FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting
February 26, 2020

BLA 125477 / S34
CYRAMZA (ramucirumab)
Applicant: Eli Lilly and Company

DISCLAIMER STATEMENT

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

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1 Proposed Indication

The Applicant, Eli Lilly and Company (Lilly), is seeking approval for the following indication:

> *Ramucirumab, in combination with erlotinib, is indicated for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.*

2 Executive Summary

This supplemental application to BLA 125477 contains the results of a single, randomized, placebo-controlled trial (RELAY) assessing the safety and efficacy of ramucirumab, a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, in combination with erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). RELAY enrolled 449 patients with previously untreated metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations and randomized them (1:1) to receive ramucirumab and erlotinib or placebo and erlotinib. The primary endpoint is progression-free survival (PFS) assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The trial demonstrated a statistically significant improvement in investigator-assessed PFS [hazard ratio (HR): 0.59 (95% confidence interval (CI): 0.46, 0.76); p=<0.0001] corresponding to a 7-month improvement in median PFS as compared to the placebo arm (median PFS: 19.4 vs.12.4 months). At the time of data cut-off (January 23, 2019), 79 deaths had occurred, resulting in an information fraction of 26% for overall survival (OS), with a HR of 0.83 (95% CI: 0.53, 1.30; p=0.4209).

On January 14, 2020, FDA requested a descriptive update on overall survival. Lilly submitted updated survival data on January 27, 2020, corresponding to a data cut-off of December 31, 2019. At this time, 125 deaths had occurred, resulting in an information fraction of 42% for OS. The medians were not reached in either arm, and the HR is 0.92 (95% CI: 0.65, 1.32).

Based on these data, Lilly seeks approval for the indication cited above.

The specific issues identified by FDA are summarized below:

Can the risk benefit profile of this combination be adequately assessed in the absence of mature overall survival data?

Ramucirumab is a VEGFR2 Inhibitor that does not specifically target an oncogenic driver mutation. Over the last decade, demonstrated improvements in OS have formed the basis for first-line approvals for metastatic NSCLC therapies which do not specifically target oncogenic driver mutations. PFS has been used as the primary endpoint to support regular approval for the first-line treatment of NSCLC for drugs that specifically target oncogenic driver mutations. In studies of earlier generation EGFR TKIs, such as afatinib, gefitinib and erlotinib, the control arm consisted of platinum-based chemotherapy, and a large proportion of patients who received chemotherapy as the study treatment went on to receive an EGFR-TKI as subsequent anti-cancer therapy. Therefore, OS results were potentially confounded by subsequent treatment of patients in the control arms. This is not an issue for the RELAY study, as only 4% of patients in the control arm received ramucirumab as subsequent treatment. It is also notable that in more recent studies comparing third-generation EGFR TKIs to first-generation EGFR TKIs, improvement in OS has been observed[1,2].

Several approvals in the first-line metastatic setting for other tumors types have been based on a statistically significant and clinically meaningful benefit in PFS. FDA acknowledges that a difference in PFS favoring the ramucirumab arm has been demonstrated in the RELAY trial. While the RELAY study met its primary endpoint of improved PFS compared to placebo plus erlotinib, the OS data was immature with 26% information fraction as of the January 23, 2019 (final PFS analysis) data cut-off. With further follow-up (42% information as of December 31, 2019), the updated OS HR is 0.92 (95% CI: 0.65, 1.32).

Given the upper limit of the confidence interval of 1.3, the results suggest a possible detrimental effect on survival for patients treated with the combination of ramucirumab and erlotinib. In the context of an add-on therapy associated with increased toxicity, FDA considers this a safety concern. While the first-line treatment of patients with EGFR-positive NSCLC remains an unmet medical need, there are therapies currently approved for which an improvement in OS has been observed when compared to first generation EGFR TKI.

What is the clinical meaningfulness of the observed effect on PFS in the context of additive toxicity associated with the combination of ramucirumab and erlotinib?

