CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125547/0
Priority or Standard	Standard
Submit Date(s)	December 2, 2014
Received Date(s)	December 2, 2014
PDUFA Goal Date	December 2, 2015
Division / Office	DOP2/OHOP
Reviewer Name(s)	Lee Pai-Scherf, MD
Review Completion Date	August 8, 2015
Established Name	Necitumumab
(Proposed) Trade Name	PORTRAZZA
Therapeutic Class	Monoclonal Antibody targeting EGFR
Applicant	Eli Lilly and Company
Formulation(s)	800mg/50mL single dose vial
Dosing Regimen	Necitumumab 800 mg, (b) (4) min IV on days 1, 8 of 3-week cycle
Indication(s)	In combination with gemcitabine and cisplatin for first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer
Intended Population(s)	(b) (4) patients with metastatic squamous non-small cell lung cancer

Template Version: March 6, 2009

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List of Abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASBI	Average Symptom Burden Index
AUC	area under the concentration
BLA	Biologics License Application
BMI	body mass index
CAD	coronary artery disease
CABG	coronary artery bypass grafting
CBC	complete blood count
CHF	congestive heart failure
CI	confidence interval
CDISC	Clinical Data Interchange Standards Consortium
Cmax	maximum concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete remission
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
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
eCRF	electronic case report form
EF	ejection fraction
EIR	establishment inspection report

FDA	Food and Drug Administration
F/U	follow-up
GC	gemcitabine plus cisplatin
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
HR	hazard ratio
HTN	hypertension
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
KRAS	Kistern rat Sarcoma
LCSS	Lung Cancer Symptom Scale
LDH	lactate dehydrogenase
LLN	lower limit of normal
mAb	monoclonal antibody
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
mTTP	median time-to-progression
MTD	maximum tolerated dose
N	number of subjects
N+GC	necitumumab plus gemcitabine and cisplatin
N+PC	necitumumab plus pemetrexed and cisplatin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NOS	not otherwise specified
NSCLC	Non-Small Cell Lung Cancer
ODAC	Oncology Drug Advisory Committee
ORR	objective response rate
OS	overall survival
PC	pemetrexed and cisplatin
PD	progressive disease
PE	pulmonary embolism
PI	package insert
PFS	progression free survival
PK	pharmacokinetics
PP	per protocol
PR	partial response
PRO	patient reported outcome
PS	performance status
QOL	Quality of Life
QTc	corrected QT interval
QTcF	QT interval corrected using the Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SOC	system organ class
TE	thromboembolic event
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
Tmax	time to maximum concentration
TSH	thyroid stimulating hormone
TTF	time to treatment failure
ULN	upper limit of the normal range
U.S.	United States
USPI	United States Prescribing Information
VTE	venous thromboembolic event

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval for necitumumab in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC).

1.2 Risk Benefit Assessment

The recommendation for approval is based on the demonstration of improved overall survival (OS) and improved progression-free-survival (PFS) in a single, randomized, open-label, multicenter study, I4X-IE-JFCC (SQUIRE). The SQUIRE study enrolled 1093 patients with metastatic NSCLC who were randomized (1:1) to receive either necitumumab 800 mg intravenously on days 1 and 8 in combination gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 on day 1 of every 3-week cycle (N+GC) or gemcitabine and cisplatin (GC) alone. Randomization was stratified by ECOG (Eastern Cooperative Oncology Group) performance status and geographic region.

Analysis of Condition

Lung cancer is the leading cause of cancer related deaths in the US. It is estimated that there will be 158,040 deaths due to lung cancer in 2015, comprising 26.8%% of all cancer deaths in the US[1]. Squamous cell carcinoma comprises 30-35% of all lung cancers. The majority of patients 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%.

Treatment options for first-line treatment of squamous NSCLC has not appreciably changed in decades. Platinum-doublet chemotherapy is the accepted standard-of-care for first-line treatment for metastatic squamous NSCLC in the US. Platinum combination with vinorelbine, paclitaxel, docetaxel, or gemcitabine yields similar improvements in survival. The median OS for patients receiving platinum –doublet chemotherapy ranges from 8 to 13 months, with a 1- year survival rate of approximately 33% [2].

For patients who progress after platinum based therapy, treatment options include single agent docetaxel, erlotinib and two recently approved agents, ramucirumab in combination with docetaxel and nivolumab. Despite these recent advances, patients with metastatic squamous cell lung cancer eventually relapse and succumb to their disease within one year. The median survival for patients treated with ramucirumab[3] and nivolumab[4] is 10.5 months (95% CI 9.5, 11.2) and 9.2 months (95% CI 7.3, 13.3), respectively.

Given the relative lack of efficacious treatment, additional therapeutic options are needed for patients with metastatic squamous NSCL.

Benefit

The addition of necitumumab to GC resulted in a 1.6 month improvement in median OS and a 0.2 month improvement in median progression-free-survival compared to GC alone, both were 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)].

Risk

The safety profile of necitumumab is in general consistent with the adverse events (AEs) observed with anti-EGFR antibody class products. Serious (grade 3–4) necitumumab related adverse events (AE) were hypomagnesemia (19%), skin rash (8%), conjunctivitis (0.4%) and infusion related reactions (0.4%). The incidence of venous thromboembolic events (VTE) of any severity was 9% in patients receiving necitumumab plus chemotherapy versus 5% in patients receiving chemotherapy alone. Fatal cardiopulmonary arrest and/or sudden death, in some cases likely exacerbated by inadequate electrolyte replacement, were observed in 2.2 % of the patients in the N+GC arm compared to 0.5 % in the control arm. The most common AEs in the SQUIRE trial occurring at a ≥ 25 % frequency were nausea, skin rash, neutropenia, anemia, decrease appetite, hypomagnesemia, and vomiting.

Uncertainties

The key issues concerning this application were:

- The modest 1.6 month median improvement in OS, a 0.2 month median improvement in PFS, and no improvement in response rate in a single trial to support the proposed indication of necitumumab in combination with gemcitabine and cisplatin for metastatic squamous NSCLC (SQUIRE study) relative to the increased risk for severe skin rash, hypomagnesemia, thromboembolic events and sudden cardiac deaths associated with necitumumab.
- The results of a second randomized controlled trial in patients with non-squamous NSCLC (INSPIRE study) which showed no improvement in OS, PFS or ORR with the addition of necitumumab to pemetrexed and cisplatin. The INSPIRE study was closed prematurely due to an increase in death of all causes and thromboembolic events observed in the necitumumab containing arm.

Given these uncertainties, an Oncologic Drug Advisory Committee (ODAC) was convened by the review Division on July 9, 2015 to advise and offer insight on the overall benefit: risk of necitumumab in combination with gemcitabine and cisplatin for the proposed population [5].

The vast majority of the 12-member voting committee agreed that the efficacy and safety results of SQUIRE support a positive benefit: risk assessment of necitumumab for the proposed population. Committee members noted that the median 1.6 month survival benefit is modest yet clinically meaningful. It was also noted that the overall survival endpoint and the consistency of the results from various sensitivity analysis conducted by the FDA offer compelling and robust evidence of a positive benefit: risk assessment based on a single trial.

The committee agreed that the lack of efficacy in the non-squamous NSCLC population did not impact on the robustness of the findings in the SQUIRE trial in the squamous NSCLC population.

The reviewer agrees with ODAC members' assessment that results of the SQUIRE trial support a positive benefit: risk assessment of necitumumab in combination with gemcitabine and cisplatin for the proposed indication. While the safety issues identified in the SQUIRE trial are of concern, the reviewer notes that the overall incidence and severity of hypomagnesemia, skin reactions, conjunctivitis and infusion reactions are in general, consistent with what has been reported with other anti-EGFR monoclonal antibodies currently on the market[6,7]. Patients with lung cancer have several inherent risk factors for thromboembolic events[8]. Treating physicians should be made aware of the increased risk of these events with necitumumab. In patients with a previous history of thromboembolic events, the benefits of therapy with necitumumab versus the risk for serious or life-threatening vascular complications must be carefully considered.

It is noted that in a pre-specified, retrospective analysis of EGFR tumor protein expression conducted by the Applicant in the SQUIRE trial, EGFR expression, as determined by immunohistochemical staining, was not predictive for efficacy outcome. Future efforts to identify biomarkers with predictive power to discern subgroup of patients more likely to derive benefit from necitumumab are needed.

Conclusion

Taking into consideration the totally of data submitted in the BLA125547 and commentaries from ODAC members, the reviewer concludes that the results of the SQUIRE trial support a positive benefit: risk assessment of necitumumab and recommends its approval in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous NSCLC

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At the time of completion of this review, the clinical team determined that a Risk Evaluation and Mitigation Strategy (REMS) would not be required for this approval.

The applicant did not submit a REMS with the application.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of completion of this review, the clinical team determined there was no need for post market requirements or commitments studies to ensure the safety use of necitumumab in the indicated patient population.

The reader is referred to the action letter and cross-discipline team leader (CDTL) reviews for the final requirements of the postmarketing requirement.

2 Introduction and Regulatory Background

2.1 Product Information

Necitumumab is a recombinant human DNA-derived mAb of IgG1 that blocks the ligand binding site of EGFR.

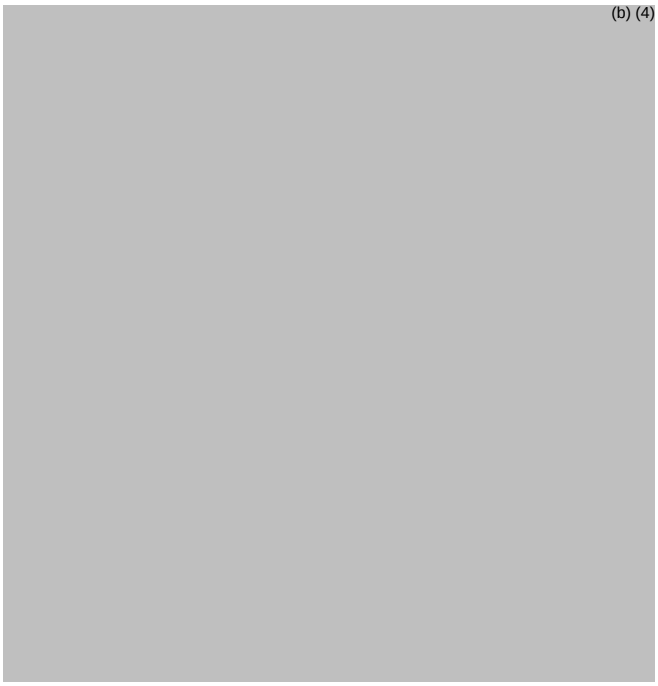
Code Name:	NECITUMUMAB; LY3012211
Generic Name:	Necitumumab
Proprietary Name:	PORTRAZZA
Drug Class:	Monoclonal antibody
Pharmacologic Class:	Epidermal growth factor receptor (EGFR) antagonist
Chemical Name:	Immunoglobulin G1, anti-(human endothelial growth factor receptor (receptor tyrosine protein kinase ErbB1, EC 2.7.10.1)); human monoclonal NECITUMUMAB γ1 heavy chain 224-214')-disulfide with human monoclonal NECITUMUMAB κ light chain dimer (230- 230":233-233")-bidisulfide

Structure and Molecular Weight:

Necitumumab is composed (b) (4)

(Figure 1). The molecular weight for the entire antibody is (b) (4) kilo Daltons (kDa) (b) (4)

Figure 1 Schematic Structure of Necitumumab



Formulation: Necitumumab Injection is to be marketed as a 16 mg/mL (800 mg/50 mL) sterile solution in single dose vials for intravenous (IV) infusion.

2.2 Tables of Currently Available Treatments for Proposed Indications

The current standard first-line treatment for patients with advanced, metastatic squamous NSCLC is cytotoxic chemotherapy with cisplatin or carboplatin-based doublets[9]. Platinum combination with vinorelbine, paclitaxel, docetaxel, or gemcitabine yields similar improvements in survival. In historic front-line platinum based chemotherapy trials[2], the ORR range from 25%-35%%, time to progression range from 4 to 6 months, median OS range from 8 to 10 months, with a 1- year survival rate of 30 to 40%.

In recent years, identification of driver mutations in the kinase domain of the EGFR gene and alterations of Anaplastic Lymphoma Kinase (ALK) gene in lung cancer[10] 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[11], afatinib[12] and gefitinib[13] and ALK inhibitors such as crizotinib[14] 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[3] (approved in December 2014) and nivolumab[4] (approved in 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 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) m, 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)

2.3 Availability of Proposed Active Ingredient in the United States

Necitumumab is a new molecular entity and is not currently marketed in the United States or any other country at the time of this review (August 2015).

2.4 Important Safety Issues with Consideration to Related Drugs

Necitumumab is a drug in the class known as anti-EGFR monoclonal antibodies (mAbs). The currently marketed anti-EGFR mAbs used for treatment of squamous cell carcinoma of the head and neck or K-Ras wild-type, EGFR-expressing colorectal cancer have the following WARNINGS and PRECAUTIONS in the US Prescribing Information (USPI):

Erbitux (cetuximab)

Boxed warning: Serious infusion reactions, some fatal. Cardiopulmonary arrest and/or sudden death. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux administration.

- Infusion reactions
- Cardiopulmonary Arrest
- Pulmonary toxicity
- Dermatologic toxicity
- Hypomagnesemia
- Increased tumor progression, increased mortality, or lack of benefit in patients with *Ras*-mutant mCRC

Vectibix (panitumumab)

Boxed warning: Severe dermatologic toxicities

- Dermatologic and Soft Tissue Toxicity
- Increased tumor progression, increased mortality, or lack of benefit in patients with *RAS*-mutant mCRC
- Electrolyte Depletion
- Infusion Reactions
- Pulmonary Fibrosis/Interstitial Lung Disease
- Ocular Toxicities

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

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

Table 2 Key Regulatory Activities Related to Clinical Development

DATE	MILESTONE
2008-12-5	Type B Pre-IND/End-of-Phase 2 meeting • Discussion held regarding ImClone/Lilly's proposed [redacted] to support approval of IMC-11F8 (necitumumab) • FDA recommended [redacted]
2008-11-19	New IND 102512 - ImClone/Lilly submitted new IND with Study CP11-0806/INSPIRE, RCT of pemetrexed/cisplatin with or without necitumumab for 1st-line treatment of patients with stage IV non-squamous NSCLC. - FDA found the overall design of the study acceptable. FDA provided non-hold comments. These were addressed by the Applicant in a subsequent amendment to the IND
2008-12-19	IND activated Study CP11-0805/INSPIRE for non-squamous NSCL was allowed to proceed
2009-09-21	- Protocol CP11-0806/JFCC/ SQUIRE, a RCT of gemcitabine/cisplatin with or without necitumumab for 1s-line treatment of patients with stage IV squamous NSCLC was submitted to the IND - FDA found the overall design and plan acceptable and provided non-hold comments that were addressed by the Applicant in a subsequent amendment to the IND
2011-02-11	Lilly informed the FDA of IDMC's recommendation to close study INSPIRE due to an imbalance in the incidence of deaths of all causes and fatal thromboembolic events observed in the necitumumab arm. Interim safety results of the SQUIRE trial was also reviewed. The IDMC recommended continuation of the SQUIRE trial without modification.
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

DATE	MILESTONE
2014-01-31	Type C meeting - Discussion held regarding Lilly's plan to submit a BLA for necitumumab supported by the results of SQUIRE - FDA found Lilly's proposed rolling BLA submission acceptable - FDA asked Lilly to provide datasets for INSPIRE study in the BLA
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 - Discussion held concerning the results of EGFR expression exploratory analyses for SQUIRE. - (b) (4) FDA considers the finding exploratory in nature and did not support (b) (4)
2014-10-22	BLA 125547 submitted (rolling submission)

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The BLA submission contains all the required components of the electronic Common Technical Document (eCTD). The overall integrity and quality of the submission was acceptable to allow for substantive review of the contents.

3.2 Compliance with Good Clinical Practices

The clinical studies submitted to the BLA were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), and, applicable laws and regulations and where applicable, Food and Drug Administration (FDA) regulations (21 Code of Federal Regulations, Parts 50 a and 56) for the protection of the rights and welfare of human t participating in biomedical research.

All protocols, amendments and patients informed consent forms (ICF) were reviewed and approved by local regulatory authorities and ethics review boards (ERBs).

3.2.1 Clinical Site Inspections

Three clinical sites were selected for inspection based on enrollment of large numbers of study subjects, significant primary efficacy results and general safety reports pertinent to decision making. The study sponsor, Eli Lilly and Company, was also inspected (Table 3). Inspection was carried out by the Division of Good Clinical Practice Compliance, Office of Scientific Investigations (OSI), CDER, FDA as part of the BLA review:

Table 3 Clinical Sites Inspected for Study SQUIRE

Site No. Investigator	No. of Subjects Enrolled	Inspection Date and Final Classification*
No. 321 Dr. Tudor Ciuleanu Cluj-Napoca, Romania	39	April 27 to May 1, 2015 - Final classification pending - Interim classification: VAI
No. 324 Dr. Mircea Dediu Bucharest, Romania	27	April 20 to 24, 2015 - Final classification pending - Interim classification: VAI
No. 133 Dr. Perrine Crequit Paris, France	10	April 20 to 24, 2015 Final classification: NAI
Eli Lilly & Co Lilly Corporate Center Indianapolis, IN 46285	Sites 321, 133, 324, 156 and 702	May 4 – 12, 2015 Final classification: NAI

*Key to Classifications:

- NAI = No deviation from regulations
- VAI = Deviation(s) from regulations
- OAI = Significant deviations from regulations. Data unreliable.
- Pending = Preliminary classification based on information in 483 or preliminary communication with the field; establishment inspection report (EIR) has not been received from the field, and complete review of EIR is pending.

At the time of this review, preliminary inspectional findings for Site 321 (Dr. Tudor Eliade Ciuleanu), Site 133 (Dr. Perrine Crequit), Site 324 (Dr. Mircea Dediu) and the study sponsor, Eli Lilly and Company, the SQUIRE study data submitted to the Agency in support of BLA 125547 appear reliable based on available information.
With respect to Dr. Ciuleanu's site, the inspection revealed a number of protocol deviations, as well as two incidences where a drug accountability log failed to document the disposition of unused test article for two study subjects. Dr. Ciuleanu provided a written response, dated May 21, 2015, to the Form FDA 483 inspectional observations.

The written response provided adequate explanations and detailed corrective actions to prevent reoccurrences moving forward. The observations noted for Dr. Ciuleanu's site should not importantly impact overall study outcome or have placed study subjects at increased risk.
Please refer to the final OSI review for details regarding the inspection results and recommendations.

3.2.2 Study Protocol Violations

Data from the SQUIRE study was reviewed for possible significant protocol violations that might impact on the integrity and reliability of the study outcome. A total of ten patients (0.9%), five in each treatment arm were found to have had a protocol-specified major protocol violation. The site, patient ID and violations are listed in Table 4.

Table 4 Major Protocol Violations

SITE	PATIENT ID	MAJOR PROTOCOL VIOLATION
N+GC Arm		
111	6001	Additional concurrent prohibited therapies
175	6004	No histologically cytologically confirmed squamous NSCLC
179	6001	No advanced stage IV disseat the time of study entry
245	6005	No histologically cytologically confirmed squamous NSCLC
324	6023	No advanced stage IV disseat the time of study entry
GC Arm		
321	6011	ECOG PS >2 No advanced stage IV disease at the time of study entry
604	6002	No histologically cytologically confirmed squamous NSCLC
604	6003	No histologically cytologically confirmed squamous NSCLC
172	6003	No advanced stage IV disseat the time of study entry
301	6001	No histologically cytologically confirmed squamous NSCLC

Important protocol violations occurred in 75 patients (6.9%). Violations were more frequent in the necitumumab + GC arm (N=47) compared to the control arm (N=28). The reasons for the violations are summarized in Table 5.

Table 5 Important Protocol Violations

VIOLATIONS	N+GC N=545	GC N=548
All	47 (8.6%)	28 (5.1%)
Inclusion/exclusion criteria		
- Inadequate hepatic, renal or hematologic function	9 (1.7)	7 (1.1)
- Received prior chemotherapy for metastatic disease	1 (0.2)	1 (0.2)
Incorrect dosing		
- Study drug dose > 10% than protocol defined dose	3 (0.6)	5 (0.9)
- Dose of gemcitabine /cisplatin escalated after prior reduction	8 (1.5)	12 (2.2)
- Next cycle started < 18 days after previous cycle	5 (0.9)	1 (0.2)
Study specific violations	20 (3.7)	3 (0.5)
- Study treatment continued after PD	1 (0.2)	-
- Study treatment continued after Grade 3-4 infusion reaction	1 (0.2)	-
- Received more than 2 dose reductions		

Reviewer's comment

Major protocol violations occurred in equal number in the treatment arms and do not appear to impact the final efficacy results. A sensitivity analysis of OS was conducted by excluding all patients with major protocol deviations (per-protocol population). Results were similar to the primary findings (refer to Section 6.4.1).

Although the number of important protocol deviations was higher in the treatment arm, the majority (N=20) was due to continued necitumumab treatment after radiographic progression date). Other causes of violation were evenly distributed between the two treatment arms. These protocol deviations do not change the overall benefit: risk assessment for necitumumab.

3.3 Financial Disclosures

The Applicant submitted Certification of Financial Interests and Arrangement of Clinical Investigators (Form 3454) for (b) (6) study with a list of all investigators, sub-investigators and members of the IDMC who provided information that they had no financial conflicts of interest as defined in 21 CFR 54.2(1)(b).

For two investigators, (b) (6) information could not be obtained despite due diligence performed by the Applicant. Eli Lilly states that based on company's records of payment, the above investigators did not have a disclosable financial interest as defined in 21 CFR Part 54.

Seven investigators reported significant financial interest:

- Dr. [redacted] disclosed that he has speaker fees and scientific reviews totaling $43,848. [redacted] enrolled [redacted] patients in study [redacted]
- Dr. [redacted] disclosed honoraria fees, consulting and speaker fees totaling $ 42,150. [redacted] site enrolled [redacted] patients in study [redacted]
- Dr. [redacted] disclosed honoraria and consulting fees totaling $ 27,000. [redacted] site enrolled [redacted] patients in study [redacted]
- Dr. [redacted] disclosed "payments of other sorts" totaling $ 49,487. [redacted] enrolled [redacted] patients in study [redacted]
- Dr. [redacted] disclosed speaker and consultant fees totaling $61,626. [redacted] enrolled [redacted] patients in study [redacted]
- Dr. [redacted] disclosed speaker fees totaling $ 28,350. [redacted] site enrolled [redacted] patients in Study [redacted]
- [redacted] Dr. [redacted] disclosed speaker and consultant fees totaling $25,038. [redacted] site enrolled [redacted] patients in study [redacted]

Reviewer's Comment

The financial interests of the investigators and sub-investigators identified above have a low likelihood of affecting the outcome of the study due to small numbers of patients enrolled at each respective site. It is also noted that site inspection was conducted by OSI at [redacted] site (site [redacted]). OSI found no deviations from regulations and has concluded that data quality and integrity is acceptable for consideration for licensure.

One member [redacted] reported significant financial interest:

- Dr. [redacted] disclosed honoraria and speaker fees totaling $196,391. Eli Lilly states that "[redacted] Eli

Lilly believes that the financial payments [redacted] received did not influence the outcome [redacted]

Reviewer's Comment

Because [redacted] it is unlikely that the financial interests disclosed [redacted] would affect the study results. The reviewer notes [redacted] Conflicts of interest, the most obvious being financial interest, could substantially affect the outcome of the trial. In this regard, this reviewer questions the Applicant's decision to include individuals with financial ties with the company to provide independent advice on the conduct of this and other trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The following section summarizes issues identified by other review discipline during the ongoing review of this application. The reader is referred to the final review of the respective disciplines for a detailed description of the issues identified.

4.1 Chemistry Manufacturing and Controls

Necitumumab (IMC-11F8 [LY3012211]) drug substance is a recombinant human DNA-derived mAb of IgG1 that blocks the ligand binding site of EGFR. It is composed [redacted] The measured molecular weight for the entire antibody is ca. [redacted] kilo Daltons (kDa) [redacted]

Necitumumab Injection, Solution for Intravenous Infusion, 16 mg/mL, is a sterile solution intended for single use. Necitumumab Injection is formulated in an aqueous [redacted] solution at pH 6.0, containing [redacted] 40mM sodium chloride, 133mM glycine, 50mMmannitol, and 0.01% w/v polysorbate 80.
Necitumumab drug substance (DS) has been manufactured [redacted] yielding comparable DS/drug product (DP). Phase-appropriate analyses of necitumumab were used throughout development to demonstrate comparability of DS manufacturing processes [redacted] clinical PK was collected in a study (Study I4X-IE-JFCJ [JFCJ]) that used DP manufactured

with DS produced (b) (4) to provide additional assessments of comparability.

CMC review of the submission is ongoing at the time of the review. Comparability of DS manufacturing processes, (b) (4) and the results of I4X-IE-JFCJ [JFCJ study comparing the PK of necitumumab DS produced (b) (4) has been reviewed by the Clinical Pharmacology team. PK data from subjects exposed to necitumumab manufactured using (b) (4) was comparable to PK data from subjects exposed to necitumumab manufactures using (b) (4)

4.2 Clinical Microbiology

Microbiology reviews of necitumumab drug product and drug substance quality are ongoing at the time of this review.

Please refer to Microbiology Assessment Branch's final reviews for a full description of Microbiology quality review issues.

