CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 20, 2015
From	Gideon M. Blumenthal, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 125547
Applicant	Eli Lilly and Company
Date of Submission	December 2, 2014
PDUFA Goal Date	December 2, 2015 (standard review)
Proprietary Name / Established (USAN) names	Necitumumab (Portrazza)
Formulation/ Dosing Regimen	(b) (4) single dose vial; 800 mg, (b) (4) minute intravenously on days 1, 8 of a 3 week cycle
Proposed 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
Recommended:	*Approval (pending satisfactory resolution of CMC review)*

Discipline and Consultants	**Primary/ Secondary Reviewer**
Clinical Review	Lee Pai-Scherf, M.D./ Gideon Blumenthal, M.D.
Statistical Review	Lijun Zhang, Ph.D./ Shenghui Tang, Ph.D.
Regulatory Project Manager	Mimi Biable, M.S., R.P.M.
Pharmacology Toxicology Review	Margaret Brower, Ph.D., Shawna Weis, Ph.D./ Whitney Helms, Ph.D.
CMC Reviews	Micro: Candace Gomez-Broughton, Ph.D., Lakshmi Narashimhan, Ph.D/ Patricia Hughes, Ph.D. Regulatory Business Process: Andrew Shiber Drug Substance: Ying-Xin Fan, Ph.D Drug Product: Yan Wang, Ph.D. Assay Validation and Immunogenicity: Ralph Bernstein, Ph.D. Quality Labeling: Jibril Abdus-Samad, PharmD Quality Assessment Lead: Chana Fuchs, Ph.D.
Clinical Pharmacology Review	Clin Pharm: Safaa Burns, Ph.D./ Hong Zhao, Ph.D. Pharmacometrics: Hongshan Li, Ph.D./Jingyu Yu, Ph.D. Genomics: Sarah Dorff, Ph.D./Rosane Charlab Orbach, Ph.D.
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OPDP	Nazia Fatima, PharmD, MBA
PMHS	Amy Taylor M.D./ Tamara Johnson M.D.

1. Introduction

On December 2, 2014, Eli Lilly and Co (Heretofore referred to as the Applicant) submitted BLA 125547, for the new molecular entity necitumumab (Portrazza). The proposed indication is necitumumab in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced squamous (SQ) non small cell lung cancer (NSCLC). At the time of this review, necitumumab is not marketed in any country.

Necitumumab is a humanized IgG1 monoclonal antibody which binds to the extracellular domain of the protein epidermal growth factor receptor (EGFR). EGFR is over-expressed in SQ NSCLC and is thought to contribute to cancer invasion, metastasis and proliferation. The basis of the BLA submission are the results of the SQUIRE trial, a large randomized, add-on trial of necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone for the first-line treatment of patients with SQ NSCLC.

2. Background

Lung cancer is the leading cause of cancer death in the U.S. It is estimated that there will be 158,040 deaths due to lung cancer in 2015, comprising 27% of all cancer deaths in the U.S. Lung cancer can be broadly divided into Small Cell Lung Cancer, and NSCLC. NSCLC can be further divided by histology: SQ NSCLC, and non-squamous NSCLC, the latter comprised mainly of adenocarcinoma histology. SQ NSCLC comprises roughly 30 to 35% of NSCLC. Unfortunately, the majority of patients with SQ NSCLC present with locally advanced or metastatic disease at the time of diagnosis, which is incurable with currently available therapeutic options. The 5-year survival for this population is less than 5%.

Options for first-line treatment of metastatic SQ NSCLC has not changed appreciably in the past several decades. Platinum-doublet chemotherapy is the accepted standard-of-care for first line treatment of metastatic SQ NSCLC in the U.S. Platinim (either cisplatin or carboplatin) in combination with vinorelbine, paclitaxel, docetaxel, or gemcitabine yields similar improvements in overall survival (OS). The median OS for patients enrolled in clinical trials who receive first-line platinum- doublet chemotherapy for metastatic NSCLC (all histology) is approximately 8 to 13 months, and in patients with metastatic SQ NSCLC is about 8 to 10 months. The one-year survival rate is approximately 33%.

For patients who progress after platinum-based therapy, second line treatment options for SQ NSCLC include single agent docetaxel, erlotinib, and two recently approved agents, ramucirumab in combination with docetaxel, and nivolumab. The median OS for metastatic 2nd line SQ NSCLC patients treated with ramucirumab and docetaxel was 9.5 months (Larkins et al, Oncologist 2015) and for nivolumab was 9.2 months (Kazandjian et al JamaOnc 2015).

