CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Summary Review
BLA #	BLA 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**
Division Director	Patricia Keegan
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

1. Introduction

On December 2, 2014, Eli Lilly and Company submitted a BLA for Portrazza (necitumumab) for the proposed indication of: *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.* Necitumumab is a recombinant human IgG1 kappa monoclonal antibody that 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.

2. Background

Indication Population and Available Therapy

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. 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.

3. CMC

There are no issues that would preclude approval from a CMC perspective. Chemistry reviewers have provided an overall 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.

4. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. 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.

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[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.

Nonclinical toxicity was assessed in 5- and 26-week repeat dose studies in cynomolgus monkeys. No significant drug-related findings were identified in the 5-week study; however, 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 was 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 which 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 BLA relied on findings observed with cetuximab, which binds to a similar epitope in the EGFR III domain, which resulted in embryolethality in animals.

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

There are no issues that would preclude approval from a clinical pharmacology perspective. The application contained pharmacokinetic (PK) 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 PK of necitumumab. In addition, there was no significant impact of renal or hepatic impairment or of manufacturing process (b) (4) on the PK of necitumumab. Also 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 generally attributable to necitumumab (e.g., rash, hypomagnesemia) rather than gemcitabine (nausea/vomiting, cytopenia) therefore 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. 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.

7. Clinical/Statistical-Efficacy

This BLA was supported by the results of a single, randomized, multi-center open-label trial (SQUIRE) 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 VEGF receptor; and archived tumor tissue available for analysis of EGFR and KRAS mutation status and EGFR gene copy numbers .

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 of 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.

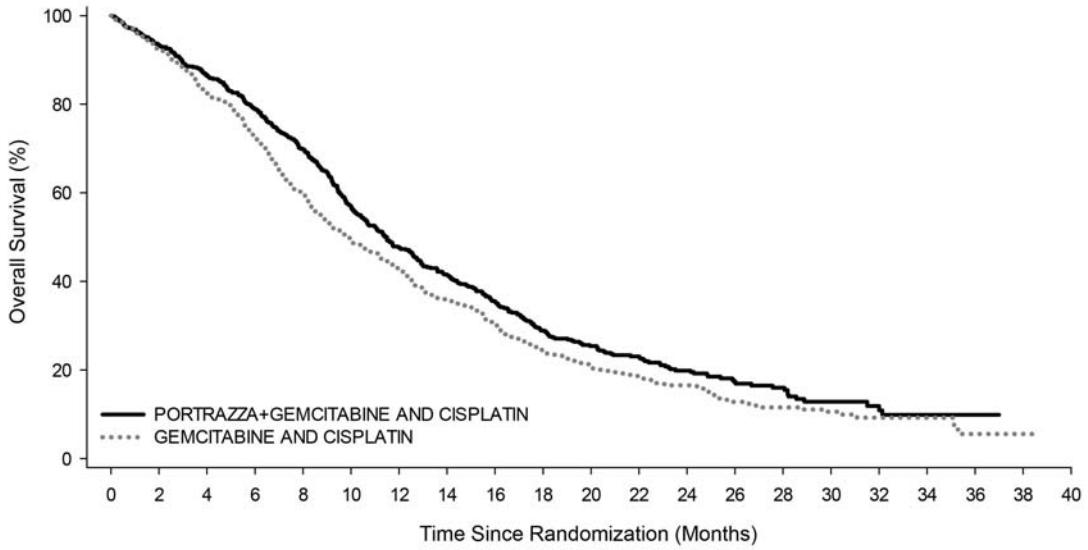
A total of 1093 patients were enrolled and randomized to necitumumab, cisplatin, and gemcitabine (n=545) or cisplatin and gemcitabine (n=548) between January 2010 and February 2012, across 184 clinical study sites internationally.

The trial demonstrated a statistically significant improvement in OS [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%).

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



INSPIRE trial
The INSPIRE 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 OS; secondary endpoints were PFS, ORR, time-to-treatment failure, safety, PK, and safety.

Patients were randomized (1:1) to the following treatment arms.

- 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.

Results
The INSPIRE trial was closed prematurely at the recommendation of the DMC due to an imbalance on the number of deaths attributed to potential thromboembolic events (TE) and fatal TE SAEs 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 OS 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 OS, PFS, 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.

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.

9. Advisory Committee Meeting

This BLA was referred to the Oncologic Drugs Advisory Committee (ODAC) 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 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

Necitumumab was granted Orphan Drug Designation for this indication and is therefore exempt from the requirements of PREA.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- 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 OS [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 established the clinical benefits of necitumumab based on statistically robust effects on OS. 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.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter.

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

/s/

TAMY E KIM
11/24/2015

RICHARD PAZDUR
11/24/2015