CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	November 23, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
BLA #	STN BL 125547
Applicant Name	Eli Lilly and Company (Lilly)
Date of Submission	December 2, 2014
PDUFA Goal Date	December 2, 2015
Proprietary Name / Established (USAN) Name	Portrazza/ necitumumab
Dosage Forms / Strength	Injection for intravenous administration/ 800 mg/50 mL (16 mg/mL) in single use vials
Proposed Indication(s)	"PORTRAZZA in combination with gemcitabine and cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer."
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Mimi Biable
Medical Officer Review	Lee Pai-Scherf
Statistical Review	Lijun Zhang
Pharmacology Toxicology Review	Margaret E. Brower & Shawna L. Weis
Clinical Pharmacology Review	Safaa Burns
Quality Review	Chana Fuchs (Technical Lead); Ying-Xin Fan (Drug Substance); Yan Wang (, Drug Product); Ralph Bernstein (Assay Validation and Immunogenicity)
Microbiology Review	Lakshmi Rani Narasimhan; Candace Gomez-Broughton; Patricia Hughes
Carton/Container Labeling Review	Jabril Abdus-Samad
OPDP	Nazia Fatima
OSI	Lauren C. Iacono-Connors
OSE/DMEPA	Otto Townsend
OSE/DRISK	Mona Patel
Maternal Health Team	Tamara N. Johnson
QT IRT Review	Jiang Liu
CDTL Review	Gideon Blumenthal

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
QT IRT=QT Interdisciplinary Review Team
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

Portrazza (necitumumab, Eli Lilly) is a recombinant human IgG1 kappa monoclonal antibody that specifically binds to the ligand binding site of the human epidermal growth factor receptor (EGFR). Necitumumab blocks the binding of EGFR to its ligands, induces EGFR internalization and degradation, and mediates antibody-dependent cellular cytotoxicity (ADCC) in EGFR-expressing cells.

This BLA was supported by the results of a single, randomized, multi-center open-label trial [SQUIRE (I4X-IEJFCC)] conducted in patients receiving first-line chemotherapy for metastatic squamous NSCLC. Key eligibility criteria were histologically or cytologically confirmed squamous NSCLC, Stage IV, no prior chemotherapy other than adjuvant chemotherapy administered ≥ 1 year prior to randomization; no prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factors (VEGF), or VEFG receptor; and archived tumor tissue available for analysis of EGFR and KRAS mutation status (by PCR) and EGFR gene copy numbers (by FISH). Patients were randomized (1:1) to receive necitumumab, gemcitabine and cisplatin or gemcitabine and cisplatin. Stratification factors were ECOG performance status (0, 1 versus 2) and geographic region (North America, Europe, and Australia versus South America, South Africa, and India versus Eastern Asia). Background chemotherapy consisted of gemcitabine 1250 mg/m^2 administered as an intravenous infusion on days 1 and 8 and cisplatin 75 mg/m^2 as an intravenous infusion day 1 of each 21-day treatment cycle until disease progression, unacceptable toxicity, or a maximum of 6 cycles. For those randomized to the necitumumab arm, necitumumab was administered at a dose 800 mg by intravenous infusion on days 1 and 8 of each cycle, prior to infusion of gemcitabine and cisplatin, and as a single agent following completion of chemotherapy disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS); key secondary efficacy endpoints were investigator-assessed progression-free survival (PFS) and overall response rate (ORR).

The baseline demographics of the study population was median age of 62 years (range 32 to 86), 83% were male; 84% were Caucasian; 91% were smokers, ECOG performance status was 0 or 1 in 91% of patients, and 91% had metastatic disease in 2 or more sites. In the PORTRAZZA plus gemcitabine and cisplatin arm, 51% of patients continued necitumumab after completion or discontinuation of planned cisplatin/gemcitabine chemotherapy. Use of post-study systemic therapy was similar between arms.

The trial demonstrated a statistically significant improvement in overall survival [HR 0.84 (0.74, 0.96); p=0.01], with median survival of 11.5 months and 9.9 months in the necitumumab plus chemotherapy and chemotherapy arms, respectively. In addition, there was a statistically significant improvement in PFS [HR 0.85 (0.74, 0.98); p=0.02], with median

PFS of 5.7 and 5.5 months in the necitumumab plus chemotherapy and chemotherapy arms, respectively. There was no significant difference in ORR between arms (31% vs. 29%).

The major issues considered during review of this application was whether the risk:benefit analysis was favorable and how to weigh the results of the INSPIRE (I4X-IE-JFBB) trial, a randomized, open-label, multicenter trial conducted in patients with non-squamous, NSCLC, which was terminated prematurely due to a numerically higher rate of fatal thromboembolic events and of serious thromboembolic adverse events. The INSPIRE trial demonstrated no evidence of an effect on overall survival, progression-free survival, or overall response rate for patients randomized to necitumumab, pemetrexed, and cisplatin as compared to those randomized to pemetrexed and cisplatin. The BLA was referred to the Oncologic Drugs Advisory Committee for advice on these issues.