4.3 Preclinical Pharmacology/Toxicology

Necitumumab was evaluated in 5- and 26-week repeat dose studies in Cynomolgus monkeys. There were no significant drug-related findings following dosing for 5 weeks at doses as high as 40 mg/kg. In the 26-week study, monkeys were treated at dose levels of 0, 6, 19, or 60 mg/kg weekly for 26 weeks. Refer to section 7.2.3. Special Animal and/or In Vitro Testing, for a summary of the findings and discussion.

Reproductive toxicity studies, including embryofetal development studies, with necitumumab were not conducted. The Applicant provided surrogate data by right of reference to the reproductive toxicology study conducted as a post-marketing requirement for the anti-EGFR antibody cetuximab. Cetuximab and necitumumab bind to the same domain of EGFR with similar affinities and have comparable effects on EGFR ligand binding, downstream signaling, and anti-tumor activities. Cetuximab was detected in amniotic fluid and the serum of embryos from treated dams and, as suggested by the available data from knockout animals, caused embryo lethality and abortions at clinically relevant doses.

The Pharmacology/Toxicology review team did not identify issues precluding approval of necitumumab for the proposed indication but concludes that a warning for embryofetal risk is warranted in the necitumumab label based on the potential risk of reproductive toxicity.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Necitumumab is a fully human IgG1 mAb that binds to the human epidermal growth factor receptor-1 (EGFR-1) and antagonizes binding of its cognate ligands including transforming growth factor α (TGFα), epidermal growth factor (EGF), heparin- binding epidermal growth factor (HB-EGF), betacellulin, amphiregulin, epiregulin, and epigen. Necitumumab selectively blocks ligand-induced phosphorylation of EGFR and consequent phosphorylation of downstream signaling molecules. Furthermore, necitumumab inhibits EGFR-dependent tumor cell proliferation and targets EGFR-expressing tumor cells for killing through an antibody-dependent cell cytotoxicity response (ADCC).

4.4.2 Pharmacodynamics

Exploratory exposure-efficacy relationship was evaluated using the population PK (PopPK) data from the SQUIRE study.

Using the final PopPK model, simulations of survival time predicted necitumumab average concentration at steady state ($C_{ss,ave}$) of 216 µg/mL resulted in an increase in survival time of approximately 48 days relative to control and an E_{max} of 42 days. The 90% predicted interval of $C_{ss,ave}$ for the 800 mg dose regimen was 110-360 µg/mL, an exposure range covering the efficacy range of 70%-100% E_{max} in the $C_{ss,ave}$ -OS curve.

Refer to Clinical Pharmacology review for this and other exploratory pharmacodynamics analyses.

4.4.3 Pharmacokinetics

Population pharmacokinetics analysis was performed to estimate PK parameters for necitumumab.

Absorption: necitumumab is administered intravenously.

Distribution: following a 800 mg dose administered over 50 min IV on Day 1 and Day 8 of every 3-week cycle, necitumumab distribution followed a biphasic decline, while drug clearance was non-linear. Total systemic clearance (CL_{tot}) and steady state volume of distribution (V_{ss}) were 14.1 mL/h (CV=39%) and 6.9 L (CV=31%), respectively. This corresponds to a half-life of approximately 14 days. The predicted time to reach steady state was approximately 100 days. Inter-patient variability in PK parameters was 21.1-55.4%.

Metabolism: Since monoclonal antibodies are degraded into amino acids that are then recycled into other proteins, no metabolism studies are usually performed

Elimination: Excretion studies are not generally performed for monoclonal antibodies because their large molecular size prevents them from kidney elimination.

Special Population

- Renal Impairment: no specific studies of necitumumab in patients with renal impairment have been conducted. As a mAb with a 144.8 kDa molecular weight, necitumumab is not expected to be excreted via the kidney, but rather through proteolytic degradation. Thus a renal impairment study is considered unnecessary. PopPK analysis conducted by the Clinical Pharmacology review team indicates that renal function (as assessed by Cockcroft-Gault creatinine clearance [CGCL = 11-250 mL/min]) has no significant effect on the PK of necitumumab
- Hepatic Impairment: No specific studies of necitumumab in patients with hepatic impairment have been conducted. Necitumumab is a mAb that is eliminated by proteolytic degradation not by hepatic CYP enzyme metabolism, thus a hepatic impairment study is considered unnecessary. PopPK analysis indicates that hepatic function (as assessed by alanine aminotransferase [ALT=2-615 U/L], aspartate transaminase [AST=1.2-619 U/L] and total bilirubin [Total Bilirubin=0.1-106 µmol/L]) has no significant effect on the PK of necitumumab.

4.4.4. Interdisciplinary Review of Through QT Study

A phase 2 study (I4X-IE-JFCI, entitled: "A Study to determine whether Necitumumab (NECITUMUMAB) Monotherapy affects the Corrected QT (QTc) Interval in Patients with Advanced Solid Tumors" with the primary objective of evaluating the effect of necitumumab on the QTc interval is ongoing. The study planned to enroll 60 patients with advanced solid tumors to received necitumumab 800 mg IV every week of a 6-week cycle.

At the time of the BLA submission, accrual has been completed and interim data from 40 patients was submitted and reviewed. CDER's QT-Interdisciplinary Review Team found the interim QTc data analysis for the ongoing study reasonable (b) (4)

(b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following tables lists the clinical trials submitted in support of the BLA application. Data from study SQUIRE serves as the primary basis for the efficacy and safety evaluation, supported by safety information from the INSPIRE study. Three studies were submitted as synopses (I4X-IE-JFCK and I4X-IE-JFCL) or interim reports (I4X-IE-JFCI) because they were ongoing. An interim report for study I4X-IE-JFCK was submitted with the 120-safety update and has been reviewed as in a separate amendment.

Table 6 Clinical Studies to Support Efficacy and/or Safety of Necitumumab

TRIAL IDENTITY	TRIAL DESIGN	STUDY POPULATION	REGIMEN/ SCHEDULE/ ROUTE	STUDY ENDPOINTS	TREATMENT DURATION/ FOLLOW UP	NO. OF PATIENTS ENROLLED	NO. OF CENTERS AND COUNTRIES
Randomized Controlled Study to Support Efficacy and Safety							
SQUIRE (I4X-IE-JFCC, IMCL CP11-0806)	Phase III open-label, multicenter, multinational, controlled, randomized, stratified	Stage IV squamous NSCLC	Treatment arm: N+GC Necitumumab 800 mg IV d1 and D8 Gemcitabine 1250 mg IV d1, 8 Cisplatin 75 mg/m2 IV d1 of 3-wk cycle Control arm: GC (gemcitabine + cisplatin)	Primary: OS Secondary: PFS, ORR, TTF, safety, PK, immunogenicity, health status Exploratory: relationship between biomarkers and efficacy and safety	Both arms: chemotherapy up to 6 cycle Necitumumab until disease progression or unacceptable toxicity Follow-up every 3 months until death	N=1093 randomized N+GC=545 GC=548	184 centers in 26 countries in North America, Europe, Australia, Eastern Asia, South America, South Africa and India
Randomized Controlled Study to Support Safety							
INSPIRE (I4X-IE-JFCB, IMCL CP11-0805)	Phase III open-label, multicenter, multinational, controlled, randomized, stratified	Stage IV non-squamous NSCLC	Treatment arm: N+PC (necitumumab 800 mg IV d1 and 8 of 3-wk cycle + pemetrexed + cisplatin Control arm: PC (pemetrexed + cisplatin)	Primary: OS Secondary: PFS, ORR, TTF, safety, PK, immunogenicity, health status Exploratory: relationship between biomarkers and efficacy and safety	Both arms: chemotherapy up to 6 cycle Necitumumab until disease progression or unacceptable toxicity Follow-up every 3 months until death	N=633 randomized N+PC=315 PC=318	103 sites in 20 countries in North America, Europe, Australia, New Zealand, Central/South America, Africa and India)

CONT. OTHER STUDIES TO SUPPORT SAFETY AND EFFICACY							
I4X-IE-JFCE, IMCL CP11-0401	Dose-escalation	Advanced solid tumors	Arm A Necitumumab IV every wk. of each 6-wk cycle Arm B Necitumumab every other week of 6-wk cycle	Primary: safety, MTD Secondary: PK, immunogenicity, antitumor activity	Until PD or unacceptable toxicity	N=60 Arm A = 29 Arm B = 31	Netherlands
I4X-IE-JFCA, IMCL CP11-0907	Phase I	Advanced solid tumors	Necitumumab 600 or 800 mg IV d1 and D8 every 3 or 6 wks, or 800 mg IV every 2k of 6-wk cycle	Primary: safety and PK Secondary: immunogenicity Exploratory: antitumor activity	Until PD or unacceptable toxicity	N= 15	Japan
I4X-IE-JFCJ, IMCL CP11-1115	DDI Study CSR Data set	Advanced solid tumors	Necitumumab 800 mg IV D3 of a 3-wk PK, D1,8 q3w Gemcitabine and Cisplatin	Primary: PK, DDI Secondary: safety PK, immunogenicity Antitumor activity	Until PD or unacceptable toxicity	Planned: 30 Treated 37	United States
Study in Other Indications							
I4X-IE-JFCD, IMCL CP11-0602	Phase 2, single arm	Unresectable or metastatic colorectal adenocarcinoma	Necitumumab 800 mg IV D3 q 2-wk Oxaliplatin 85 mg/m^2 IV d1 5-FU 400 mg/m^2 bolus d1, 2400 mg/m^2 infus46hrs every 2 wk. cycle	Primary: ORR Secondary: OS, PFS, DOR, safety, PK, immunogenicity, association efficacy and KRAS mutation status		Planned: 40 Treated:44	Belgium and Spain
Ongoing Studies							
I4X-IE-JFCI, IMCL CP11-1114	QTc study	Advanced solid tumors	Necitumumab 800 mg IV every week of a 6-wk cycle	Primary: effect of necitumumab on QTc interval Secondary: other ECG parameters, safety, immunogenicity,	Until PD or unacceptable toxicity	Planned: 60 Ongoing (data available in N=40 as of Jan 2014)	United States

				PK, anti-tumor activity			
I4X-IE-JFCK	Phase 2, single arm, multicenter	Stage IV squamous NSCLC	Necitumumab 800 mg IV d1 and D8 Gemcitabine 1250 mg IV d1 and 8 Cisplatin 75 mg/m2 IV d1 of 3-wk cycle	Primary: ORR Secondary: Osaka PFS, DCR, CTS, safety, PK, immunogenicity	Both arms: chemotherapy up to 6 cycle Necitumumab until disease progression or unacceptable toxicity Follow-up every 3 months until death	Planned: 60 Ongoing	Canada, France, Korea, Mexico, Netherlands, Spain, Taiwan, United States
I4X-IE-JFCL	Phase 2, randomized, open-label, multicenter	Stage IV squamous NSCLC	Arm A Necitumumab 800 mg iv d1 and d8 Paclitaxel 200 mg/m2 IV d1 Carboplatin AUC=6 IV d1 of 3-wk cycle Arm B: paclitaxel and carboplatin	Primary: ORR Secondary: biomarker, PFS, DCR, OS, PFS, safety, PK, immunogenicity	Both arms: chemotherapy up to 6 cycle Necitumumab until disease progression or unacceptable toxicity Follow-up every 3 months until death	Planned: 162 Ongoing	Germany, Korea, Mexico, Poland, Russia, United States

5.2 Review Strategy

Review of Technical Integrity
FDA's JumpStart service was used to evaluate the technical integrity of SQUIRE and INSPIRE Study Data Tabulation Model (SDTM) data sets and conformity to Clinical Data Interchange Standards Consortium (CDISC).

Review of Application Quality and Reliability
Data were assessed based on random cross-validation of datasets with CRF forms. Inspection of selected investigational sites was conducted by the Office of Scientific Investigations to support the reliability of the data. In addition, conflict of interest information and protocol deviations data were analyzed and taken into account to establish the reliability and quality of the submission.

Clinical Review and Analysis
Clinical Study Reports, datasets, Data Monitoring Committee report, case report forms, case narratives and supportive analyses and risk: benefit assessment submitted by the Applicant were reviewed. Key safety and efficacy data were analyzed using the datasets provided. A collaborative statistical review was conducted by the Biometrics review team, Dr. Lijun Zhang and Dr. Shenghui Tang. Sensitivity analyses and subgroups analyses were performed as necessary to establish the robustness of the findings.

This application is primary supported by the efficacy and safety results of a single study, SQUIRE (I4X-IE-JFCC, IMCL CP11-0806). Data from a second study conducted in the non-squamous lung cancer population, INSPIRE (I4X-IE-JFCB, IMCL CP11-0805) has been submitted to provide additional safety data. Review of data from SQUIRE and INSPIRE studies are the primary focus of this clinical review.

Data pooling was not used in the review of this application because of the differences in choice of control and population or differences in dose and schedule of necitumumab.

Clinical study reports from two phase 1, necitumumab dose findings studies (I4X-IE-JFCE, IMCL CP11-0401 and I4X-IE-JFCA, IMCL CP11-0907) and one phase 2 study conducted in patients with metastatic colorectal cancer are summarized and presented in Appendix 9.4. The findings from study I4X-IE-JFCE are discussed in section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Studies assessing drug-drug interaction (I4X-IE-JFCJ, IMCL CP11-1115) and effect on QTC interval (I4X-IE-JFCI, IMCL CP11-1114) are reviewed in detail by the Clinical Pharmacology and QTc-Interdisciplinary review teams. A summary of the findings can be found in Section 4.4 and 7.5. Please refer to the review by the respective disciplines for a detailed description of the issues identified.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 SQUIRE (I4X-IE-JFCC, IMCL CP11-0806)

Study Title
"A Randomized, Multicenter, Open-Lable, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (NECITUMUMAB) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)"

SQUIRE is an open-label, randomized, multicenter, multinational study comparing overall survival of patients with histologically or cytologically confirmed stage IV squamous NSCLC treated with necitumumab with gemcitabine and cisplatin (N+GC) with gemcitabine and cisplatin (GC) alone.

The original protocol was submitted on July 23, 2009 and amended six times. Key protocol changes are listed below:

- Original Protocol (July 2009)
- Version 2.0 (April 2010):
  - References to "stage IIIb or IV" NSCLC revised to "stage IV" to reflect the Jan 2010 AJCC Staging Manual v.7 in which patients with Stage IIIB with malignant pleural effusion are now defined as stage IV
- Version 2.1: Editorial changes
- Version 3.0 (June 2011)
  - Study sample size increased from 947 to 1080 in order to increase the power of the study from 85% to 90%, thereby reducing the Type II-error from 15% to10%.
  - Add information regarding thromboembolic events from the INSPIRE study
- Version 4.0 (October 2011): Administrative changes only
- Version 5.0
  - Added description of assessment of immunogenicity results using validated immunogenicity assay
  - Define biomarker analyses as exploratory objectives. Update list of biomarkers that are considered potentially predictive in the study setting
- Version 6.0: editorial changes

Applicant's rational for conducting the SQUIRE study:

Previous results from two randomized controlled studies using another anti-EGFR mAb, cetuximab in combination with either carboplatin-taxanes or vinorelbine-cisplatin as the chemotherapy backbone in patients with all histological subtypes of advanced metastatic NSCLC resulted in a statistically significant improvement in ORR with both regimens[15,16]. A statistically significant survival benefit was also

reported in the FLEX study only[16]. No statistically significant improvement of PFS was observed in either trial. Subgroup analysis of both studies by tumor histology resulted in better OS hazard ratio (HR) estimates in squamous cell, leading to Eli Lilly to explore the activity of necitumumab in combination with gemcitabine and cisplatin in the squamous NSCLC subgroup in the current trial.

The primary objective of the study was to evaluate the overall survival (OS) in patients with Stage IV squamous NSCLC (per AJCC Staging Manual, 7th Edition) treated with necitumumab plus gemcitabine and cisplatin chemotherapy (N+GC arm) versus gemcitabine and cisplatin chemotherapy alone (GC Arm) in the first-line metastatic setting.

Secondary objectives were to evaluate progression-free survival (PFS), objective response rate (ORR), time to treatment failure (TTF) in each treatment arm, to evaluate the safety profile of necitumumab in combination with gemcitabine and cisplatin, to evaluate the pharmacokinetics (PK), the immunogenicity of necitumumab and to evaluate Health Status.

The study exploratory objectives to evaluate the relationship between biomarkers related to the EGFR-pathway and the mechanism of action of necitumumab and efficacy and safety outcomes using tumor tissue, whole blood and plasma proteomics.

Reviewer's comment concerning the overall study design

The study is well designed with the appropriate regulatory endpoints. The primary endpoint point of overall survival is the preferred basis for oncology drug approval. Demonstration of prolongation of survival is an unequivocal, direct measurement of clinical benefit and it reflects efficacy as well as safety of the drug. PFS is an acceptable secondary endpoint because it is not affected by post-progression treatment. The proposed methods for measurement of PFS were adequate, with the same methods and intervals of tumor assessments in both treatment arms, however, the open-label design of the study may result in assessment bias. The reviewer agrees with the Applicants assertion that a placebo-controlled, blinded study would not have value. The high incidence of skin toxicity observed with necitumumab would have likely unblinded most patients and investigators to treatment assignment.

Eligibility Criteria

Inclusion Criteria

- Patients with histologically or cytologically confirmed squamous NSCLC
- The patient has Stave IV disease (per the AJCC Staging Manual, 7th Edition) at the time of study entry
- Measurable or nonmeasurable disseat the time of the study entry as defined by the RECIST 1.0

- Must be ≥ 18 of age
- The patient has resolution to Grade ≤ 1 by NCI-CTCAE v. 3.0 of all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy
- The patients has an ECOG performance status score of 0-2
- The patient has adequate hepatic, renal hematologic function defined by: total bilirubin ≤ 1.5x ULN, and aspartate transaminase (AST) and alanine transaminase (ALT) ≤5.0 x the ULN in the presence of liver metastasis or ≤ 2.5 x the ULN in the absence of liver metastases; serum creatinine ≤ 1.2 x the ULN or calculated creatinine clearance > 50 mL/min; white blood cell count ≥ 3000/µl, and absolute neutrophil cell count (ANC) ≥ 1500/µL, hemoglobin ≥ 9.5 g/dL, and platelets ≥ 100,000/µL.
- If female, is surgically sterile, postmenopausal, or compliant with a highly effective contraceptive method during and for 6 months after the treatment period. If male, the patien is surgically sterile or compliant with a highly effective contraceptive regimen during and for 6 months after the treatment period.
- Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to randomization
- The patient is able to provide informed written consent and is amenable to compliance with protocol schedules and testing
- The patients has archived tumor tissue available for analysis of EGFR and KRAs mutation status (by PCR) and EGFR gene copy numbers (by FISH)

Exclusion Criteria

- The patient has nonsquamous NSCLC (adenocarcinoma/large cell or other)
- Received prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factors (VEGF), or VEFG receptor
- The patients received prior chemotherapy for advanced NSCLC (adjuvant chemotherapy are eligible if the last administration of the prior adjuvant regimen occurred at least 1 year prior to randomization).
- The patient has undergone major surgery or received any investigational therapy in the 4 weeks prior to randomization
- The patient has undergone chest irradiation within 12 weeks prior to randomization (except palliative irradiation of bone lesions, which is allowed)
- The patient has brain metastases that are symptomatic or require ongoing treatment with steroids or anticonvulsants. Patient who are nonsymptomatic and no longer require treatment with steroids or anticonvulsants eligible
- Patient has superior vena cava syndrome contraindicating hydration
- Clinically relevant coronary artery disease or uncontrolled congestive heart failure (NYHA III or IV), myocardial infarction within 6 months prior to randomization

- The patient has an ongoing active infection including active tuberculosis or known HIV infection
- History of significant neurological or psychiatric disorders
- The patient has any NCI-CTCAE v 3.0 grade ≥ 2 peripheral neuropathy
- The patient has significant third space fluid retention, requiring repeated drainage
- The patients has any other serious uncontrolled medical disorders or psychological conditions that would limit the patient's ability to complete the study sign an informed consent document
- The patient has a known allergy/history of hypersensitivity reactions to any of the treatment components, including any ingredient used in the formulation of I MC-11F8, or any other contraindications to one of the administered treatments
- The patient is pregnant or breastfeeding
- The patient has a known history of drug abuse
- The patient has a concurrent active malignancy other than adequately-treated basal cell carcinoma of the skin or preinvasive carcinoma of the cervix. A patient with previous history of malignancy other than NSCLC is eligible, provided that he/she has been free of disease for ≥ 3 years.

Randomization and Study Treatment

Eligible patients were randomized 1:1 to either Arm A (necitumumab plus gemcitabine-cisplatin) or arm B (GC) via a call-in Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS).

Randomization was stratified by ECOG performances status (ECOG PS; 0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia). A stratified permutated block randomization was used and incorporated into the IVRS/IWRS to balance the treatment allocation among the stratification factors.

Treatment in Arms A and B consists of:

Arm A: N+GC

- Necitumumab 800 mg I.V. on Days 1 and 8 of each 3-week cycle
- Gemcitabine 1250 mg/m^2 I.V on Day 1 and 8 of each 3-week cycle (maximum of six cycles)
- Cisplatin 75 mg/m^2 I.V. on Day 1 of each 3-week cycle (maximum of six cycles)

Arm B: GC

- Gemcitabine 1250 mg/m^2 IV on Day 1 of each 3-week cycle (maximum of six cycles)
- Cisplatin 75 mg/m^2 IV on Day 1 of each 3-week cycle (maximum of six cycles)

Chemotherapy continued for a maximum of six cycles in each arm (or until there is radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance or withdrawal of consent). Patients in Arm A will continue to receive necitumumab until there is radiographic documentation of PD, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

Pretreatment antiemetics and hydration was administered according to local standards. Following premedication, patients received necitumumab (Arm A), followed by gemcitabine (Arms A and B). Cisplatin was administered at least 30 minutes following the end of the gemcitabine infusion (Arms A and B).

Necitumumab 800mg in 250 mL normal saline (0.9%) was administered via I.V. infusion over a minimum of 50 minutes. The infusion rate must never exceed 25 mg/minute. Refer to section below concerning infusion reaction management guidelines.

Reviewer's comment 1

Acceptability of the back-bone chemotherapy regimen: Gemcitabine and cisplatin is an accepted standard-of-care chemotherapy regimen in the U.S. for the first-line treatment of advanced NSCL and is therefore, is acceptable as add-on regimen and control for necitumumab. Gemcitabine and cisplatin in combination with cetuximab, another anti-EGFR mAb, had also been previously evaluated in a phase II study[17] was found to have anti-tumor activity with an acceptable safety profile. In addition, pre-clinical supportive data provided by the Applicant demonstrates antitumor activity of necitumumab as a single agent and in combination with multiple platinum-based doublets in mouse xenograft models of squamous NSCLC.

Reviewer's comment 2

Acceptability of the proposed dose and schedule: the proposed dose and schedule of necitumumab +GC for this trial is acceptable and supported by safety and PK data obtained from the first-in-human dose-finding, phase 1 study (I4X-IE-JFCE). The appropriateness of the dose and schedule are discussed in section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations. A synopsis of study I4X-IE-JFCE is presented in Appendix 9.4

Dose Delays and Modifications
This section summarizes necitumumab and chemotherapy dose delay and modification guidelines for treatment toxicity, graded according to NCI CTCAE 3.0

Necitumumab related Adverse Events:

In the event of grade 3 or 4 non-life-threatening, reversible AEs (i.e., fatigue, anorexia, fever) necitumumab can be delayed for up to 6 weeks and resumed at a reduced dose (600 mg). A second dose reduction (400 mg) is permitted. Necitumumab should be permanently discontinued for events that require more than two dose reductions.

In the event of necitumumab related toxicity, necitumumab will be interrupted, but treatment with gemcitabine and cisplatin will continue according to the planned schedule. For chemotherapy related toxicity, treatment cycle should be delayed until recovery; however treatment with necitumumab should be continued. Necitumumab, gemcitabine and/or cisplatin should be permanently discontinued if treatment is delayed for more than 2 cycles (6 weeks) due to toxicity.

Infusion Reaction:

General guidelines for necitumumab related infusion reactions are summarized here:

- Grade 1: decrease infusion rate by 50% and monitor patient for worsening of condition.
- Grade 2: temporarily stop necitumumab infusion and resume when the infusion reaction has resolved to ≤ grade 1. Resume infusion at 50% rate. For all subsequent infusions, premedication with diphenhydramine hydrochloride 50 mg I.V. (or equivalent) may be administered at the investigator's discretion.
- Grade 3 or 4: stop infusion and disconnect the infusion tubing from the patients. Administer antihistamine, dexamethasone, epinephrine and bronchodilators as indicated. Hospitalization may be indicated following initial improvement. Discontinue necitumumab permanently.

Skin Reactions

Table 7 describes the management recommendations for necitumumab related skin reactions. The protocol recommends continuing necitumumab in the event of grade 1 or 2 skin reaction. Necitumumab is to be held for grade 3 skin reaction for a maximum of 6 weeks and resumed at 400 mg when skin reaction improved to grade ≤ 2. Necitumumab is to be permanently discontinued in the event of a recurrence despite dose reduction, grade 3 skin reaction with fibrosis/enduration, grade 4 toxicity. The protocol recommends reactive treatment with clindamycin and hydrocortisone based on Canadian recommendations for Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies.[18]

Table 7 Skin Reactions: Management Recommendations

(Source: BLA125547, I4X-IE-JFCC clinical protocol, version 6.0, page 77/121, with editorial changes and modifications for brevity)

NCI CTCAE GRADE	MANAGEMENT RECOMMENDATIONS
1	• Administer topical clindamycin 2% and hydrocortisone 1% in lotion base twice daily until resolution of reaction. • Patients are advised to take appropriate protective measures prior to sun exposure to avoid exacerbation of rash severity.
2	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base BID daily 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.
3	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily 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, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade ≤ 2. • Following improvement to Grade ≤ 2, necitumumab may be re-administered, 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 (i.e., after withholding two consecutive doses of necitumumab), or if reactions recur or become intolerable at 50% of the original dose, necitumumab should be permanently discontinued. • Patients who experience Grade 3 skin induration / fibrosis will be immediately discontinued from necitumumab.
4	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily until resolution of reaction. • Administer oral minocycline or doxycycline 100 mg BID, 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 permanently discontinued.