The combination of ramucirumab plus erlotinib is associated with increased toxicity compared to placebo plus erlotinib. There was a higher incidence of Grade ≥3 adverse events (72% vs. 54%) and serious adverse events (29% vs 21%) in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm. Adverse events of special interest occurring at a higher incidence in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm in the RELAY study included bleeding/hemorrhage, hypertension, and proteinuria. There was also a higher incidence of severe infections in the ramucirumab plus erlotinib arm.

Bleeding/hemorrhage occurred in 55% of patients treated with ramucirumab plus erlotinib and 26% of patients treated with placebo plus erlotinib. Most of these events were low grade; the incidence of grade 3-5 bleeding was 1% in the ramucirumab plus erlotinib arm and 0 in placebo plus erlotinib arm.

Grade 3 hypertension occurred in 24% of patients treated with ramucirumab plus erlotinib and 5% of patients treated with placebo plus erlotinib (All Grade hypertension 45% vs 12%, respectively). Of the patients with a treatment-emergent adverse event of hypertension, 22% of such patients on ramucirumab plus erlotinib required three or more antihypertensives vs. 2% of such patients on the placebo plus erlotinib arm.

All Grade proteinuria occurred in 34% of patients treated with ramucirumab plus erlotinib and 8% of patients treated with placebo plus erlotinib. Grade 3-4 proteinuria occurred in 3% of patients treated with ramucirumab plus erlotinib vs. 0 treated with placebo plus erlotinib.

The incidence of Grade 3-5 infection was 17% in the ramucirumab plus erlotinib arm vs. 7% in the placebo plus erlotinib arm.

There were more deaths due to adverse events on study or within 30 days of treatment discontinuation reported in the ramucirumab plus erlotinib arm (n=6 compared to none in the erlotinib plus placebo arm). Of these six deaths in the ramucirumab plus erlotinib arm, FDA considers one death (attributed to hemothorax) related to treatment with the combination and one (attributed to encephalitis influenza) possibly related / cannot be ruled out.

3 Background

3.1 Non-small Cell Lung Cancer (NSCLC)

NSCLC is the most commonly diagnosed cancer world-wide with 2.1 million new cases diagnosed and an estimated 1.76 million lung cancer deaths in 2018[3]. Lung cancer occurs most often in patients between the ages of 50-70 years and is more common in men[3]. Typically, there are no symptoms of lung cancer until the disease is metastatic. The 5-year survival for metastatic NSCLC is 5%[3].

3.2 EGFR-positive NSCLC

NSCLC has three major histologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma[3]. Treatment is determined by the histologic type and by the presence of actionable oncogenic driver mutations. EGFR mutations are targetable oncogenic drivers found in approximately 16% of NSCLC with adenocarcinoma histology[3]. EGFR-mutated NSCLC is more common in Asians, women, and never smokers. The National Comprehensive Cancer Network (NCCN) guidelines recommend that all adenocarcinomas should be molecularly profiled to determine the presence of oncogenic driver mutations[4].

3.3 Available Therapies for EGFR-mutated NSCLC

First-line treatments for metastatic EGFR-positive NSCLC are tyrosine kinase inhibitors (TKIs) that target EGFR driver mutations. The following drugs are considered available therapy for the first-line treatment of patients with EGFR-positive NSCLC:

- Afatinib was approved in 2013 for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by the diagnostic companion test *therascreen* EGFR RGQ PCR kit[5]. Approval was based on data from the LUX-Lung 3 trial in which 345 patients were randomized (2:1) to receive afatinib 40 mg orally once daily (n=230) or intravenous pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) once every 21 days for up to 6 cycles (n=115). The trial demonstrated a 4.2-month improvement in PFS in patients receiving afatinib (11.1 months) compared patients treated with pemetrexed/cisplatin (6.9 months), [HR=0.58 (95% CI: 0.43, 0.78)]. The trial demonstrated no improvement in OS for afatinib (28.2 months) compared to pemetrexed/cisplatin (28.2 months) with a HR of 0.88 (95% CI: 0.66, 1.17, p-value 0.39). While the LUX-Lung 3 study did not allow on-study

crossover, upon disease progression 64.9% of patients in the control arm received an EGFR-TKI as a single agent as subsequent therapy and 7.2% received an EGFR-TKI-containing combination.

