC, in patients who are not candidates for curative surgery or radiation	Nab-paclitaxel + carboplatin vs paclitaxel + carboplatin • **ORR: 33% (28.6-36.7) vs 25% (21.2- 28.5) p=0.005** • m DoR: 6.9 (5.6-8.0) vs 6.0 (5.6-7.1) months

FOR SECOND-LINE TREATMENT		
DEC- 1999	**DOCETAXEL** Single agent for locally advanced or metastatic NSCLC after platinum therapy failure	1. Docetaxel (n=55) vs. BSC (n=49) • **mOS 7.5 m (5.5, 12.8) vs 4.6 (3.7, 6.1); HR 0.56 (0.35, 0.88); p=0.01** • mTTP 12.3 (9.0, 18.3) wks vs. 7.0 wks (6, 9.3) • ORR 5.5% (1.1, 15.1) vs N/A 2. Docetaxel vs. Vinorelbine/Ifosfamide • m OS 5.7 m (5.1, 7.1) vs. 5.6 m (4.4, 7.9); HR 0.82 (0.63, 1.06); p=0.13 • mTTP 8.3 wks (7.0, 11.7) vs. 7.6 wks (6.7, 10.1) • ORR 5.7% (2.3, 11.3) vs. 0.8% (0.0, 4.5)
NOV 2004	**ERLOTINIB** Treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen	Erlotinib vs placebo • **mOS 6.7 vs. 4.7 m; HR 0.73 (0.61, 0.86); p <0.001** • mPFS 9.9 wks vs. 7.9 wks; HR 0.59 (0.5, 0.7); p < 0.001 • ORR 8.9% vs < 1%; p < 0.001
DEC-2014	**RAMUCIRUMAB** In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving ramucirumab	Ramucirumab/Docetaxel vs Placebo/Docetaxel • **mOS 10.5 (0.95, 11.2) vs 9.1 (8.4, 10.0); HR 0.86 (0.75, 0.98) p = 0.024** • mPFS 4.5 (4.2, 5.4) vs 3.0 (2.8, 3.9) ; HR 0.76 (0.68, 0.86) p < 0.001 • ORR 23% (20, 26) vs. 14% (11, 17); p < 0.001
MAR-2015	**NIVOLUMAB** Metastatic squamous NSCLC with progression on or after platinum-based chemotherapy	1. Nivolumab vs. docetaxel • **mOS 9.2 (7.3, 13.3) vs. 6.0 (5.1, 7.3); HR 0.59 (0.44, 0.79) p=0.00025** 2. Nivolumab (single arm), ≥ third-line • ORR 15% (9.0,22)

Necitumumab Regulatory History

Necitumumab is an anti-EGFR recombinant human IgG1 mAb designed to block the ligand binding site of the human EGFR and is being developed the treatment of squamous NSCLC.

The Investigation New Drug Application (IND #102512) was submitted on November 19, 2008 to support conduct of study CP11-0805/JCCB/INSPIRE.

The major U.S. regulatory milestones for necitumumab development are summarized in the following table.

Table 2 Key Regulatory Activities Related to Clinical Development

Date	Milestone
2008-10-5	Type B Pre-IND/End-of-Phase 1 meeting To discuss the Sponsor's development plan for necitumumab to support approval for KRAS wild type metastatic colorectal cancer
2008-12-19	IND activated Study CP11-0805/INSPIRE was allowed to proceed
2009-09-21	Protocol CP11-0806/JFCC/ SQUIRE submitted to the IND
2011-02-11	Lilly informed the FDA of DMC's recommendation to close study INSPIRE due to an imbalance in the incidence of fatal TE events observed in the necitumumab arm
2013-10-10	Fast Track designation granted for necitumumab in combination with gemcitabine and cisplatin in the 1st-line treatment of patients with metastatic squamous NSCLC
2014-01-16	FDA issued letter of agreement to the Agreed iPSP to request a waiver from all requirements from Pediatric Research Equity Act (PREA) for necitumumab in combination with gemcitabine and cisplatin for metastatic squamous NSCLC
2014-01-31	Type C meeting to discuss Lilly's plan to submit a BLA for necitumumab supported by the results of SQUIRE
2014-06-23	Type B pre-BLA meeting FDA stated that given the modest clinical effect demonstrated in the pivotal trial (SQUIRE), the premature closing of the INSPIRE trial due to safety concerns, the FDA anticipates discussion of the application at an ODAC meeting
2014-11-19	Type C meeting regarding results of EGFR expression exploratory analyses for SQUIRE. FDA stated that given the small sample size of patients with 0% EGFR expression by Immunohistochemistry (IHC) and the overlapping HR for the analysis of PFS, FDA considers the finding exploratory in nature and did not support inclusion in product labeling
2014-10-22	BLA 125547 submitted (rolling submission)

III Randomized Controlled Study to Support Efficacy and Safety

I4X-IE-JFCC (SQUIRE)

Study Design

SQUIRE was a randomized, open-label, controlled study of necitumumab in combination with gemcitabine and cisplatin (N+GC) compared to GC alone as first-line therapy in patients with stage IV squamous NSCLC.

The primary objective of the study was to evaluate the OS of the combination N+GC versus GC alone. Secondary objectives were to evaluate the PFS, ORR, time to treatment failure (TTF), safety, pharmacokinetic, immunogenicity and the Health Status by patient reported outcome (PRO) measure. Exploratory objectives were to evaluate the relationship between biomarkers related to the EGFR-pathway and the mechanism of action of necitumumab in tumor tissue, blood and plasma.

Eligible patients were stratified by ECOG performance status (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia) and randomized 1:1 to receive:

Arm A: Necitumumab 800 mg on Days 1 and 8 of every 3-week cycle
Gemcitabine 1250 mg/m^2 on Days 1 and 8 of every 3-week cycle
Cisplatin 75 mg/m^2 on day 1 of every 3 week cycle

Arm B: Gemcitabine 1250 mg/m^2 on Days 1 and 8 of every 3-week cycle
Cisplatin 75 mg/m^2 on day 1 of every 3 week cycle

Gemcitabine and cisplatin continued for a maximum of 6 cycles and necitumumab until disease progression, unacceptable toxicity, protocol noncompliance, or withdrawl of consent.