Conjunctivitis

- Grade 1 and 2: initiate symptomatic treatment and follow-up observation
- Grade 3 or 4 or symptoms persist for > 10 days after symptomatic treatment, refer to an ophthalmologist for further evaluation and treatment.

Chemotherapy related Adverse Events

For chemotherapy related non-hematologic toxicities of Grade ≥ 3 treatment must be delayed until resolution to grade ≤ 2 and resume at one dose reduction. If the grade 3 or 4 AE recur, the dose can be reduced a second time. Patients who experience the same toxicity after a second dose reduction must be discontinued from the agent.

Permitted dose reductions for Gemcitabine are 950mg/m^2 and 625 mg/m^2. Permitted dose reductions for Cisplatin are 56 mg/m^2 and 38 mg/m^2.

Guidelines for gemcitabine and cisplatin dose modification due to myelosuppression are summarized in the following table:

Table 8 Dose Modification for Hematologic Toxicity

ANC	PLATELETS	GEMCITABINE DOSE	CISPLATIN DOSE
< 500/mm^3	and ≥ 50,000/mm^3	↓ one dose level	↓ one dose level
Any	and < 50,000/mm^3 without bleeding	↓ one dose level	↓ one dose level
Any	and < 50,000/mm^3 with bleeding	↓ two dose level	↓ two dose level
<1000/mm^3 and fever >38.5^{o}C	any	↓ one dose level	↓ one dose level

Study Assessment

Patients underwent the following assessment during the screening, treatment and follow-up periods:

- Screening/baseline: Informed consent, medical history and physical exam, concomitant medications, toxicity assessment, vital signs, EOG performance status , ECG, laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis, pregnancy test), blood sample for biomarkers analysis, tumor imaging, tumor tissue submission and health status (LCSS and EQ-5D).
- Day 1, week 1 of every cycle: physical exam, concomitant medications, toxicity assessment, vital signs, EOG performance status , laboratory evaluations

(hematology, coagulation, serum chemistry, urinalysis), blood samples for PK, immunogenicity and plasma proteomics and health status (LCSS and EQ-5D).

- Day 8, week 2 of every cycle: concomitant medications, vital signs, toxicity assessment, hematology and serum chemistry profile, blood sample for plasma proteomics
- Every 6 weeks: ECG, coagulation profile, urinalysis, pregnant test, tumor imaging and health status (LCSS and EQ-5D).
- End of therapy: physical exam, concomitant medications, toxicity assessment, vital signs, EOG performance status, laboratory evaluations (hematology, serum chemistry, and urinalysis), and blood samples for PK, immunogenicity and plasma proteomics and health status (LCSS and EQ-5 D).
- 30-Day safety follow-up: toxicity assessment and tumor imaging
- Survival follow-up every 2 months: toxicity assessment

PK sample were obtained prior to first necitumumab infusion of cycles 1 to 6 only, serum immunogenicity analysis were conducted from blood samples collected for PK analysis at baseline, cycles 1, 3 and 5.

Health status was evaluated prior to cycles 1-6 and every 6 weeks thereafter until disease progression.

Statistical Analysis Plan

Efficacy Endpoints
The primary efficacy endpoint for study SQUIRE is overall survival, defined as the time from randomization to death from any cause based upon the intent-to-treat population (ITT). For patients who were alive at the data cut-off date (June 17, 2013) for the final analysis or are lost to follow up, OS time will be censored on the last date the patients is known to be alive.

Secondary efficacy endpoints include investigator assessed PFS, ORR, TTF, and Health Status.

Investigator-assessed PFS was defined as the time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first. Patients with no tumor progression and lost to follow-up or withdrawal of consent were censored on the date of last adequate radiological assessment. Patients with no tumor progression but died within 2 scan intervals following last radiological tumor assessment were censored on the date of death (refer to biometrics team review for a complete list of PFS censoring rules).

Objective response rate was defined as the percentage of patients who achieved either a confirmed complete response (CR) or partial response IPR) determined by

investigators. Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 was used to assess measurable disease.

Additional secondary endpoints:
Time to treatment failure (TTF) was defined as the time from randomization to the first observation of progressive disease, death due to any cause, early discontinuation of treatment (all reasons from eCRF- except "completed treatment" for the GC arm), or initiation of new anti-cancer therapies.

Health status assessment (patient reported outcome) was assessed using lung cancer symptom scale (LCSS, patient scale) measures and EuroQOL Five Dimensions questionnaire (EQ-5D). LCSS is a self-reported disease- and site-specific instrument consisting of six questions on lung cancer symptoms plus three global items (symptom distress, difficulties with daily activities, and quality of life). EQ-5D is a standardized instrument for use as a measure of self-reported health status. The instrument is not specific to lung cancer. EQ-5D included a 3-level assessment (no problem, some problem, and extreme problem) of each of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), plus a VAS rating of the patient's overall health state (100=best imaginable health state; 0=worst imaginable health state).

Sample Size

At least 844 OS events (deaths) were needed to detect a HR of 0.80 (corresponding to an increase from 11 to 13.75 months in median OS) with 90% power using a log-rank test at a two-sided 5% level of significance. Assuming 5% patient drop-out rate, a total of 1080 patients were to be randomized upon the assumption of a 27-month accrual period, a follow-up of 19 months after the last patient was enrolled, and 1:1 randomization ratio.

Interim Analyses
There was no interim efficacy analysis planned for OS. Interim analyses of safety were performed under the auspices of an IDMC, according to the specifics set forth in a separate IDMC charter.

Efficacy Analysis

The primary efficacy analysis population was the ITT population, defined as all patients randomized into the study. Patients were to be classified according to assigned treatment group, regardless of the actual treatment received.

Overall survival was estimated using the Kaplan-Meier method and compared between treatment arms 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 limit were to

be estimated from a stratified Cox proportional hazards model with stratification factors. An unstratified log-rank test was also planned.

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 for consideration to be included in the label. The study statistical analysis plan has specified using Hochberg's method to adjust for multiplicity testing for PFS and ORR.

Progression-free survival was compared using a stratified log-rank test, and the estimation of PFS curves for the two treatment groups was generated using the Kaplan-Meier method. Censoring rules for the primary PFS analysis are summarized in Table 4.

ORR per RECIST1.0 was compared between the two treatment arms for all randomized patients using the Cochran-Mantel-Haenszel test with the same stratification factors as used in the primary analysis of OS.

LCSS and EQ-5D assessments were intended per protocol to be collected once at baseline (within 14 days of randomization), once during each cycle of study chemotherapy, and once every 6 weeks thereafter until disease progression. Patients with a baseline value and at least one post-baseline value of the variable were included in the following analyses:

- Treatment hazard ratio for TTD was estimated using Cox proportional hazards models.
- The proportion of patients with responses of "sustained improvement", "deteriorated" and "stable" were compared between arms using Fisher's exact test.
- 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)

Descriptive analyses were to be performed for patients' data as collected by EQ-5D.

Trial Monitoring

An Independent Data Monitoring Committee (IDMC) was convened to monitor the safety data of this trial and the INSPIRE trial. The Committed met after 50 and 150 patients had been enrolled and received a minimum of two cycles of therapy and twice a year thereafter. Safety data, including AEs, study drop-outs san deaths were reviewed. The IDMC met to review safety data 15 times during the course of the study and recommended continuation of the trial without modification.

Reviewer's Comment

SQUIRE was a well-planned and well-designed trial and is adequate to provide data that will achieve the study objectives.

5.3.2 Supportive Study for Safety: INSPIRE (I4X-IE-JFCB)

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. At the time of the study closure, 633 patients out of 947 planned (67%) had been enrolled.*

The Applicant submitted an abbreviated Study Report and key datasets to provide supportive data for this application.

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: N+PC

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: PC

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 and cisplatin continued for a maximum of 6 cycles and necitumumab until disease progression, unacceptable toxicity, protocol noncompliance, or withdrawal 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)

Demographics and Baseline Characteristics

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.

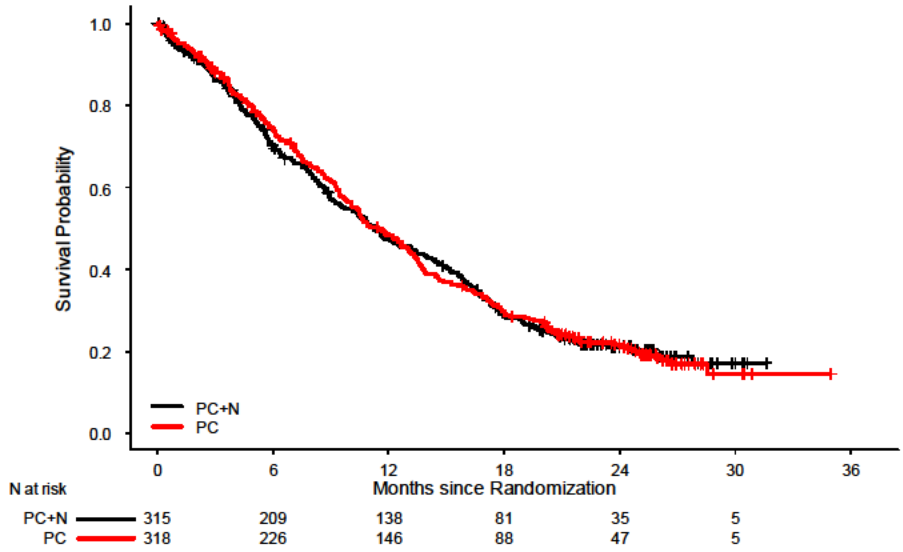
Efficacy
The INSPIRE study did not meet its primary objective of prolonging survival. There was no statistically significant or clinically relevant difference between the two arms in terms of OS (HR=1.01; 95% CI: 0.84, 1.21; p-value=0.96), with a median OS of 11.3 months in the PC+N arm and 11.5 months in the PC arm), as shown in Table 9. The Kaplan-Meier curves are shown in Figure 2.

Table 9 Study INSPIRE: Analysis of Overall Survival

	N+PC (N=315)	PC N=318)
Number of deaths, n (%)	236 (75%)	246 (77%)
Median (95% CI), in months	11.3 (9.5, 13.4)	11.5 (10.1, 13.1)
Hazard ratio (95% CI) [a]	1.01 (0.84, 1.21)	
P-value [b]	0.96	

[a] *Hazard ratio was obtained from a Cox proportional hazards model stratified by smoking history, ECOG PS, disease histology, and geographic region.*
[b] *p-value was calculated from a logrank test stratified by smoking history, ECOG PS, disease histology, and geographic region.*

Figure 2 INSPIRE: Kaplan-Meier Curves of Overall Survival



Secondary Endpoints

Results of the secondary endpoints, PFS and ORR, are summarized in Table 10. The hazard ratio of PFS between the two arms was 0.96 with a 95% confidence interval of 0.80 to 1.16. The median PFS was 5.6 months in each arm. Similar objective response rates were observed in the two arms, 31% in the PC+N arm and 32% in the PC arm.

Table 10 Study INSPIRE: PFS and ORR

	N+PC (N=315)	PC (N=318)
Progression-Free Survival		
Number of PFS Events, n (%)	231 (73%)	239 (75%)
Median (95% CI), in months	5.6 (5.1, 6.0)	5.6 (4.8, 5.7)
Hazard ratio (95% CI) [a]	0.96 (0.80, 1.16)	
Nominal P-value [a]	0.66	
Objective Response Rate		
Objective Response, n (%)	98 (31%)	102 (32%)
95% CI	(26%, 36%)	(27%, 37%)
Nominal P-value [b]	0.79	

[a] *Log-rank test as well as the hazard ratio from a proportional hazard model are stratified by smoking history, ECOG PS, disease histology, and geographic region*
[b] *Derived from two-sided test Cochran-Mantel-Haensel test adjusting for the randomization strata.*

Safety

Reviewer's Note:
The following section summarizes key safety findings for INSPIRE trial FDA's in-depth analysis of death, thromboembolic events and known anti-EGFR drug class AEs are presented and discussed in parallel with SQUIRE safety findings in section 7.3 of this review.

Safety Population

The safety population of INSPIRE 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.

An overview of treatment-emergent adverse events for the INSPIRE study is shown in Table 11:

Table 11 INSPIRE: Overview of Incidence of Adverse Events

ADVERSE EVENTS	N+ PC % (N=304)	PC % (N=312)
Patients with any AE	301 (99)	310 (99)
Patients with any Serious AE	155 (51)	127 (41)
Patients with any NCI CTCAE ≥ Grade 3 Grade 3 Grade 4 Grade 5	220 (72) 140 (46) 31 (10) 49 (16)	185 (59) 135 (43) 18 (6) 32 (10)
Deaths Disease Progression Patients with an AE with outcome of death Death on treatment or ≤ 30 days	229 (75) 185 (61) 29 (10) 16 (5)	242 (78) 206 (66) 23 (7) 13 (4)

The incidence of serious AEs (51% vs. 41%) and grade ≥ 3 AEs (72% vs. 59%) were significantly higher in the necitumumab + PC arm compared to PC alone arm. Patients in the necitumumab containing arm also experienced more grade 4 and fatal events compared to the chemotherapy alone arm.

At the time of the data cut off 75% of the patients in the N+PC arm and 78% in the PC arm had died. Death attributed to an AE and during treatment or within 30 days of last study drug were not significantly different between the two treatment arms *(Refer to FDA's review of causes of death in section 7.3.1)*

Grade ≥3 Adverse Events

Treatment emergent related adverse events of Grade ≥ 3 occurring in > 2% of patients in the N+PC arm is summarized in Table 12.

Table 12 Treatment Related AEs ≥ Grade 3 Occurring in > 2% in the N+PC arm

MedDRA PT	N+ PC N= 304 (%)			PC N=312 (%)		
	Gr ≥ 3	Gr 4	Gr 5	Gr ≥3	Gr 4	Gr 5
Any AE	**178 (59)**	**27 (9)**	**15 (5)**	**134 (42)**	**18 (6)**	**9 (3)**
Neutropenia	51 (17)	14 (5)	0	55 (18)	6 (2)	0
Rash	24 (8)	0	0	0	0	0
Anemia	17 (6)	1 (<1)	0	20 (6)	1 (<3)	0
Hypomagnesemia	17 (6)	6 (2)	0	6 (2)	3 (1)	0
Vomiting	18 (6)	1 (<1)	0	9 (3)	0	0
Leukopenia	17 (6)	4 (1)	0	16 (5)	6 (2)	1 (<1)
Nausea	15 (5)	0	0	12 (4)	0	0
Asthenia	15 (5)	1 (<1)	0	6 (2)	0	0
Thrombocytopenia	12 (4)	8 (3)	0	12 (4)	5 (2)	0
Fatigue	11 (4)	0	0	13 (4)	1 (<1)	0
Pulmonary Embolism	10 (3)	2 (1)	2 (1)	1 (<1)	0	0
Hyponatremia	9 (3)	1 (<1)	0	4 (1)	1 (<1)	0
Dermatitis Acneiform	8 (3)	0	0	0	0	0
Mucosal Information	7 (2)	0	0	1 (<1)	0	0
Rash Generalized	7 (2)	1 (<1)	0	1 (<1)	0	0

In Grade ≥ 3 AEs occurring with > 3% difference between the treatment and control arms were rash (8% vs. 0%), hypomagnesemia (6% vs.2%), vomiting (6% vs. 3%), dermatitis acneiform (3% vs. 0%). Pulmonary embolism, an event of special interest in this submission was reported in 10 patients in the necitumumab arm, with two patients experiencing grade 4 event and two patients experiencing fatal events.

Refer to section 7.3.5 for FDA's analysis and discussion of death, thromboembolic events and anti-EGFR drug class related AEs.

Reviewer's Comment:
The addition of necitumumab to platinum-doublet pemetrexed and cisplatin for patients with non-squamous cell lung cancer failed to show improvement in any of the protocol specified efficacy measures and was poorly tolerated, with a higher incidence of

adverse events related deaths, sudden deaths, thromboembolic events and necitumumab related toxicities compared to standard therapy.

Labeling Recommendation
Based on the efficacy and safety results of the INSPIRE trial, the reviewer recommends adding a Limitation of Use statement in the label stating that PORTRAZZA is not indicated for treatment of non-squamous NSCLC in Section 1 INDICATION and USAGE and Section 14 CLINICAL STUDIES of the proposed label to inform health care providers of the clinical trial findings.

5.3.3 Additional Supportive Safety Studies

The following supportive studies evaluated necitumumab in patients enrolled in studies of necitumumab using dosing schedules and indications different than that proposed for this BLA:

- Study I4X-IE-JFCE, IMCL CP11-0401: first-in-human, single-arm, dose-finding phase 1 study in subjects with refractory advanced solid tumors. A total of 60 patients were enrolled: 29 subjects received necitumumab at doses 100 to 1000 mg IV every week of each 6-week cycle and 31 subjects received necitumumab at doses 100 to 1000 mg every other week of 6-week cycles. *(Refer to Summary of the study key findings in Appendix 9.4.1)*

- Study I4X-IE-JFCA, IMCL CP11-0907: a single-arm, dose finding study in Japanese subjects with refractory advanced solid tumors. A total of 15 patients received necitumumab 600 or 800 mg IV d1 and D8 every 3 or 6 wks, or 800 mg IV every 2k of 6-wk cycle *(Refer to Summary of the study key findings in Appendix 9.4.2)*

- I4X-IE-JFCJ, IMCL CP11-1115: a single arm, DDI study in subjects with refractory advanced solid tumors. A total of 37 subjects received Necitumumab 800 mg IV D3 of a 3-wk PK, D1,8 every 3 weeks in combination with gemcitabine and cisplatin *(Refer to Clinical Pharmacology Review and summary of findings in section 7.5.4)*

- I4X-IE-JFCI, IMCL CP11-1114: a single-arm QTc study in subjects with refractory advanced solid tumors. A total of 60 subjects were enrolled to receive necitumumab 800mg IV every week of a 6 week-cycle (Refer to Clinical Pharmacology and QT-Interdisciplinary Review Team review and summary of findings in section 4.4.4)

- I4X-IE-JFCD, IMCL CP11-0602: a phase 2, single arm study in subjects with unresectable or metastatic colorectal adenocarcinoma with the primary objective

of determined the ORR of necitumumab in combination with oxaliplatin and 5-Fluorouracil (5-FU). A total of 44 patients received Necitumumab 800 mg IV Day3 every 2 weeks, Oxaliplatin 85 mg/m^2 IV Day 1 and 5-FU 400 mg/m^2 bolus Day 1, 2400 mg/m^2 infusion over 46hrs every 2-week cycle *(Refer to Summary of the study key findings in Appendix 9.4.3)*

6 Review of Efficacy

Efficacy Summary

- The addition of necitumumab to GC resulted in a 1.6 month improvement in median OS and a 0.2 month improvement in median progression-free-survival compared to GC alone, 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)].

- In patients with metastatic non-squamous NSCLC (INSPIRE trial), the addition of necitumumab to pemetrexed/cisplatin did not result in significant differences in OS [HR=1.01, 95% CI 0.84, 1.21)], PFS [HR=0.96, 95% CI (0.80, 1.16)] or ORR (32% vs. 31%).

6.1 Indication

Eli Lily proposed the following indication for necitumumab:

"Necitumumab in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer"

6.1.1 Methods

This review is primary focused on the efficacy results of the single randomized controlled trial SQUIRE submitted to support the proposed indication.

Data from the INSPIRE trial, conducted in non-squamous NSCLC population was submitted to provide supporting safety data. A review of the efficacy data was conducted and presented in section 5.3.2 of this review.

6.1.2 Demographics

From 07 January 2010 until 22 February 2012, a total of 1093 patients from 184 clinical sites in 26 countries were randomized to receive either gemcitabine-cisplatin plus necitumumab or gemcitabine-cisplatin chemotherapy in a 1:1 randomization ratio: 545 in the N+GC arm and 548 patients in the GC alone arm.

The demographic and baseline characteristics of the ITT population are summarized in Table 13. Among all randomized patients 83% were male, the median age was 62 years old (range 32–86 years, 88% were white, 8% were Asia, and 1% were black or African American. Ninety-one percent of patients were current smokers, 91% had ECOG PS 0 or 1. The study was conducted in 26 countries, with 87% of the patients from North America, Europe or Australia, 6% from South America, South Africa or India, and 8% from Eastern Asia.

Table 13 SQUIRE: Patient Demographics and Baseline Characteristics

DEMOGRAPHICS AND CHARACTERISTICS	GC+N N=545 (%)	GC N=548 (%)
Age (years)		
Median	62	62
Range	32, 84	32, 86
Age group		
< 65 years	332 (61)	340 (62)
≥ 65 years	213 (39)	208 (38)
< 70 years	437 (80)	451 (82)
≥ 70 years	108 (20)	97 (18)
Sex		
Male	450 (83)	458 (84)
Female	95 (17)	90 (16)
Race		
White	457 (84)	456 (83)
Asian	43 (8)	42 (8)
Black or African American	5 (1)	6 (1)
Others	40 (7)	44 (8)
Baseline ECOG PS		
0	164 (30)	180 (33)
1	332 (61)	320 (58)
2	49 (9)	47 (9)
Smoking History		
Ex-light smoker	18 (3)	26 (5)
Non-smoker	26 (5)	27 (5)
Smoker	500 (92)	495 (90)
Region		
North America, Europe, Australia		

DEMOGRAPHICS AND CHARACTERISTICS	GC+N N=545 (%)	GC N=548 (%)
South America, South Africa, India	(87)	475 (87)
Eastern Asia	30 (6%)	32 (6%)
Unknown	43 (8%)	41 (8%)

Reviewer's comment 1:

Discrepancies between ECOG performance status and region of origin annoted in the electronic case report forms and data collected from IVRS used for stratification were found in 60 out of 1093 (5.5%) randomized patients (Table 14). Discrepancy in ECOG PS 0-1 vs. 2 was noted in 13 patients (6 in N+GC arm and 7 in GC arm) and region of origin (Eastern Asia vs. South America, South Africa, India) in 27 patients (24 in N+GC arm and 23 in GC arm).

Table 14 Discordance of Stratification Data, between eCRF and IVRS

DISCORDANCE	N+GC N=545 (%)	GC N=548 (%)
ECOG PS		
Discordance	6 (1.1)	7 (1.3)
Concordance	539 (98.9)	541 (98.7)
Region		
Discordance	24 (4.4)	23 (4.2)
Concordance	521 (95.6)	525 (95.8)
ECOG PS or Region		
Discordance	30 (5.5)	30 (5.5
Concordance	515 (94.5)	518 (94.5)

The primary OS analysis was stratified by the stratification data collected on IVRS. A sensitivity analysis of OS per eCRF-based stratification data was performed and the results were consistent with the primary OS findings (see Section 6.1.4).

The demographics and baseline characteristics were otherwise similar between the two treatment arms and are representative of the squamous NSCLC population. It is noted that only 36 out of 1098 patients were enrolled in the U.S. Given that gemcitabine and cisplatin used in the study is an accepted standard of cared for this population in U.S. and the post-study anticancer therapies (Table 17) are in general consistent with the types of second-line therapies used in this country, the data obtained from SQUIRE can be applicable to the U.S. population and U.S. medical practice.

Reviewer's comment 2

Other baseline disease characteristics were otherwise similar between the two treatment arms. Eighteen patients (10 in N+GC arm and 8 in GC arm) had an inclusion criteria violation. The violations were evenly distributed between the treatment arms and did not impact on the final efficacy findings (Refer to section 3.2.2 for a list of the violations and discussion).

Baseline disease characteristics of the ITT population are summarized in Table 15.

Table 15 SQUIRE: Disease Characteristics

	GC+N N=545 (%)	GC N=548 (%)
Disease stage at study entry		
IIIb without malignant pleural effusion	1 (0.4)	1 (0.4)
IV	543 (99.2)	546 (99.2
Missing	1 (0.4)	1 (0.4)
Histology		
Squamous	543 (>99)	546 (>99)
Other histology	1 (<1)	1 (<1)
No. of Metastatic Sites at Study Entry		
1	51 (9)	50 (10)
2	193 (35)	193 (35)
>2	301 (55)	304 (56)

Reviewer's comment
Given that only 2 patients (one in each treatment arm) had stage IIIb disease, there is insufficient clinical experience based on the SQUIRE trial to support an indication of necitumumab for locally advanced disease squamous NCLC.

6.1.3 Subject Disposition

Patient disposition, per Applicant, at the time of the data cut-off (17 June 2013) is summarized in Table 16.