Given the poor prognosis for patients with metastatic squamous NSCLC, new treatment options are needed to cure, prolong survival, substantially delay disease progression, or alleviate lung-cancer related symptoms.

3. CMC

Drug substance is manufactured by ImClone Systems LLC, Branchburg, New Jersey and drug product is manufactured at Lilly, Indianapolis, Indiana, USA.

The application was submitted in eCTD format and included Module 1.1.2- FDA form 356h, Module 1.2-Cover letter, and Module 2 and Module 3 (drug substance and drug product sections), appendices (3.2.A.1, Facilities and Equipment and 3.2.A.2, Adventitious Agents Safety Evaluation), and a regional section (3.2.R). Letter of authorization (LOA) for Lilly's Type V DMF 21219 to reference the information regarding (b) (4) operations at the Indianapolis site and a LOA for (b) (4) Type V DMF (b) (4) were provided.

- **Drug Product Microbiology:**
  - **Storage period:** the submitted microbiological challenge study data supports a storage period of up to 24 hours at 2 to 8 centigrade for the infusion solution
  - **Container Closure Integrity (CCI):** test method qualified using worst case pressure/vacuum conditions
  - **Facilities:** Lilly's Indianapolis facility was inspected on July 27 to August 4, 2015
  - **DP manufacturing process:** adequately described

  - From microbiology memo from Dr Narasimhan dated September 22, 2015: The drug product section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval with the following PMC (agreed to by the sponsor to submit in the first annual report): "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."

Please note that final Drug Substance and Drug Product reviews are still pending at the time of completion of the CDTL review.

4. Nonclinical Pharmacology/Toxicology

- Necitumumab bound to EGFR from humans and cynomolgus monkeys with similar affinity, thus general toxicology studies were conducted in cynomolgus monkeys.

Monkeys were administered necitumumab weekly for 5 or 26 weeks. In the 26 week study the skin and injection sites were the primary targets for necitumumab-mediated toxicity. Findings included dose-dependent increases in hyperkeratosis, hyperplasia, hemorrhage, inflammation and lymphocytic infiltration at all doses tested. In monkeys, mild but persistent decreases in magnesium levels occurred following administration. Thromboembolism was not exhibited in monkeys. Mild increases in platelets and fibrinogen occurred at all dose levels compared to controls throughout the 26-week study extended until the end of the 8 week recovery period.

Consistent with ICH S6 guidance, genetic toxicology studies were not conducted or required. Carcinogenicity studies were not required given the intended population of advanced human cancer.

No dedicated studies examining the potential for reproductive toxicity were conducted. Instead, the Applicant submitted a literature-based assessment of total or partial EGFR knockout on the developing embryo. Based on the literature, disruption of EGFR has clear detrimental effects, including that on the placenta, lung, skin, cardiac and neural development which may lead to embryofetal and postnatal death, as well as teratogenicity. In order to specifically describe potential developmental effects following an anti-EGFR antibody, the Applicant provided data by right of reference to a developmental study in non-human primates conducted using cetuximab. Cetuximab binds to a similar epitope and has comparable in vitro and in vivo pharmacologic effects as necitumumab. Administration of cetuximab during development resulted in embryolethality and abortions at clinically relevant doses of the antibody. The totality of the data suggests that necitumumab has the potential to cause serious adverse reactions in a developing fetus and is not recommended for use in pregnancy. Based on the half-life of approximately 12 days, use of contraception for 3 months following the final dose is recommended.

Overall Recommendation [Margaret E Brower, Ph.D., Shawna L Weis, Ph.D. and Whitney S. Helms, Ph.D., 7/24/15]: From the nonclinical perspective, necitumumab is approvable in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

5. Clinical Pharmacology

- **Population pharmacokinetics (popPK):** pooled data from 807 patients in five clinical trials suggested that increased risk of rash and hypomagnesemia in patients who received necitumumab in combination with gemcitabine/cisplatin was independent of necitumumab concentration. Body weight was the only significant covariate in the final popPK model; however, simulations suggested that the influence of body weight on the variability of necitumumab exposure is not clinically meaningful to require a body weight based dosing. Age, sex, race, renal function (as measured by Cockcroft-Gault creatinine clearance), hepatic function (as defined by ALT, AST, and total

bilirubin) or concomitant medications (gemcitabine and cisplastin) did not appear to have a clinically meaningful effect on necitumumab exposure. No apparent correlation was identified between necitumumab exposure (Css,ave) and safety or efficacy endpoints. The exposure to gemcitabine tends to be higher when administered with necitumumab in the presence of cisplatin.