Patient Population

Key Inclusion:

- Patients must have histologically or cytologically confirmed squamous NSCLC with measurable or non-measurable disease per RECIST v 1.0
- Stage IV disease per AJCC (American Joint Committee on Cancer) 7th edition
- Age ≥ 18 years with ECOG performance status (PS) score of 0-2
- Adequate hepatic, renal, and hematologic function, defined as: aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x the upper limit of normal (uln) (≤ 5.0 x the uln in the presence of liver metastasis), total bilirubin ≤ 1.5 x uln; serum creatinine ≤ 1.2 x uln or calculated creatinine clearance > 50 mL/min; WBC ≥ 3000/µL, hemoglobin ≥ 9.5 g/dL, and platelets ≥ 100,000/µL
- Archived tumor tissue available for biomarker analysis

Key Exclusion:

- Nonsquamous NSCLC histology (adenocarcinoma, large cell or other)
- Previous chemotherapy for advanced NSCLC. Patients who received prior adjuvant therapy were eligible provided that the last regimen was administered ≥ 1 year prior to randomization.
- Prior anticancer therapy with mAb, signal transduction inhibitors, therapies targeting the EGFR, VEGF or VEGFR pathways
- No clinically relevant co-morbid conditions or serious uncontrolled medical disorder, including brain metastasis that were symptomatic or required ongoing treatment with steroids or anticonvulsants
- Major surgery or investigational therapy < 4 weeks prior to randomization
- Chest radiation <12 weeks prior to randomization.

Safety and Efficacy Measurement Assessment

Safety assessment included baseline history and physical examination, laboratory tests (CBC with diff, chemistry, coagulation profile , urinalysis), ECG, pregnancy test and blood samples for pharmacokinetics, immunogenicity and biomarker studies at baseline and on day 1 of every cycle for 6 cycles at the end of therapy and at 30-day safety follow-up. Patient Lung Cancer Symptom Scale (LCSS) and the EQ-5D instruments were assessed at baseline, every cycle for 6 cycles and every 6 weeks thereafter.

Imaging studies for tumor status assessment (CT or MRI) were performed at baseline and every 6 weeks (+/- 3 days) while on study. All radiographic assessments were performed according to RECIST 1.0.

Survival follow-up: all patients were to have a 30-day safety follow-up evaluation subsequent to last dose; follow-up evaluations were then conducted every 2 months (+/- 7 days) thereafter to obtain information about subsequent anticancer therapy and survival.

Analysis Plan

The primary endpoint OS was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a log-rank test stratified by ECOG PS (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia), as collected by the IVRS/IWRS (Interactive Voice Response System/Interactive Web Response System). The HR with a two-sided 95% CI was derived from a stratified Cox proportional hazards model with the same stratification factors used in the stratified log-rank test. There was no planned interim analysis of OS. Per the statistical analysis plan, the primary analysis of OS was to be performed when at least 844 death events had occurred.

Key secondary endpoints included PFS per RECIST criteria as assessed by the investigator and ORR. In the event that there was a statistically significant result for the primary analysis of OS, the secondary endpoints PFS and ORR would be tested. Hochberg's method was to be used to adjust for multiplicity testing for PFS and ORR.

Results

Study Conduct: 2010 – 2012

- Data cut-off date: June 17, 2013
- Enrollment: 184 sites in 26 countries (87% in North America/Europe/Australia, 8% Eastern Asia and 6% South America/South Africa/India); only 36/1093 enrolled in USA.
- Major protocol violations: 0.9% (5 each arm)

A total of 1093 patients were enrolled, 545 in the N+ GC arm and 548 in the GC alone arm. Patient demographics and disease characteristics are summarized in Table 3.

The baseline demographics and disease characteristics of the ITT (intention-to-treat) population were balanced between the two treatment arms. The median age was 62 years old, > 80% were white, > 80% were males, 60% had ECOG PS 1, > 90% were current smokers. As required by the entry criteria, patients had stage IV squamous cell cancer. More than half of the patients had two or more sites of metastasis, with lymph node, pleura, bone and liver as the most common sites of disease at the time of study entry. Prior treatment included surgery (~ 20%), radiation (8%) or adjuvant chemotherapy (< 5%).

Table 3 Demographic Parameters and Disease Characteristics of the ITT Population

Characteristics	N + GC (N=545) %	GC (N=548) %
Age median (range)	62 years (32 – 84)	62 years (32-86)
Male sex	83	84
ECOG 0, 1 /2	91 /9	91/9
Race White/Asian/African American	84/8/1	83/8/1
Smoker/ ex-light smoker/ non-smoker	92/3/5	90/5/5
Stage IV Squamous histology	99.6	99.5
Median Duration of Disease	0.72 months	0.72 months
No. of metastatic sites		
1 -2	44	44
>2	55	56
Most common sites		
Lymph nodes	79	82
Pleura	27	28
Bone	22	24
Liver	20	21
Prior therapy		
Surgery	22	19
Radiation	8	8
Adjuvant chemotherapy	4	3

Efficacy

Primary Endpoint: OS

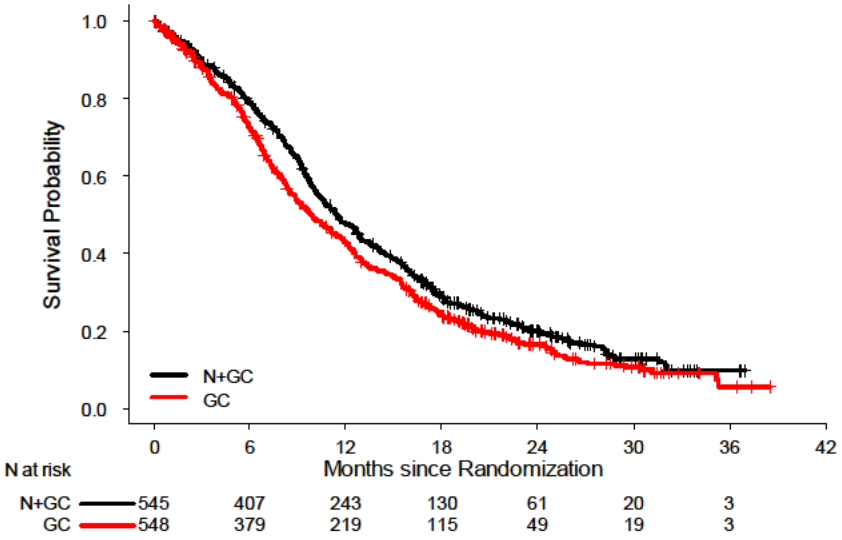
The pre-specified final OS analysis was conducted when 860 death events occurred at the study cut-off date of 17 June 2013. The median duration of follow-up was approximately 25 months for both treatment arms. There was a statistically significant improvement in OS for patients in the N+GC arm compared to patients in the GC alone arm, with a 1.6-month difference in median OS and a HR of 0.84 (95% CI: 0.74, 0.96; two-sided log rank p-value =0.012). FDA's OS analyses findings are consistent with those reported by the Applicant. These are shown in Table 4 and Figure 1.