Table 16 SQUIRE Patient Disposition

	N+GC N=545 (%)	GC N=548 (%)	TOTAL N=1093
Never Treated	7 (1)	7 (1)	14 (1)
On Treatment	9 (2)	0	9 (<1)
Discontinued From Treatment	529 (97)	541 (99)	1070 (98)
Due to Radiographic PD	314 (58)	104 (19)	418 (38)
Due to Symptomatic Deterioration	18 (3)	23 (4)	41 (4)
Due to Death	35 (6)	30 (6)	65 (6)
Due to Withdrawal of Consent	44 (8)	33 (6)	77 (7)
Due to AE	74 (14)	80 (15)	154 (14)
Due to Completion of Therapy	0	235 (43)	235 (22)
Due to Loss to FU	5 (1)	0	5 (<1)
Due to Other Reasons	39 (7)	36 (7)	75 (7)

[Source: SQUIRE CSR Table JFCC.10.1.]

Fourteen patients (7 in each arm) were randomized, but did not receive study treatment. At the time of the data cut-off, 98% of the patients had discontinued treatment. Disease progression as per RECIST was the primary reason for treatment discontinuation in the N+GC arm (58%) and treatment completion was the primary reason for treatment discontinuation in the GC arm (43%), which are attributable to the study design (patients in the N+GC arm allowed to continue with necitumumab monotherapy after 6 cycles of GC until withdrawal criteria were met, while patients in the GC arm were followed for disease progression after completion of 6 cycles of GC). An equal number of patients was reported to have discontinued from treatment due to an adverse event (14% in the N+GC arm and 15% in the GC).

Post-Study Treatment Anti-Cancer Therapy

Approximately half of patients on both treatment arms received post-study systemic anticancer therapy (47% in the N+GC arm and 45% in the GC arm), as listed in Table 17.

Table 17 Post-Study Systemic Anti-Cancer Therapy

	N+GC N=545 (%)	GC N=548 (%)
Any therapy	258 (47)	245 (45)
Carboplatin/Paclitaxel	15 (3)	14 (3)
Cisplatin/Docetaxel	1 (<1)	4 (<1)
Cisplatin/Gemcitabine	9 (2)	14 (3)
Gemcitabine/Vinorelbine	2 (<1)	0
Paclitaxel/Cisplatin	2 (<1)	0
Cisplatin/Vinorelbine	4 (<1)	1 (<1)
Docetaxel	167 (31)	127 (23)
Erlotinib	57 (11)	75 (14)
Gemcitabine	16 (3)	12 (2)
Pemetrexed	4 (<1)	1 (<1)
Vinorelbine	40 (7)	33 (6)
Other	76 (14)	86 (16)

Reviewer's comment

Post-study anti-cancer treatment chemotherapies are in general consistent with the standard of care for second-line treatment of metastatic squamous NSCLC. More patients in the necitumumab +GC arm compared to GC arm received docetaxel (31% vs. 23 %). In a randomized controlled trial of docetaxel vs. best standard of care, docetaxel showed an improvement in overall survival time [(HR 0.56 (0.35, 0.88); p=0.01][19]. A sensitivity analysis performed by the sponsor accounting for this imbalance in post-progression docetaxel did not change the OS results.

6.1.4 Analysis of Primary Endpoint

Reviewer's Comment

Efficacy analysis of this application was performed in collaboration with Dr. Lijun Zhang, Mathematical Statistician, from the Division of Biometrics, Office of Biostatistics. Please refer to Dr. Zhang's review of the application for additional statistical analysis and discussion.

Primary Endpoint: OS

Overall survival was the primary efficacy endpoint of this study. The pre-specified final OS analysis was conducted when 860 death events occurred at the study cut-off date of

17 June 2013. There was a statistically significant improvement in OS for patients in the N+GC arm compared to patients in the GC 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). The results are summarized in Table 18 and the Kaplan-Meier curves are shown in Figure 3.

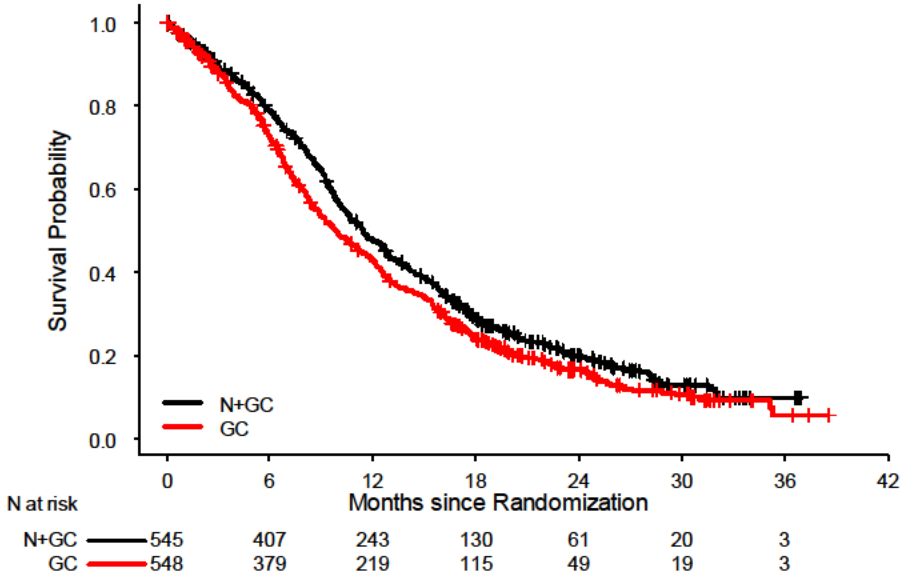
The median follow-up time was 25.2 months (95% CI: 23.7, 27.1) in the N+GC arm and 24.8 months (95% CI: 22.8, 28.3) in the GC arm. A total of 31 patients (16 in the N+GC arm and 15 in the GC arm) were lost to follow-up and 43 patients (23 in the N+GC arm and 20 in the GC arm) withdrew consent for follow-up for the primary OS analysis.

Table 18 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 3 SQUIRE: Kaplan-Meier Curves of Overall Survival



Sensitivity analysis

FDA's sensitivity analyses for OS are consistent with the primary findings and are summarized in Table 19.

Table 19 SQUIRE: Sensitivity Analyses of OS

SENSITIVITY ANALYSIS	N+GC	GC	HAZARD RATIO (95% CI)
	Median OS (months)		
ITT population, un-stratified analysis	11.5	9.9	0.85 (0.74, 0.97)
ITT population, per CRF stratification factor	11.5	9.9	0.83 (0.73,0.95)
Per-protocol population (n=1072), stratified by IVRS data	11.5	10.0	0.85 (0.74, 0.97)
Per-protocol population (n=1072), un-stratified analysis	11.5	10.0	0.86 (0.75, 0.98)
Exactly 844 events as per protocol sample size calculation	11.5	9.9	0.83 (0.73, 0.95)
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)
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.*

6.1.5 Analysis of Secondary Endpoints(s)

Progression-Free Survival

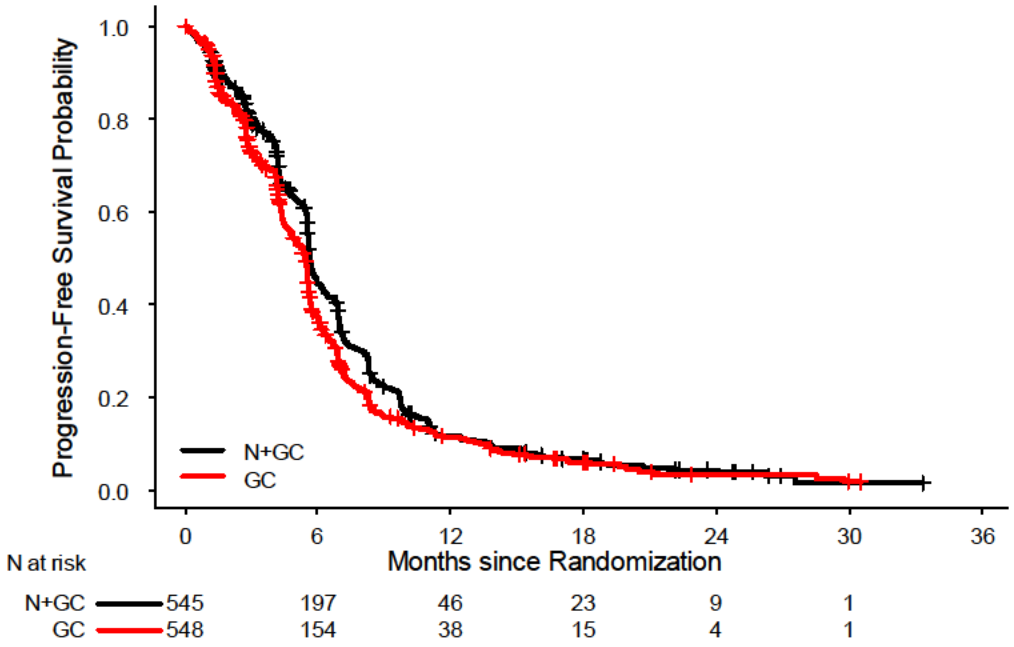
At the time of the OS analysis, PFS per investigator assessment was statistically significantly different between the N+GC arm and the GC arm, with a hazard ratio of 0.85 (95% CI: 0.74, 0.98) and a two-sided log-rank p-value of 0.02. Median PFS was 5.7 months in the N+GC arm and 5.5 months in the GC arm. FDA's PFS analyses findings are consistent with those reported by the Applicant. These results are shown in Table 20 and Figure 4.

Table 20 SQUIRE: Progression-Free Survival (ITT Population)

	N+GC N=545 (%)	GC 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 4 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 21.

Table 21 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*

6.1.6 Other Endpoints

Other Secondary Endpoints

Other secondary endpoints include time to treatment failure and health status outcomes. The study protocol did not pre-specify any multiplicity adjustment method to control the overall alpha for these endpoints.

Time to Treatment Failure

Time to treatment failure (TTF) was compared between the N+GC arm and the GC arm, and the observed hazard ratio was 0.84 (95% CI: 0.75, 0.95). The median TTF was 4.3 months in the N+GC arm and 3.6 months in the GC arm.

Reviewer's Comment

As this is an open-label study, results of time to treatment failure endpoint could be biased.

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.

Reviewer's comment:

The analyses of the LCSS and EQ-5D by the Applicant did not show a consistent or compelling difference between the two treatment arms. Because of the open-design of the study, PRO outcome results must be interpreted with caution.

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[16]) 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 ≥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 ≥ 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 22 Applicant's Summary of Efficacy Parameters by % Positive (> 0 vs. 0)

Source: SQUIRE CSR, Section 11.5.3., page 103

	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.

Reviewer's Comment

Pre-specified, retrospective EGFR protein expression analysis using tumor tissue obtained from patients enrolled in the SQUIRE trial failed to identify a subset of patients

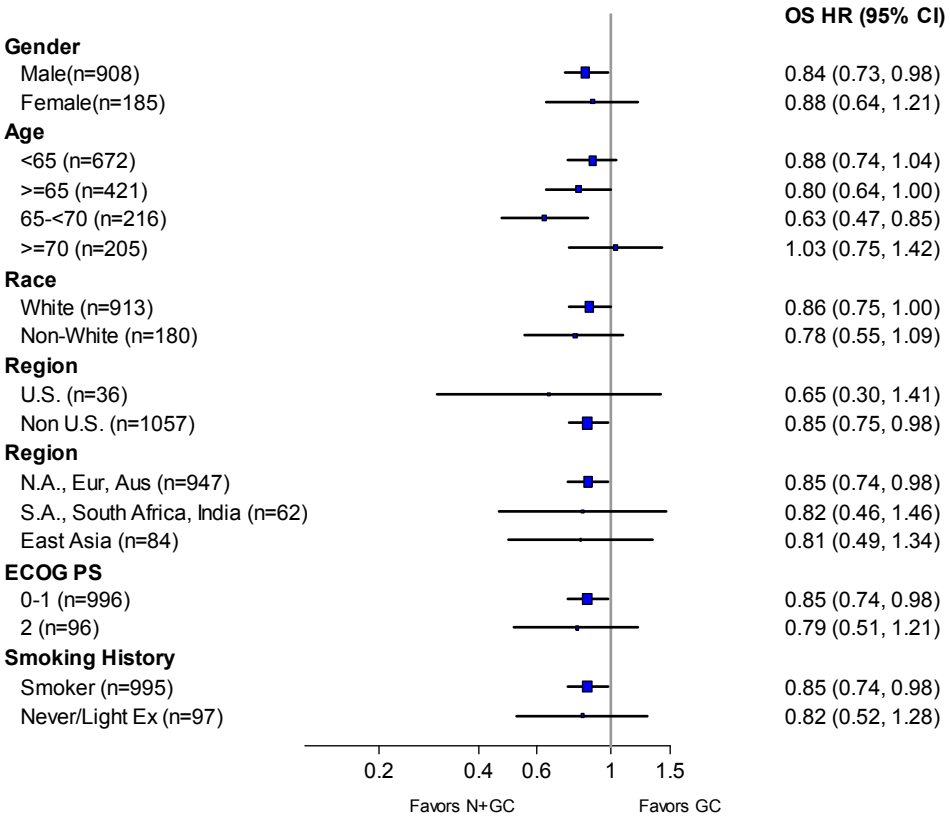
more likely to derive benefit from necitumumab based on EGFR expression measured by immunohistochemical analysis. Concerning the EGFR null (0% EGFR expression) subpopulation, FDA considers these findings exploratory and hypothesis generating. FDA noted that the sample size of patients with 0% EGFR expression by IHC is small and the confidence intervals around the observed HR for the subgroup with no expression and the confidence intervals around the observed HR for patients with any expression overlap for the subgroup analyses of PFS. In addition, no evidence is provided to support the biologic plausibility of this finding (i.e., patients whose tumors do not express EGFR are harmed by necitumumab treatment) and no supportive evidence from other appropriate cut-offs for IHC positivity was provided.

A Type C meeting was held between the Applicant and the FDA on November 19, 2014 to discuss the clinical relevance of the findings with regards to EGFR expression. FDA recommended that the Applicant conduct a confirmatory trial to verify this finding using a validated assay.

6.1.7 Subpopulations

Exploratory subgroup analyses of OS were performed for baseline factors. The Forest plot for OS is shown in Figure 5.

Figure 5 SQUIRE: Subgroup Analyses of OS



The treatment effect on OS was generally consistent and numerically favors the N+GC arm across various subgroups except for the subgroup of patients who are ≥ 70 years of age. For patients ≥ 70 years (N=205), the point estimate of HR is 1.03 with a wide 95% CI (0.75, 1.42).

Reviewer's Comment:

Exploratory subgroup analysis shows a consistent treatment effect on survival across subgroups for gender, race, ECOG PS, smoking history and region of enrollment, with the exception of subgroup of patients who are 70 years or older. Safety analysis by age group did not identify meaningful differences in toxicity between subjects < 70 years of age and ≥ 70 that would explain lack of an survival effect in the elderly subgroup (refer to Section 7.5.3).

Labeling Recommendation

The subgroup analysis findings in OS for patients 70 years and older should be included in Section 8.5 of the prescribing information.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Reviewer's Note
Refer to Clinical Pharmacology review of the PK data for studies I4X-IE-JFCE and Study I4X-IE-JFCA and Appendix 9.4 for a clinical synopsis of the Study I4X-IE-JFCE

Study I4X-IE-JFCE was the first-in-human necitumumab single-agent dose-escalation to evaluate the safety and tolerability of necitumumab in cancer patients.

The study enrolled 60 patients with advanced solid tumors that progressed on standard therapy or for which no standard therapy was available. Patients received intravenous necitumumab:

- Arm A: once a week
- Arm B: once every 2 weeks

A cycle was defined as 6 weeks for both Arm A and B

Doses from 100 mg to 1000 mg were investigated.

At the 1000mg dose level no dose-limiting toxicities (DLTs) were observed in any patient treated with weekly necitumumab.

DLT was reported in 2 out 9 patients who received 1000 mg every 2 weeks: one patient experienced grade 3 headache, grade 3 vomiting, and grade 3 nausea; the second patient experienced grade 3 headache but was able to continue necitumumab at a reduced dose of 800 mg.

Because the DLTs in both patients of the 1000 mg cohort of Arm B occurred in the immediate post-treatment period, after first dose of necitumumab, they were considered to be related to dose and not schedule. The dose level of 800 mg was defined as the maximum tolerated dose and recommended dose for both schedules.

Simulation using clinical PK data from Study JFCE was conducted to predict trough levels of necitumumab following doses of 600 or 800 mg on Days 1 and 8 of a 3-week cycle, a dosing regimen consistent with standard chemotherapy used in NSCLC. The simulation results suggested that only 800 mg (Days 1 and 8 of a 21-day cycle) would

maintain serum trough levels above 40 µg/mL (the level associated with antitumor activity in tumor xenograft models).

A second Phase 1 study (I4X-IE-JFCA; IMCL CP11-0907) was conducted in Japan to evaluate the safety, tolerability and PK in Japanese subjects. DLTs were not observed in this study during the first 6-week cycle for either the 800 mg every- 3-week regimen, or for the 800 mg every 2-week regimen. The PK data for necitumumab at a dose of 800 mg on Days 1 and 8 of a 3-week cycle showed serum trough concentrations (Cmin) above 40 µg/mL throughout the study. Based on these data, the selected Recommended Dose (RD) of necitumumab for Phase 2 and 3 studies is the same for Western and Japanese patients.

An exploratory graphical analysis was conducted based on PK data from Study JFCE to assess correlation between clearance and body weight. No apparent correlation was observed between clearance and body weight, which suggested that necitumumab clearance is independent of patient body weight. Therefore, the Applicant concluded that necitumumab can be administered with a flat dose, as adjustment based on body weight is not necessary.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please refer to Section 6.1.5 for the analysis of OS, PFS, and duration of response for the review of persistency of necitumumab efficacy effects.

6.1.10 Additional Efficacy Issues/Analyses

Supportive data from a randomized, control study of necitumumab in a non-squamous histology of NSCL population (INSPIRE study) was submitted to provide safety data to support the application. Refer to Section 5.3.2 for a description of the study design and efficacy results. Briefly, 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 study enrolled 633 patients with metastatic non-squamous, NSCLC, 315 in the N+PC arm and 318 in the PC arm. The study did not meet the primary endpoint of improved OS (HR = 1.01 (0.84, 1.21). 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.

7 Review of Safety

Safety Summary

- The safety profile of necitumumab is in general consistent with the adverse events (AEs) observed with anti-EGFR antibody class products.
- Serious (grade 3–4) necitumumab related AE were hypomagnesemia (19%), skin rash (8%), conjunctivitis (0.4%) and infusion related reactions (0.4%). The incidence of venous thromboembolic events (VTE) of any severity was 9% in patients receiving necitumumab plus chemotherapy versus 5% in patients receiving chemotherapy alone.
- Fatal cardiopulmonary arrest and/or sudden death, in some cases likely exacerbated by inadequate electrolyte replacement, were observed in 2.2 % of the patients in the N+GC arm compared to 0.5 % in the control arm.
- The most common AEs in the SQUIRE trial occurring at a ≥ 25 % frequency were nausea, skin rash, neutropenia, anemia, decrease appetite, hypomagnesemia, and vomiting.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review of this application is primarily focused on the results of the single randomized controlled trial SQUIRE submitted to support the efficacy and safety of the proposed indication. Safety data from a second randomized controlled trial conducted in the non-squamous NSCLC population was also reviewed.

The databased used to evaluate safety of necitumumab reflected adverse events collected from a total of1695 patients (1079 from SQUIRE and 616 from INSPIRE) in which 842 patients (538 from SQUIRE and 304 from INSPIRE) received necitumumab at the proposed dose and schedule.

The primary safety analysis was performed using the AE dataset from the SQUIRE study and selected analysis from the INSPIRE study.

Clinical Study Reports for two single-arm dose finding studies (I4X-IE-JFCE, I4X-IE-JFCA) and one phase 2 study in colorectal cancer (I4X-IE-JFCD) were reviewed and findings summarized in the Section 9.4. Findings from studies I4X-IE-JFCE, I4X-IE-JFCA are also discussed in Section 6.1.8 Analysis of Clinical Information Relevant to Dose Recommendations.

7.1.2 Categorization of Adverse Events

Adverse event coding for SQUIRE and INSPIRE studies was based on Medical Dictionary for Regulatory Activities (MedDRA) version 13.0.

Adverse event severity grading was coded based on the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0

Case report forms for selected patients enrolled in the SQUIRE study were reviewed to determine the accuracy of the adverse events entry in the safety database. No significant discrepancies between the CRFs and database were identified.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Data pooling was not implemented in this review due to differences in the chemotherapy used in the trials (gemcitabine/cisplatin vs. pemetrexed/cisplatin) and population (squamous carcinoma vs. non-squamous carcinoma).

The primary safety analysis was performed using the AE dataset from the SQUIRE study and selected analysis from the INSPIRE study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the SQUIRE study, a total of 538 patients with previously untreated metastatic squamous NSCLC received necitumumab at the target dose/schedule of 800 mg IV on Day 1 and Day 8 of a 3-week cycle in combination with gemcitabine and cisplatin. Supportive safety data is also available for 304 patients with metastatic non-squamous NSCLC exposed to necitumumab at the target dose/schedule in combination with pemetrexed and cisplatin.

The following table summarized the exposure data for patients enrolled in the SQUIRE trial.

Table 23 SQUIRE: Study Drug Exposure

	N+GC N=538	GC N=541
NECITUMUMAB		
No. Cycles (median, range)	6.0 (1-45)	-
Duration of therapy (median, range)	25 weeks (2.0-148.6)	-
No. of infusions (mean, range)	12 (1-89)	-
Relative dose intensity (median, range)	94.4% (33-114)	-
GEMCITABINE		
No. Cycles (median, range)	6 (1-6)	5 (1-6)
Duration of therapy (median, range)	17.9 weeks (2.0-27.0)	17.0 weeks (2.0-26.0)
No. of infusions (median, range)	9.0 (1-12)	9 (1-12)
Relative dose intensity (median, range)	86.4% (36 – 104)	86.2% (38-105)
CISPLATIN		
No. Cycles (median, range)	6 (1-6)	5 (1-6)
Duration of therapy (median, range)	18 (3- 26.4)	16.9 (3- 25)
no. of infusions (mean, range)	6 (1-6)	5 (1-6)
Relative dose intensity (median, range)	**95% (51 – 113)**	**95.3 (45 – 110)**

In the SQUIRE trial, 538 patients received a median of 6.0 cycles (range 1 – 45) of necitumumab 800mg IV on days 1 and 8 of every 3-week cycle with 94.4% relative intensity (range 33-114). The gemcitabine and cisplatin exposure was similar in both treatment arms.

Of the 538 patients randomized to N+GC arm, 275 (51%) received necitumumab monotherapy upon completion of 6 cycles of N+GC. Patients in this group received a median of 4 cycles of necitumumab (median 12 weeks duration).

In the INSPIRE trial, 304 patients received a median of 8 infusions (4.0 cycles) of necitumumab 800mg IV on days 1 and 8 of every 3-week cycle with 92.9% median relative dose intensity. The pemetrexed and cisplatin exposure was similar in both treatment arms. *(Source: INSPIRE Abbreviated Clinical Study Report)*

Reviewer's comment:

The safety database contains an adequate number of patients exposed to necitumumab at the target doses/duration to permit a substantive safety review of the application for necitumumab in combination with gemcitabine and cisplatin for metastatic squamous cell NSCLC administered at 800mg IV on days 1 and 8 of every 3-week cycle.

It is noted that in both SQUIRE and INSPIRE studies, the enrollment was limited to patients with adequate renal, hepatic and hematologic function. Patients were required to have ECOG performance status of 0 or 2 and no significant co-morbidities. The patient selection criteria of SQUIRE and INSPIRE studies are consistent with clinical trials for oncology products. There is currently no data to assess the safety of necitumumab in combination with chemotherapy in patients who do not have these characteristics.

7.2.2 Explorations for Dose Response

The primary safety review was conducted in the SQUIRE trial where all patients received the same dose and schedule, i.e., necitumumab 800 mg on Day 1 and Day 8, gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 on day 1 of every 3-week cycle.

7.2.3 Special Animal and/or In Vitro Testing

Refer to review by the Pharmacology/Toxicology team for detail of the findings. Necitumumab was evaluated in 5- and 26-week repeat dose studies in Cynomolgus monkeys. There were no significant drug-related findings following dosing for 5 weeks at doses as high as 40 mg/kg. In the 26-week study, monkeys were treated at dose levels of 0, 6, 19, or 60 mg/kg weekly for 26 weeks.

Following are the key findings from the pre-clinical toxicology studies

- Dermatologic toxicities: following 26 weeks of dosing, the skin was found to be the primary target site. Hyperplastic dermatitis, characterized by epidermal hyperplasia, hyperkeratosis, and inflammatory infiltration was observed grossly and microscopically in the skin of the abdomen, inguinal area, ears /nose/mouth, and to a lesser extent, skin of the mammary glands. These findings were observed at all dose levels with a higher incidence at 19 and 60 mg/kg. Skin at the injection

site exhibited hyperkeratosis, hyperplasia, hemorrhage, inflammation, and lymphocytic infiltration at all doses with a greater incidence at the 60 mg/kg dose level.

The Pharmacology/Toxicology team concludes that that the clinical observations were consistent with dose-related skin toxicity and included erythema, scaling, dry skin, and rash. Skin toxicity has previously been observed with similar EGFR inhibitors (e.g. cetuximab) and is a major adverse reaction clinically.

- Degeneration of renal tubular epithelium was observed in monkeys administered necitumumab; this finding was consistent with findings observed with cetuximab. Diffuse inflammation and lymphocytic infiltration was observed in multiple organs and tissues following dosing and recovery at all dose groups. Magnesium levels were marginally depressed in males and depressed in females at doses ≥ 19 mg/kg. This finding is consistent with hypomagnesemia observed in the clinic. Magnesium levels in monkeys remained marginally depressed at the end of the recovery period.