- **Exposure comparisons between manufacturing process:** The exposure of the commercial formulation manufactured with (b) (4) is comparable to the clinical formulation manufactured by (b) (4)
- **Immunogenicity:** A total of 14.4% (141/981) of patients in six clinical trials with necitumumab tested positive for ADAs at baseline with 2.9% (28/981) having neutralizing antibodies. After treatment, 8.7% (71/814) tested positive for ADAs. The incidence of treatment emergent ADA was 4.1% (33/814). For patients with post-treatment ADAs, mean CLtot was 26% higher and mean Css,ave was 34% lower than in those without ADAs. No obvious relationship was observed between ADAs and infusion related reactions.

Overall Recommendation from Clinical Pharmacology (8/7/2015): BLA 125547 is acceptable from a clinical pharmacology perspective provided the Applicant and the Agency come into mutual agreement regarding the labeling language.

6. Clinical Microbiology

The application did not include clinical microbiology information. Refer to Section 3 for product quality microbiology information.

7. Clinical/Statistical- Efficacy

I agree with the conclusions of the statistical reviewer (Dr. Lijun Zhang) and clinical reviewer (Dr. Lee Pai-Scherf) regarding the efficacy of necitumumab for the first-line treatment of patients with metastatic squamous NSCLC in combination with cisplatin and gemcitabine.

The following summarizes the key milestones in the regulatory history.

- December 5, 2008: Type B pre-IND/ End of Phase 2 meeting
  - Discussion on phase 3 trial to support approval of IMC-11F8 (necitumumab) (b) (4)
- December 19, 2008: IND 102512 activated. FDA allowed study INSPIRE for non-squamous NSCLC to proceed

- September 21, 2009: Study SQUIRE for squamous NSCLC was submitted to the IND. Non-hold comments were conveyed by FDA to the sponsor.
- February 11, 2011: Lilly informed FDA of the IDMC recommendation to close study INSPIRE due to an imbalance in the incidence of deaths of all causes and fatal thromboembolic events in the necitumumab arm. Interim safety results of SQUIRE was also reviewed, and the IDMC recommended continuation of SQUIRE without modifications
- October 10, 2013: Fast Track designation granted for necitumumab in combination with gemcitabine and cisplatin for the 1st line treatment of patients with metastatic SQ NSCLC.
- January 16, 2014: FDA issued letter of agreement to the agreed iPSP to request a waiver from PREA for the metastatic SQ NSCLC indication.
- January 31, 2014: Type C meeting to discuss BLA content and format. FDA found Lilly's proposed rolling BLA submission acceptable. FDA requested submission of INSPIRE datasets in the BLA.
- June 23, 2014: Type B pre-BLA meeting. FDA stated that given the modest clinical effect demonstrated in SQUIRE and the premature closing of INSPIRE due to safety concerns, an ODAC discussion is anticipated.
- November 19, 2014: Discussion held concerning the results of EGFR expression exploratory analyses for SQUIRE. FDE stated (b) (4) FDA considers the finding exploratory in nature (b) (4) .
- October 22, 2014: initial component of BLA 125547 submitted (rolling submission).

SQUIRE 1st line squamous study:

The pivotal study submitted to support the first line metastatic SQ NSCLC indication was SQUIRE (14X-IE-JFCC, IMCL CP11-0806). Squire was an open-label, multicenter, multinational study comparing overall survival of patients with stage IV squamous NSCLC treated with necitumumab with gemcitabine and cisplatin (N + GC) or gemcitabine and cisplatin GC alone. The primary endpoint was superiority in OS for patients randomized to N + GC. Secondary endpoints included PFS and ORR.

Key eligibility included: measurable or non measurable disease, ECOF PS 0 to 2, last adjuvant therapy at least 1 year prior to randomization, no chest irradiation within 12 weeks prior to randomization, asymptomatic and stable brain metastases. Patients were randomized 1:1 to either N+ GC or GC. Randomization was stratified by ECOG PS (O-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa and India vs. Eastern Asia). N+ GC consisted of: Necitumumab 800 mg IV days 1 and 8 of each 3 week cycle; Gemcitabine 1250 mg/m2 IV on days 1 and 8 of each 3 week cycle (maximum six cycles) and cisplatin 75 mg/m2 IV on day 1 of each 3 week cycle (maximum of six cycles). GC was the same dose and schedule of gemcitabine and cisplatin.