Table 4 SQUIRE: Overall Survival (ITT Population)

	N+GC (N=545)	GC (N=548)
Number of deaths, n (%)	418 (77)	442 (81)
Median (95% CI), in months	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Hazard ratio (95% CI) [a]	0.84 (0.74, 0.96)	
P-value [b]	0.012	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS and region information collected by IVRS.
[b] p-value was calculated from a logrank test stratified by ECOG PS and region information collected by IVRS.

Figure 1 SQUIRE: Kaplan-Meier Curves of Overall Survival (ITT Population)



FDA's sensitivity analyses for OS are consistent with the primary findings and are summarized below.

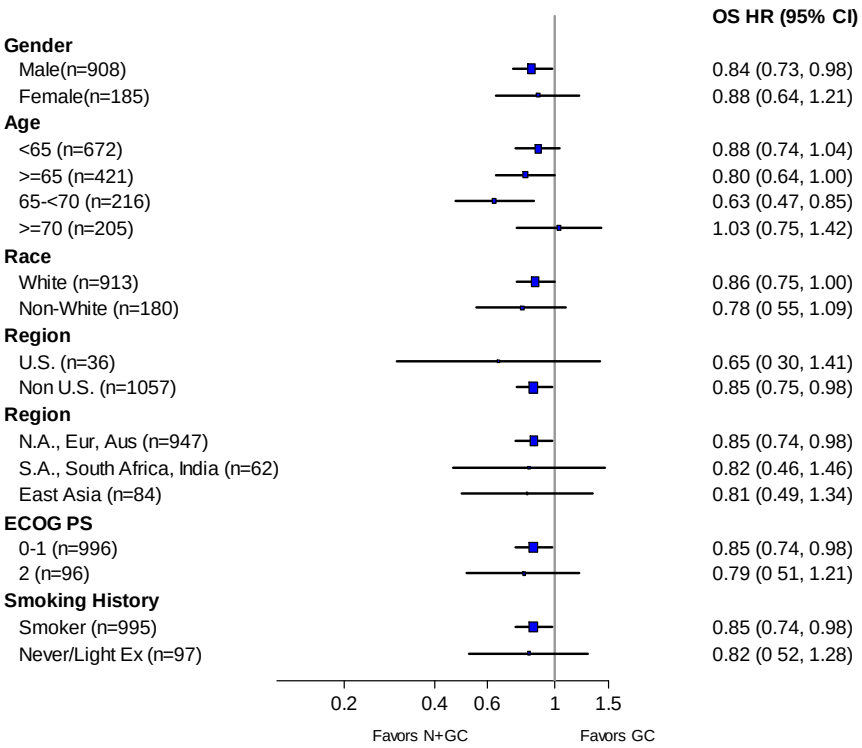
Table 5 SQUIRE: Sensitivity Analyses of OS

Sensitivity Analysis	N+GC	GC	Hazard Ratio (95% CI)
	Median OS (months)		
1. ITT population, un-stratified analysis	11.5	9.9	0.85 (0.74, 0.97)
2. ITT population, per CRF stratification factor	11.5	9.9	0.83 (0.73,0.95)
3. Per-protocol population (n=1072), stratified by IVRS data	11.5	10.0	0.85 (0.74, 0.97)
4.Per-protocol population (n=1072), un-stratified analysis	11.5	10.0	0.86 (0.75, 0.98)
5. Exactly 844 events as per protocol sample size calculation	11.5	9.9	0.83 (0.73, 0.95)
6. Considering patients lost to follow-up or withdrawing consent as events at 2 months after the date of last known alive[a]	10.7	9.2	0.86 (0.75, 0.97)
7. Censoring patients lost to follow-up or withdrawing consent at the study cutoff date[a]	12.1	10.5	0.84 (0.74, 0.96)

[a]*A total of 31 patients (16 in the N+GC arm and 15 in the GC arm) were lost to follow-up and 43 patients (23 in the N+GC arm and 20 in the GC arm) have withdrawn consent for follow-up.*

Exploratory subgroup analyses of OS were performed for baseline factors. The Forest plot for OS is shown in Figure 2. The treatment effect on OS was generally consistent and numerically favors the N+GC arm across various subgroups except for the subgroup of patients ≥ 70 years of age. For patients ≥ 70 years (N=205), the point estimate of HR is 1.03 with a wide 95% CI including 1.

Figure 2 SQUIRE: Subgroup Analyses of OS



Secondary Endpoints: PFS and ORR

Progression-Free Survival

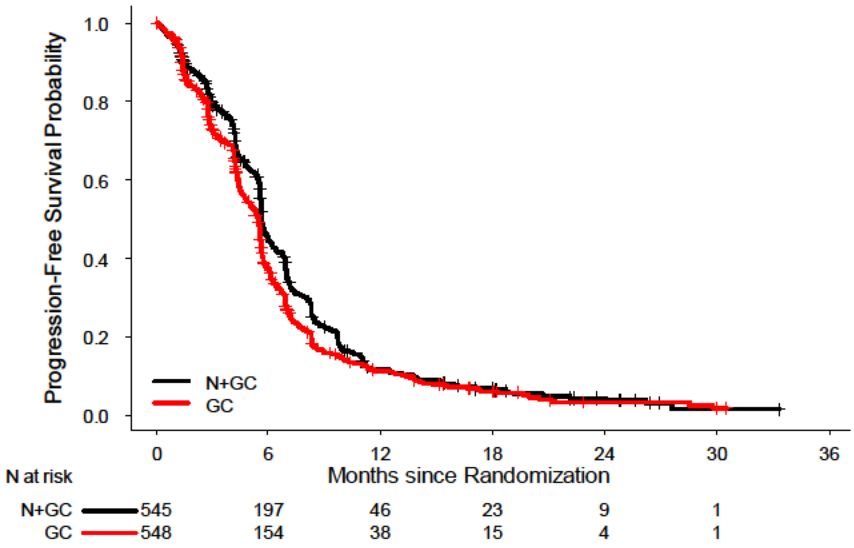
At the time of the OS analysis, PFS per investigator assessment was statistically significantly different between the N+GC arm and the GC arm, with a hazard ratio of 0.85 (95% CI: 0.74, 0.98) and a two-sided log-rank p-value of 0.02. Median PFS was 5.7 months in the N+GC arm and 5.5 months in the GC arm. FDA's PFS analyses findings are consistent with those reported by the Applicant. These results are shown in Table 6 and Figure 3.