- Mild increases in platelets and fibrinogen occurred at all dose levels compared to controls throughout the 26-week study and extending until the end of the recovery period, suggesting the potential for effects on coagulation. Thromboembolism observed in the clinic did not occur in monkeys,

Reviewer's comment:

Skin toxicity and hypomagnesemia observed in pre-clinical toxicity studies are consistent with those observed in necitumumab clinical studies and with other anti-EGFR monoclonal antibodies (cetuximab and panitumumab). The significance of coagulation abnormalities observed in monkeys exposed to necitumumab is unclear as no thromboembolic events were reported in these animals. In the SQUIRE trial, 42% of the patients experienced thrombocytopenia attributed to chemotherapy. Fibrinogen was not routinely measured in the trial.

7.2.4 Routine Clinical Testing

The reader is referred to section 7.4.2 for review and discussion on the adequacy of routine clinical testing in the SQUIRE trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology review of the application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Evaluations of adverse reactions associated with anti-EGFR class drugs are presented in section 7.3.5 of the review: skin rash/acneiform rash, hypomagnesemia, infusion reaction, conjunctivitis and interstitial lung disease.

7.3 Major Safety Results

An overview of incidence of AEs and serious AEs (SAE) reported in the SQUIRE trial is shown in Table 24.

Table 24 Overview of Incidence of Adverse Events

ADVERSE EVENTS	N+ GC % (N=538)	GC % (N=541)
Patients with Any AE	535 (99)	929 (98)
Patients with 1ny Serious AE	257 (48)	203 (38)
Patients with any NCI CTCAE ≥ Grade 3	388 (72)	333 (62)
Patients with an AE with outcome of death	66 (12)	57 (11)

7.3.1 Deaths

SQUIRE Study

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. Death was attributed to disease progression in 63% of the patients in the treatment arm and 68% in the control arm. The incidence of death due to an AE as the primary cause of death, per investigator was similar between the arms (7.4% and 7.9%). Equal number of patients died during the treatment period or within 30 days of last study drug dose.
Deaths and causes of death on treatment of within 30 days of last dose as assigned by the investigator are shown in Table 25 and 26.

Table 25 Deaths

	N+ GC N=538 (%)	GC N=541 (%)
All Deaths	**414 (77.0)**	**437 (80.8)**
Disease Progression	339 (63.0)	367 (67.8)
Adverse Events	40 (7.4)	43 (7.9)
Other causes	35 (6.5)	27 (5.0)
Death on Treatment or < 30 days of last dose	**60 (11.2)**	**57 (10.5)**
Disease Progression	18 (3.3)	18 (3.3)
Adverse Event	35 (6.5)	38 (7.0)
Other Causes	7 (1.3)	1 (0.2)

(Source: SQUIRE CSR, Section 12.3.1, Table JFCC.12.21)

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 26 AEs leading to Death on Treatment or within 30 days of the Last Dose

MEDDRA PT	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

Source: Adapted from SQUIRE CSR, Section 12.3.1, Table JFCC.14.183

Seventeen patients in the N+GC arm and 5 patients in the GC arm had causes of death assigned by the investigator as sudden death, death NOS, cardiac arrest, cardiopulmonary arrest or respiratory arrest. FDA reviewed the case report forms and narratives of these patients to further investigate the circumstances of death. A

summary of the review with days of treatment, events leading to death, co-morbid conditions and FDA's assessment of death are summarized in Table 27.

Of the seventeen patients in the N+GC arm, causes of death could be attributed to an AE in five patients upon review of the available information: ID 169-6002, gastric hemorrhage, ID197-6005, acute renal failure following vomiting, ID 220-6020, cardiac failure due to pericardial metastasis found on autopsy, ID 324-6012 history of malignant pericardial effusion, ID 553-6003 cerebellar metastasis with obstructive hydrocephalus. Of the five patients in the GC arm, two patients experienced AEs that could have led to death: ID221-6003, underlying congestive heart failure, ID551-6003 grade 4 diarrhea leading to acute renal failure and multiorgan failure.

The exact cause of death was unknown in 12 patients in the N+GC arm and 3 patients in the GC arm (Table 27). Uncorrected hypomagnesemia, a known anti-EGFR drug class toxicity, was observed in several patients (i.e. ID 159-6005, ID 371-6005, ID 160-6008, ID 224-6003), prior to death and may have contributed to the cardio-pulmonary arrest in some patients.

Table 27 SQUIRE Trial: Sudden Death/Death NOS while on Treatment or within 30-Days of Last study Drug FDA's Attribution of Cause of Death

	Necitumumab + Gemcitabine/Cisplatin ARM						
	ID	**Age**	**Day of therapy/ day since last study drug**	**Primary Cause of Death**	**Pertinent Information from CRF**	**Risk factors**	**Reviewer's Comment**
1	159-6005	61m	D85 /D13 C4 D8	Unknown (Sudden Death)	Found dead at home (b) (6) Mg++: (Normal 0.7 – 1.1 mmol) 0.77 (10/14/10) 0.61 mmol/L (11/16/10) 0.4 mmol/L (12/8/10) 0.37 mmol/L (12/21/10), **0.34 mmol (12/29/10),** K and Ca normal on 12/29/10 Electrolytes on the day of death (b) (6) not known.	HTN, COPD, ECG abnormal (LPHB), Other AEs: Gr 3 Syncope Gr 3 diarrhea, Dehydration	+ Risk factors for sudden death. Progressive worsening of hypomagnesemia (from normal baseline to grade 3 C4D8) 6 weeks prior to death, apparently untreated. Untreated hypomagnesemia and other electrolyte disturbances most likely contributed to death
2	160-6008	63mw	D111 , D19d C5D8	Unknown (Sudden Death)	Found death in his flat, no further info (b) (6) Mg++: (Normal 0.7 – 1.1 mmol) 0.71 4/7/11 0.68 4.20.11 0.47 4.28.11 0.45 5/11/11 0.48 5/20/11 0.47 6/8/11 0.49 6/16/11 0.52 6/29/1 0.51 7/8/11 (despite oral replacement)	History of alcohol abuse, gastric ulcer, hemoptysis, COPD, Parkinson's disease AEs: Grade 2 hypomagnesemia, oral replacement , rash	Attribution of sudden death to study drug cannot be ruled out Chronic persistent grade 2 hypomagnesemia despite oral replacement.

	Necitumumab + Gemcitabine/Cisplatin ARM						
3	169-6002	66fw	C2/D2	Asystole	Not related to study drug, autopsy (b) (6) – major gastric hemorrhage	SAE gastric hemorrhage Hx COPD, bronchitis, thrombosis prophylaxis	Autopsy: massive gastric hemorrhage
4	197-6005	45mw	D 85/D10 C4 D1	Cardiopulmonary arrest	Hospitalized with vomiting, acute renal failure 7 days after last dose (oliguria, anuria). Hemodialysis, acute tubular necrosis. Cardiopulmonary arrest during hospitalization (renal failure and electrolyte imbalance)	Peptic ulcer, tobacco use, alcohol use. No HTN, DM, no prior renal failure.	Study drug discontinued Renal failure attributed to study treatment (cisplatin, gemcitabine and necitumumab?)
5	220-6020	67m	D16/D9	Heart failure	Died at home on (b) (6) of CHF	Not known	Autopsy: pericardial metastatic
6	224-6003	57wm	D245/D8 (on monotherapy)	Unknown (Sudden death)	Verbal report death at home on (b) (6) Narrative statement: "Patient seen 8 days prior to death, normal. Labs reported for 7/26/11) – K elevated at 6.0 (nil 3.4 – 5) No other information.	COPD, arteriosclerosis, hepatomegaly	Causal relationship to study drug cannot be ruled out. Grade 2 K 8 days prior to death (?)
7	271-6016	64mw	D21/D14 C1 d8	Death NOS (Sudden death)	Died at home. (b) (6) Labs 9/21/10 - OK	HTN, DM2, COPD, obesity	Multiple risk factors. Causal relationship to study drug cannot be ruled out due to temporal association.
8	273-6023	62wm	59/11	Unknown	Died (b) (6) Only registry office report available No major lab abnormalities 3/30	Stable CAD (medications: ramipril, bisoprolol)	+ Risk factor of CAD, Causal relationship to study drug cannot be ruled out due to temporal association.
Cont.							

	Necitumumab + Gemcitabine/Cisplatin ARM						
9	273-6043	54wm	148/28 C6 d1	Unknown	PD on 4/12/12, last visit 4/16/12 Information from registry patient died on (b) (6) No other information available	No known risk factors (lipoma, gout, back pain)	Causal relationship to study drug cannot be ruled out due to temporal association.
10	273-6044	80wm	D90/D24 C2 d8	Unknown	Loss to follow-up, last seen 3/30/12 in stable condition. Only report from a registry office patient died on (b) (6) Mg level 0.47 mmol/L 2/22/12	HTN, chronic atrial fibrillation, thrombosis (atenolol, nitrazepam, enoxaparin, etc.) AE from rx: elevated creatinine	Pre-existing risk-factors. Causal relationship to study drug cannot be completed ruled out due to temporal association. Grade 2 hypo Mg
11	277-6001	55wm	D16/D9 C1 D8	Death (NOS) (Sudden death)	Sudden death at home 16 days after initiation of therapy (b) (6) Other AEs: anorexia and skin rash 10 days after initiation of therapy.	Hx of CAD and MI (atorvasterol, hydrochlorothiazide, pantoprazole, polpril, and others)	Investigator and ImClone consider death NOS to be related to progressive disease. No diagnostic test to confirm PD was performed. Reviewer comment: Pre-existing risk-factors. Causal relationship to study drug cannot be completed ruled out due to temporal association.
12	324-6012	53wm	D164/D31 C7 d8	Cardiopulmonary arrest	(b) (6) discontinued treatment, continue follow-up Died at home 31 days after last study drug	HTN, pericardial drainage, asthenia	Disease progression
Cont.							

	Necitumumab + Gemcitabine/Cisplatin ARM						
13	371-6005	62wm	81/18 C3 d 8	Cardiac arrest	Died at home, after feeling weak and fatigued cause of death cardiac arrest (b) (6) **3/20/12 –** **Mg 0.39 (grade 3)** **K 3.1** **Ca 1.97** **Action taken –none– CSR page 436/2759 – see below**	COPD, HTN (bisoprolol, fluticasone, salmeterol, aminophylline, tramadol)	Investigator assessed cause of death as disease progression Reviewer disagrees – Pre-existing risk-factors. Untreated severe electrolyte imbalance most likely contributed to death. No documentation of PD
14	**406-6005**	61wm	D31/D8 C2 d1	Unknown	Died at home. Cause unknown Did not report for c2 d8. Family informed of patient's death (b) (6) No other information available. Mg no done on 9/16/10 (c2 d1), other labs normal	COPD	Causal relationship to study drug cannot be completely ruled out
15	**542-6002**	74asian m	D9/D9 C1 d1	Unknown	Sudden death at home 9 days after 1st dose (b) (6) No other information available. C1d8 held due to severe mucositis and dizziness	COPD	Investigator considers death unrelated to study drug but to progressive disease. Reviewer's comment: Causal relationship to study drug cannot be completely ruled out.
16	553-6003	52aian f	D78/D8	AE cardio-pulmonary arrest	Cerebellar metastasis/obstructive hydrocephalus, hyponatremia, Died in hospital cardiorespiratory arrest (b) (6)		Disease progression
17	**653-6001**	63wm	D10/D3 C1 d8	Sudden death	Respiratory and cardiac arrest at home (b) (6) Did not response do resuscitative measures in route to hospital	CAD, HTN, Hodgkin's disease, alcohol abuse (metoprolol, ranitidine, clodpidogrel, lisinopril and finasteride),	Multiple risk factors. Causal relationship to study drug cannot be ruled out

Gemcitabine/ Cisplatin ARM							
1	221-6003	67mw	69/20	Cardiac failure		COPD, CHF, cardiomegaly	Underlying disease of CHF
2	272-6004	62wm	74/11	Unknown	Sudden death at home (b) (6) Mg++ (Normal1.3-2.7 mg/dL) 7/6 1.3 mg/dL (1.3-2.7) (b) (6) 0.5 mg/dL(grade 4) ten days prior to sudden death - untreated	varices	Reviewer's comment: untreated hypomagnesemia likely contributed to sudden death
3	324-6007	46wm	6/6	AE death NOS	Sudden death at home 6 days after c1d1 GC	Meningitis, diabetes	Death NOS
4	551-6001	64asian m	50/8	Cardiopulmonary arrest	Grade 4 diarrhea, dehydration, acute renal failure, multi-organ failure and cardiopulmonary arrest	COPD, HTN, intercurrent acute gastroenteritis	Causes of death multi-organ failure precipitated by gastroenteritis.
5	643-6003	56b m 4/28	3/3 C1/D1	Unknown	Family found patient dead (b) (6) (b) (6) ECG = atrial fibrillation with rapid ventricular response, left axis deviation, R ventricular conduction delay, septal infarct	Atrial fibrillation/ arrhythmia prior to enrollment warfarin NSCLC, cholecystectomy, ankle operation	New onset atrial fib 21 days prior to enrollment. Resolved on (b) (6) per CRF .

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

INSPIRE Study

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 Tables 28 and 29.

Table 28 Causes of Death in Patients during 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

Death 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 10 patients in the necitumumab arm (3.2%) compared to only 3 in the control arm 1.3%. 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.

Table 29 INSPIRE Trial: Sudden Death/Death NOS while on Treatment or within 30-Days of Last study Drug FDA's Attribution of Cause of Death

	PATIENT ID	AGE	DAY ON STUDY	CAUSE OF DEATH PER CRF	PERTINENT INFORMATION FROM CRF	RISK FACTORS	REVIEWER'S ATTRIBUTION
Necitumumab + Pemetrexed/Cisplatin ARM							
1	156-5011	70YoM	Day 31 C2, D2	PD	Died at home	COPD, HTN, carotid stenosis	Sudden Death
2	156-5024	71yoM	Day 103	PD	Uncorrected grade 4 hypomagnesemia, hypocalcemia prior to death	COPD, DM, CAD	Death NOS
3	160-5011	60yoF	Day 80 C2 D8	Suspected PE	Hospitalized for hypocalcemia, agitation Mg++ 0.26 mmol/L (Lab Range: 0.77 – 1)	N/A	Sudden death
4	165-5008	65yo F	Day 19 C1D19	Unknown	Cardiac decompensation after 1 dose of stud drug Died at home	COPD, HTN	Sudden death
5	320-5001	50yoM	Day 10 C1D8	Sudden death	Died 2 days after C1D8	Hepatitis C Tb	Sudden Death
6	275-5014	58yoF	Day 11 C1D8	Death NOS	No information, Uncorrected hypo Mg 1.37	N/A	Death NOS
7	220-5004	73yoM	Day 14 C1D8	PD	Hospitalized with grade 2 diarrhea, grad 4 weakness while in hospital	COPD, HTN	Death NOS
8	222-5003	58yoM	Day 5 C1D1	Sudden death due to PD	"4 days from initial study drug, condition worsened and died"	N/A	Death NOS
9	324-5002	55yoF	Day 7 C1D7	PD	Sudden Death at home	HTN	Sudden Death
10	707-5005	74yoM	Day 22 C1D8	PD	Sudden death at home	N/A	Sudden death

	PATIENT ID	AGE	DAY ON STUDY	CAUSE OF DEATH PER CRF	PERTINENT INFORMATION FROM CRF	RISK FACTORS	REVIEWER'S ATTRIBUTION
Pemetrexed/Cisplatin ARM							
1	160-5012	63yoF	Day 42	AE	Sudden death at home while walking	-	Sudden Death
2	406-5002	71yoM	Day 2 C1D1	PD	Sudden death at home	-	Sudden death
3	406-5013	51yoM	Day 11 C1D8	AE	Sudden death at home, unconfirmed PE	-	Sudden death
4	161-5001	78yoF	110	AE	Sudden death	-	Sudden Death

Reviewer's comment:

Sudden death and death of unknown cause occurred at a higher incidence in the patients exposed to necitumumab and chemotherapy compared to chemotherapy alone in both SQUIRE (2.2% vs. 0.5%) and INSPIRE (3.2% vs.1.3%) trials. The exact cause(s) of death in these patients are unclear. Uncorrected hypomagnesemia with associated electrolyte imbalance, a known adverse event associated with anti-EGFR class products, was observed in several patients prior to death and may have contributed to the cardio-pulmonary arrest in some patients. Other possible causes of death are thromboembolic events such as pulmonary emboli and myocardial infarction.

Labeling Recommendation

Box warning is recommended for increased risk of sudden death. Physicians should carefully consider use of necitumumab in combination with gemcitabine and platinum in patients with history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Close monitoring of serum electrolytes, including magnesium, potassium, and calcium, during and after necitumumab treatment, with aggressive replacement when necessary, should be strongly recommended.

7.3.2 Serious Adverse Events

Serious Adverse Event is defined per protocol as any events that results in death, is life-threatening, requires inpatient hospitalization or cause prolongation of existing hospitalization, results in persistent or significant disability incapacity, cause a congenital anomaly/birth defect or is an important medical event of requires intervention to prevent permanent impairment/damage. Any grade 3, 4 or 5 event, as graded by NCI CTCAE v3.0 is considered to be a SAE.

Serious adverse events occurred at a higher incidence in the N+GC (47.8%) arm compared to GC alone arm (37.5%). SAEs occurring in ≥ 2% of patients in the N+GC arm are listed in Table 30.

Table 30 SQUIRE: Serious Adverse Events occurring in ≥ 1% of Patients in N+GC arm

ADVERSE EVENTS (MEDDRA PREFERRED TERM)	N+ GC N=538 (%)	GC N=541(%)
All Serious AEs	**257 (47.8)**	**203 (37.5)**
Non-small cell lung cancer	26 (4.8)	23 (4.3)
Anemia	22 (4.1)	17 (3.1)
Neutropenia	20 (3.7)	33 (6.1)
Pulmonary Embolism	19 (3.5)	9 (1.7)
Thrombocytopenia	17 (3.2)	20 (3.7)
Vomiting	12 (2.2)	2 (0.4)
Medication Error*	12 (2.2)	21 (3.9)
Pneumonia	11 (2.0)	19 (3.5)
Hemoptysis	11 (2.0)	9 (1.7)
Diarrhea	8 (1.5)	2 (0.4)
Death	8 (1.5)	2 (0.4)
General physical Health Deterioration	8 (1.5)	7 (1.3)
Pyrexia	7 (1.3)	3 (0.6)
Bronchitis	6 (1.1)	3 (0.6)
Elevated creatinine	6 (1.1)	1 (0.2)
Renal failure	8 (1.5)	6 (1.1)
Febrile neutropenia	6 (1.1)	7 (1.3)
Leukopenia	6 (1.1)	4 (0.7)
Pancytopenia	6 (1.1)	3 (0.6)

The most common SAEs that occur in both treatment arms in similar frequency can in general, be attributed to either toxicities commonly related to chemotherapy (anemia,

neutropenia, thrombocytopenia and leucopenia) or the underlying disease (non-small cell lung cancer, pneumonia, hemoptysis, bronchitis).

Serious AEs that occur at a higher frequency in the N+GC arm include: pulmonary embolism and diarrhea. These AEs are discussed in section 7.3.5 of this review.

Medication errors were reported in 12 patients in N+GC arm and 21 patients in the GC alone arm. Medication errors, as specified in the protocol, are to be reported as serious AEs regardless of the seriousness or outcome. The most common causes of medication error in the N+GC arm were improper storage of necitumumab and continued dosing beyond radiographic disease progression date. The most common medication errors in the GC arm were improper dose reduction or improper dosing of either cisplatin or gemcitabine.

Improper medication error resulted a grade 3 AE in a patient who received necitumumab after radiographic disease progression (ID 416-6003) and in 2 patients in the GC arm who received lower than planned doses of either gemcitabine (ID 406-6002) or cisplatin (ID 298-6001), however, the reported AEs were unrelated to the error and all patients recovered without sequelae.

NCI CTCAE ≥ 3 Grade Events

Adverse events were graded using NCIC CTCAE version 3.0 for the SQUIRE study.

Grade ≥ 3 AEs observed in more than 15% of patients in the SQUIRE study by MedDRA preferred term (PT) are shown in Table 31.

More patients in the N+GC arm experienced a grade ≥ 3 AE compared to GC alone (72% vs. 62%). Grade ≥ 3 AEs that occurred at a >1% frequency in the necitumumab arm compared to control arm were: hypomagnesemia (8.7% vs. 1.1%), pulmonary embolism (3.5% vs. 1.8%), rash (3.7% vs. 0.2%), hypokalemia (2.8% vs. 1.5%) and dyspnea (2.8% vs. 0.9%).

Table 31 Incidence of Grade ≥3 AE Occurring in > 2% of Patients in N+GC Arm

MEDDRA PT	N+ GC N=538 (%)	GC N=541 (%)
ANY GRADE ≥ 3 AE	**388 (72.1)**	**333 (62.5)**
Neutropenia	128 (23.8)	146 (27)
Anemia	56 (10.4)	59 (10.9)
Thrombocytopenia	53 (9.9)	54 (10.0)
Hypomagnesemia	**47 (8.7)**	**6 (111)**
NSCLC	26 (4.8)	22 (4.1)
Pulmonary Embolism	**19 (3.5)**	**10 (1.8)**
Asthenia	23 (4.3)	20 (3.7)
Leukopenia	20 (3.7)	36 (6.7)
Rash	**20 (3.7)**	**1 (0.2)**
Hyponatremia	17 (3.2)	22 (4.1)
Fatigue	16 (3.0)	18 (3.3)
Hypokalemia	**15 (2.8)**	**8 (1.5)**
Vomiting	15 (2.8)	14 (2.6)
Dyspnea	**15 (2.8)**	**5 (0.9)**

7.3.3 Dropouts and/or Discontinuations

Twelve percent of the patients in N+GC arm and 15% in GC arm discontinued from all study drugs due to an adverse events.
MedDRA PT adverse events leading to study drug discontinuation are listed in Table 32 The most common AEs leading to drug discontinuation in either treatment arm were myelosuppression related AEs (neutropenia and thrombocytopenia). In the N+GC arm, rash was the cause for necitumumab discontinuation in 6 patients (1.1%).

Table 32 Adverse Events Leading to Study Drug Discontinuation

MEDDRA PT	N+ GC N=538 (%)			GC N=541 (%)	
	All drugs	Necitumumab	Any chemo	All drugs	Any chemo
All drop out and/or discontinuation	**63 (12)**	**109 (20)**	**135 (25)**	**80 (15)**	**133 (25)**
Neutropenia	22 (0.4)	2 (0.4)	29 (5.4)	8 (1.5)	36 (6.7)
Thrombocytopenia	7 (1.3)	7 (1.3)	19 (3.5)	2 (0.4)	8 (1.5)
Anemia	1 (0.2)	3 (0.6)	8 (1.5)	3 (0.6)	4 (0.7)
Elev. Creatinine	3 (0.6)	3 (0.6)	8 (1.5)	10 (1.8)	13 (2.4)
NSCLC	8 (1.5)	7 (1.3)	6 (1.1)	2 (0.4)	3 (0.6)
Leukopenia	0	0	6 (1.1)	0	5 (0.9)
Asthenia	0	2 (0.4)	4 (0.7)	2 (0.4)	5 (0.9)
Fatigue	2 (0.4)	2 (0.4)	6 (1.1)	4 (0.7)	5 (0.9)
Rash	0	6 (1.1)	0	0	0

Adverse Events Leading to Drug Dose Modification

In the SQUIRE trial, 8% (43/538) patients required a necitumumab dose reduction and 28% (151/538) required a dose delay of more than 1 week.
The frequency of dose reduction or delay for gemcitabine and cisplatin were similar between the treatment arms.

The following Table from the Applicant summarizes all dose delays and modifications for the SQUIRE trial.

Table 33 Dose Delays and Modifications (Safety Population)

	Necitumumab	Gemcitabine		Cisplatin	
	GC+N N = 538 n (%)	GC+N N = 538 n (%)	GC N = 541 n (%)	GC+N N = 538 n (%)	GC N = 541 n (%)
Any Dose Reduction	43 (8.0)	71 (13.2)	84 (15.5)	73 (13.6)	86 (15.9)
1 Reduction Step	41 (7.6)	61 (11.3)	65 (12.0)	63 (11.7)	65 (12.0)
2 Reduction Steps	2 (0.4)	10 (1.9)	19 (3.5)	10 (1.9)	21 (3.9)
Any Dose Delay[a]	292 (54.3)	259 (48.1)	259 (47.9)	260 (48.3)	257 (47.5)
Maximum Delay 4-7 Days	141 (26.2)	150 (27.9)	156 (28.8)	148 (27.5)	155 (28.7)
Maximum Delay > 7 Days	151 (28.1)	109 (20.3)	103 (19.0)	112 (20.8)	102 (18.9)
Any Infusion Modification	23 (4.3)	33 (6.1)	48 (8.9)	22 (4.1)	30 (5.5)
Infusion Rate Modification	17 (3.2)	33 (6.1)	42 (7.8)	20 (3.7)	28 (5.2)
Infusion Interrupted	8 (1.5)	4 (0.7)	8 (1.5)	2 (0.4)	2 (0.4)

Source: SQUIRE CSR, section 12.1, Table JFCC.12.2

The following AEs were identified as AEs leading to dose delays and modifications in the SQUIRE safety dataset:

Adverse events leading to delay/modification of:

- Necitumumab: rash (N=17, 3.2%), hypomagnesemia (N=13, 2.4%). Infusion related reactions that required infusion rate modification occurred in 23 patients (4.3%).