2. Background

Indication Population and Available Therapy

The proposed indication for necitumumab is

> *PORTRAZZA in combination with gemcitabine and cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.*

The American Cancer Society estimated that there were 224,210 new cases of lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and an estimated 159,260 deaths due to lung cancer in the US in 2014.[1] The 5-year relative survival rate between 2010 and 2014 was 4.5% for patients with metastatic, non-small cell lung cancer.[2]

The current standard first-line treatment for patients with advanced, metastatic squamous NSCLC is cisplatin- or carboplatin-based doublet chemotherapy. In 2002, the published results of a 4-arm, open-label, randomized (1:1:1:1) trial directly compared the safety and efficacy of platinum-double regiments. The "control" arm was the paclitaxel/carboplatin arm, which was the most commonly used platinum-doublet in the US at the time of this trial and the regimen for which paclitaxel is approved for the treatment of NSCLC. The trial demonstrated similar outcomes for the following regimens:

- Cisplatin plus paclitaxel (control), consisting of paclitaxel, 135 mg/m^2 over 24-hr period on day 1 and cisplatin, 75 mg/m^2 on day 2 of each 21-day cycle
- Cisplatin plus gemcitabine, consisting of gemcitabine, 1000 mg/m^2 on days 1, 8, and 15 and cisplatin, 100 mg/m^2 on day 1 of each 28-day cycle
- Cisplatin plus docetaxel, consisting of docetaxel, 75 mg/m^2 on day 1 and cisplatin, 75 mg/m^2 on day 1 of each 21-day cycle

[1] American Cancer Society: Cancer Facts and Figures 2014. Atlanta, Ga: American Cancer Society, 2014.
[2] Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

- Carboplatin plus paclitaxel consisting of paclitaxel, 225 mg/m^2 over 3-hr period on day 1 and carboplatin, AUC 6.0 mg/mL/min on day 1 of each 21-day cycle

The authors concluded that all the combinations have similar efficacy.[3] However, because of its more favorable safety profile, the Eastern Collaborative Oncology Group (ECOG) selected carboplatin/paclitaxel as its reference regimen for future studies.

The following drugs are approved for the treatment of NSCLC

Paclitaxel is approved, 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.

Gemcitabine is indicated, in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced Stage IIIA or IIIB, or metastatic (Stage IV) NSCLC.

Vinorelbine is indicated, in combination with cisplatin or as single agent, for the first-line treatment of ambulatory patients with unresectable, advanced NSCLC.

Docetaxel is indicated in combination with cisplatin, unresectable, locally advanced or metastatic untreated NSCLC.

Nab-paclitaxel is indicated 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.

Pre-submission Regulatory History

On November 5, 2008, a preIND meeting was held to present the results of Phase 1 and 2 studies of IMC-11F8 (necitumumab) conducted in Europe and discuss the proposed development program (b) (4)

On November 17, 2008, ImClone LLC submitted IND 102512 for the investigation of IMC-11F8 (necitumumab) for the treatment of non-squamous, non-small cell lung cancer (NSCLC) under Protocol IMCL CP11-0805, titled "A Randomized, Multicenter, Open-Label Phase 3 Study of Pemetrexed-Cisplatin Chemotherapy Plus IMC-11F8 Versus Pemetrexed-Cisplatin Chemotherapy Alone in Patients with Nonsquamous Stage IIIb or IV

[3] Schiller JH, Harrington D, Belani CP, et al: Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 346:92-98, 2002.

Non-Small Cell Lung Cancer (NSCLC). On December 19, 2008, FDA issued a communication indicated that the proposed study may proceed.

On September 21, 2009, ImClone submitted an IND amendment containing a new clinical protocol, Protocol IMCL CP11-0806, entitled "A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus IMC-11F8 Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients with Squamous Stage IIIb or IV Non-Small Cell Lung Cancer (NSCLC)"

On February 11, 2011, FDA requested a tabular listing by protocol and within protocol, by study arm, for Study CP11-0805 and Study CP11-0806: total number of patients enrolled, deaths, deaths within 30 days of receiving study drug, serious adverse events (SAEs); thromboembolic SAEs; thromboembolic SAEs occurring within the first 2 cycles of therapy; thromboembolic events by severity grade.

On July 1, 2011, ImClone submitted the protocol for assessment of pharmacokinetic drug-drug interactions among necitumumab, gemcitabine and cisplatin.

On July 15, 2011, ImClone submitted a proposed study design for a QT/QTc protocol, CP11-1114, "A Study to Determine Whether Necitumumab (IMC-11 F8) Monotherapy Affects the Corrected QT (QTc) Interval in Patients with Advanced Solid Tumors." On October 14, 2011, FDA provided comments on the proposed protocol.

On November 29, 2012, ImClone submitted preliminary analytical results of the comparability protocol to support manufacturing changes (drug substance (DS) manufactured using (b) (4) and DS manufactured using (b) (4)). On February 28, 2013, FDA issued a letter requesting additional information to be included in the final study report for this comparability assessment.

On October 10, 2013, FDA issued a letter designating as a Fast Track development program, the investigation of necitumumab, in combination with gemcitabine-cisplatin chemotherapy, to improve survival, as compared to gemcitabine-cisplatin chemotherapy alone, in the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.

On January 31, 2014, FDA provided written responses to a Type C meeting request. In this communication, FDA stated under the PDUFA V Program, applicants were strongly encouraged to discuss the planned content of their application with the appropriate FDA review division at a pre-BLA meeting. FDA stated that the efficacy datasets for the INSPIRE study were required to allow a complete assessment of the efficacy of necitumumab and to allow inclusion of these data in product labeling, if appropriate. In addition, Lilly was asked to provide the specific contents of each database at the interdisciplinary pre-BLA meeting.