- Gefitinib was approved in 2014 for first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test[6]. Approval was based on data from the IFUM study (IRESSA Follow-Up Measure), in which 106 patients received IRESSA at a dose of 250 mg once daily until disease progression or intolerable toxicity. The trial demonstrated an overall response rate (ORR) of 50% with a median duration of response of 6 months. This approval was supported by an exploratory analysis of a subset of patients in the IPASS study (IRESSA Pan-ASia Study), a randomized study of first-line treatment with gefitinib compared to carboplatin plus paclitaxel in 1217 patients with metastatic NSCLC of adenocarcinoma histology. The exploratory analysis included 186 patients with EGFR mutation-positive NSCLC and radiographic scans available for a retrospective assessment by BICR; 88 received gefitinib and 98 received carboplatin and paclitaxel. This subset analysis demonstrated a 3.5-month improvement in PFS for patients treated with gefitinib (10.9 months) compared to carboplatin/paclitaxel (7.4 months) [HR=0.54 (95% CI: 0.38, 0.79)] and an ORR of 67% with gefitinib vs 41% with carboplatin/paclitaxel. While the IPASS study did not allow crossover upon disease progression, based on information available for the total study population, among the 608 patients in the chemotherapy arm, 40% received an EGFR-TKI as subsequent therapy.
- Erlotinib was initially approved in 2004 for treatment of metastatic NSCLC after failure of at least one prior chemotherapy regimen[7]. In 2013, the indication was broadened to include first-line treatment for NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. as detected by an FDA-approved test[4]. The first-line approval was based on the EURTAC trial, an open-label study that randomized 174 patients 1:1 to receive erlotinib 150 mg once daily until disease progression (n = 86) or four cycles of a standard platinum-based doublet chemotherapy (n = 88); standard chemotherapy regimens (cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel). The trial demonstrated a 5.2-month improvement in PFS for patients treated with erlotinib (10.4 months) compared to chemotherapy (5.2 months) [HR=0.34 (95% CI: 0.23, 0.49)]. The EURTAC study allowed subsequent anti-cancer treatment after disease progression at the discretion of the investigator. Based on data available at the time of approval, 82% of patients in the chemotherapy arm had received subsequent treatment with an EGFR-TKI. Median OS was 22.9 months in the erlotinib arm compared to 19.5 months in the chemotherapy arm [HR=0.93 (95% CI: 0.64, 1.35)].
- Dacomitinib was approved in 2018 for the treatment of first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R

substitution mutations as detected by an FDA-approved test[1]. The approval was based on the ARCHER 1050 trial that randomized 452 patients 1:1 to receive dacomitinib 45 mg orally once daily (n=227) or gefitinib 250 mg orally once daily (n=225) until disease progression. The trial demonstrated an improvement in PFS of 5.5 months for patients treated with dacomitinib (14.7 months) compared to gefitinib (9.2 months). Though OS was not formally tested due to the hierarchically earlier endpoints having failed hypothesis tests, a 7.3-month improvement in median OS was observed for patients treated with dacomitinib (34.1 months) compared to patients treated with gefitinib (26.8 months).

- Osimertinib was approved in 2018 for the treatment of first-line metastatic NSCLC whose tumors express EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test[8]. The approval was based on the FLAURA study that randomized 556 untreated patients 1:1 to receive osimertinib 80 mg orally once daily (n=279) or to receive gefitinib 250 mg orally once daily or erlotinib 150 mg orally once daily (n=277) until disease progression. The trial demonstrated an improvement in PFS of 8.7 months for patients treated with osimertinib (18.9 months) compared to patients who received gefitinib or erlotinib (10.2 months) [HR=0.46 (95% CI: 0.37, 0.57)]. At the time of approval, OS data was immature with 44% information, and an interim analysis of OS was not statistically significant. The median OS had not been reached on either arm and the OS HR was 0.63 (95% CI: 0.45, 0.88). Updated OS results for this trial were recently published, showing a statistically significant 6.8-month improvement in OS [HR 0.80 (0.64, 1.00), p=0.046] for patients treated with osimertinib (38.6 months) compared to erlotinib or gefitinib (31.8 months).