Table 6 SQUIRE: Progression-Free Survival (ITT Population)

	N+GC	GC
	(N=545)	**(N=548)**
Number of PFS events, n (%)	431 (79)	417 (76)
Disease progression	357 (66)	332 (61)
Deaths without progression	74 (14)	85 (16)
Median (95% CI), in months	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Hazard ratio (95% CI) [a]	0.85 (0.74, 0.98)	
P-value [b]	0.02	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS and region information collected by IVRS.
[b] p-value was calculated from a log-rank test stratified by ECOG PS and region information collected by IVRS.

Figure 3 SQUIRE: Kaplan-Meier Curves of PFS (ITT Population)



Objective Response Rate

As per investigator assessment, the objective response rate was 31% and 29% in the N+GC arm and the GC arm, respectively. There was no statistically significant difference in ORR between the two treatment arms. The median response duration was 5.6 months in the N+GC arm and 4.9 months in the GC arm. FDA's ORR analyses findings are consistent with those reported by the Applicant. These results are summarized in Table 7.

Table 7 SQUIRE: Objective Response Rate (ITT population)

	N+GC (n=545)	GC (n=548)
Objective Response Rate, n (%)	170 (31%)	158 (29%)
(95% CI)	(27%, 35%)	(25%, 33%)
P-value [a]	0.40	
Duration of response (95% CI), in months	5.6 (5.1, 6.6)	4.9 (4.3, 5.5)

[a] *p-value from CMH test adjusting for ECOG PS and region as collected by IVRS*

Health Status (Patient Reported Outcome)

Analyses of Health Status variables derived from the LCSS consisted of the average symptom burden index (ASBI), the global composite index; the LCSS total score, and each of the 9 individual item scores. For each variable, the proportion of patients with responses of "sustained improvement", "deteriorated" and "stable" were compared between arms using Fisher's exact test. The time to first deterioration was compared between arms for each variable, using a Cox proportional hazards model. In addition, the mean value of patients' best and worst change-from-

baseline scores were summarized and compared between treatment arms using analysis of covariance (with baseline score as the covariate). Similarly, the best and worst change-from-baseline mean score for index score and Visual Analogue Scale of EQ-5D were compared between the treatment arms following the same methods as those for the LCSS. Per the statistical analysis plan, there were no alpha (type-I error rate) adjustments for the multiple tests for the PRO endpoints.

Findings: The analyses of the LCSS and EQ-5D have not shown a consistent or compelling difference between the two treatment arms. Please note that no differences in PRO outcomes in this open-label study do not mean that the addition of necitumumab to gemcitabine and cisplatin had no decrement in patient's health-related quality of life since the Applicant did not plan to test specific hypotheses related to the PRO outcomes.

Exploratory EGFR Results

Results of a post-hoc analysis conducted by the Applicant on EGFR IHC findings from a phase 3 study of cetuximab plus chemotherapy in first-line metastatic NSCLC (FLEX study[9]) had shown a potential correlation with EGFR mAb efficacy in NSCLC.

In the SQUIRE study, tumor samples evaluable for EGFR protein expression were available from 982 patients (89.8%) which included 486 patients in the N+GC arm and 496 patients in the GC arm. EGFR protein expression was evaluated using the Dako EGFR pharmDx Kit which is marketed as an aid in identifying colorectal cancer patients eligible for treatment with cetuximab or panitumumab.

EGFR membrane staining was recorded via H-score, calculated as = [0% x (% cells with no staining) + 1 + (% cells with staining intensity of + 1) + 2 x (% cells with staining intensity of +2) + 3x (% cells with staining of +3)].

As part of the pre-specified statistical analysis plan, the primary analysis of the EGF IHC data dichotomized H-scores into two mutually exclusive subgroups: H score $\geq$ 200 and H-score < 200 (on a scale of 1-300). The cutpoint value of 200 was chosen based on a post-hoc subgroup analysis of the FLEX study, in which NSCLC patients with EGFR H-score $\geq$200 had an OS hazard ratio indicating greater cetuximab benefit relative to the HR within the group of patients with H-score < 200.

Results per Applicant: There were no relevant differences in terms of baseline demographics and disease characteristics between arms or between the subset of patients included in the analysis and the intent-to-treat population. Efficacy outcomes in the EGFR IHC population closely mirrored those in the ITT population. The majority of patients (95.2%) had tumor samples expressing EGFR; only 4.8% had tumors with undetectable EGFR protein. The H-score was evenly distributed in both arms. The Applicant's analysis of OS and PFS by EGFR subgroup (H-score $\geq$ 200 vs. H-score < 200) showed inconsistent results with no treatment by cutpoint interaction; the H-score with a cut-off of 200 was thus not predictive of efficacy outcomes in this study.

Patients whose tumors lacked detectable EGFR expression by IHC (24 in the N+GC arm; 23 in the GC arm), did not appear to benefit in terms of OS or PFS from the addition of necitumumab to gemcitabine and cisplatin compared to gemcitabine and cisplatin alone. Results of the key efficacy endpoints by percent of EGFR expression by IHC (0% vs. > 0% positive) are summarized in the following table provided by the Applicant.

Table 8 Summary of Efficacy Parameters by % Positive (> 0 vs. 0) – Per Applicant
(Translational Research Population)

	Percent Positive >0		Percent Positive =0[d]	
	GC+N N = 462	GC N = 473	GC+N N = 24	GC N = 23
Overall Survival				
p-value[a]	0.004		0.072	
HR (95% CI)[b]	0.81 (0.70, 0.93)		1.86 (0.94, 3.65)	
Median – months	11.73	9.99	6.47	17.35
Interaction p-value[a]	0.018			
Progression-free Survival				
p-value[a]	0.015		0.611	
HR (95% CI)[c]	0.83 (0.72, 0.97)		1.19 (0.61, 2.30)	
Median– months	5.72	5.49	4.24	5.59
Interaction p-value[a]	0.305			

a= p-value from Likelihood Ratio chi-square test of significance; b and c = HR for death (b) or death or progressive disease (c) from any cause comparing N+GC to GC within protein expression subgroup; d = 0 % positive is equivalent to H-score=0 for EGFr staining.