On March 31, 2014, FDA provided comments via email communication that, based on the summary results submitted to the IND, additional PK data would not be required to support comparability of DS manufactured by (b) (4)

On June 23, 2014, a pre-BLA meeting was held; key advice and agreements reached were:

- The results of the SQUIRE study appeared acceptable to support the filing of the BLA. FDA expressed concern regarding the modest treatment effect on OS observed in SQUIRE [HR of 0.84 (95% CI: 0.74, 0.96), p =0.01], with a difference in median OS of 1.6 months (11.5 months vs. 9.9 months). The effect on PFS, a secondary endpoint, was also modest [HR 0.85 (95% CI 0.74, 0.98), p= 0.02] with a difference in median PFS of 2 months (median 5.7 vs. 5.5 months), and the effect on ORR, although numerically higher in the treatment arm, was neither statistically significant nor clinically meaningful (31.2 % vs. 28.8%; p= 0.39).
- Given the modest clinical effects demonstrated in this single trial intended to support this NME, the premature closing of the INSPIRE trial due to safety concerns, and the uncertain risk/benefit assessment, please be advised that FDA anticipates discussion of the approvability of necitumumab at an Oncologic Drugs Advisory Committee (ODAC) meeting.
- Lilly stated that submission of the clinical module might be delayed in order to include the results of further exploratory analyses regarding the role of EGFR protein expression. If these exploratory analyses looked promising, further discussions with DAKO would occur. FDA also advised further discussion (b) (4)
- The literature based reproductive toxicity assessment provided by Lilly was insufficient to adequately describe the potential for necitumumab to cause reproductive toxicity, but if supported by the nonclinical data used to support the submission of the BLA for cetuximab and data demonstrating that the pharmacokinetic, pharmacodynamic and toxicologic profiles of necitumumab were similar to cetuximab, an embryo-fetal development study may not be required.
- The clinical pharmacology data package would support filing.
- Lilly agreed that the extent and location in the BLA of CMC data for the (b) (4) manufacturing site would be determined based on whether this manufacturing site will be approved in the BLA or a supplement. The BLA should include a more robust data package to support elimination of the Biacore binding potency assay from release and stability specifications. FDA agreed that an ADCC assay is not required as an additional potency assay if sufficient data are available from other assays that will ensure that the quality attributes associated with ADCC functionality would be measured and controlled.
- Lilly agreed to provide SMQs or a safety analysis based on a defined composite concept (that includes multiple terms) for adverse drug reactions common to EGFR-directed antibodies and will provide a list of terms to be included in a defined composite concept when an SMQ is not available. Lilly will include an analysis of thromboembolic events as an SMQ in the BLA.

On August 26, 2014, FDA issued a letter of agreement with the schedule for rolling submission and review of the proposed BLA in three components to be submitted in October, November, and December 2014.

On November 19, 2014, Lilly received FDA's preliminary responses regarding questions posed with regard to the analyses investigating the role of EGFR protein expression in the study results from SQUIRE (CP11-0806, I4X-IE-JFCC). FDA stated that these analyses were exploratory, using a non-pre-specified definition and should be confirmed prospectively. FDA did not agree (b) (4)

BLA Regulatory History

On October 22, 2014, Lilly submitted the first component of BLA 125547, containing Module 4, associated sections of Module 2, administrative items in Module 1, and in support of the nonclinical reproductive toxicity assessment, authorization to a cross reference BLA 125084 in support of BLA 125547, and request for priority review designation.

On November 25, 2014, Lilly submitted the second component of BLA 125547, containing Module 5, associated sections of Module 2, and administrative items in Module 1.

On December 2, 2014, Lilly submitted the third (final) component of the BLA 12554 (b) (4) containing Module 3, associated sections of Module 2, related administrative items in Module 1, the final request for Proprietary Name Review, and the manufacturing schedule to allow scheduling of manufacturing inspections.

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months from the date of manufacture when stored at 2-8 °C. There are no outstanding CMC issues that preclude approval.

The following post-marketing commitments have been agreed-upon:

- Qualification of the endotoxin and sterility test methods was performed with two nonclinical demonstration/engineering batches of drug product. As a post-marketing commitment, perform the endotoxin and sterility test method qualification studies with two additional drug product batches and submit the information and summary data in the first annual report.
- Conduct and submit the results (including of the analytical and statistical plan used to evaluate specifications) of an evaluation of all necitumumab drug substance lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug

substance manufactured by [redacted] (b) (4) and any proposed changes to the specifications.

- Conduct and submit a re-evaluation of all necitumumab drug product lot release and stability data after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process, include corresponding data and the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications, based on the available drug substance and drug product data.
- To further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the nonclinical pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

The BLA contained the results of in vitro and in vivo pharmacology studies, nonclinical toxicology studies, human and cynomolgus tissue cross-reactivity studies, comparative in vitro pharmacology assessment of cetuximab and necitumumab, and literature assessment of the potential for reproductive toxicology.

Since necitumumab binds to the EGFR in human and cynomolgus monkey tissues with similar affinity and patterns of staining, nonclinical toxicity was assessed in 5- and 26-week repeat dose studies in cynomolgus monkeys. While no significant drug-related findings were identified in the 5-week study, evidence of dermatologic toxicity (pathologic findings of hyperplastic dermatitis and clinical findings of rash, dry skin, scaling, and erythema), degeneration of renal tubular epithelium, proteinuria, and hypomagnesemia were observed in the 26-week study. Thromboembolism observed in cynomolgus monkeys.