3.4 Regulatory History of Ramucirumab

Prior Approvals of Ramucirumab

The original Biologics Licensing Application (BLA) for Cyramza (ramucirumab) was approved on April 21, 2014. This approval was based on the results of the REGARD trial, a randomized, double-blind, placebo-controlled trial in which 355 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction [GEJ]) who previously received platinum- or fluoropyrimidine-containing chemotherapy were randomized (2:1) to receive either an intravenous infusion of Cyramza 8 mg/kg (n=238) or placebo solution (n=117) every 2 weeks until unacceptable toxicity or progressive disease. The approval was based on the demonstration of a statistically significant improvement in OS and PFS. The HR for OS was 0.78 (95% CI: 0.60, 0.998; p =0.047), corresponding to a 1.4-month improvement in median OS (3.8 vs. 5.2 months). The HR for PFS was 0.48 (95%CI: 0.38, 0.62;

p<0.001), corresponding to a 0.8-month improvement in PFS (1.3 vs. 2.1 months).

On October 2, 2014, FDA approved Cyramza (BLA 1255477/S-2) in combination with paclitaxel for the treatment of patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine or platinum-containing chemotherapy.
This approval was based on the results of the RAINBOW trial, a randomized double-blind, placebo-controlled trial in which 665 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the GEJ) who previously received platinum- and fluoropyrimidine-containing chemotherapy were randomized (1:1) to receive either Cyramza 8 mg/kg or placebo as an intravenous infusion every 2 weeks (on Days 1 and 15) of each 28-day cycle until unacceptable toxicity or progressive disease. The approval was based on the demonstration of a statistically significant improvement in OS. The HR for OS was 0.81 (95% CI: 0.68, 0.96; p <0.017), corresponding to a 2.2-month improvement in median OS (7.4 vs. 9.6 months). Based on this data, FDA determined that the results verified the clinical benefit of Cyramza in combination with paclitaxel in patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the GEJ) who previously received platinum- and fluoropyrimidine-containing chemotherapy.

On December 12, 2014, FDA approved Cyramza (BLA 125477/S-7) in combination with docetaxel for the treatment of patients with metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. This approval was based on the results of the REVEL trial, a randomized, placebo-controlled trial in which 1253 patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease were randomized to receive either Cyramza at 10 mg/kg or placebo by intravenous infusion, in combination with docetaxel at 75 mg/m^2 every 21 days until unacceptable toxicity or progressive disease. The approval was based on the demonstration of statistically significant improvements in OS and PFS. The OS HR was 0.86 (95% CI: 0.75, 0.98; p=0.024) corresponding to a 1.4-month improvement in median OS (9.1 vs. 10.5 months). The PFS HR was 0.76 (95% CI: 0.68, 0.86; p<0.001) corresponding to a 1.5-month improvement in median PFS (3 vs. 4.5 months). Based on this data, FDA determined that the results verified the clinical benefit of Cyramza in combination with docetaxel for

the treatment of patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease.

On April 24, 2015, FDA approved Cyramza (BLA 125477/S11) in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. This approval was based on the results of the RAISE trial in which 1072 patients with metastatic colorectal cancer with disease progression within 6 months of the last dose of first-line therapy were randomized to receive either Cyramza 8 mg/kg as an intravenous infusion or placebo in combination with FOLFIRI: irinotecan 180 mg/m^2 administered intravenously over 90 minutes and folinic acid 400 mg/m^2 administered intravenously simultaneously over 120 minutes; followed by 5-fluorouracil 400 mg/m^2 intravenous bolus over 2 to 4 minutes; followed by 5-fluorouracil 2400 mg/m^2 administered intravenously by continuous infusion over 46 to 48 hours given until disease progression or unacceptable toxicity. The approval was based on the demonstration of a statistically significant improvement in OS. The OS HR was 0.85 (95% CI: 0.73, 0.98; p=0.023) corresponding to a 1.6-month improvement in median OS (11.7 vs. 13.3 months). Based on this data, FDA determined that the results verified the clinical benefit of Cyramza in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

On May 10, 2019, FDA approved Cyramza (BLA 125477/S-29) for the treatment of patients with hepatocellular carcinoma who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.