- Gemcitabine or Cisplatin: neutropenia (N=168, 31% in N+GC arm and N=173, 32% in GC arm), thrombocytopenia (N=46, 8.6% vs. N=50, 9.2%), anemia (N=40, 7.4% vs. N= 46, 8.5%), elevated creatinine (N=26, 4.8% vs. N=23, 4.3%)

Other AEs requiring dose delay or modification of any study drug in ≤ 2% of patients in either arm were fatigue, viral respiratory infection, nausea and vomiting.

Reviewer's comment

The incidence of necitumumab related toxicities leading to treatment discontinuation (rash) or modification (rash, hypomagnesemia, and infusion related reaction) in the SQUIRE trial does not appear to impact significantly on the adequate delivery of the planned dose of necitumumab in this trial.

7.3.4 Significant Adverse Events

Refer to:

- *Section 7.3.1 for Adverse Events Leading to Death*
- *Section 7.3.2 Serious Adverse Events and Grade ≥ 3 Adverse Events*
- *Section 7.4.3 Adverse Events Leading to Study Drug Discontinuation, Delay or Modification*
- *Section 7.3.5 Submission Specific Primary Safety Concerns for Significant AEs*

7.3.5 Submission Specific Primary Safety Concerns

Adverse events known to occur in anti-EGFR mAb drug class including dermatologic toxicities, hypomagnesemia, hypersensitivity reactions and interstitial lung disease are analyzed by the Applicant using composite MedDRA PT terms in order to capture additional PT events not included in the MedDRA SOC and are presented in the following section, following reviewer's analysis based on MedDRA PT.

7.3.5.1 Dermatologic Toxicities

Skin disorders occurred in 78% of the patients in who received necitumumab in the SQUIRE trial with 7.8 % grade 3 events (Table 34). Common skin disorders as defined by MedDRA preferred term that occurs in more than 5% of the patients were: rash (42.2%), dermatitis acneiform (15.1%), acne (8.7%), dry skin (5.9%) and pruritus (5.9%)

Table 34 Incidence of Skin Toxicities by MedDRA PT observed in > 5% of the Patients in the N+GC arm

MEDDRA SOC/PT	N+GC N= 538 (%)		GC N=541 (%)	
	All grade	Grade 3	All grades	Grade 3
Skin and Subcutaneous Tissue Disorders	**420 (78.1)**	**42 (7.8)**	**100 (18.5)**	**4 (0.7)**
Rash	227 (42.2)	20 (3.7)	22 (4.1)	1 (0.2)
Dermatitis Acneiform	81 (15.1)	7 (1.3)	2 (0.4)	0
Acne	27 (8.7)	2 (0.4)	2 (0.4)	0
Dry skin	32 (5.9)	0	4 (0.7)	0
Pruritus	32 (5.9)	1 (0.2)	3 (0.6)	1 (0.2)
Rash Generalized	26 (4.8)	5 (0.9)	2 (0.4)	0
Skin Fissures	25 (4.6)	2 (0.4)	0	0
Rash Maculo-Papular	14 (2.6)	3 (0.6)	1 (0.2)	1 (0.2)
Erythema	12 (2.2)	0	1 (0.2)	1 (0.2)

Paronychia was reported in 34 patients (6.3%), with 2/34 patients reporting a grade 3 event.

Grade 3 dermatologic toxicity occurred in 42 (7.8%) of the patients and required discontinuation from necitumumab treatment. There were no grade 4 or 5 skin related events in the SQUIRE trial.

The Applicant further analyzed the incidence of skin related events using composite MedDRA PT terms as follow:

Table 35 Applicant's Analyses of Skin Reactions using Composite MedDRA PT

Composite Terms	N+GC N= 538 (%)		GC N=541 (%)	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Skin Reaction[a]	424 (79.8%)	44 (8.2)	64 (11.8)	3 (0.6)
Rash[b]	410 (76.2)	38 (7.1)	55 (10.2)	2 (0.4)

[a] **Skin Reactions**: rash, dermatitis acneiform, acne. Pruritus, paronychia, dry skin, rash generalized, skin fissures, erythema, rash maculo-papular, palmar-plantar Erythrodysaesthesia syndrome, folliculitis, rash macular, skin exfoliation, nail disorder, rash erythematous, skin infection, skin lesion, skin toxicity, urticaria, skin ulcer, exfoliative rash, fungal skin infection, hirsutism, hypertrichosis, ingrowing nail. Nail bed inflammation, onycholysis. Rash follicular., dermatitis, dermatitis allergic, laceration, nail bed infection, nail dystrophy, nail infection, onychalgia, palmar erythema, plantar erythema, pruritus generalized, scab, skin disorder, skin erosion, skin reaction, subcutaneous abscess, cellulitis, erythema

multiforme, nail discoloration, generalized erythema, rash papular, rash pruritic, eczema, nail toxicity, rash pustular, hair growth abnormal, impetigo, photosensitivity, reaction, pigmentation disorder

[b]. **Rash:** rash, dermatitis acneiform, acne, pruritus, dry skin, rash generalized, Rash maculo-papular, Macular Erythematous, papular pruritic, exfoliative follicular, rash dermatitis allergic, drug eruption, generalized erythema, planar erythema, pruritus generalized, erythema multiform, pigmentation disorder

Time-to-event analysis was conducted by the Applicant (Table 36 and 37). The majority of the skin events occurred within 4 weeks from the initiation of treatment, with 34.2% occurring in the first two weeks of starting necitumumab.

Table 36 Time to First Occurrence of Rash in the N+GC arm

	N+GC N= 538 (%)
1-7 days	68 (12.5)
8-14	118 (21.7)
15-21	75 (13.8)
22-28	62 (11.4)
29-35	22 (4.0)
36-42	9 (1.7)
43-49	15 (2.8)
≥ 50 days	41 (7.5)
No rash during the study	135 (24.8)

Source: Adapted from BLA Appendix to Clinical Safety Summary SQNSCLC,

Of the 424 patients who experienced a skin reaction, AE was reported as resolved/recovered in 41% and not resolved/recovered in 59%. Median time-to-resolution for those who recovered was 17 weeks. Necitumumab dose was delayed/modified in 43 patients (10%) and permanently discontinued in 12 (2.8%). Treatment for skin toxicity included topical antibiotics (47%), antipruritics (25%), steroids (31%) and/or sunscreen (3%).

Table 37 Skin Reactions in N=GC Arm: Time-to-Event and Outcome

SKIN REACTIONS	***N+GC ARM N= 538***
Time-to-onset (weeks)	N=424
Median	2.1
Q1-Q3	1.1-3.3
Event outcome	N=424
Resolved/recovered	173 (40.8%)
Not resolved/recovered	251 (59.2%)
Time-to-resolution (weeks)	N=173
Median	17.1
Q1-Q3	6.4 – 30.0
Action taken with Necitumumab	43 (10.1%)
Dose delay/modification	12 (2.8%)
Discontinuation	2 (0.5%)
Hospitalization	
Treatment for skin toxicity	N=424
Any	339 (80%)
Antibiotics	200 (47%)
Antipruritic	104 (25%)
Steroid	130 (31%)
Sunscreen	11 (3%)
Topical	278 (66%)

In the INSPIRE trial, skin rash (MedDRA PT) was reported in 38% of the patients, 7.9% with a grade 3 event.

Reviewer's Comment:

Dermatologic toxicities including MedDRA PT terms rash, acneiform rash, generalized rash, maculo-papular rash and skin fissures were the most common toxicity related to necitumumab therapy. Severe skin toxicity occurred in 7.8% of patients and resulted in treatment discontinuation in 2.8% of patients.

***Labeling Recommendation**: Warning and Precautions section should be revised to provide more granular information regarding clinical course for skin toxicity. Dose modification section should be modified for clarity. Incidence of dermatologic toxicities should be revised based on MedDRA SOC and PT.*

7.3.5.2 Hypomagnesemia

The incidence of hypomagnesemia reported as an AE and based on laboratory measurements are shown in t Table 38.

Table 38 Incidence of Hypomagnesemia in the SQUIRE Trial

HYPOMAGNESEMIA	N+GC			GC		
	N= 538 (%)			N=541 (%)		
	All Gr	Gr 3	Gr 4	All Gr	Gr 3	Gr 4
Adverse Event	**168 (31)**	**37 (22)**	**13 (7.7)**	**85 (16)**	**6 (7.1)**	**0**
	N=461 (%)			N=457 (%)		
	All Gr	Gr 3	Gr 4	All Gr	Gr 3	Gr 4
Clinical Laboratory*	**406 (88)**	**69 (17)**	**27 (6.7)**	**342 (75)**	**29 (8.5)**	**8 (2.3)**

**only patients with laboratory results are included*

The incidence of hypomagnesemia as reported as an AE was 31%, 22% grade 3 and 7.7 % grade 4 event in the N+GC arm. In the GC arm, all-grade hypomagnesemia was reported in 16% of the patients, with 7% grade 3.

The incidence of hypomagnesemia as assessed by laboratory measurement was significantly higher, with 88% in the N+GC arm, 17% grade 3 and 6.7% grade 4. In the GC alone arm 75% of the patients had hypomagnesemia all-grades, 8.5% grade 3, and 2.3% grade 4.

Time-to-event and outcome of hypomagnesemia reported as an AE and as assessed by laboratory testing in the SQUIRE trial, are shown in Tables 39 and 40.

The median onset of hypomagnesemia in the N+GC arm was 7.1 weeks (25% and 75% occurring around 4.1 – 11.1 weeks). Hypomagnesemia was reported as resolved in only 43.5% of the patients in the N+GC arm. Necitumumab was delayed in 8% of the subjects who experienced a hypomagnesemia AE and only 64% received magnesium replacement.

Only 31% of the patients in the N+GC arm and 17% of the patients in the GC arm with laboratory-assessed hypomagnesemia was reported as having received magnesium replacement.

Table 39 Hypomagnesemia as an AE: Time-to-Event and Outcome

HYPOMAGNESEMIA	N+GC ARM N= 538 (%)	GC ARM N=841 (%)
Time-to-onset (weeks)		
Median	7.1	9.1
Q1-Q3	4.1-11.1	6.1-13.1
Event outcome	N=168	N=85
Resolved/recovered	73 (43.5)	45 (52.9)
Not resolved/recovered	95 (56.5)	39 (45.9)
Time-to-resolution (weeks)	N=73	N=45
Median	10.3	2.9
Q1-Q3	4.3-17.1	1.4-10.4
Action taken with Necitumumab	N=168	N=85
Dose delay/modification	13 (7.7)	0
Discontinuation	2 (1.2)	0
Hospitalization	-	0
Treatment		
YES	108 (64.3)	47 (55.3)
NO	60 (35.7)	38 (44.7)

Source: Applicant's submission to BLA

Table 40 Hypomagnesemia by Laboratory Assessment: Time-to-Event Outcome

HYPOMAGNESEMIA	N+GC ARM N= 538 (%)	GC ARM N=841 (%)
Time-to-onset (weeks)		
Median	6.0	7.1
Q1-Q3	3.9-9.3	4.0-10.3
Event outcome		
Resolved/recovered	5 (1.20	9 (2.6)
Not resolved/recovered	401 (98.8)	333 (97.4)
Time-to-resolution (weeks)	N=5	9
Median	21.3	11.1
Q1-Q3	18.3-45.1	10.4-12.4
Action taken with Necitumumab		
Dose delay/modification	None	None
Discontinuation		
Hospitalization		
Treatment		
YES	126 (31)	57 (16.7

Source: Applicant's submission to BLA

Reviewer's Comment:

Hypomagnesemia is a known toxicity associated with anti-EGFR monoclonal antibodies and cisplatin[6,7,20] due to impairment of magnesium reabsorption in the kidney. Magnesium wasting may lead to clinically significant hypomagnesemia and associated hypocalcemia and hypokalemia (refer to section 7.4.2 for laboratory findings).

In the SQUIRE, the incidence of hypomagnesemia was greatly underestimated by treating physicians as only 20 to 35 % of the laboratory assessed hypomagnesemia were reported as an adverse event. More alarmingly, only a third of patients with laboratory assessed hypomagnesemia received magnesium replacement in the SQUIRE trial. Clinical manifestations of hypomagnesemia include anorexia, nausea, vomiting, lethargy, weakness, and personality changes and tremor[21]. The diagnosis of hypomagnesemia can be overlooked, as these symptoms and signs are also commonly observed in patients with advanced cancer undergoing chemotherapy. In both the SQUIRE and INSPIRE studies, severe hypomagnesemia and associated electrolyte disturbances were observed in several patients who died during treatment or within 30 days of last treatment dose of unknown causes or sudden death (refer to section 7.3.1 Death). Several patients had co-morbid conditions that might have contributed to death. The causal relationship of severe hypomagnesemia and sudden death in some of patients cannot be ruled out.

Labeling Recommendation

Add Box Warning and Warnings and Precautions for hypomagnesemia, with recommendation to monitor patients for hypomagnesemia, hypocalcemia, hypokalemia, prior to each dose of necitumumab during treatment and for at least 8 weeks following the completion of necitumumab. Treatment with necitumumab should be held for grade 3 or 4 hypomagnesemia and associated electrolyte abnormalities until corrected.

7.3.5.3 Thromboembolic Events

Thromboembolic events was an early safety signal during the conduct of the INSPIRE study.

In the SQUIRE trial, the incidence of thromboembolic events (Table 41) was significantly higher in the N+GC arm compared to GC alone arm (14.5% vs. 9%).

Venous thromboembolic events (VTE) account for the majority of the TE events in the necitumumab arm (Table 41). 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).

Death attributed to VTE was reported in one patients (pulmonary embolism) in the N+GC arm (0.2%) and two patients (pulmonary embolism and mesenteric vein thrombosis) in the GC arm (0.4%)

The incidence of all grade arterial TEs did not appear to substantially differ between the treatments arms. 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).

Death attributed to an arterial thromboembolic event was reported in three patients in the N+GC arm (2 myocardial infarction and ischemic stroke) and one patient in the GC arm (myocardial infarction).

Table 41 Incidence of Thromboembolic Events (MedDRA Composite Terms) by Treatment Arm Occurring in ≥ 2 Patients in the N+GC Arm

MEDDRA COMPOSITE TERM AND PT	N + GC N=538 N (%)		GC N=541 N (%)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Venous TE*	**49 (9.1)**	**27 (5)**	**29 (5.4)**	**14 (2.6)**
Pulmonary Embolism	26 (4.8)	19 (3.5)	13 (2.4)	10 (0.8)
Deep Venous Thrombosis	10 (1.9)	5 (0.9)	5 (0.9)	0
Thrombosis	4 (0.7)	1 (0/2)	3 (0.6)	0
Mesenteric Vein Thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Pulmonary Artery Thrombosis	2 (0.4)	0	2 (0.4)	1 (0.2)
Pulmonary venous thrombosis	2 (0.4)	1 (0.)	0	0
Venous Thrombosis limb	2 (0.4)	0	0	0
Arterial TE^	**29 (5.4)**	**21 (3.9)**	**21 (3.9)**	**11 (2.0)**
Ischemic stroke	4 (0.7)	4 (0.7)	0	0
Cerebral ischemia	3 (0.6)	2 (0.4)	0	0
Acute myocardial infarction	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
Aortic thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	0
Cerebral infarction	2 (0.4)	1 (0.2)	0	0
Myocardial infarction	2 (0.4)	2 (0.4)	3 (0.6)	2 (0.4)
Peripheral arterial occlusive disease	2 (0.4)	1 (0.2)	1 (0.2)	0
Peripheral artery thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Transient Ischemic Attack	2 (0.4)	2 (0.4)	3 (0.6)	3 (0.6)
TOTAL	**78 (14.5)**	**48(8.9)**	**50 (9.3)**	**25 (4.6)**

**Composite VTE MedDRA PT terms: pulmonary embolism, deep vein thrombosis, thrombosis, mesenteric veins thrombosis, pulmonary artery thrombosis, pulmonary venous thrombosis, venous thrombosis limb, axillary vein thrombosis, thrombophlebitis, thrombosis s in device, vena*

(cont.) cava thrombosis, venous thrombosis, subclavian vein thrombosis, superior vena cava syndrome, thrombophlebitis superficial,
^Composite ATE MedDRA PT terms: ischemic stroke, aortic thrombosis, cerebral ischemia, peripheral arterial occlusive disease, peripheral artery thrombosis, transient ischemic attack, acute myocardial infarction, angina pectoris, cerebrovascular accident, colitis ischemic, coronary artery disease, myocardial infarction, peripheral artery stenosis, peripheral embolism, peripheral ischemia, renal infarct, splenic infarction acute coronary syndrome, coronary artery stenosis, ECG signs of myocardial ischemia, embolism, femoral artery occlusion, myocardial ischemia,

Time –to-event and outcome of TE in the SQUIRE trial was analyzed by the Applicant and are summarized in Table 42. The median time to onset was 9 weeks in the necitumumab arm (25% - 75 % 5.6 – 14.4 weeks). The event was reported as resolved in 53% of the patients in the necitumumab arm and necitumumab was permanently discontinued in 20% of the TE events.

Table 42 Thromboembolic Events: Time-to-Event and Outcome

VENOUS THROMBOEMBOLIC EVENT	N+GC ARM N= 538 (%)	GC ARM N=841 (%)
Time-to-onset (weeks)	N=49	N=29
Median	9.1	6.1
Q1-Q3	5.6-14.4	2.6-11.7
Event outcome	N=49	N=29
Resolved/recovered	26 (53.1)	18 (62)
Not resolved/recovered	22 (44.9)	10 (34.5)
Fatal	1 (2.)	1 (3.4)
Time-to-resolution (weeks)	N=26	18
Median	3.4	3.5
Q1-Q3	11.-9.1	1.3-6.1
Action taken	N=49	N=29
Dose delay/modification	15 (30.6)	4 (13.8)
Discontinuation	11 (22.4)	2 (6.9)
Hospitalization	19 (38.8)	11 (37.9)
Treatment (any anticoagulant) YES	44 (89.8)	25 (86.2)

Source: Applicant's submission to BLA125547

In the INSPIRE trial (Table 43) 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 43 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)

Reviewer's comment:

In the SQUIRE and INSPIRE trials, the overall incidence of TEs were significantly higher in the necitumumab arms compared to the 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.

Lung cancer patients have 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[8, 22, 23, 24, 25]. 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]. Recently, anti-EGFR mAbs have been implicated in the development of thromboembolic events, however, the incidence and level of risk remains unclear[26]. Tumor histology differences (adenocarcinoma vs. squamous) might account for the higher incidence of VTEs observed in the INSPIRE trial.

Labeling Recommendation

Add Thromboembolic Events to WARNINGS and PRECAUTIONS section to discontinue necitumumab for patients with serious or life threatening thromboembolic events.

7.3.5.4 Infusion Related Reactions

Infusion related reaction was reported in 8 patients (1.5%) in the N+GC arm. Infusion reaction was grade 3 in severity in two patients (0.4%).

Subject ID 176-6003 developed a grade 3 infusion reaction during necitumumab infusion on cycle 2, day 1. Subject ID 622-6001 developed thoracic pressure, asthmatic symptoms and back pain after receiving cycle 1, day 8 necitumumab. He was

diagnosed with a grade 3 allergic drug reaction. Both patients recovered from the event without sequelae. Necitumumab was permanently discontinued

In the INSPIRE study, grade 1-2 infusion related reaction was observed in 6 patients (2.0%) in the N+GC arm and 4 (1.3%) in the GC alone arm. There were no grade ≥ 3 IRRs in either arm.

Reviewer's Comment:

Labeling recommendation
Revise Premedication and DOSE AND MODIFICATIONS section for clarity. Revise WARNINGS and PRECAUTIONS section to provide incidence and severity of infusion-related reactions observed in the SQUIRE trial.

7.3.5.5 Conjunctivitis

A total of 23 patients (4.3%) developed conjunctivitis (MedDRA PT) during the course of treatment in the N+GC arm compared to 12 patients (2.2%) in the GC alone arm.

The majority of the events was grade 1-2 and reported as "recovered". Grade 3 conjunctivitis was reported in two patients (0.37%) in the necitumumab arm:

- Patient ID273-6002 was 72 yo white male randomized to N+GC arm developed grade 3 conjunctivitis on cycle 5, day 13 of therapy. Treatment for conjunctivitis included levofloxacin. The event was reported as improved to grade 2 a month after onset but not resolved. Necitumumab was permanently discontinued due to the event.
- Patient ID141-6001 was a 62 yo male, randomized to N+GC arm, who developed grade 3 conjunctivitis on cycle 10, day 9. Action taken with study drug was "delayed/modified". Outcome of the event was not reported.

The Applicant further analyzed the incidence of conjunctivitis using the following composite MedDRA PT:

Conjunctivitis, eye irritation, vision blurred, conjunctivitis, bacterial, dry eye, visual acuity reduced, Blepharitis, Blepharitis allergic, conjunctiva hemorrhage, eye infection, eye pain, lacrimation increased ocular hyperemia, Sjogren's Syndrome, visual impairment and eye pruritus.

Using the composite terms analysis, 40 patients (7.4%) were included in the category of 'conjunctivitis" with 4.8% grade 1 (N=26), 2.2% grade 2 (N=12) and 0.4% grade 3 (N=2).

In the INSPIRE trial, grade 1-2 conjunctivitis was reported in 31 patients (10.2%%) in the N+PC arm and 6 patients (1.9%), in PC arm with one instance of grade 3 events reported in the PC alone arm.

Reviewer's Comment:

Eye disorder and conjunctivitis (MedDRA PT composite terms) occurred in 7.4% and 4.3% of patients treated with necitumumab. Conjunctivitis can occur late in the course of therapy and be severe in 0.4% of patients.

Labeling recommendation

Recommend adding conjunctivitis to WARNINGS and PRECAUTIONS section to provide guidance regarding monitoring, Interrupt or discontinue necitumumab for severe, or worsening ocular disorders.

7.3.5.6 Interstitial Lung Disease

In the SQURIE trial, interstitial lung disease was reported in five patients (0.9%), one fatal (0.2%), in the N+GC arm and four patients (0.7%) in the GC arm.

Subject ID 540-6017 was a 67 years-old Asian male with a medical history of idiopathic pulmonary fibrosis and arteriosclerosis coronary disease. He had completed 6 cycles of chemotherapy and received a total of 18 doses of necitumumab monotherapy (C9D8). CT scan had shown increased primary tumor mass. He was hospitalized with fever, chills and hypoxia and diagnosed with interstitial lung disease combined with pneumonia. He was started on antibiotics and corticosteroids but progressed with respiratory failure and died. The event was considered as possibly related to necitumumab.

Subject ID 417-6001 randomized to N+GC arm was hospitalized on cycle 3 day 5 with the diagnosis of grade 3 necrotizing pneumonia of infectious origin. The event was considered to be unrelated to necitumumab. The patient recovered from the event without sequelae.

In the INSPIRE study, grade 1-2 interstitial lung disease was reported in 4 patients (1.3%) in the N+PC arm and 3 patients (1.0%) in the PC arm, with one fatal.

Reviewer's Comment:

Fatal and non-fatal interstitial lung disease can occur with anti-EGFR monoclonal antibody class drugs at a incidence of 1 %, consistent with the what is observed in the SQUIRE trial.

Labeling Recommendation

Add interstitial lung disease to WARNINGS and PRECAUTIONS section to raise awareness in the event of acute onset or worsening of pulmonary symptoms and to recommend interrupting or discontinue necitumumab if interstitial lung disease is confirmed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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 44 lists AE (all grades and grade ≥ 3) that were observed in either treatment arm in > 5 % of the patients in the SQUIRE study.