The study was powered for 844 deaths to detect a HR of 0.8 (corresponding increase from 11 to 13.8 months median OS) with 90% power using a log-rank test at two-sided alpha of 5%. Assuming a 5% drop-out rate, a total of 1080 patients were to be randomized up on the assumption of a 27-month accrual period, follow-up period of 19 months, and 1:1 randomization ratio.

From January 2010 until February 2012, a total of 1093 patients from 184 clinical sites in 26 countries enrolled in SQUIRE: 545 in the N+GC arm and 548 in the GC alone arm. The demographic and baseline characteristics were well balanced and were: 83% male, median age 62 years, 88% white, 8% Asian, 91% current smokers, 31% ECOG PS 0, 60% PS 1, 9% PS 2, 87% of patients were from North America, Europe, or Australia.

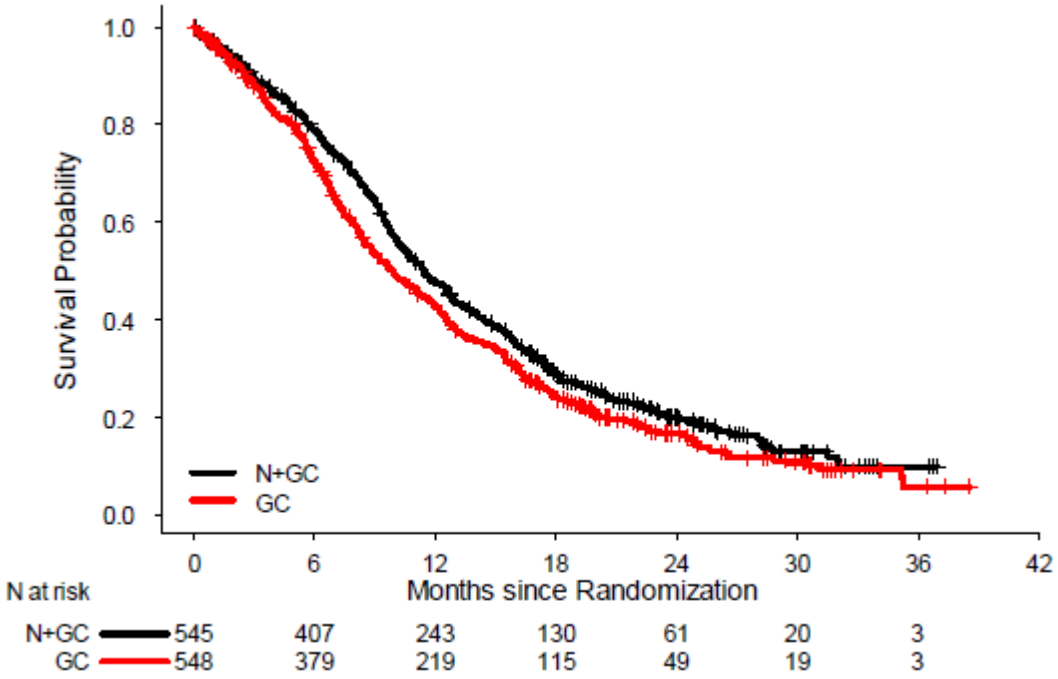
At a median follow-up time of 25 months, patients allocated to N+GC had a modest but statistically significant improvement in OS as compared to patients allocated to GC alone (Table 1 and Figure 1). In addition, a number of OS sensitivity analyses were conducted by the Applicant and FDA, including ITT un-stratified analysis, ITT per CRF stratification, per protocol population (n=1072) stratified and un-stratified, exactly 844 events as per protocol sample size calculation, considering patients lost to follow-up (n=31) or withdrawing consent (n=43) as events (date last known alive) or censoring at study cut-off. The results of these sensitivity analyses corroborated the robustness of the modest OS findings, with HR ranging from 0.83 to 0.86, and the upper bound of the 95% CI always less than 1.