Pertinent Regulatory History

Table 1 summarizes the pertinent regulatory history related to this supplemental biologic licensing application.

Table 1. Regulatory Milestones

Date	Discussion
11/4/2014	A meeting between Lilly and FDA was held to discuss Study 14T-MC-JVCY (RELAY) Regarding the use of investigator-assessed PFS as the primary endpoint for registration, FDA stated "In general a substantial, robust improvement in progression-free survival (PFS) that is clinically meaningful and statistically persuasive with an acceptable risk-benefit profile and with consistent treatment effects in relevant subpopulations for PFS and consistent effects in key secondary endpoints, including no evidence of a decrement in OS, would support a regulatory application for marketing." FDA also noted that investigator-assessed PFS would require compelling evidence that study blinding remained intact. FDA proposed that "Prior to the initiation of the trial, Lilly should propose a plan for a full or partial audit of investigator PFS by an independent radiologic review committee and archive all scans." Lilly response: The addition of blinded independent review of all imaging scans for determination of PFS and the analysis of PFS based on blinded independent radiologic review for prespecified sensitivity analysis was made. The following measures were taken to ensure blinding during the study: 1) patients and investigators remain blinded at the time of disease progression, 2) placebo and ramucirumab are identical in appearance with equivalent volume, 3) investigators and all other personnel involved in study conduct are blinded to treatment assignment, and 4) the same imaging assessment frequency was planned for both treatment arms to avoid bias.
12/18/2014	Lilly submitted JVCY 05 Protocol (RELAY) to IND 115613
06/10/2019	A teleconference between Lilly and FDA was held to discuss the proposed sBLA for ramucirumab and erlotinib. In the preliminary meeting responses to Lilly's questions, FDA stated, "In general, regular approval for the first-line treatment of metastatic NSCLC has been based on demonstration of improvement in OS, with the exception of therapies specifically targeting oncogenic driver mutations, which have received approval based on clinically meaningful improvements on PFS. Although the intended population is patients with tumors harboring oncogenic driver mutations, ramucirumab does not specifically target these driver mutations. In addition, the finding of an improvement in PFS in the RELAY study is not supported by a

	difference in overall response rate. Finally, the addition of ramucirumab to erlotinib results in a clinically important increase in toxicity, including more deaths due to adverse drug reactions (six vs. none on the erlotinib arm), a higher incidence of Grade 3-4 adverse reactions (72% vs. 54%) and a higher incidence of certain AESI (bleeding/hemorrhage events, hypertension, and proteinuria). Taking all of this into consideration, the observed improvement in PFS would not be sufficient to support regular approval of ramucirumab, in combination with erlotinib, for the proposed indication. FDA recommends that Lilly wait for the mature, pre-specified analysis of OS in the RELAY trial before filing an sBLA for the proposed indication." Following discussion during the meeting, Lilly stated that it was their intent to submit the sBLA by the end of July. FDA stated that they will conduct a complete review of the application, if filed, and may seek the advice of the ODAC. Lilly acknowledged FDA's comments.
7/29/2019	Lilly submitted the sBLA application (S-34) to BLA 125477