Reproductive toxicity studies with necitumumab were not conducted; the requirement to assess for reproductive toxicity was satisfactorily addressed by a literature-based assessment of the potential for inhibition of EGFR signaling to result in reproductive toxicity. The literature supported a conclusion that inhibitory effects on EGFR signaling would result in clinically significant developmental effects on placental, lung, cardiac, skin, and neural development. In addition, the NDA relied on findings observed with cetuximab, which binds to a similar epitope in the EGFR III domain, which resulted in embryolethality in animals.

As discussed prior to submission of the BLA, no studies were conducted to assess the potential of necitumumab for genotoxicity, which are not required for monoclonal antibodies. Based on the intended patient population (patients with metastatic NSCLC with an expected 5-year survival of less than 5%), carcinogenicity and fertility were not required for approval and none were conducted by the Applicant.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology and pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The application contained pharmacokinetic data from 5 clinical trials enrolling 807 patients, which were used to conduct population pharmacokinetics (popPK) analyses and exposure-response analyses for safety and efficacy. Based on popPK analyses, body weight was a statistically significant but clinically unimportant covariate and there were no significant effects of gender, age, or race on the pharmacokinetics of necitumumab. In addition, there was no significant impact of renal or hepatic impairment or of manufacturing process (b) (4) on the pharmacokinetics of necitumumab. Based on popPK analyses, there appeared to be an increased risk of rash and of hypomagnesemia in patients who received necitumumab with gemcitabine/cisplatin as compared to necitumumab alone, independent of necitumumab concentration.

There was a trend suggesting an E-R relationship for efficacy (increasing exposure and longer survival) and safety (increasing exposure and hypomagnesemia) but not for severe rash of severe arterial and venous thromboembolic events in the SQUIRE study.

Gemcitabine and cisplatin administered had no effects on necitumumab exposure; however, it was noted that gemcitabine exposure was higher in the necitumumab arm. While the clinical pharmacology review postulated that the increased gemcitabine exposure may have contributed to the higher incidence of adverse reactions in the necitumumab-containing arm, the toxicities observed were most often attributable to necitumumab (e.g., rash, hypomagnesemia) rather than gemcitabine (nausea/vomiting, cytopenia) thus this hypothesis is unlikely.

The incidence of treatment-emergent anti-necitumumab antibodies was, 8.7% (71/814) across patients with a baseline and post-treatment assessment for anti-drug antibodies (ADA) in 6 clinical trials. The development of ADA appeared to correlate with increased clearance and decreased exposures as compared to patients without ADA. The effect of ADA on efficacy could not be assessed due to the limited number of patients with treatment-emergent ADA. As expected, there was no correlation between development of anti-necitumumab antibodies and the risk of infusion reactions; infusion reactions occurred with the first or second exposure, prior to the expected development of anti-drug antibodies, and are attributable to cytokine release rather than a hypersensitivity reaction.

6. Clinical Microbiology

Not applicable. The assessment of quality microbiology and CMC sterility issues are summarized in Section 3 of this Summary Review.

7. Clinical/Statistical-Efficacy

The BLA is supported by a single, large, multicenter trial for efficacy, the SQUIRE trial. Bioresearch Monitoring Inspections were performed at three clinical sites, chosen based on enrollment of large numbers of patients, potential impact on primary efficacy results, and safety reports pertinent to assessment of the risk:benefit. In addition, the BLA applicant, Eli Lilly and Company, was also inspected. Based on these inspections, the data submitted in BLA 125547 appear reliable based on available information.

Protocol Design
Protocol I4X-IE-JFCC/IMCL CP11-0806 (SQUIRE), titled "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)."

The primary endpoint was overall survival; secondary efficacy endpoints were PFS as determined by investigator assessment, objective response rate as determined by investigator assessment per RECIST, time to treatment failure (TTF); and health-related quality of life assessment as captured by the EQ-5D instrument.

Key eligibility criteria were adults with histologically or cytologically confirmed squamous NSCLC, Stage IV (AJCC 7th Edition), ECOG performance status 0-2, no prior chemotherapy other than adjuvant chemotherapy administered ≥ 1 year prior to randomization; no prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factors (VEGF), or VEFG receptor; and archived tumor tissue available for analysis of EGFR and KRAS mutation status (by PCR) and EGFR gene copy numbers (by FISH).

Patients were randomized (1:1) to the following two treatment regimens. Randomization was stratified by ECOG performance status (0, 1 versus 2) and geographic region (North America, Europe, and Australia versus South America, South Africa, and India versus Eastern Asia).

- Necitumumab 800 mg intravenously on days 1 and 8, gemcitabine 1250 mg intravenously on days 1 and 8, and cisplatin 75 mg/m^2 intravenously on day 1 of each 21-day cycle.
- Gemcitabine 1250 mg intravenously on days 1 and 8 and cisplatin 75 mg/m^2 intravenously on day 1 of each 21-day cycle.

Chemotherapy was administered until disease progression, unacceptable toxicity, or a maximum of 6 cycles; necitumumab was administered following completion of chemotherapy until disease progression or unacceptable toxicity.