Table 1: SQUIRE OS Results (Source: Dr Pai-Scherf clinical review page 59)

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

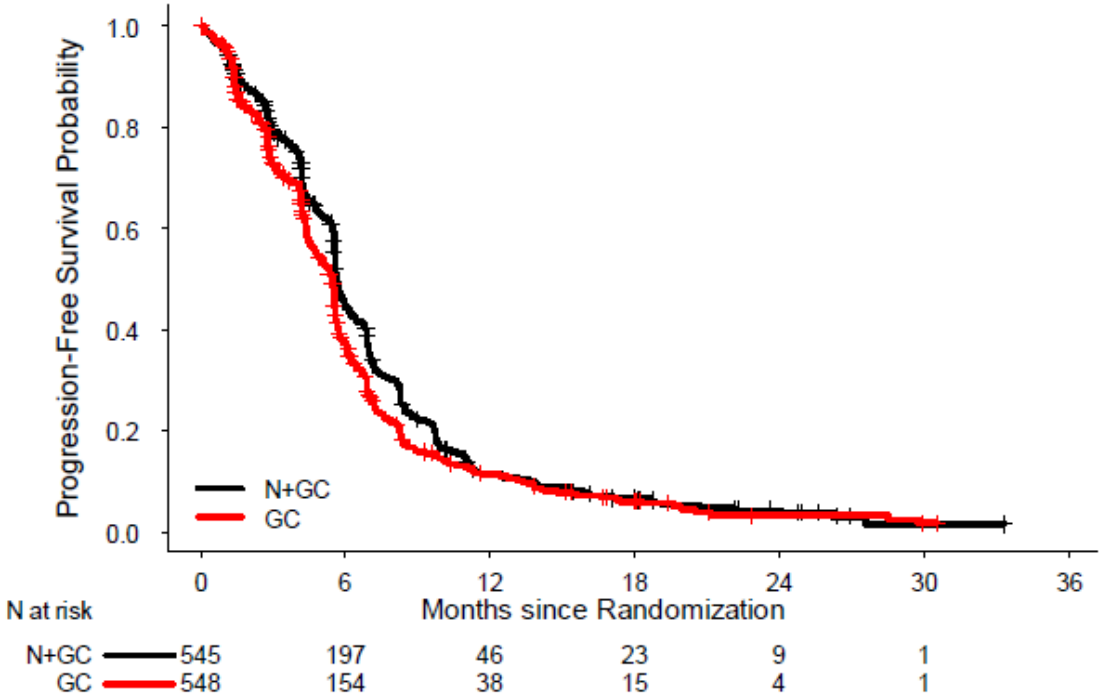
[a] *Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS and region information collected by IVRS.*
[b] *p-value was calculated from a logrank test stratified by ECOG PS and region information collected by IVRS.*

Figure 1: SQUIRE: Kaplan-Meier Curves OS (Source: Dr Pai-Scherf clinical review page 59)



SQUIRE Secondary Endpoints:
At the time of OS analysis, PFS per investigator was statistically significantly dfferent between the N+GC arm and the GC arm, with a HR 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 (Figure 2). There was no statistical difference in ORR (31% N+GC with a median DOR of 5.6 months versus 29% GC with a median DOR of 4.9 months).

Figure 2: SQUIRE KM PFS (Source: Dr Pai-Scherf Clinical Review page 61)



SQUIRE PRO:
The Applicant also submitted PRO analyses of the LCSS and EQ-5D. These analyses did not show a consistent or compelling difference between the two treatment arms.

SQUIRE EGFR expression:
Tumor samples evaluable for EGFR protein expression using the Dako EGFR pharmDx Kit were available in 982 patients (90%), including 486 in the N+GC arm and 496 in the GC arm.

EGFR membrane staining was recorded via H-score, calculated as =[0% x (% cells with no staining + 1 x (%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 EGFR 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 cut-point value of 200 was chosen based on a post-hoc subgroup analysis of the FLEX study, in which NSCLC patients with EGFR H Score $\geq$ 200 had an OS HR indicating greater cetuximab benefit relative to the HR within the group of patients with H-score <200.

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. The majority (95%) of patients had tumors with detectable 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 cut-point interaction; the H-score with a cut-off of 200 was thus not predictive of efficacy outcomes in this study.

The 5% of 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. The HR for OS was 1.86 (0.94,3.65) and for PFS was 1.19 (0.61, 2.3) favoring GC over N+GC in the EGFR null expression subgroup. The findings in the EGFR null subpopulation are considered exploratory and hypothesis generating.

INSPIRE 1st line non squamous study:

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 non squamous NSCLC. The primary objective was OS; secondary objectives included PFS and ORR. Eligible patients were stratified by smoking status (nonsmokers versus light smokers versus smokers), ECOG PS (0 to 1 versus 2), histology (adeno/large cell versus others); geographic region (North America, Europe, Australia vs. South America, South Africa, India vs. Eastern Asia) Patients were randomized 1:1 tor receive Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2 on day 1 of every 3 week cycle with or without Necitumumab 800 mg on days 1 and 8 of every 3-week cycle. PC was continued for a maximum of 6 cycles and N until disease progression, unacceptable toxicity, noncompliance, or withdrawal of consent.