4 Clinical Study Supporting the Application

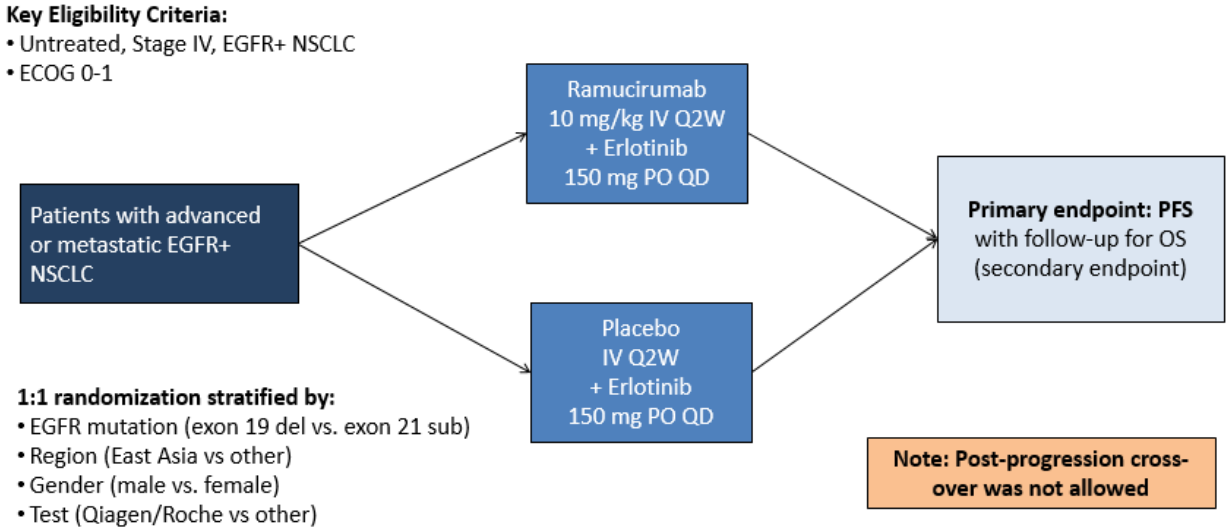
4.1 RELAY Study Design

RELAY is a two-part, global, multicenter randomized, placebo controlled, double-blinded study comparing the combination of ramucirumab with erlotinib to placebo with erlotinib in patients with untreated metastatic NSCLC whose tumors harbor EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The first part (Part A) of the study was a safety lead-in that enrolled 12 patients to establish the dose and schedule to be used in Part B. Part A will not be further described here.

Part B of the study is randomized, placebo controlled and blinded to evaluate the benefit of adding ramucirumab to erlotinib compared to single-agent erlotinib. Key study inclusion was the diagnosis of metastatic EGFR-positive NSCLC and Eastern Cooperative Oncology Group [ECOG] performance status of 0-1. The key exclusion criteria included known T790M-positive NSCLC, any prior treatment for metastatic NSCLC, and the presence of brain metastases. Approximately 450 patients were randomized 1:1 to receive either the combination of ramucirumab 10mg/kg IV every 14 days with erlotinib 150mg orally daily or placebo IV every 14 days with erlotinib 150 mg orally daily. Treatment will continue until intolerable toxicity or disease progression. The stratification factors were EGFR mutation type (exon 19 deletion or exon 21 substitution), geographic region (east Asia versus other), gender, and test used for

study enrollment (Qiagen or Roche versus other). Figure 1 depicts the RELAY study design.

Figure 1 RELAY (Part B) Study Design



Source: Reviewer-generated figure

Statistical Analysis Plan

The primary endpoint of the RELAY study was investigator-assessed PFS, defined as the time from the date of randomization until the date of radiographic documentation of progression (as defined by RECIST v1.1) or the date of death due to any cause, whichever was earlier. The primary analysis of PFS was a stratified log-rank test performed on the intent-to-treat (ITT) population. The PFS HR and its associated 95% confidence interval (CI) were to be estimated using the log-rank test and stratified Cox model.

The pre-specified sample size was 450 patients. Assuming a median PFS of 11 months in the control arm and 15.5 months in the experimental arm, a total of 270 events were needed to detect a HR of 0.71 with 80% power at a one-sided alpha level of 0.025. One PFS interim analysis for futility was planned to be performed when 114 (25%) PFS events were observed.

The key secondary endpoint of RELAY was OS, defined as the time from the date of randomization to the date of death from any cause. The final analysis of OS was planned to occur after approximately 300 deaths are observed. An interim analysis was planned for the time of the final PFS analysis with an alpha boundary calculated using a Haybittle-Peto type spending function. However, this study did not pre-specify effect-size assumptions for the OS analysis.

Other secondary endpoints include overall response rate (ORR) and duration of response (DOR). Exploratory efficacy endpoints include time to second disease progression (PFS2) and analyses of PFS by clinical and biomarker subgroups, as well as exploratory patient-reported outcome (PRO) analyses.