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.

Secondary endpoints included PFS, ORR, TTF, and Health Status Assessment. 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 the 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. Compliance rates for each patient reported outcome instrument were to be calculated for each of these planned periods of assessment. Compliance for each of these assessment periods was defined as the number of patients assessed at that period, divided by the number of patients eligible to provide assessment at that period. A patient was eligible to provide an assessment if the patient was known to be alive without disease progression for that period.

Descriptive analyses were to be performed for patients' data as collected by EQ-5D. Best and worst change-from-baseline mean scores for index score. LCSS, and Visual Analogue Scale (VAS) were to be compared between treatment arms.

Results

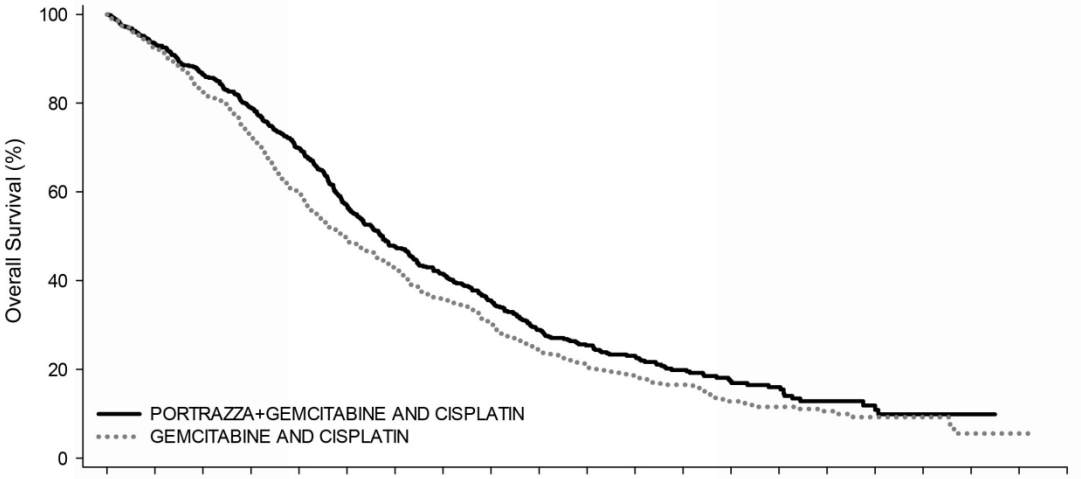
A total of 1093 patients were enrolled and randomized to necitumumab, cisplatin, and gemcitabine (n=545) or cisplatin and gemcitabine (n=548) between January 2010 and February 2012, across 184 clinical study sites internationally. The majority of the patients (87%) were enrolled in North America, Europe and Australia, however only 36 patients (3%) were enrolled at clinical sites in the U.S. Additionally, 6% of the patients were enrolled in South America, South Africa and India and 8% enrolled at clinical sites in Eastern Asia.

Across the study population, the median age was 62 years (range 32 to 86), 83% were male; 84% were Caucasian; and 91% were smokers. Baseline ECOG performance status was 0 or 1 for 91%, and 2 for 9% of patients; 91% had metastatic disease in 2 or more sites. In the PORTRAZZA plus gemcitabine and cisplatin arm, 51% of patients continued PORTRAZZA after completion or discontinuation of chemotherapy. Use of post-study systemic therapy was 47% in the PORTRAZZA plus gemcitabine and cisplatin arm, and 45% in the gemcitabine and cisplatin arm.

Efficacy Results for the SQUIRE Trial		
Efficacy Parameter	**Necitumumab plus Gemcitabine–Cisplatin (n=545)**	**Gemcitabine–Cisplatin (N=548)**
Overall Survival		
Number of deaths	418 (77%)	442 (81%)
Median in months (95% CI)	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Stratified[1] HR (95% CI)	0.84 (0.74, 0.96)	
p-value (stratified log-rank)[2]	0.01	
Progression-free survival		
Number of PFS events	431 (79%)	417 (76%)
Median in months (95% CI)	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Stratified HR (95% CI)	0.85 (0.74, 0.98)	
p-value (stratified log-rank)	0.02	
Overall Response Rate	31%	29%
95 % CI	(27, 35)	(25, 33)
p-value	0.40	

[1] Hazard ratio using Cox proportional hazards model stratified by ECOG PS and region information as captured in the IVRS
[2] stratified by ECOG PS and region information as captured in IVRS.

Kaplan-Meier Curves for Overall Survival in the SQUIRE Trial



Number at Risk

PORTRAZZA+GEMCITABINE AND CISPLATIN	545	496	450	407	358	291	243	208	176	130	101	84	61	42	32	20	11	3	3	0	0
GEMCITABINE AND CISPLATIN	548	494	435	379	308	254	219	182	153	115	80	63	49	33	27	19	9	7	3	1	0

Sensitivity analyses were conducted in the following populations: unstratified analysis in the ITT population; stratified analysis using data captured on CRF in the ITT population; stratified by IVRS data in the per-protocol population (n=1072); unstratified analysis in the per-protocol population; and pre-specified timing of 844 events (cutoff 20 May 2013).

INSPIRE trial

The INSPIRE (I4X-IE-JFBB) trial is a randomized, open-label, multicenter, trial conducted in patients with metastatic, squamous NSCLC who had not received chemotherapy for metastatic disease.