Safety

The safety population in the SQUIRE trial consists of a total 1079 randomized patients who received any dose of study treatment with allocation to treatment group based on the first actual treatment a patient received. An overview of incidence of AEs and serious AEs (SAE) reported in the SQUIRE trial is shown in Table 9.

Table 9 Overview of Incidence of AEs

Adverse Events	N+ GC* % (N=538)	GC % (N=541)
Any AE	99	98
Any SAE	48	38
≥ Grade 3	72	62
AE leading to Deaths	12	11

* Include AEs post chemotherapy, 50% continued Necitumumab monotherapy

AEs and Grade ≥ 3 AEs

AEs observed in more than 15% of patients in the SQUIRE study by MedDRA preferred term (PT) are shown in the following table. More patients in the N+GC arm experienced a grade ≥ 3 AE compared to GC alone (72% vs. 62%). The most common grade ≥ 3 AEs observed in the N

+ GC arm was hypomagnesemia (9% vs. 1%). The most common Grade ≥ 3 AEs observed in both treatment arms were myelosuppression, neutropenia (26%), anemia (11%) and thrombocytopenia (10%). Grade ≥ 3 pulmonary embolism was reported in 3.5% vs. 2% respectively.

The most common necitumumab related AEs were hypomagnesemia (30%) and dermatitis acneiform (15%). Common AEs in both treatment arms (>20%) were gastrointestinal (nausea, anorexia, vomiting, constipation), myelosuppression (neutropenia, anemia, thrombocytopenia) and constitutional symptoms (asthenia and fatigue).

Table 10 AEs Observed in > 15% of Patients by MedDRA Preferred Term

MedDRA PT	N+ GC (N=538)		GC (N=541)	
	All grade %	Grade ≥ 3 %	All grade %	Grade ≥ 3 %
Patients with AE	**99**	**72**	**98**	**62**
Nausea	50	3	52	3
Rash	44	4	6	< 1
Neutropenia	42	24	45	27
Anemia	41	10	46	11
Decreased appetite	30	1	28	2
Hypomagnesemia	30	9	15	1
Vomiting	30	3	25	1
Asthenia	23	4	21	4
Fatigue	21	3	23	3
Constipation	21	<1	18	< 1
Thrombocytopenia	20	10	24	10
Cough	16	0	13	< 1
Dyspnea	16	3	15	4
Diarrhea	16	2	11	2
Alopecia	14	0	13	0
Dermatitis acneiform	15	1	<1	0

Necitumumab-related skin rash and hypomagnesemia lead to treatment delays and modifications in 3% and 2% of patients in the N+GC arm. The most common AEs leading to GC dose delays and modifications in both arms were, as expected, myelosuppression (neutropenia and thrombocytopenia).

Adverse Events Known to be associated with anti-EGFR Class Drugs
Adverse events known to be related to anti-EGFR class drugs were analyzed using composite MedDRA prefer terms and are summarized in Table 11. Skin reaction/rash and hypomagnesemia are the two most common AEs associated with necitumumab, occurring in 79% and 31% of the patients, with 8% and 9% grade ≥ 3.

Table 11 SQUIRE: AEs known to be Associated with anti-EGFR Class Drugs

	N+ GC		GC	
AEs (composite terms)	**N=538 (%)**		**N=541 (%)**	
	All grades	**≥ Gr 3**	**All grades**	**≥ Gr 3**
Skin Reactions	424 (79)	44 (8)	64 (12)	3 (0.6)
- **Rash**	410 (76)	38 (7)	55 (10)	2 (0.4)
Hypomagnesemia	168 (31)	50 (9)	85 (16)	6 (1)
Conjunctivitis	40 (7)	2 (0.3)	12 (2)	0
Diarrhea	84 (16)	9 (2)	61 (11)	8 (2)
Hypersensitivity/infusion reactions	8 (2)	2 (0.3)	12 (2)	0
Interstitial Lung Disease	5 (1)	2 (0.3)	4 (0.7)	3 (0.6)

Thromboembolic Events (TE)

Thromboembolic events were considered an AE of interest due to early signals in the INSPIRE study. An increased incidence of venous TEs (Table 12) was noted in the necitumumab containing arm (9% vs. 5%). Confirmed and unconfirmed diagnosis of pulmonary embolism accounted for more than half (26/49 patients) of the VTEs (5% of patients treated with N+ GC overall) and deep venous thrombosis accounted for 20% (10/49 patients) of VTEs (2% of patients overall).

The incidence of all grade arterial TEs did not appear to differ between the treatment arms (Table 12). The most common ATE events with N+ GC were ischemic stroke/cerebral infarction/TIA (11/29 patients, 2.1% of patients overall) and myocardial infarction (4/29, 0.8% of patients overall).

Table 12 SQUIRE: Thromboembolic Events

	N+ GC N=538 (%)		GC N=541 (%)	
Thromboembolic Events	**All grades**	**≥ Gr 3**	**All grades**	**≥ Gr 3**
ALL TEs	78 (14.5)	48 (9)	50 (9)	25 (5)
Arterial	29 (5)	21 (4)	21 (4)	11 (2)
Venous	49 (9)	27 (5)	29 (5)	14 (3)

**for the list of MedDRA PTs included in the composite term refer to the Appendix.*

Deaths

At the time of the data cut-off, 77% of the patients in the N+GC arm and 81% in the GC arm had died. The incidence of death due to an AE as the primary cause of death, per investigator was reported in 7.4% of N+GC-treated patients and 7.9% of GC-treated patients.

Death on treatment or within 30 days of the last dose of study drug occurred in 11% of the patients in both arms. AEs leading to death in ≥ 3 subjects were death NOS, hemoptysis/hemorrhage, pneumonia or respiratory infection, and cardio-respiratory arrest (Table 13).

Table 13 AEs leading to Death on Treatment or within 30 days of the last dose (≥ 2 patients)

MedDRA Preferred Term	Neci + GC * N=538	GC N=541
Due to an AE	66 (12%)	57 (10.5%)
NSCLC	22	19
Death NOS	8	2
Hemoptysis/hemorrhage	5	11
Pneumonia/respiratory infection	6	5
Cardio-Respiratory arrest	3	1
Myocardial infarction	2	1
Sudden death	2	0
Septic shock	0	2
Cardiac arrest	2	0
Cardiac failure	0	2
Encephalopathy	0	2

A review of the case report forms and narratives revealed an imbalance in the number of sudden deaths and deaths NOS (unknown cause) in the necitumumab arm compared to control (12/538, 2.25 % vs. 3/541, 0.5%). Baseline characteristics, co-morbid conditions and days on study for these patients are listed in the following table.