The study was initially planned to enroll 947 patients and primary analysis of OS was to be conducted when at least 723 deaths occurred, yielding 85% power to detect a HR of 0.80 at two-sided alpha of 0.05. Due to early closure of study enrollment by the IDMC for safety concerns, the final sample size was 633 patients. The statistical analysis plan was revised to analyze OS at 474 deaths, yielding 68% power to detect a HR of 0.80 at two-side alpha of 0.05.

Inspire was conducted from November 2009 to February 2011 (terminated early) at 103 sites in 20 countries. Randomization was balanced in terms of demographics and baseline characteristics. The median age was 61 years, 67% male, 94% had ECOG PS 0 or 1, 93% were Caucasian, 75% were smokers, 89% had adenocarcinoma, 8% had large cell carcinoma, and 3% had received prior adjuvant chemotherapy.

INSPIRE did not meet its primary objective of prolonging survival (see table 2). In addition, there appeared to be no difference in terms of PFS (5.6 month median N+PC vs. 5.6 month PC; HR 0.96, p=0.66) nor ORR (31% N+PC vs 32% PC).

Table 2: INSPIRE OS results in non-squamous population (Source: Dr Pai-Scherf clinical review)

	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.*

Primary Reviewers Conclusions:
Based on the totality of the data, Dr Pai-Scherf and Dr Zhang have concluded the SQUIRE is an adequate and well controlled study and that the OS results with the addition of necitumumab to platinum chemotherapy in first-line metastatic SQ NSCLC patients, though modest, are robust. In addition, the lack of an effect when necitumumab is added to platinum doublet chemotherapy in first-line NSQ NSCLC do not deter from the findings in SQ NSCLC since these are different diseases. I concur with this assessment.

8. Safety

Safety Summary:

- The safety profile of necitumumab is in general consistent with the adverse events observed with anti-EGFR antibody class products
- Serious (grade 3-4) necitumumab related AEs included 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 patients on the N+GC arm compared to 0.5% on the GC arm.

I concur with the clinical reviewer's (Dr. Lee Pai-Scherf's) conclusions regarding the relative safety of necitumumab.

The safety review primarily focused on the SQUIRE study; safety data from INSPIRE was also reviewed.

In SQUIRE, the median number of necitumumab cycles was 6.0 with a median relative dose intensity of 94%. With respect to the chemotherapy backbone, patients treated with N+GC had a slightly higher median number of cycles of chemotherapy compared to the GC arm (6 vs. 5) with a similar median relative dose intensity (86% both arms for gemcitabine, 95% both arms for cisplatin). More patients on the N+GC arm had at least 1 SAE compared to the GC arm (48% vs 38%).

Dr. Pai-Scherf conducted a thorough review of treatment related deaths within 30 days for both SQUIRE and INSPIRE. On the SQUIRE trial, 12% of N+GC patients and 10.5% of GC patients had a death on treatment or within 30 days of the last dose. The exact cause of death was unknown in 12 patients (2.2%) in the N+GC arm and 3 patients (0.5%) in the GC arm. Uncorrected hypomagnesemia, a known anti-EGFR mAB drug class toxicity, was observed in several patients prior to death and may have contributed to cardiopulmonary arrest in some patients. In the INSPIRE trial, sudden death and death of unknown cause occurred in 3.2% of patients on the necitumumab arm and 1.3% of patients in the chemotherapy arm.

In the SQUIRE trial, the incidence of thromboembolic events was higher in the N+GC arm compared to the GC alone arm (15% vs. 9%). Death attributed to VTE was reported in one patient on N+GC and two patients on GC. The incidence of all grade arterial TEs did not appear to substantially differ between treatment arms (5.4% vs 3.9%). In the INSPIRE trial, the overall incidence of TE and grade > 3 TEs were higher in the necitumumab arm compared to control (17% vs. 14%), with VTE accounting for most of the events. All-grade arterial TEs were higher in the control arm (4% vs 6%).

Lung cancer patients have several risk factors for arterial and venous thromboembolic events, including smoking, underlying advanced cancer, age and co-morbid conditions such as hypertension and diabetes mellitus. Chemotherapy, particularly cisplatin, is known to be associated with a 2- to 6- fold increase in VTE risk, especially in the first 3 to 6 months of treatment. Recently, anti-EGFR mABs have been implicated in the development of thromboembolic events, however the incidence and risk remains unclear. Tumor histology differences (adenocarcinoma versus squamous) may account for the higher incidence of VTEs observed in INSPIRE. It is unknown whether routine venous thromboprophylaxis would decrease the risk of serious VTE and/or death in this patient population.