Table 44 Adverse Events Observed in > 5% of Patients in SQUIRE

	N+ GC N=538 (%)		GC N=541 (%)	
AE (MedDRA) System Organ Class and Preferred Term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥ 3**
Any AE	**533 (99)**	**388 (72)**	**529 (98)**	**333 (62)**
Blood and Lymphatic System Disorders	**371 (69)**	**185 (34)**	**396 (73)**	**213 (39)**
Neutropenia	228 (42)	128 (24)	242 (45)	146 (27)
Anemia	223 (41)	56 (10)	248 (46)	59 (11)
Thrombocytopenia	110 (20)	53 (10)	132 (24)	54 (10)
Leukopenia	73 (14)	22 (4)	87 (16)	36 (7)
Eye Disorders	**47 (8.7**	**2 (0.4)**	**16 (3.0**	**0**
Conjunctivitis	23 (4.3)	2 (0.4)	1 (0.2)	**0**
Gastrointestinal Disorders	**365 (68)**	**57 (11)**	**375 (69)**	**35 (7)**
Nausea	267 (50)	15 (3)	283 (52)	14 (3)
Vomiting	157 (29)	15 (3)	135 (25)	5 (1)
Constipation	111 (21)	3 (0.6)	98 (18)	1 (<1)
Diarrhea	84 (16)	9 (2)	61 (11)	8 (2)
Stomatitis	59 (11)	6 (1)	34 (6)	2(0.6)
Abdominal pain upper	32 (6)	1 (<1)	28 (5)	0
Dyspepsia	27 (5)	1 (<1)	22 (4)	0
General Disorders and Adm. Site Cond	**304 (57)**	**64 (12)**	**294 (54)**	**50 (9)**
Asthenia	125 (23)	23 (4)	113 (21)	20 (4)
Fatigue	114 (21)	17 3)	122 (27)	18 (3)
Pyrexia	74 (14)	6 (1)	60 (11)	2 (0.4)
Edema Peripheral	43 (8)	1 (<1)	41 (8)	0
Infections and Infestations	**207 (39)**	**33 (6)**	**139 (26)**	**35 (7)**
Paronychia	36 (7)	2 (<1)	1 (<2)	0
Urinary Tract Infection	28 (5)	1 (<1)	9 (2)	1 (<1)
Investigations	**191 (36)**	**33 (6)**	**146 (27)**	**19 (4)**
Weight decreased	72 (13)	4 (1)	34 (6)	3 (0.6)
Blood creatinine Increased	52 (10)	0	41 (8)	1 (<1)
Alanine Aminotransferase increased	27 (5)	3 (0.6)	19 4)	2 (<1)
Metabolism and Nutrition Disorders	**321 (60)**	**102 (19)**	**262 (48)**	**58 (11)**
Decreased Appetite	159 (30)	5 (1)	151 (28)	8 (2)
Hypomagnesemia	159 (30)	47 (9)	82 (15)	6 (1)
Hypokalemia	38 (7)	16 (3)	28 (5)	8 (2)
Hyperglycemia	27 (5)	9 (2)	17 (3)	8 (2)
Musculoskeletal, Connective Tissue Dis	**123 (23)**	**11 (2)**	**115 (21)**	**14 (3)**
Back pain	39 (7)	6 (1)	28 (5)	4 (1)
Pain in Extremity	27 5)	1 (<1)	21 (4)	4(1)
Nervous System Disorders	**203 (38)**	**30 (6)**	**143 (26)**	**18 (3)**
Dizziness	58 (11)	2 (<1)	42 (8)	2 (<1)
Headache	57 (11)	0	31 (6)	2 (<1)
Dysgeusia	33 (6)	1 (<1)	18 (3)	0
Psychiatric Disorders	**67 (13)**	**3 (0.6)**	**61 (11)**	**2 (<1)**

	N+ GC N=538 (%)		GC N=541 (%)	
AE (MedDRA) System Organ Class and Preferred Term	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥ 3**
Insomnia	28 (5)	0	27 (5)	1 (<1)
Respiratory, Thoracic and Mediastinal Dis	**240 (45)**	**53 (10)**	**204 (38)**	**58 (11)**
Cough	87 (16)	0	69 (13)	3 (1)
Dyspnea	87 (16)	15 (3)	79 (15)	21 (4)
Hemoptysis	53 (10)	7 (1)	27 (5)	5 (1)
Epistasis	40 (7)	0	17 (3)	1 (<1)
Productive Cough	27 (5)	0	12 (2)	0
Pulmonary embolism	26 (5)	19 (4)	13 (2)	10 (2)
Skin and Subcutaneous Tissue Disorders	**432 (80)**	**44 (8)**	**128 (24)**	**4 (1)**
Rash	235 (44)	20 (4)	30 (6)	1 (<2)
Dermatitis Acneiform	81 (15)	7 (1)	3 (0.6)	0
Alopecia	76 (14)	0	70 (13)	0
Acne	47 (8)	2 (<1)	3 (0.6)	0
Pruritus	38 (7)	1 (<1)	5 (1)	1 (<1)
Dry Skin	35 (7)	0	5 (2)	0
Rash Generalized	28 (5)	(1)	2 (<1)	0
Skin fissures	27 (5)	2 (<1)	0	0

7.4.2 Laboratory Findings

Routine clinical laboratories were assessed at baseline on day 1, week 1, day 8, week 2 of each treatment cycle, at the end of therapy, at the 30-day safety follow-up, and as indicated during treatment in the SQUIRE trial.

The incidences of post-baseline alterations in laboratory parameters, graded according to NCI CTCAE version 4.0 were analyzed and the findings for hematologic, hepatic, renal and electrolytes as listed in the following tables.

Electrolytes, Serum Creatinine and Glucose

The most significant laboratory findings in patient treated with necitumumab + GC compared to GC alone are electrolyte abnormalities associated with necitumumab induced hypomagnesemia. Hypomagnesemia based on laboratory findings occurred at high incidence in both treatment arms, but significantly higher in N+GC arm. Laboratory hypomagnesemia occurred in 81% of patients in N+GC arm with 19% grade a 3 or 4 event. In the GC arm, 70% of the patients had low magnesium post-baseline, with 7% grade 3 or 4.

Other electrolyte abnormalities know not be associated with hypomagnesemia including hypocalcemia, hypokalemia and hypophosphatemia, also occurred at a higher

incidence in patients exposed to necitumumab. Significant laboratory parameter changes are highlighted in the following table.

Renal function assessment based on serum creatinine parameter was no significantly different between the treatment arms.

Table 45 Post-Baseline Renal and Electrolyte Alterations Graded according to NCI CTCAE 4.0

LABORATORY PARAMETER	CTCAE GRADE	N+ GC N=538	GC N=541
Calcium High (mmol/L)	N Any grade Grade 3 or 4	503 54 (11) 3 (0.6)	497 73 (15) 7 (1)
Calcium Low (mmol/L)	N Any grade Grade 3 or 4	502 203 (40) 30 (6)	499 151 (30) 12 (2)
Corrected Calcium High (mmol/L)	N Any grade Grade 3 or 4	476 58 (12) 8 (2)	479 77 (16) 7 (2)
Corrected Calcium Low (mmol/L)	N Any grade Grade 3 or 4	476 157 (33) 20 (4)	480 110 (23) 11 (2)
Creatinine High (µmol/L)	N Any grade Grade 3 or 4	514 137 (27) 6 (1)	516 175 (34) 3 (0.6)
Glucose High (mmol/L)	N Any grade Grade 3 or 4	488 247 (51) 20 (4)	485 250 (52) 30 (6)
Glucose Low (mmol/L)	N Any grade Grade 3 or 4	489 47 (10) 1 (<1)	485 38 (8) 4 (1)
Magnesium High (mmol/L)	N Any grade Grade 3 or 4	460 18 (4) 11 (2)	457 22 (5) 8 (2)
Magnesium Low (mmol/L)	N Any grade Grade 3 or 4	461 375 (81) 86 (19)	457 321 (70) 33 (7)
Phosphate Low (mmol/L)	N Any grade Grade 3 or 4	461 133 (29) 29 (6)	454 103 (23) 26 (6)
Potassium High (mmol/L)	N Any grade Grade 3 or 4	505 150 (39) 18 (4)	505 162 (32) 24 (5)
Cont.			

LABORATORY PARAMETER	CTCAE GRADE	N+ GC N=538	GC N=541
Potassium Low (mmol/L)	N	505	505
	Any grade	119 (24)	89 (18)
	Grade 3 or 4	22 (4)	16 (3)
Sodium High (mmol/L)	N	508	512
	Any grade	24 (5)	17 (3)
	Grade 3 or 4	3 (0.6)	0
Sodium Low (mmol/L)	N	508	511
	Any grade	221 (44)	233 (46)
	Grade 3 or 4	59 (12)	73 (14)
Urate High (µmol/L	N	461	454
	Any grade	63 (14)	115 (25)
	Grade 3 or 4	11 (2)	15 (3)

**only patients with at least one post-baseline results are included in the analysis.*

Reviewer's comment

Refer to further analysis and discussion of hypomagnesemia in Section 7.3.4 Significant Adverse Events.

***Labeling Recommendation**:*

Refer to Section 7.3.4.for labeling recommendations for hypomagnesemia.

Hematology Assessment

The analysis of post-baseline hematology laboratory assessment is shown in Table 46.Anemia, neutropenia, leukopenia and thrombocytopenia occurred at higher incidence in both treatment arms, with no significant differences between necitumumab + GC compared to GC alone, and are likely to be related to both gemcitabine and cisplatin.

Table 46 Post-Baseline Hematology Parameter Alterations Graded according to NCI CTCAE 3.0

LABORATORY PARAMETER	N/CTCAE GRADE	N+ GC N=538	GC N=541
Hemoglobin low (mml/L)	N Any grade Grade 3 or 4	524 401 (77) 42 (8)	529 429 (81) 36 (7)
Leucocytes Low 10^9/L	N Any grade Grade 3 or 4	524 304 (58) 44 (8)	529 318 (60) 61 (12)
Lymphocyte Low 10^9/L	N Any grade Grade 3 or 4	466 223 (48) 35 (8)	468 200 (43) 43 (9)
Neutrophils Low 10^9/L	N Any grade Grade 3 or 4	516 304 (59) 110 (21)	512 305 (60) 137 (27)
Platelets Low 10^9/L	N Any grade Grade 3 or 4	524 218 (42) 35 (7)	528 274 (52) 37 (7)

**only patients with at least one post-baseline results are included in the analysis.*

Hepatic Function and Coagulation Assessment

Post-baseline hepatic and coagulation laboratory assessments were analyzed and the results summarized in Table 47. Although the incidence of hepatic enzyme elevation (all grades) was numerically higher in the N+GC arm compared to GC arm, the difference is small. The number of patients who had a post-baseline grade 3 or 4 liver enzyme elevation was similar between the treatment arms. Liver enzyme elevation and hepatic impairment are known toxic effects of gemcitabine and cisplatin. Necitumumab is eliminated by proteolytic degradation and not hepatic CYP enzyme metabolism, direct hepatic impairment is considered unlikely.

No significant differences in coagulation parameters were observed between the arms based on the available information.

Table 47 Post-Baseline Hepatic and Coagulation Laboratory Alterations Graded according to NCI CTCAE 4.0

LABORATORY PARAMETER	N/CTCAE GRADE	N+ GC N=538	GC N=541
Alanine Aminotransferase High (*U/L)	N*	507	506
	Any grade	178 (35)	159 (31)
	Grade 3 or 4	3 (0.6)	5 (1)
Albumin Low (g/L)	N	486	492
	Any grade	154 (32)	146 (30)
	Grade 3 or 4	4 (1)	3 (0.6)
Alkaline Phosphatase High (U/L)	N	504	503
	Any grade	131 (26)	116 (23)
	Grade 3 or 4	2 (<1)	4 (1)
Aspartate Aminotransferase High (U/L	N	505	503
	Any grade	148 (29)	123 (25)
	Grade 3 or 4	5 (1)	3 (1)
Bilirubin High (µmol/L)	N	507	505
	Any grade	48 (10)	33 (7)
	Grade 3 or 4	4 (1)	5 (1)
Activated PTT high	N	415	378
	Any grade	25 (6)	20 (5)
	Grade 3 or 4	5 (1)	0
PT INR High	N	426	396
	Any grade	35 (8)	28 (7)
	Grade 3 or 4	7 (2)	3 (1)

*Only patients with at least one post-baseline result are included in the analysis.

7.4.3 Vital Signs

Vital signs, including temperature, pulse rate, respiration rate, and blood pressure, were collected at baseline, on days 1 and 8 of each cycle, at the end of therapy, at 30-day safety follow-up and as warranted during the course of the study.

Pyrexia
In the SQUIRE trial, elevated temperature, reported as pyrexia (MedDRA preferred term) was reported in 74 patients (13.8%) in the N+GC arm, with 17 (3.2%) patients experiencing a grade 3 or 4 event compared to 60 patients (11.1%) in the GC arm, with 2 patients reported as experiencing grade 3 or 4 pyrexia.
Blood Pressure
Hypotension as an AE (MedDRA PT) was reported in 14 patients (2.6%), with 5 (0.9%) grade 3 or 4 in the N+GC arm and 14 patients (2.6%), 2 patients (0.4%) grade 3 or 4 in the GC arm.

Hypertension as an AE (MedDRA PT) was reported in 23 patients (4.3%) with 5 (0.9%) grade 3 or 4 in the N+GC arm and 25 patients (4.6%), 5 patients (0.9%) grade 3 or 4 in the GC arm.

The Applicant conducted an analysis of the shift in blood pressure from pre-treatment dosing to post-treatment dosing, per cycle for necitumumab, gemcitabine and cisplatin (SQUIRE CSR, Table JFCC.14.190). No clinically significant conclusions can be drawn from the data.

7.4.4 Electrocardiograms (ECGs)

Refer to QT-IRT and Clinical Pharmacology Team review.

The Applicant submitted interim ECG data from 40 patients enrolled in study I4X-IE-JFCI, with the primary objective of evaluating the effect of necitumumab on QTc interval Interim analysis was based on data available in 20 patients who completed the QT assessment period.

CDER's QT-IRT agrees with the Applicants assertion that due to its large molecular size necitumumab has a low likelihood of direct ion channel interaction and thus a small QT prolongation risk.

(b) (4)

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7.4.5 Special Safety Studies/Clinical Trials

Please refer to Clinical Pharmacology review of dedicated DDI study I4X-IE-JFCJ and section 7.4.4 for a summary of QT-IRT review of study I4X-IE-JFCI.

7.4.6 Immunogenicity

Refer to Clinical Pharmacology Review for detail analysis of the immunogenicity. Key findings by the Clinical Pharmacology team are summarized below:

The immunogenicity of necitumumab was assessed in 981 patients from 6 clinical trials. Of 814 patients who had samples collected and analyzed for anti-necitumumab antibodies (ADA) at baseline and post-treatment, 71 patients (8.7%) had samples positive for ADAs. Treatment-emergent ADAs (TE-ADAs) were detected for 33 patients (4.1%). Neutralizing antibodies were detected in 28 patients (2.9%) at baseline and in 11 patients (1.4%) post treatment. Out of the 981 patients, 17 (1.7%) experienced IRRs and among them 2 patients (0.2%) were ADA-positive.

The development of TEADAs, and neutralizing antibodies showed no correlation with safety outcomes. The incidence of skin rash and hypomagnesemia was similar between patients with ADAs detected and the overall population (81.5 versus 79% and 32.1 versus 31%, respectively). ADA-positive patients tended to have a 26% higher CL_{tot} and a 34% lower $C_{ss,ave}$ than those without ADAs. The percent increase in OS appears to be lower in ADA-positive patients with ADA tested both pre- and post- treatment than those without ADA detected.

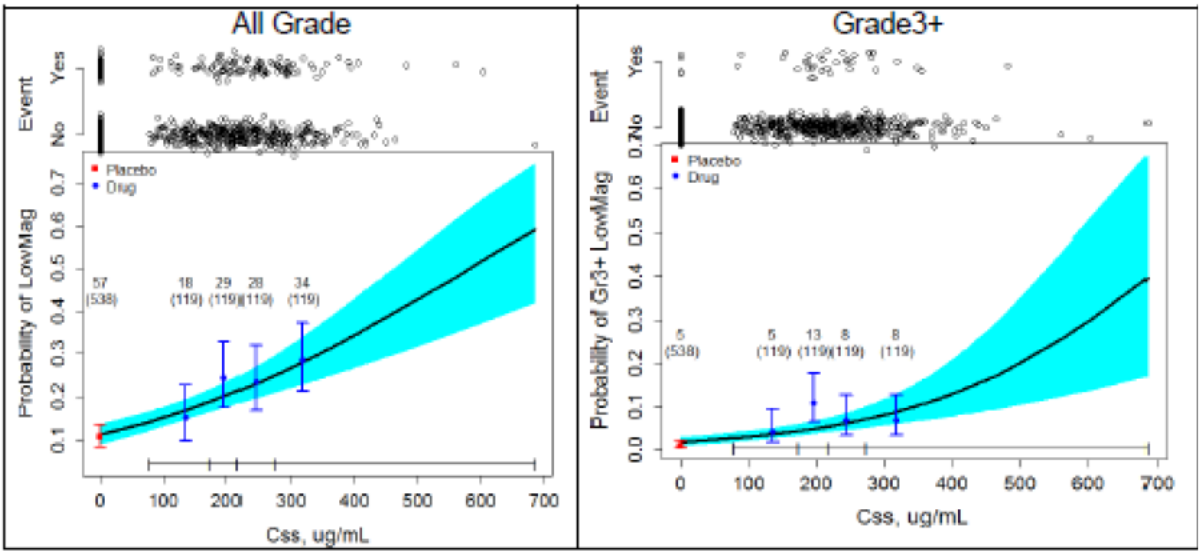
7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Analysis of dose dependency for adverse events was not conducted because all patients in the SQURIE and INSPIRE studies were treated with an uniform dose regimen of necitumumab.

Exploratory exposure-safety relationship for hypomagnesemia, skin toxicity and thromboembolic events was evaluated by the Clinical Pharmacology review team using the PopPK analysis of the data from the SQUIRE trial after excluding the patient with no PK sampling. A positive correlation between occurrence of hypomagnesemia (all grade) and necitumumab exposure was observed (Figure 8).

Figure 8 Probability of Hypomagnesemia versus Exposure



Source: Clinical Pharmacology Review, CDER. FDA

No necitumumab exposure-safety relationship was observed with skin toxicity or thromboembolic events. The reader is referred to the Clinical Pharmacology review for detailed description of the exploratory analysis.

7.5.2 Time Dependency for Adverse Events

Time-to-event analyses for skin reaction, hypomagnesemia and thromboembolic events were integrated in Section 7.3.4

7.5.3 Drug-Demographic Interactions

Exploratory subgroup analysis of treatment-emergent adverse events was conducted in the SQUIRE safety population based on age, gender and race.

Age

In the SQUIRE trial, 203 (19%) who received necitumumab were 70 years or older. Table 34 shows the analysis of adverse events in patients 70 years or older compared to patients < 70 years of age (Table 48).

In necitumumab + GC arm, grade 3 AE was numerically higher in the < 70 age group, while in the GC arm, grade 3 AE was higher in the ≥ 70 years old age group. AEs that

Table 48 Adverse Events by Age Group < 70 years and ≥ 70 years of age

MedDRA PT	< 70 YEARS-OLD (N=876)				≥ 70 YEARS OLD (N=203)			
	N+GC N=432 (%)		GC N=444 (%)		N+GC N=106 (%)		GC N=97 (%)	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3
All AEs	**429 (99)**	**315 (73)**	**435(98)**	**267 (60)**	**104 (98)**	**73 (69)**	**94 (97)**	**66 (68)**
Neutropenia	182 (42)	104 (25)	193 (44)	119 (27)	46 (43)	21 (20)	49 (51)	27 (28)
Thrombocytopenia	79 (18)	34 (8)	107 (24)	42 (10)	31 (29)	19 (18)	25 (26)	12 (12)
Anemia	172 (40)	45 (10)	201 (45)	46 (10)	51 (48)	11 (10)	47 (49)	13 (13)
Skin disorders	356 (82)	38 (9)	107 (24)	4 (1)	76 (72)	6 (6)	21 (22)	0
Rash	196 (45)	19 (4)	24 (5)	1 (<1)	39 (37)	1 (1)	6 (6)	0
Hypomagnesemia	130 (30)	40 (9)	67 (15)	5 (1)	29 (27)	7 (7)	15 (16)	1 (1)
Fatigue	90 (21)	14 (3)	102 (23)	13 (3)	24 (23)	3 (3)	20 (21)	5 (5)
Asthenia	99 (23)	18(4)	88 (20)	15 (3)	26 (25)	5 (5)	25 (26)	5 (5)
Nausea	292 (68)	48 (11)	313 (71)	26 (6)	53 (50)	2 (2)	42 (43)	3 (3)
Vomiting	127 (29)	14 (3)	113 (26)	4 (1)	30 (28)	1 (1)	22 (23)	1 (1)
Constipation	87 (20)	1 (<1)	82 (19)	0	24 (23)	2 (2)	16 (17)	1 (1)
Diarrhea	71 (16)	8 (2)	51 (12)	7 (2)	13 (12)	1 (1)	10(10	1 (1)
Stomatitis	48 (11)	4 (1)	28 (6)	1 (<1)	11 (10)	2(2)	6 (6)	2 (2)
Weight decreased	57 (13)	3 (1)	28 (6)	3 (1)	15 (14)	1 (1)	6 (6)	0
Decreased appetite	127 (30)	4 (1)	121 (27)	5 (1)	32 (30)	1 (1)	30 (31)	3 (3)
Dyspnea	75 (17)	12 (3)	64 (14)	17 (4)	12 (11)	3 (3)	15 (16)	4 (4)
Cough	70 (16)	0	56 (13)	2 (<1)	17 (16)	0	13 (13)	1 (1)
Creatinine increased	37 (9)	0	32 (7)	0	15 (14)	0	9 (9)	1 (1)
Back pain	27 (6)	3 (1)	23 (5)	4 (1)	12 (11)	3 (3)	5 (5)	0
Dizziness	42 (10)	0	33 (7)	2 (<1)	16 (15)	2 (2)	9 (9)	0

occurred at a > 5% incidence in the > 70 age group are: anemia, thrombocytopenia, creatinine elevation, back pain, dizziness. AEs that occurred at a > 5% incidence in the < 70 age group are: skin reactions, dyspnea and nausea.

In the N+GC arm, patients who are 70 years or older, experienced more thrombocytopenia (29 % vs. 18% all grades and 18% vs. 8% grade 3/4) and anemia (48 % vs. 40% all grades, with equal number of grade 3/4) and elevated creatinine (14% vs. 9% all grades).

Patients who are < 70 years of age experienced more necitumumab related skin disorders compared to those who are ≥ 70 years old (82% vs. 72 % all grades, 9% vs. 6% grade 3/4).

Gender

In the SQUIRE trial, 92 patients (17%) who received necitumumab were female. In the necitumumab-containing arm, the incidence of AEs were similar between male and female patients. In the control arm, female patients had higher incidence of grade ≥ 3 AEs compared to males. Because the number of female patients is small, definite conclusions cannot be made (Table 49).

Table 49 Adverse Events by Gender in SQUIRE trial (Safety Population)

	N+GC			GC		
	N	All grades	Grade ≥ 3	N	All grades	Grade ≥ 3
Male	446	443 (99)	323 (72)	452	441 (98)	267 (59)
Female	92	90 (98)	65 (71)	89	88 (99)	66 (74)

Race

More than 80% of the patients enrolled in the SQUIRE trial were Caucasian. An exploratory analysis of adverse events in non-white subjects compared to white subjects showed a numerically higher incidence of grade ≥ 3 AEs in the non-white subgroup (Table 50). Because the number of non-white subjects exposed to necitumumab is small, no definite conclusions can be made regarding the safety of necitumumab in non-white patients.

Table 50 Adverse Events by Race in SQUIRE trial (Safety Population)

	N+GC			GC		
	N	All grades	Grade ≥ 3	N	All grades	Grade ≥ 3
White	452	447 (99)	317 (70)	452	442 (98)	273 (60)
Non-white	86	86 (100)	71 (83)	89	87 (98)	60 (67)

7.5.4 Drug-Disease Interactions

Refer to section 4.4.3 for a discussion of the effects of hepatic and renal impairment on necitumumab pharmacokinetics.

7.5.5 Drug-Drug Interactions

Refer to Clinical Pharmacology detailed review of drug-drug-interaction PK studies.

The PopPK analysis performed in 807 patients from 5 clinical trials including Trial JFCJ indicate that gemcitabine and cisplatin have no impact on the exposure to necitumumab.

The data from Trial JFCJ in 12 patients with advanced solid tumors indicate that the co-administration of necitumumab (800 mg over 50 min IV infusion) with gemcitabine (1250 mg/m^2) and cisplatin increased the geometric mean dose-normalized gemcitabine AUC_{INF} by 22% and dose-normalized C_{max} by 63% compared to co-administration of gemcitabine and cisplatin alone This increased exposure to gemcitabine may have contributed to the higher toxicity observed with the necitumumab containing arm. The co-administration of necitumumab did not have an impact on the exposure to cisplatin (as measured by dose-normalized AUC_{0-5h} and dose-normalized C_{max} for total platinum) in the presence of gemcitabine.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been conducted with necitumumab.

7.6.2 Human Reproduction and Pregnancy Data

There are no clinical studies of necitumumab in pregnant or lactating women. Pregnant and lactating women were excluded from all studies with necitumumab.

The Applicant provided surrogate data by right of reference to the reproductive toxicology study conducted as a post-marketing requirement for the anti-EGFR antibody cetuximab. Cetuximab was detected in amniotic fluid and the serum of embryos from treated dams and, as suggested by the available data from knockout animals, caused embryo lethality and abortions at clinically relevant doses. Based on this information, the Pharmacology/Toxicology review team concluded that a warning for embryofetal risk is warranted in the necitumumab label based on the potential risk reproductive toxicity.

7.6.3 Pediatrics and Assessment of Effects on Growth

Eli Lilly requested a full waiver of the requirement for pediatric use studies under the Pediatric Research Equity Act. The Pediatric Review Committee (PeRC) granted the waiver January 16, 2014 because of the rarity of lung cancer in the pediatric population, which renders conduct of the necessary studies impossible or highly impractical.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is limited clinical trial experience with necitumumab overdose. In the SQUIRE trial, one patient received an overdose of necitumumab. Patient ID 195-6003, was a 54 years-old white male with metastatic NSCLC who was randomized to receive necitumumab plus gemcitabine and cisplatin. On cycle 1, day 1 he received necitumumab 1600mg, gemcitabine 2512 mg and cisplatin 150 mg. The dose of necitumumab was administered in error as the dose should have been 800mg. No relevant laboratory tests were performed. The patient experienced grade 1 rash 2 days after the infusion which resolved on day 8 after the infusion. He received cycle 1 day 8 necitumumab 800 mg. The event of grade I rash was attributed to necitumumab and not to gemcitabine or cisplatin. The patient was discontinued from study a month later due to progressive disease.

Necitumumab is administered IV in a clinic/hospital setting and there is low abuse potential.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the 120-day safety report on April 13, 2015. The updated data cut-off date was November 24, 2014. No notable safety signals were identified in the 120-day safety update report beyond those reported in this BLA submission.