The primary efficacy endpoint was overall survival; secondary endpoints were progression-free survival, overall response rate, time-to-treatment failure, safety, pharmacokinetics, and safety.

Patients were randomized (1:1) to the following treatment arms. Randomization was stratified by smoking status (non-smokers versus light smokers versus smokers), ECOG performance status (0 - 1 versus 2), histology (adenocarcinoma/large cell versus others), and geographic region.

- Necitumumab 800 mg intravenously on days 1 and 8, pemetrexed 500 mg/m^2 intravenously on day 1, and cisplatin 75 mg/m^2 intravenously on day 1 of each 21-day cycle.

- Pemetrexed 500 mg/m^2 intravenously on day 1, and cisplatin 75 mg/m^2 intravenously on day 1 of each 21-day cycle.

Chemotherapy was administered until disease progression, unacceptable toxicity, or a maximum of 6 cycles; necitumumab was administered following completion of chemotherapy until disease progression or unacceptable toxicity.

Statistical analysis plan: the planned sample size of 947 patients was based on the following assumptions: 723 deaths would be required to detect a HR of 0.80 with a two-sided alpha of 0.05 and a power of 85%.

Results

The INSPIRE trial was closed prematurely at the recommendation of the data monitoring committee (DMC) due to an imbalance on the number of deaths attributed to potential thromboembolic events (TE) and fatal TE observed in the necitumumab-containing arm as compared to chemotherapy alone, following enrollment of 633 patients who were randomized to necitumumab plus chemotherapy (n=315) or chemotherapy alone (n=318). The analysis of overall survival was conducted at 474 deaths (of the planned 723 deaths), resulting in 68% power to detect a hazard ratio for survival of 0.80 as a two-sided alpha of 0.05.

Across the study population, the median age was 61 years, 67 % were male, 93% were Caucasian and 94% had ECOG PS 0 or 1. More than 75% were smokers and 89% had adenocarcinoma histology.

The efficacy results are summarized in the table below and demonstrate no statistically significant differences in overall survival, progression-free survival, and ORR between treatment arms.

Efficacy Results for the INSPIRE Trial		
Efficacy Parameter	**Pemetrexed –Cisplatin Plus Necitumumab (n=315)**	**Pemetrexed –Cisplatin (N=318)**
Overall Survival		
Number of deaths	236 (75%)	246 (77%)
Median in months (95% CI)	11.3 (9.5, 13.4)	11.5 (10.1, 13.1)
Stratified HR (95% CI)	1.01 (0.84, 1.21)	
p-value (stratified log-rank)	0.96	
Progression-free survival		
Number of PFS events	231 (73%)	239 (75%)
Median in months (95% CI)	5.6 (5.1, 6.0)	5.6 (4.8, 5.7)
Stratified HR (95% CI)	0.96 (0.80, 1.16)	
p-value (stratified log-rank)	0.7	
Overall Response Rate	31% (98/315)	32% (102/318)
95 % CI	(26%, 36%)	(27%, 37%)
p-value	0.8	

[a] Stratified log-rank test as well as the hazard ratio from a stratified proportional hazard model are stratified by the randomization strata: smoking history (never smoker vs. light ex-smoker vs. smoker), ECOG PS (0-1 vs. 2), disease histology (adeno/large cell carcinoma vs. other), and geographic region (North America, Europe, and Australia/New Zealand vs. Central/South America, South Africa, and India).
[b] Derived from two-sided test Cochran-Mantel-Haenszel test adjusting for the randomization strata.

8. Safety

Size of the database
The safety of necitumumab was evaluated in two randomized, open-label trials, SQUIRE and INSPIRE. The SQUIRE trial randomized patients with previously untreated, metastatic, squamous, NSCLC to necitumumab, gemcitabine, and cisplatin or to gemcitabine and cisplatin. The median duration of exposure to necitumumab in 538 patients was 4.6 months (range 0.5 months to 34 months), including 182 patients exposed for at least 6 months; 41 patients exposed for greater than 1 year. Since the adverse reaction profile for necitumumab in the INSPIRE trial are similar to those identified in the SQUIRE trial, product labeling provides the results only of the SQUIRE trial.

The most common adverse reactions (≥15%) of necitumumab were rash (44%), vomiting (29%), diarrhea (16%), and dermatitis acneiform (15%). The most common severe (Grade 3 or higher) adverse reactions of necitumumab were venous thromboembolic events (5%; including pulmonary embolism), rash (4%), and vomiting (3%). Twelve percent of patients discontinued

treatment due to an adverse reaction; the most common adverse reaction leading to discontinuation of necitumumab was skin rash.