Table 14 Sudden Death/unknown Cause while on Treatment or within 30 days of the last dose of study drug (FDA's attribution of cause of death)

N+ GC arm	Age/Sex	Days on study	Cause of death	Co-morbidities and AEs
1	61yo M	85	Sudden death	COPD, HTN, ECG abnl, Gr 3 ↓ Mg^{++}
2	63yo M	111	Sudden Death	COPD, alcohol, Gr 2 ↓ Mg^{++}
3	57yo M	245	Sudden Death	COPD, atherosclerosis
4	64yo M	21	Sudden Death	HTN, DM, COPD
5	55yo M	16	Sudden Death	CAD, MI
6	74yo M	9	Sudden death	COPD
7	63yo M	3	Sudden death	CAD, HTN, Hodgkin's
8	62yo M	81	Cardiac arrest	COPD, HTN, Gr 3 ↓ Mg^{++}
9	62yo M	59	Unknown	CAD
10	54yo M	148	Unknown	No known risk
11	80yo M	90	Unknown	HTN, atrial fibrillation, Gr 2 ↓Mg^{++}
12	61yo M	31	Unknown	COPD
GC arm				
1	62yo M	74	Sudden death	No known risk
2	46yo M	6	Sudden death	DM, meningitis
3	56yo M	3	Sudden death	Atrial fibrillation

COPD, chronic obstructive pulmonary disease; HTN, hypertension, ECG, electrocardiogram, DM diabetes mellitus, CAD, coronary artery disease, MI, myocardial infarction

The exact cause of death in these patients is unknown. The majority of the patients died at home with no other information available. The vast majority had co-morbid conditions that might have

contributed to the death. It is possible that the electrolyte disturbances known to be associated with both necitumumab and platinum therapy play a role in the etiology of some of these events. Several patients had uncorrected or suboptimally corrected hypomagnesemia prior to death.

IV Study to Support Safety

I4X-IE-JFCB (INSPIRE)

FDA Reviewer's note: the overall design of the INSPIRE study is similar to that of SQUIRE, with the major differences being the patient population (nonsquamous vs. squamous NSCLC) and the control chemotherapy (pemetrexed and cisplatin vs. gemcitabine and cisplatin). INSPIRE was the first study initiated by Lilly to support a NSCLC indication for necitumumab. The study was closed prematurely at the recommendation of an Independent DMC due to an imbalance in the number of deaths due to thromboembolic events and deaths of all causes *observed in the treatment arm (N=16 vs. 6). At the time of the study closure 633 patients out of 947 planned (67%) had been enrolled.*

Study Design

INSPIRE was a randomized, open-label, controlled study of necitumumab in combination with pemetrexed and cisplatin (N+PC) compared to PC alone as first-line therapy in patients with stage IV nonsquamous NSCLC.

The primary objective of the study was to evaluate the OS of the combination N+PC versus PC alone. Secondary objectives were to evaluate the PFS, ORR, time to treatment failure (TTF), safety, pharmacokinetic, immunogenicity and Health Status by PRO. Exploratory objectives were to evaluate the relationship between biomarkers related to the EGFR-pathway and the mechanism of action of necitumumab in tumor tissue, blood and plasma.

Eligible patients were stratified by smoking status (nonsmokers vs. light smokers vs. smokers), ECOG performance status (0-1 vs. 2), histology (adeno/large cell vs. others); geographic region (North America, Europe, Australia vs. South America, South Africa, India vs. Eastern Asia) and randomized 1:1 to receive:

Arm A

Necitumumab 800 mg on Days 1 and 8 of every 3-week cycle
Pemetrexed 500 mg/m^2 on Day 1 of every 3-week cycle

- Corticosteroid on the day prior to, on the day of and the day after (equivalent of 4 mg dexamethasone BID)
- Folic acid 350 to 1000, daily beginning 1 week before 1st dose until 21 days after the last dose of pemetrexed
- Vitamin B12 1000 μg IM starting 1 week before the 1st dose of pemetrexed and continuing on day 1 of every 3rd cycle until discontinuation of pemetrexed therapy.

Cisplatin 75 mg/m^2 on day 1 of every 3 week cycle

Arm B

Pemetrexed 500 mg/m^2 on Day 1 of every 3-week cycle

- Corticosteroid, folic acid and vitamin B12 at the same doses as Arm A

Cisplatin 75 mg/m^2 on day 1 of every 3 week cycle

Pemetrexed, corticosteroids, folic acid, Vit B12 and cisplatin continued for a maximum of 6 cycles and necitumumab until disease progression, unacceptable toxicity, protocol noncompliance, or withdrawl of consent.

Patient Population

Patients with histologically or cytologically confirmed nonsquamous NSCLC with measurable or non-measurable disease per RECIST were eligible. Patients must have stage IV disease, age ≥ 18 years, ECOG PS score of 0-2, adequate hepatic, renal, and hematologic function and no clinically-relevant co-morbid illnesses. Patients with squamous NSCLC histology were excluded.

Safety and Efficacy Measurement Assessment

Safety assessment included baseline history and physical examination, laboratory tests (CBC with diff, chemistry, coagulation profile , urinalysis), ECG, pregnancy test and blood samples for PK, immunogenicity and biomarker studies at baseline and on day 1 of every cycle for 6 cycles at the end of therapy and at 30-day safety follow-up. Patient Lung Cancer Symptom Scale and the EQ-5D instruments were assessed at baseline, every cycle for 6 cycles and every 6 weeks thereafter.

Imaging studies for tumor status assessment (CT/MRI) were performed at baseline and every 6 weeks (+/- 3 days) while on study. All radiographic assessments were performed according to RECIST 1.0.

Survival follow-up: all patients were to have a 30-day safety follow-up evaluation subsequent to the last dose; follow-up was then conducted every 2 months (+/- 7 days) thereafter to obtain information about subsequent anticancer therapy and survival.

Analysis Plan

The study was initially planned to enroll 947 patients and the primary analysis of OS was to be conducted when at least 723 death events were observed. That sample size would have allowed detection of a HR of 0.80 with a two-sided alpha of 0.05 and a power of 85%. Due to the early closure of study enrollment, the final sample size was 633 patients based upon the actual number of patients who were enrolled prior to the halting of further enrollment. Per the statistical analysis plan, the event number required for the primary OS analysis was revised to 474 death events. This sample size allowed detection of a HR of 0.80 at a two-sided alpha of 0.05 and a power of 68%.