8 Postmarket Experience

Necitumumab is a new molecular entity in the United States. Necitumumab is not marketed in any country at the time of this review. No postmarketing information is available.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling recommendations are integrated in the review.

9.3 Advisory Committee Meeting

Given the modest improvement in OS observed in the SQUIRE trial, the lack of efficacy in patients with non-squamous NSCLC observed in the INSPIRE trial and the safety concerns discussed in the above sections the Oncology Drug Advisory Committee was convened on July 9, 2015 to discuss and provide advice on this BLA.
The committee was presented with the following issues for discussion:

Efficacy Summary

- In patients with metastatic squamous NSCLC (SQUIRE trial), the addition of necitumumab to gemcitabine/cisplatin resulted in: 1.6 month improvement in median Overall Survival (OS), [HR=0.84 (95% CI 0.74; 0.96); log-rank p=0.012]; 0.2 month improvement in median Progression-Free Survival (PFS), [HR=0.85 (95% CI 0.74, 0.98); log-rank p=0.02)]. No statistically significant difference in objective response rate (ORR) (31% vs. 29%).
- In patients with metastatic non-squamous NSCLC (INSPIRE trial), the addition of necitumumab to pemetrexed/cisplatin did not result in significant differences in OS [HR=1.01, 95% CI 0.84; 1.21)], PFS [HR=0.96; 95% CI (0.80, 1.16)] or ORR (32% vs.31%).

Safety Summary

- Anti-EGFR related serious toxicities with the addition of necitumumab to platinum based chemotherapy: hypomagnesemia and skin rash
- Increase incidence of sudden deaths/death not otherwise specified (NOS) (2.2% vs. 0.5% in SQUIRE, 3.3% vs.1.6% in INSPIRE)
- Increased incidence of venous thromboembolic events (9% vs. 5% in SQUIRE, 13% vs. 8% in INSPIRE), some fatal.

ODAC members were asked to discuss the following issues:

1. Please discuss whether the INSPIRE trial results in the non-squamous NSCLC population impact the benefit: risk assessment of necitumumab for squamous NSCLC.

Committee Discussion

The majority of the committee agreed that the lack of efficacy in the INSPIRE trial in the non-squamous NSCLC population did not appear to impact the robustness of the findings in the SQUIRE trial in the squamous NSCLC population. Committee members were concerned about the toxicity of hypomagnesemia and suggested clear guidance either in the labeling or educational resources on how to manage this in a clinical setting. The committee was also concerned with potential over-anticoagulation in clinical practice in response to the increased deaths attributed to thromboembolic events shown in the INSPIRE trial and suggested further studies to assess how to prevent venous thromboembolic events in this high risk population. Please see the transcript for details of the committee discussion.

2. Please discuss whether 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.

Committee Discussion

The majority of the committee agreed that 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. Most of the committee members noted that the 16% reduced risk of death and median 1.6-month survival benefit with necitumumab in the pivotal SQUIRE study is modest yet significant and noteworthy. Some committee members advised that consideration should be given to recommending against use in patient subgroups that appeared to gain little or no benefit from the anti-EGFR monoclonal antibody, such as patients over age 70 years and those whose tumors do not express EFGR proteins. Please see the transcript for details of the committee discussion.

The reader is referred to the meeting documents and transcript for detailed discussion at FDA's Oncology Advisory website:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm426351.h

9.4 Summary of Additional Studies with Necitumumab

The following Clinical Study Reports, relevant safety data (deaths, grade ≥ 3 AEs and necitumumab related AEs) and selected narratives were reviewed by FDA. Refer to Clinical Pharmacology detailed review and discussion of the PK data findings.

9.4.1 Study I4X-IE-JFCE (IMCL CP11-0401)

Study Title

Phase I Study of the Fully Human Anti-Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody IMC-11F8 in Patients with Solid Tumors Who Have Failed Standard Therapy

Objectives

The primary objective was to establish the safety profile and the maximum tolerated dose (MTD) of the fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody IMC- 11F8 (necitumumab) in patients with solid tumors who no longer respond to standard therapy or for whom no standard therapy is available.

Secondary objectives were to:

- Determine the pharmacokinetic (PK) profile of IMC-11F8;
- Screen for the development of antibodies against IMC-11F8 (immunogenicity);
- Assess the antitumor activity of IMC-11F8 as monotherapy.

Study Population and Design

Patients at least 18 years of age with histologically-confirmed, unidimensionally-measurable and/or evaluable solid tumors who no longer responded to standard therapy or for whom no standard therapy was available, with adequate organ function and an ECOG PS 0 to 2, were assigned to one of the two study arms:

- **Arm A**: escalating doses of IMC- 11F8, once a week during each treatment cycle for a total of 6 doses per cycle (6-week cycle). The starting dose was 100 mg/week in Cohort 1, with planned escalation to 200 mg/week in Cohort 2. Dose escalation in successive cohorts was to be in 200-mg increments thereafter, to 400 mg, 600 mg, 800 mg, and 1000 mg.

- **Arm B**: escalating doses of IMC- 11F8, every 2 weeks for a total of 3 doses per cycle (6-week cycle). In Arm B, the starting dose was 100 mg every other week in Cohort 1, with planned escalation to 200 mg every other week in Cohort 2.

Dose escalation in Cohorts 3, 4, 5, and 6 was to 400 mg, 600 mg, 800 mg, and 1000 mg every other week, respectively.

Prior to each cycle, patients received an initial infusion of IMC-11F8 at their assigned cohort dose level, followed by a 2-week PK sampling period, prior to the first cycle of therapy.

Dose escalation followed the standard 3+3 design. A DLT was defined as any Grade 3 or 4 major organ toxicity considered to be definitely, probably, or possibly related to IMC-11F8.

Summary of Results

From November 2004 to February 28, 3007, the study enrolled a total of 60 patients at two clinical sites in Netherlands, 29 patients in Arm A and 31 patients in Arm B.

Demographics and Baseline Characteristics

- In Arm A, 18/29 patients were male, median age was 60 years, 96.5% had ECOG PS 0 or 1 and 3.4% ECOG 2. The most common type of cancer was colorectal (28%), renal cancer (17%), pancreatic, melanoma and prostate cancer (10% each).

- In Arm B, 17 patients were male, with a median age of 59 years, 89% had ECOG PS 0 or 1 and 13 % ECOG PS of 2. The most common type of cancer was colorectal cancer (45%).

Exposure

- In Arm A, the median duration of treatment for all cohorts combined was 8.0 weeks, and the mean duration of treatment was 15.1 weeks (range: 2.0 weeks - 83.1 weeks). Nine of 29 patients (31%) underwent treatment beyond the initial PK sampling period and first cycle of therapy. In all, patients received a mean of 13.5 infusions per patient (range: 1 to 74). The median relative dose intensity was 100% (mean: 98.1%).
- In Arm B, the mean and median durations of treatment for all cohorts combined were 11.2 weeks and 8.0 weeks, respectively; duration of treatment ranged from 2.0 weeks to 40.0 weeks in this cohort. Duration of treatment extended beyond the 2-week PK period and initial 6-week treatment cycle for nine patients. The mean number of infusions per patient was 5.5 (range: 1 to 21), and the median relative dose intensity was 100% (mean: 97.3%).

Safety

A summary of adverse events by dose group is shown in the following table, as per Applicant.

Table 51 I4X-IE-JFCE: Summary of Adverse Events by Dose Group (per Applicant)

	Arm A (IMC-11F8 Weekly)					
	100 mg N = 4	200 mg N = 3	400 mg N = 3	600 mg N = 3	800 mg N = 7	1000 mg N = 9
All Adverse Events	4 (100%)	3 (100%)	3 (100%)	3 (100%)	7 (100%)	9 (100%)
AEs ≥ Grade 3	3 (75.0%)	1 (33.3%)	2 (66.7%)	1 (33.3%)	3 (42.9%)	6 (66.7%)
IMC-11F8-Related AEs	1 (25.0%)	3 (100%)	3 (100%)	3 (100%)	7 (100%)	6 (66.7%)
Related AEs ≥ Grade 3	0	0	2 (66.7%)	0	1 (14.3%)	0
	Arm B (IMC-11F8 Every Other Week)					
	100 mg N = 3	200 mg N = 4	400 mg N = 3	600 mg N = 5	800 mg N = 7	1000 mg N = 9
All Adverse Events	3 (100%)	4 (100%)	3 (100%)	5 (100%)	7 (100%)	9 (100%)
AEs ≥ Grade 3	2 (66.6%)	3 (75.0%)	1 (33.3%)	3 (60.0%)	2 (28.6%)	5 (55.5%)
IMC-11F8-Related AEs	0	4 (100%)	3 (100%)	5 (100%)	7 (100%)	9 (100%)
Related AEs ≥ Grade 3	0	0	1 (33.3%)	2 (40.0%)	1 (14.3%)	3 (33.3%)

Source: IMCL CP11-0401 CSR

Dose-Limiting Toxicity: Two patients receiving IMC-11F8 at a dose of 1000 mg every 2 weeks (Arm B) experienced dose-limiting toxicities (one patient with Grade 3 headache and a second patient with Grade 3 headache, nausea, and vomiting) following the first infusion of IMC-11F8. The maximum tolerated dose for every other week administration of IMC-11F8 was therefore set at 800 mg. No MTD was reached for weekly administration in this study.

Sixteen patients in each arm experienced an AE of Grade 3-5; common Grade 3-5 AEs in Arm A included fatigue, ascites, back pain, and pleural effusion (three cases each), while the most common Grade 3-5 AE in Arm B was fatigue (four cases). Grade 4 AEs was reported in 4 patients: hypomagnesemia, cerebrovascular accident, ileus, fatigue, and 3 Grade 5 AEs (euthanasia, hepatic failure, gastrointestinal perforation).

Skin and subcutaneous tissue disorders (MedDRA SOC) was reported in 79% of the patients. Grade 1 or 2 acne, dry skin, dermatitis Acneiforme were the most common AEs reported in all dose levels, in both treatment arms. Grade 3 acne was reported in only 1 patients. Dose related hypomagnesemia was reported in 19/29 patients in arm A and 22/31 In arm B with the highest incidence observed at 800mg and 1000 mg dose levels, Grade 3-4 hypomagnesemia was reported in 2 patients in this trial. Other related adverse events, all grades, included nausea (62%) , vomiting (59%) , pyrexia (31%), and headache (61%0.
The most common AEs were nausea (62.1%), vomiting (58.6%), acne (55.2%), fatigue (51.7%), and dry skin (41.4%) in Arm A and headache (61.3%), pyrexia (58.1%), nausea (38.7%), dermatitis acneiform (35.5%), and acne (32.3%) in Arm B.

Pharmacokinetics

Refer to analysis of the PK and PopPK data by Clinical Pharmacology Review team

Noncompartmental analysis of IMC-11F8 concentration-time data following single doses ranging from 100-1000 mg revealed greater-than-dose-proportional increases in exposure, consistent with saturable clearance mechanism(s). Over the 10-fold dose range, geometric mean clearance decreased approximately 80%, while geometric mean Cmax and AUC(0-α) increased approximately 20 and 40 fold, respectively. Following single-dose administration, geometric mean half-life ranged from nearly 3 days to more than 6 days. As with a single dose, measures of exposure (including Cmax, Cmin and AUC□) following multiple doses showed greater-than dose- proportional increases over the 10-fold range, with CLss (Arm A) showing dose-dependent decreases. Multiple dose CLss was slower than single dose clearance. Following seven weekly doses, geometric mean accumulation ratio (RA,AUC) ranged from 1.6 to 3.2. At doses of 600 mg weekly or 800 mg every other week, geometric mean trough concentrations of IMC-11F8 were above 40 µg/mL (target associated with antitumor activity in preclinical models) throughout.

Anti-tumor Activity (as per Applicant)

Twenty-three of 29 patients and 24 or 31 patients in Arms A and B were evaluable for response, respectively. Partial objective response was reported in two patients (melanoma and colorectal cancer), with response durations of 15.6 and 5.6 months, respectively.

Reviewer's Comment

In this first-in-human study, IMC-11F8 related AE were in general consistent with what has been observed with other anti-EGFR monoclonal antibodies. The dose level of 800 mg was defined as the maximum tolerated dose and the recommended dose for both schedules based on the safety findings. IMC-11F8 showed preliminary activity in patients with advanced solid tumors who had progressed after standard therapy.

9.4.2. Study I4X-IE-JFCA (IMCL CP11-0907)

Study Title

A Phase 1 Study of IMC-11F8 in Patients with Advanced Solid Tumors

Objectives

The primary objective was to establish the safety and PK profile necitumumab, administered either: (1) in a 3-week cycle; or (2) in a 2-week cycle to Japanese patients with advanced solid tumors that have not responded to standard therapy or for which no standard therapy is available.

Secondary objective of this study was to screen for the development of circulating antibodies against necitumumab (immunogenicity).

Exploratory analyses included preliminary assessment of the antitumor activity of necitumumab as monotherapy in the treatment of advanced solid tumors.

Study Population and Design

Adult Japanese patients (age ≥ 20 years) with advanced primary or recurrent solid tumors not responsive to standard therapy or for which no standard therapy was available, with measurable and/or evaluable disease, an ECOG performance status of 0-1, and adequate hematologic, hepatic, and renal function. were enrolled into each of 3 dose cohorts, with doses of 600 mg necitumumab on Days 1 and 8 of a 3- week cycle, 800 mg necitumumab every 2 weeks, and 800 mg necitumumab on Days 1 and 8 of a 3-week cycle, respectively.

Summary of Results

From January 13, 2010 to February 28, 2012 a total of 15 patients were enrolled at the National Cancer Center Hospital, Tokyo, Japan.

Patient Demographics and Baseline Characteristics

The Safety population included 7 males and 8 females, at a median age of 61.2 years. The lung (n = 4) and esophagus (n = 4) were the most common sites of primary tumor; the most common metastatic sites were the lung (n = 10), the lymph nodes (n = 8), and the liver (n = 5). All 15 patients received prior chemotherapy; no patients had received prior hormonal, immunotherapeutic, or biologic therapy. All patients have discontinued treatment, with all discontinuations due to progression of disease.

Three patients was enrolled in Cohort 1 (600 mg D1, 8 every 3 weeks), 6 patients each were enrolled in Cohort 2 (800 mg D1, 8 every 2 weeks and Cohort 3 (800 mg D1, 8 every 3 weeks). Fourteen of 15 patients completed Cycle 1, and 9 of 15 patients received at least 1 dose in Cycle 2 or beyond

Safety

Dose-limiting toxicities were not observed in any cohort, and the MTD was not reached at the maximum planned doses (800 mg every 2 weeks, 800 mg on Days 1 and 8 every 3 weeks).

The most common AEs related to necitumumab were headache (66.7%), dry skin (66.7%), pruritus (53.3%), and rash (53.3%), nearly all of severity Grade 1-2. Grade 3 skin reactions consisting of rash and dry skin were seen in1 (7%) of 15 patients after administration of multiple cycles. Infusion-related reaction was observed in 3 patients (grade 1 hot flush) and 2 patients experienced grade 1 hypomagnesemia. Conjunctivitis and thromboembolic events were not reported in this study. One patient in Cohort 3 experienced Grade 3 abnormal liver function during the first cycle, but this event resolved while treatment was continued and was not considered related to study therapy.

No deaths were reported on study or within 60 days of the last dose of study drug.

Anti-Tumor Activity (as per Applicant)

No objective responses were observed in this study. Stable disease was reported in 67% of the patients (95% CI = 38.4% - 88.2%) in all cohorts.

Pharmacokinetics

Refer to analysis of the PK and PopPK data by Clinical Pharmacology Review team

The PK of necitumumab were evaluated following single and multiple doses administered every 2 weeks (800 mg) or on Days 1 and 8 every 3 weeks (600 or 800 mg). Mean exposure parameters were higher with the 800-mg regimens. Maximum concentrations were most often observed 1 to 2 hours after the end of infusion. Though sampling data were limited, individual values of t1/2 were estimated with a range from approximately 1 to 2 weeks. When able to be estimated, CL was less than 15 mL/L, and Vd was approximately 3 liters. All 3 regimens generated through concentrations above 40µg/mL (target concentration associated with antitumor activity in preclinical models) throughout the study.

Reviewer's Comment

Based on the PK and limited safety data from this study, it appears that necitumumab can be safely administered to Japanese patients at the same dose regimen recommended for Western patients.

9.4.3. Study I4X-IE-JFCD (IMCL CP11-0602)

Study Title

Open Label, Multicenter, Phase II study Evaluating the Efficacy and Safety of IMC-11F8 in Combination with 5-FU/FA and Oxaliplatin (mGOLFOX-6) in Patients with Treatment –Naïve Locally Advanced or Metastatic Colorectal Cancer.

Objectives

The primary objective was to evaluate the antitumor activity of necitumumab administered in combination with mFOLFOX-6 in treatment0-vaive, locally advanced or metastatic colorectal cancer patients

Secondary objectives were to evaluate the OS, PFS, the safety profile ,the duration of response, the PK profile of necitumumab and immunogenicity of necitumumab and the association between response to treatment and the presence or absence of KRAS mutations in tumor tissue.

Study Population and Design

Study I4X-IE-JFCD was an open-label, single-arm, multicenter study in which eligible patients received necitumumab in combination with mFOLFOX-6 chemotherapy every 2 weeks (one cycle).

On day of each cycle, patients received:

- Necitumumab 800 mg
- Oxaliplatin (85 mg/m^2)
- Folinic acid (400 mg/m^2)
- 5-FU (400 mg/m^2 as a bolus injection), and
- A 46-hour continuous IV infusion of 5-FU at 2400 mg/m^2, beginning immediately following the bolus infusion.

Treatment were to be administration every 2 weeks until disease progression or unacceptable toxicity.

Eligibility criteria included the following:

Key Inclusion Criteria

- Histologically confirmed, EGFR-detectable or EGFR-undetectable colorectal cancer.
- Locally advanced unresectable or metastatic adenocarcinoma of the colon or rectum.
- At least one unidimensionally measurable target lesion.
- Age ≥ 18 years, life expectancy ≥ 6 months, and ECOG PS ≤ 2.
- Adequate hematologic, hepatic, and renal function.
- Adequate recovery from toxicities/effects of prior therapy

Key exclusion criteria

- Prior systemic chemotherapy for locally advanced unresectable or mCRC. Prior adjuvant chemotherapy was allowed if disease progression was documented > 6 months after the end of the last cycle of adjuvant chemotherapy or ≥ 12 months for oxaliplatin-containing regimens.
- Prior radiotherapy to > 25% of bone marrow.
- Documented and/or symptomatic brain metastases.
- Previous therapy with monoclonal antibodies, or any agent targeting the EGFR.
- Current use of chronic non-topical corticosteroid treatment for > 6 months at doses > 10 mg/day of prednisolone or equivalent before study entry, which in the opinion of the investigator could compromise the patient or the study.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Acute or subacute intestinal occlusion.
- History of other malignancies, with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix.
- Pregnancy or breastfeeding.
- Prior autologous or allogeneic organ or tissue transplantation.
- Interstitial pneumonia or interstitial fibrosis of the lung.

Patients were assessed for safety throughout the study and for at least 30 days after discontinuation of study therapy. Following treatment discontinuation and progression of disease, survival status follow-up was to continue as long as the patient remained alive. Tumor assessment was to be evaluated at baseline, every 8 weeks while on therapy, and at least every 3 months after discontinuation of treatment, until progression.

Summary of Results

From August 2007 to June 2008, the study enrolled a total of 44 patients in 5 investigation sites in Belgium and Spain.

Patient Demographics and Baseline Characteristics

The ITT population was 57% male, 96% white, median age 64 years (range 33 to 81 years). All patients had a diagnosis of adenocarcinoma, with 66% originating from the colon and 34% from the rectum and 96% had metastatic disease, 93% had a baseline ECOG PS of 0 or 1.

Efficacy (as reported by the Applicant)

The primary efficacy endpoint of the study was ORR. All 44 patients were evaluable for response. The ORR was 64% (95% Ci 47,8, 77,6%), with 4 patients (9%) achieving a CR and 24 patients achieving a PR (54.5%). The median duration of response for all responders was 10 months (95% CI 7, 16 months)

The median OS was 22.5 months (95% CI 11, 30 months). The reported one- and two-year overall survival rates were 63.6% and 42.9%, respectively. The median PFS was 10 months (95% CI 7, 12 months).

Safety

All 44 patients received at least one dose of study therapy. The median number of infusions of necitumumab was 9.5 (range 1 – 47) and 75% of the patietns received ≥ 80% of the intended dose and median number of infusions for Oxaliplatin, FA and 5-FU were 10 to 11 and 75% of the patients received the intended dose.

A total of 38 patients (86.4%) experienced at least one TEAE of Grade ≥ 3, regardless of relationship to study therapy. The most common Grade ≥ 3 TEAE were neutropenia (n = 13; 29.5%), asthenia (n = 12; 27.3%), and rash (n = 9; 20.5%);

There were seven patients (15.9%) with Grade 4 events: four patients with Grade 4 neutropenia and one patient each with febrile neutropenia, sepsis, and hypocalcemia. Four patients (9.1%) experienced TEAE of Grade 5: one patient each with intestinal obstruction, general health deterioration (secondary to PD), organizing pneumonia, and respiratory failure.

Deaths: 30 patients had died at the time of the study cut off, 25 (57%) due to disease progression, 3 due to an adverse event and 2 due to other cause (intestinal obstruction and acute respiratory failure secondary to pneumonia) . Three patients died within 30 days of last dose of study drug (two patients died due to respiratory failure and one patient with intestinal obstruction).

Table 53 summarize the incidence and severity of necitumumab related AEs observed in the I4X-IE-JFCD trial.

Table 52 I4X-IE-JFCD: Necitumumab Related Adverse Events

MedDRA PT	Necitumumab + mFOLFOX6 N=44 (%)	
	All grades	Grade ≥ 3
Skin and Subcutaneous	41 (93)	13 (30)
Rash	31 (71)	9 (21)
Acneiform Rash	5 (1)	1 (2)
Conjunctivitis	11 (25)	1 (2)
Palmar-plantar erythrodysesthesia Sy	10 (23)	2 (5)
Hypersensitivity reaction	3 (7)	-
Hypomagnesaemia	5 (11)	-
Thromboembolic events	8 (20)	2 (5)
Cerebrovascular accident	1 (2)	1 (2)
Thrombosis in device	2 (5)	-
Deep vein thrombosis	2 (5)	-
Jugular Vein Thrombosis	2 (5)	-
Thrombosis	1 (2)	1 (2)

The most common necitumumab related AE was skin rash (71%) with 21% grade 3 AE. Conjunctivitis was reported in 25% (11/44), with one patient experiencing grade 3 event. Grade 1 or 2 hypomagnesemia was reported in 5 patients. Thromboembolic events occurred in 8/44 patients, with 6 venous TEs. There were no deaths directly attributed to study drug.

Reviewer's Comment

In this single-arm trial, the addition of necitumumab to mFOLFOX6 chemotherapy for patients with advanced colorectal cancer resulted in an ORR of 63% (95% CI 47.8, 77.6), with an acceptable safety profile.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEE HONG PAI SCHERF
08/08/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125547 **Applicant: Eli Lilly** **Stamp Date: December 2, 2014**

Drug Name: Necitumumab **NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				N/A
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				N/A
15.	Describe the scientific bridge (e.g., BA/BE studies)				N/A
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: I4X-IE-JFCE Study Title: Phase I Study of the Fully Human Anti-Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody IMC-11F8 in Patients With Solid Tumors Who Have Failed Standard Therapy Sample Size: 60 Arms: 2 Location in submission: 5.3.3.2	X			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and				

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 SQUIRE (I4X-IE-JFCC; IMCL CP11-0806), A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Squamous Non- Small Cell Lung Cancer (NSCLC) Indication: Combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		The applicant must submit a rationale
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			The applicant must submit as listing of the narratives in tabular format with patient ID and reason for the narrative.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		The applicant must submit a rationale
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			The applicant must submit as listing of the CRF in tabular format with patient ID and reason for the submission
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes ____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Concerning Patient Narratives and Case Report Forms, for each study, provide a Table of Significant and Notable Patients (ToSNP) consisting of a listing of all patients who experienced notable events with links to narratives and CRFs for those patients. Categorize the narratives and CRFs as:
    a. Death while on study or within 30 days after the date of last dose
    b. Discontinuation due to AE
    c. Suspected unexpected serious AEs
    d. Thromboembolic SAEs and SAEs of potential thromboembolic origin (that is, fatal and nonfatal cases where thromboembolism was not proven but could be suspected based on the data available [including cases of unexplained death]) from the Lilly safety database, defined by the Global Patient Safety physician as per case review applying medical judgment and using standardized MedDRA queries for embolic/thrombotic events as supportive tool

2. In reference to 14X-IE-JFCC/IMCL CP11-0806 (SQUIRE) study, 14X-IE-JFCC/IMCL CP11-0806 (SQUIRE) provide all information submitted to the Data Monitoring Committee (DMC) at the time of the study closure, and minutes of the DMC, as requested during the June 23, 2014 pre-BLA meeting.

3. In the pivotal study 14IX-IE-JFCC (CP11-0806), ESQUIRE, only 35 out of 1093 patients were from an U.S. investigational site. The Applicant must provide rationale for assuming the foreign data will be applicable to the U.S. population/practice of medicine.

If the above listed items have been previously submitted, identify the section and page where the information can be found.

Lee Pai-Scherf, MD — January 23, 2015
Reviewing Medical Officer — Date

Gideon Blumenthal, MD
Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEE HONG PAI SCHERF
01/26/2015

GIDEON M BLUMENTHAL
01/26/2015