Major safety concerns related to labeling
Major safety concerns, which are included in the Boxed Warnings or the Warnings and Precautions sections of the USPI, are briefly summarized below:

- *Cardiopulmonary arrest or sudden death* was higher (3% vs. 0.6%) in patients who received necitumumab/gemcitabine/cisplatin as compared to those receiving gemcitabine/ cisplatin; 12 of the 15 (80%) deaths due to cardiopulmonary arrest or sudden death occurred within 30 days of the last dose of necitumumab. Since patients with significant coronary artery disease, myocardial infarction within 6 months, uncontrolled hypertension, and uncontrolled congestive heart failure were not eligible for enrollment in the SQUIRE trial, the risks of cardiopulmonary arrest or sudden death have not been characterized in patients with these co-morbid conditions.
- *Hypomagnesemia* of any severity [83% (461/538) vs. 70% (457/541)] and of Grade 3-4 severity [20% vs. 7%] for those receiving necitumumab plus gemcitabine/cisplatin compared with gemcitabine/cisplatin alone in the subgroup patients with available laboratory results. The median time to development of hypomagnesemia was 6 weeks after initiation of necitumumab-containing therapy.
- *Venous and arterial thromboembolic events (VTE and ATE):* The overall incidence (9% vs. 5 %) of VTE, which included deep venous thrombosis and pulmonary emboli, and of ≥ Grade 3 VTE (5% versus 3%), was higher in the necitumumab plus gemcitabine/ cisplatin arm compared with gemcitabine/cisplatin alone arm, however the incidence of fatal VTEs was similar between arms (0.2% versus 0.2%). The overall incidence (5% vs. 4%) of ATEs and of ≥ Grade 3 ATE (4% vs 2%) were higher in the necitumumab plus gemcitabine/ cisplatin arm compared with gemcitabine/cisplatin alone arm. The most common ATEs were cerebral stroke and ischemia (2%) and myocardial infarction (1%).
- *Dermatologic toxicity* characterized as rash, dermatitis acneiform, acne, dry skin, pruritus, generalized rash, skin fissures, maculo-papular rash and erythema, occurred in 79% of patients receiving necitumumab in the SQUIRE trial, with Grade 3-4 skin toxicity in 8% of patients. The time to onset was early (within the first 2 weeks of the first dose of necitumumab) with improvement or resolution while continuing therapy in most patients after approximately 4 months.
- *Infusion-related reactions* of any severity occurred in 1.5% of patients receiving necitumumab in the SQUIRE trial (which did not require premedication to prevent infusion reactions); most cases occurred during/after the first or second dose. The incidence of Grade 3 infusion reactions was 0.4% Grade 3 infusion-related reactions.

REMS
I concur with the recommendations of the clinical review team and DRISK reviewer that risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of necitumumab. The risks of necitumumab are qualitatively similar other anti-EGFR directed antibodies, thus special educational efforts are not required and product labeling provides adequate information regarding incidence of these risks, including a Boxed Warning, and provides adequate directions for dose adjustment and monitoring for early detection of the risks of electrolyte abnormalities to mitigate this risk.

PMRs and PMCs
There were no post-marketing requirements (PMRs) required under the FD&C Act 505(o) to further investigate serious risks of necitumumab. Several post-marketing commitments were identified by the Quality reviewers however none were identified by the non-clinical pharmacology/toxicity, clinical pharmacology, and clinical reviewers.

9. Advisory Committee Meeting

This BLA was referred to the Oncologic Drugs Advisory Committee (ODAC) for advice and presented on July 9, 2015. The ODAC was asked to discuss two questions. A summary of this discussion, from the minutes of the ODAC meeting, are reproduced below:

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

  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 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.

  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.

10. Pediatrics

The BLA contained a request for waiver from the requirements of the Pediatric Research Equity Act (PREA) for all age groups because this disease (NSCLC) predominately occurs in adults, and is included by FDA in its list of adult-related conditions that may qualify the drug product for disease-specific waivers (FDA 2005). This waiver request was reviewed by the Pediatric Review Committee (PeRC) on February 11, 2015. The PeRC agreed that the waiver be granted for the proposed indication (for the treatment of locally advanced or metastatic, squamous, non-small cell lung cancer).

On November 20, 2015, FDA granted orphan drug designation for necitumumab for the "treatment of squamous, non-small cell lung cancer (NSCLC)."

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proposed proprietary name of Portrazza were determined to be acceptable (i.e., low risk of medication errors, not promotional) based on the assessment of potential look-alike/sound-alike errors conducted by DMEPA and the assessment of OPDP and clinical review team.

- Physician labeling
  - Boxed Warning: As recommended by the ODAC, a Boxed Warning was incorporated in product labeling to highlight the serious risks of Cardiopulmonary Arrest and Hypomagnesemia.
  - Indications and Usage: the proposed indication was modified to indicate that necitumumab is indicated as part of "first-line chemotherapy" as there are no data on the efficacy of necitumumab when administered as second-line therapy (e.g., after nivolumab). In addition, a limitation of use was added based on the results of the INSPIRE trial, stating that necitumumab is not indicated for use in patients with non-squamous, NSCLC.
  - Dosage and Administrations: Modified to recommend infusion of 60 minutes to avoid sound-alike medication errors (b) (4) included direction to administered necitumumab "prior to gemcitabine and cisplatin infusion;" provided specific details regarding recommended premeditation to reduce the incidence/severity of infusion-related reactions; editorial changes to the dose modifications subsection.
  - Dosage Forms and Strengths: added dosage form (Injection)
  - Contraindications: Deleted (b) (4) in accordance with FDA Guidance on this section of product labeling.