Table 3 summarizes all-grade and grade 3-4 adverse reactions more common on the necitumumab arm. Table 4 summarizes laboratory abnormalities more common in patients treated with necitumumab.

Table 3: Adverse Reactions Occurring at Incidence Rate ≥5% All Grades or a ≥2% Grade 3-4 Difference Between Arms in Patients Receiving Necitumumab in SQUIRE

Adverse Reactions (MedDRA) System Organ Class	NECITUMUMAB PLUS GEMCITABINE AND CISPLATIN N=538 (%)		GEMCITABINE AND CISPLATIN N=541 (%)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Skin and Subcutaneous Tissue Disorders				
Rash	44	4	6	0.2
Dermatitis Acneiform	15	1	0.6	0
Acne	9	0.4	0.6	0
Pruritus	7	0.2	0.9	0.2
Dry Skin	7	0	1	0
Skin fissures	5	0.4	0	0
Gastrointestinal Disorders				
Vomiting	29	3	25	0.9
Diarrhea	16	2	11	1
Stomatitis	11	1	6	0.6
Investigations				
Weight decreased	13	0.7	6	0.6
Respiratory				
Hemoptysis	10	1	5	0.9
Pulmonary embolism[a]	5	4	2	2
Nervous System Disorders				
Headache	11	0	6	0.4
Vascular Disorders				
Venous Thromboembolic Events[b]	9	5	5	3
Infections and Infestations				
Paronychia	7	0.4	0.2	0
Eye Disorders				
Conjunctivitis[c]	7	0.4	2	0

[a] Pulmonary embolism is also included in the composite term venous thromboembolic events under system organ class vascular disorders.

[b] VTE is a composite term which includes: pulmonary embolism, deep vein thrombosis, thrombosis, mesenteric veins thrombosis, pulmonary artery thrombosis, pulmonary venous thrombosis, venous thrombosis limb, axillary vein thrombosis, thrombophlebitis, thrombosis in device, vena cava thrombosis, venous thrombosis, subclavian vein thrombosis, superior vena cava syndrome, and thrombophlebitis superficial.

[c] Conjunctivitis is a composite term that includes conjunctivitis, eye irritation, vision blurred, conjunctivitis bacterial, dry eye, visual acuity reduced, blepharitis, allergic blepharitis, conjunctiva hemorrhage, eye infection, eye pain, lacrimation increased, ocular hyperemia, sjogren's syndrome, visual impairment, and eye pruritus.

Table 4: Electrolyte Abnormalities according to Laboratory Assessment at Incidence Rate >10% and a >2% Difference between Arms in Patients Receiving Necitumumab in SQUIRE[a]

LABORATORY PARAMETER	PORTRAZZA PLUS GEMCITABINE AND CISPLATIN N=538			GEMCITABINE AND CISPLATIN N=541		
	N[a]	All Grades (Frequency %)	Grade 3 or 4 (Frequency %)	N[a]	All Grades (Frequency %)	Grade 3 or 4 (Frequency %)
Magnesium Low	461	83	20	457	70	7
Potassium Low	505	28	5	505	18	3
Potassium High	505	33	5	505	32	5
Calcium Low	502	45	6	499	30	2
Corrected Calcium Low	477	36	4	480	23	2
Phosphate Low	462	31	8	454	23	6

[a] Only patients with baseline and at least one post-baseline result are included.

Overall Safety Assessment: I concur with Dr Pai-Scherf that the overall safety assessment is consistent with that observed with other EGFR monoclonal antibodies and risks can be mitigated through product labeling.

9. Advisory Committee Meeting

On July 9, 2015, the review Division convened an Oncologic Drug Advisory Committee (ODAC) to advise and offer insight on the overall benefit-risk of necitumumab in combination with gemcitabine and cisplatin in the proposed population.

The majority of the 12-member 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 could be considered clinically meaningful. It was noted that the OS endpoint and the consistency of results from various sensitivity analyses conducted by 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 the robustness of the findings in the SQUIRE trial in the squamous NSCLC population.

10. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues
- **Exclusivity or Patent Issues of Concern:** No issues

- **Financial Disclosures:** No issues

- **Other GCP Issues:** None

- **Pediatrics:** a full waiver of pediatric studies was requested by the Applicant. On February 11, 2015, the PeRC agreed to a full waiver.