The primary endpoint (OS) was to be estimated using the Kaplan-Meier method, and compared between treatment groups in the intent-to-treat population using the log-rank test, stratified by the randomization strata. The overall significance level was set at 0.05. The HR and its 95% confidence interval were to be estimated from a stratified Cox proportional hazard model stratified by the randomization strata.

Results

Study Conduct: November 2009 – February 2011 (early termination of enrollment)
Data cut-off date: November 14, 2012
Enrollment: 103 sites in 20 countries (87% in North America, Europe, Australia, New Zealand, 13% in Central/South America, Africa and India)

A total of 633 patients were enrolled, 315 in the N+PC arm and 318 in the PC arm. Randomization was balanced in terms of demographics and baseline characteristics. In the ITT population, the median age was 61.0 years (range 26 – 88), 67% were male, 94% had ECOG PS 0 or 1 and 93% Caucasian. More than 75% of subjects were smokers, 89% had adenocarcinoma histology and 8% large cell carcinoma. Nearly a third of the patients had prior surgery, 12 % prior radiation and 3% had received prior adjuvant chemotherapy.

Efficacy

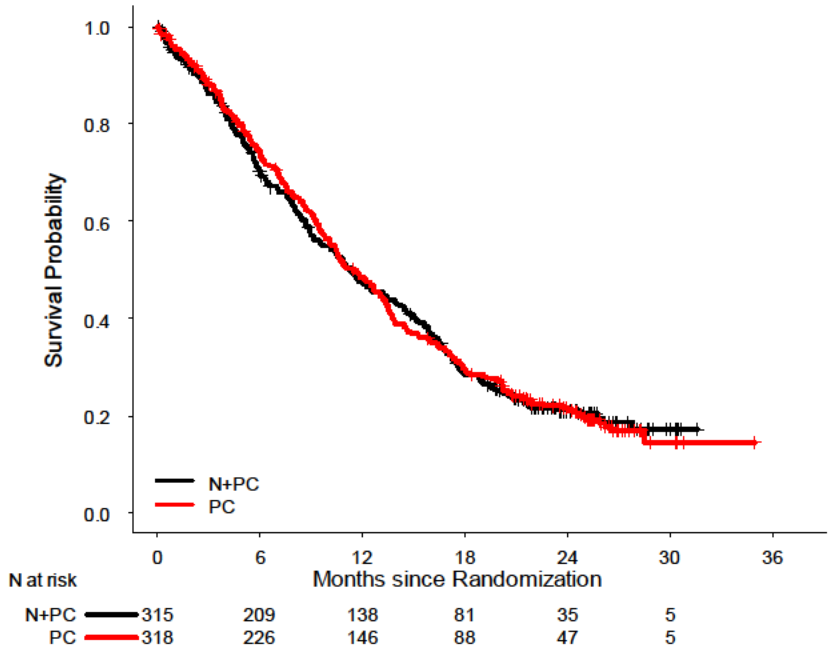
The INSPIRE study did not meet the primary endpoint of improved OS.

Analysis of the data from the 633 patients showed no statistically significant differences in OS, PFS, or ORR. FDA's analyses findings are consistent with those reported by the Applicant.

The median OS was 11.3 months in the PC+N arm and 11.5 months in the PC arm [HR=1.01; 95% CI: 0.84, 1.21; p-value=0.960]. The Kaplan-Meier curves for OS are shown in Figure 4.

The median PFS was 5.6 months in each arm [HR=0.96; 95% CI (0.8, 1.16)]. ORR was similar, 32% in the N+PC arm and 31% in the PC arm.

Figure 4 INSPIRE: Kaplan-Meier Curves of Overall Survival (ITT Population)



Safety

Safety Population

The safety population consists of a total of 616 patients (304 in the N+PC arm and 312 in the PC arm) that includes all patients who received any quantity of study drug.

Incidence of overall AEs and Grade ≥ 3AE
The overall incidence of AEs (all AEs, SAEs, AEs ≥ grade 3) as reported in the safety dataset and CRFs was not significantly different than that reported in the SQUIRE trial.

The most common AEs (all grades) observed in both treatment arms were gastrointestinal, myelosuppression and constitutional symptoms, observed at similar incidence between arms, with the exception of diarrhea (31% vs. 17%). These AEs are consistent with what is expected of the chemotherapy regimen.

The most common grade ≥ 3 AEs occurring with > 3% difference between the treatment and control arms were rash (8% vs. 0%), hypomagnesemia (8% vs. 2%), vomiting (7% vs. 3%), dermatitis acneiform (3% vs. 0%) and hypocalcemia (4% vs. 1%).

AEs known to be related to anti-EGFR class

AEs known to be related to the anti-EGFR class of drugs were analyzed using composite MedDRA preferred terms. The incidence of all grade skin reaction, hypomagnesemia, conjunctivitis, diarrhea, infusion reaction and interstitial lung disease are summarized in table 15. Overall, the incidence and severity of the events are consistent with what was observed in the SQUIRE trial and what has been observed with other mAbs of this class.

Table 15 INSPIRE: AEs known to be Associated with anti-EGFR Class of Drugs

	N + PC		**PC**	
AEs	**N = 304 (%)**		**N = 312 (%)**	
	All grades	**≥ Gr 3**	**All grades**	**≥ Gr 3**
Skin Reactions*	237 (78)	49 (16)	59 (19)	2 (0.6)
- **Rash**	230 (76)	45 (15)	49 (16)	1 (0.3)
Hypomagnesemia	81 (27)	23 (7)	40 (13)	7 (2)
Eye disorders (conjunctivitis)	49 (16)	0	36 (12)	0
Diarrhea	93 (31)	13 (4)	54 (17)	7 (2)
Hypersensitivity/infusion reactions*	6 (2)	0	4 (1)	0
Interstitial Lung Disease	4 (1)	0	3 (1)	2 (0.6)

**for the list of MedDRA PTs included in the composite term refer to the Appendix.*

Thromboembolic Events

Similar to SQUIRE, the overall incidence of TE and grade ≥ 3 TEs were higher in the necitumumab arm compared to control (17.4% vs.14%). Venous TE accounts for most to the TE events (40/53 in the N+PC arm). The most common VTEs were confirmed or suspected pulmonary embolism (20/40) and DVT (8/40).