- Warnings and Precautions: Revised to add new subsections to describe the incidence of the risks of on Cardiopulmonary arrest, Hypomagnesemia, Increased toxicity/mortality in patients with non-squamous NSCLC, and Embryofetal toxicity; removed (b) (4) provided detail on the incidence and time to development of dermatologic toxicity; and expanded description of timing and risks of severe infusion-related reactions.
- Adverse Reactions: Expanded description of the safety population enrolled in SQUIRE; expanded description of the incidence and type of AEs resulting in necitumumab dose modification; added tabular listing of treatment-emergent laboratory abnormalities to enhance legibility; removed (b) (4) ; described in Warnings and Precautions; and added information regarding the clinical sequelae, where known, of the development of anti-drug antibodies (No relationship was found between the presence of ADA and incidence of infusion-related reactions. The impact of ADA on efficacy (overall survival) could not be assessed due to the limited number of patients with treatment-emergent ADA. In Study 1, the exposure to necitumumab was lower in patients with ADA post-treatment than in patients without detectable ADA).
- (b) (4)
- Use in Specific Populations: Edited for conformance with requirements for content and format described in the Pregnancy and Lactation Labeling Rule (PLLR); added a description of regarding apparent lack of efficacy in exploratory subgroup analyses in elderly patients (hazard ratio for overall survival in patients 70 years or older was 1.03 (95% CI: 0.75, 1.42); and added subsections on Renal and Hepatic Impairment, stating that there are no recommended dose adjustments for organ impairment.
- Overdosage: editorial changes.
- Description: Removed (b) (4)
- Clinical Pharmacology: Modified subsection 12.1 to (b) (4) provide more details on nonclinical studies supporting mechanism of action; modified subsection 12.3 to (b) (4) provide greater description of the results of popPK studies in specific populations and drug interactions; added information on effects of immunogenicity on pharmacokinetics.
- Nonclinical Pharmacology/Toxicology: Edited for brevity.
- Clinical Studies: Expanded the description of the design of the SQUIRE trial and of the study population and included results of ORR by treatment arm in the text; Added a new subsection to describe the results of the INSPIRE trial, which supports the limitation of use proposed by FDA.
- How Supplied/Storage and Handling: edited for brevity
- Patient Counseling: Edited for conformance with FDA Guidance on this section of labeling with regard to format and content.

- Carton and immediate container labels: Final carton and container labeling, with increased prominence of required information, are acceptable.

- Patient labeling/Medication guide: None was proposed and FDA did not request that patient labeling be developed for this product administered by in a healthcare setting by intravenous infusion.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that this BLA be approved with the agreed-upon product labeling.

- Risk Benefit Assessment
  Non-small cell lung cancer is a serious and life-threatening disease with a projected 5-year survival rate of 4.5%. The results of the SQUIRE trial demonstrated a statistically significant improvement in overall survival [HR 0.84 (0.74, 0.96); p=0.01], with median survival of 11.5 months and 9.9 months in the necitumumab plus chemotherapy and chemotherapy arms, respectively, and a statistically significant improvement in PFS [HR 0.85 (0.74, 0.98); p=0.02], with median PFS of 5.7 and 5.5 months in the necitumumab plus chemotherapy and chemotherapy arms, respectively. There was no significant difference in ORR between arms (31% vs. 29%). While the benefits are modest in light of the large treatment effects on survival observed with nivolumab as second-line treatment of squamous NSCLC, the SQUIRE trial has definitively establish the clinical benefits of necitumumab based on statistically robust effects on overall survival. As discussed at ODAC, lack of efficacy in the INSPIRE trial did not alter confidence in the results of the SQUIRE trial, as squamous and non-squamous NSCLC should be considered different diseases in which efficacy may differ, as has been seen with pemetrexed.

  The most common adverse reactions (≥15%) of necitumumab were rash (44%), vomiting (29%), diarrhea (16%), and dermatitis acneiform (15%). The most common severe (Grade 3 or higher) adverse reactions of necitumumab were venous thromboembolic events (5%; including pulmonary embolism), rash (4%), and vomiting (3%). Twelve percent of patients discontinued treatment due to an adverse reaction; the most common adverse reaction leading to discontinuation of necitumumab was skin rash. Additional serious risks, resulting in increased mortality, are cardiopulmonary arrest, severe electrolyte imbalances including hypomagnesemia, which predispose patients to the risks of cardiac arrhythmias, severe dermatologic toxicity, and serious infusion reactions generally occurring during the first or second dose.

  These risks, which are similar to those reported with other monoclonal antibodies directed against and blocking the interactions of EGFR with its ligands, are acceptable only in the indicated population. In clinical settings where necitumumab has not been shown to be effective (i.e., in patients with non-squamous, NSCLC), these risks are not only

unacceptable but may shorten survival, with the upper 95% confidence interval around the observed hazard ratio for OS of 1.21. Based on these concerns, a limitation of use has been included in product labeling and the indication is limited to the population studied, i.e., receiving first-line treatment for squamous, NSCLC.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  Risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of necitumumab. The risks of necitumumab are qualitatively similar other anti-EGFR directed antibodies, thus special educational efforts are not required and product labeling provides adequate information regarding incidence of these risks, including a Boxed Warning, and provides adequate directions for dose adjustment and monitoring for early detection of the risks of electrolyte abnormalities to mitigate this risk.

- Recommendation for other Postmarketing Requirements and Commitments
  Lilly will re-evaluate all necitumumab drug substance lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured by (b) (4) Lilly will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

  - Lilly will re-evaluate all necitumumab drug product lot release and stability data after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process. Lilly will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications, based on the available drug substance and drug product data.

  - To further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly.

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/s/

PATRICIA KEEGAN
11/23/2015