- **Office of Scientific Investigation (OSI) Audits:** Three clinical sites were chosen for inspection: Site 321 (Dr Tudor Eliade Ciulianu, Romania), Site 133 (Dr. Perrine Crequit, France) and Site 324 (Dr. Mircea Dediu, Romania) based on enrollment of large numbers of study subjects, and significant study drug primary efficacy results and general safety reports pertinent to decision making. The study sponsor, Eli Lilly and Company, was also inspected.

  Based on Dr Iacono-Connors memos dated July 28 2015, and August 14 2015, Dr. Diuleanu's site had an interim classification of VAI, Dr Crequit NAI, Dr Dediu NAI and the sponsor NAI.

  From the July 28, 2015 Memo: "Based on the review of 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 Study 14X-IE-JFCC (CP11-0806) 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."

- **Division of Risk Management:** DRISK and DOP-2 concur at this time that a REMS for necitumumab is not necessary to ensure that the benefits outweigh the risks for the FDA proposed indication of the first-line treatment of metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin. The risks associated with necitumumab treatment will be communicated through professional labeling and routine pharmacovigilance.

- **Other Discipline Consults:** None

- **Other Outstanding Regulatory Issues:** None

11. Labeling

- **Proprietary name:** OSE/DMEPA concluded that the proposed proprietary name, PORTRAZZA, is acceptable.

- **OSE/ Division of Medication Error Prevention and Analysis (DMEPA):** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.

- **Patient Labeling Team:** The patient labeling team participated in labeling discussions.

- **Office of Prescription Drug Promotion (OPDP):** OPDP participated in labeling discussions. Refer to OPDP review in DARRTS for OPDP labeling recommendations.

- **Maternal Health**: participated in labeling discussions. Refer to Maternal Health review in DARRTS for their labeling recommendations.

- **Clinical labeling summary:**

    - Boxed Warning: Clinical team recommended adding a boxed warning for cardiopulmonary arrest and hypomagnesemia
    - Indications and Usage: remove (b) (4) and add that it is indicated for the first-line treatment of patients with SQ NSCLC (as this was the population studied)
    - Warnings and Precautions: add Cardiopulmonary Arrest, Hypomagnesemia, Venous and Arterial Thromboembolic Events, and Increased Toxicity and Increased Mortality in Non-Squamous NSCLC. Remove (b) (4)
    - Adverse Reactions: Include VTE and PE in AR table.
    - Geriatric Use: include exploratory subgroup analysis suggesting no OS benefit for patients older than 70 years of age in SQUIRE. Include safety data on increased incidence of VTE in patients older than age 70 as compared to patients younger than age 70.
    - Clinical Studies- add a section of Lack of Efficacy in Non Squamous NSCLC based on results of INSPIRE.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Traditional Approval, contingent on satisfactory completion of CMC review

- Risk Benefit Assessment

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 in the N+GC arm compared to 9.9 months in the GC arm, HR=0.84 (95% CI 0.74; 0.96; logrank p=0.012). The median PFS was 5.7 months in the N+GC arm compared to 5.5 months in the GC 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 skin rash, neutropenia, anemia, and hypomagnesemia.

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.

CDTL conclusions: After multi-disciplinary BLA review and with input from the ODAC, I agree that the benefit-risk profile of necitumumab in combination with gemcitabine and cisplatin for the first line treatment of patients with SQ metastatic NSCLC is favorable. Although the OS advantage is modest, OS is a direct and objective measure of clinical benefit, a composite of safety and efficacy, and some patients may be willing to incur an increased risk of toxicities such as rash and VTE in order to increase the likelihood of modestly improving survival. Although the lack of efficacy in the INSPIRE study did not support the findings of the SQUIRE, SQ NSCLC and NSQ NSCLC can be considered separate disease entities, with different underlying genomic characteristics, different prognosis, and different responses to

various anti-cancer agents. Oncologists are quite familiar in managing the toxicities of anti-EGFR mAbs, and necitumumab toxicity can be adequately addressed through product labeling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)

At the time of completion of this review, the clinical team determined that a REMS would not be required for the safe and effective use of necitumumab in the indicated patient population.

- Recommendation for other Postmarketing Requirements and Commitments

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

The following is a proposed product quality microbiology PMC:

(b) (4)

Please note that the CMC review has not been finalized, and additional PMR/PMCs may be warranted.

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/s/

GIDEON M BLUMENTHAL
10/20/2015