Of 13 patients who experienced an ATE, 4/13 had a cardiac event (angina, myocardial infarction) and 4/13 had a cerebral event (CVA, ischemia).

Table 16 INSPIRE: Thromboembolic Events

	N + PC N = 304 (%)		**PC N = 312 (%)**	
Thromboembolic Events	**All grades**	**≥ Gr 3**	**All grades**	**≥ Gr 3**
All TEs	53 (17.4)	31 (11)	44 (14)	16 (6)
Venous	40 (13)	23 (8)	26 (8)	11 (4)
Arterial	13 (4)	8 (3)	18 (6)	5 (2)

**for the list of MedDRA PTs included in the composite term refer to the Appendix.*

Deaths

At the time of the data cut-off, 75% of the patients in the treatment arm and 78% in the control arm had died. Death was attributed to disease progression by the investigator and Sponsor in the majority of patients (61% vs. 66%).

More deaths were observed in the treatment arm attributed to an AE or "other causes" than in the control arm (14.5% vs.11.6%), the majority occurred during study or within < 30 days of study drug (14.1% vs. 9.0% in the control arm had died during the study or within 30 days of study drug). The causes of death are discussed in the following section.

Deaths during Study and within < 30 days of Study Drug
A total of 43 patients in the treatment arm and 28 patients in the control arm died during study or within < 30 days of study drug. The causes of death, based on FDA's review of case report forms and case narratives are summarized in the following table.

Table 17 Causes of Death in Patients during study or within < 30 days of Study Drug (FDA's attribution of cause of death)

Cause of Death	**N+PC N=304**	**PC N=312**
Necitumumab + PC	**N=43 (14.1%)**	**N=28 (9.0%)**
Disease progression	14	7
Respiratory failure	5	3
Death NOS	5	-
Sudden death (died at home)	5	5
Infection:		
Sepsis/Neutropenic sepsis	4	-
Pneumonia	2	4
Viral Hepatitis B	1	-
Thromboembolic event		
Pulmonary emboli	1	-
Intestinal Infarction	1	-
Myocardial infarction	1	3
Cerebrovascular accident	-	1
Gastrointestinal perforation	2	1
Worsening of general condition	1	1
Cardiac arrhythmia (supraventricular)	1	-
Renal failure	-	1
Leukopenia	-	1
Pulmonary hemorrhage	-	1

The incidence of deaths during study and within < 30 days of study drug was higher in the treatment arm compared to control (14% vs. 9%). Sudden death and death NOS occurred in 11 (3.6%) patients in the necitumumab arm compared to 5 (1.6%) in the control arm. Similar to the SQUIRE trial, several patients in the necitumumab arm had uncorrected electrolyte disturbances prior to death, including hypomagnesemia and hypocalcemia that might have contributed to the event.

IV Summary

In patients with metastatic squamous NSCLC (SQUIRE trial), the addition of necitumumab to gemcitabine/cisplatin resulted in a 1.6 month median improvement in OS [HR=0.84 (95% CI 0.74; 0.96); logrank p=0.012] and a 0.2 month median improvement in PFS [HR=0.85 (95% CI 0.74, 0.98); logrank p=0.02)]. No significant difference in ORR was observed (31% vs. 29%).

In patients with metastatic nonsquamous NSCLC (INSPIRE trial), the addition of necitumumab to pemetrexed/cisplatin did not result in improvement in OS [HR=1.01, 95% CI 0.84; 1.21)], PFS or ORR.

Patients enrolled in the necitumumab containing arms experienced an increased risk of serious skin reactions, hypomagnesemia and thromboembolic events. A small increase in risk of sudden death (2.2 % vs. 0.5% in SQUIRE and 3.6 % vs. 1.6% in INSPIRE) was observed. The exact cause(s) of death in these patients are unclear; it is possible that the electrolyte disturbances known to be associated with both necitumumab and platinum therapy, couple with co-morbid illnesses, play a role in the etiology of some of these events. Several patients had uncorrected or suboptimally corrected hypomagnesemia prior to death. Careful consideration should be given for use of necitumumab in combination with platinum in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias. Close monitoring of serum electrolytes, including magnesium, potassium, and calcium, during and after necitumumab treatment, with aggressive replacement when necessary, should be strongly recommended.

Although the safety profile of necitumumab appears to be similar to other anti-EGFR mAbs currently marketed, i.e., cetuximab[10] and panitumumab[11], a higher than expected incidence of TE events were observed in both trials. TEs emerged as an early safety signal in the INSPIRE trial and lead to premature closure of the trial.

The target population of lung cancer has several inherent risk factors for arterial and venous thromboembolic events, including smoking, underlying advanced cancer, age and frequent co-morbid conditions such as hypertension and diabetes mellitus[1, 2, 4]. Chemotherapy, in particular cisplatinum, is known to be associated with 2- to 6- fold increase in VTE risk, especially in the first 3-6 months of treatment[3,12]. Tumor histology differences (adenocarcinoma vs. squamous) might account for the higher incidence of TEs observed in the INSPIRE trial.

Recently, anti-EGFR mAbs have been implicated in the development of thromboembolic events, however, the incidence and level of risk remains unclear. In a meta–analysis conducted by Petrelli et al, anti-EGFR therapy results in < 2% absolute increased risk for venous TEs (5% vs. 3.7%, p=0.0136) but not arterial TEs (4.5% vs. 3.4%) or cardiac events. The slight increase of venous TE events appears to be more evident with anti-EGFR mAb than anti-EGFR TKIs and is thought to be due to an indirect anti-vascular endothelial growth factor (VEGF) signaling inhibition by anti-EGFR antibodies[13].

The overall incidence of TEs was higher in the necitumumab arms in both SQUIRE (9% vs. 5%) and INSPIRE (11% vs. 6%) trials compared to control arms. The most common venous TE events, some fatal, were pulmonary emboli and deep vein thrombosis while the most common arterial TEs were myocardial infarction and cerebrovascular accidents.

V Issues for the Advisory Committee

The Division of Oncology Products 2 seeks the advice of the ODAC regarding the pending BLA for necitumumab on the following issues:

1. Do the efficacy and safety results of SQUIRE in squamous cell NSCLC support a positive benefit: risk assessment of necitumumab in combination with gemcitabine/cisplatin in the proposed population?

2. Do the INSPIRE trial results in the nonsquamous NSCLC population impact the benefit: risk assessment of necitumumab for squamous NSCLC?

VI References

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