Clinical Outcome Assessment

The RELAY study included two PRO as exploratory endpoints; the Lung Cancer Symptom Scale (LCSS) and EuroQol-5 Dimension 5 Level questionnaire (EQ-5D-5L). The FDA analysis focused primarily on the LCSS as the EQ-5D is a generic questionnaire primarily used for health technology assessment.

The LCSS includes 9 items, 6 measuring major symptoms for lung cancer (appetite loss, fatigue, cough, dyspnea, hemoptysis, pain), and 3 summary items related to total symptom severity, activity status, and overall quality of life. Each item is captured using a visual analog (VAS) with zero corresponding to the lowest rating (best status) and 100 representing the highest rating (worst status). The total score is the average of all 9 items, a sub-score using the mean of all 6 major symptoms or average symptom burden index (ASBI) can also be created. Patients completed the LCSS and EQ-5D-5L at baseline, at Cycle 2, thereafter at every other cycle, and at the 30-day short-term follow-up visit.

The LCSS data (both the total score and individual items) were to be summarized descriptively at baseline and for each cycle by treatment arm. Change from baseline for each cycle by treatment arm was also summarized. In addition, time to deterioration (TtD) for each of the 9 LCSS items, ASBI, and the LCSS total score was defined as the time from the date of randomization until the date of the first ≥15-mm increase from baseline.

4.2 RELAY Study Results

4.2.1 Study Population

At the time of the final PFS analysis based on a January 23, 2019 data cut-off date, a total of 449 patients (224 in the ramucirumab plus erlotinib arm and 225 in the placebo plus erlotinib arm) were randomized. Three patients were enrolled but not treated due to adverse event (1 patient), physician's decision (1 patient) and patient withdraw (1 patient).

The patient demographics and baseline disease characteristics of patients in the ITT population were balanced between treatment arms.

Table 2. RELAY Patient Demographic and Baseline Disease Characteristics

	Ramucirumab + Erlotinib N=224 n (%)	Placebo + Erlotinib N=225 n (%)
Sex		
Male	83 (37)	83 (37)
Female	141 (63)	142 (63)
Age		
Median (range)	65 (27-86)	64 (23-89)
<65	102 (46)	114 (51)
≥65	122 (54)	111 (49)
Race[1]		
Asian	172 (77)	174 (77)
White	52 (23)	48 (21)
Other	0	2 (1)
Unknown	0	1 (0.4)
Smoking History		
Ever	64 (29)	73 (32)
Never	134 (60)	139 (62)
Unknown	26 (12)	13 (6)
ECOG		
0	116 (52)	119 (53)
1	108 (48)	106 (47)
Disease Stage at Diagnosis		
Metastatic	195 (87)	189 (84)
Others	29 (13)	36 (16)
Pathological Diagnosis		
Adenocarcinoma	215 (96)	218 (97)
NSCLC NOS	9 (4)	7 (3)
EGFR Mutation Type[2]		
Exon 19 del	123 (55)	120 (53)
Exon 21 L858R	99 (44)	105 (47)
Other or Unknown	2 (1)	0
EGFR Testing Method[3]		
Qiagen/Roche	96 (43)	101 (45)
Other	128 (57)	124 (55)

[1]One patient was Black/African American, and one patient was American Indian/Alaskan Native, and One patient did not have information on race collected; [2]One patient had an EGFR mutation other than L858R as a protocol deviation and one patient had missing data; [3]One patient in the "other" category had missing information for EGFR testing method;
Source: FDA generated table – summarizing patient characteristics using analysis datasets (ADSL and ADPTDC, January 23, 2019 data cutoff date, submitted by Applicant)

3.2.2. Efficacy Results

3.2.2.1. Results of the Primary Endpoint

At the time of the final analysis of PFS as assessed by investigator, a total of 280 PFS events were observed. The median duration of follow-up was 20.7 months (range: 0.1, 35.4).

As presented in Table 3, a statistically significant improvement in PFS per investigator assessment was observed for patients in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm. The difference in median PFS assessed by investigator was 7.0 months.

Figure 2 provides a plot of the Kaplan-Meier estimates of PFS.

Table 3. Results of the Primary Efficacy Endpoint in RELAY

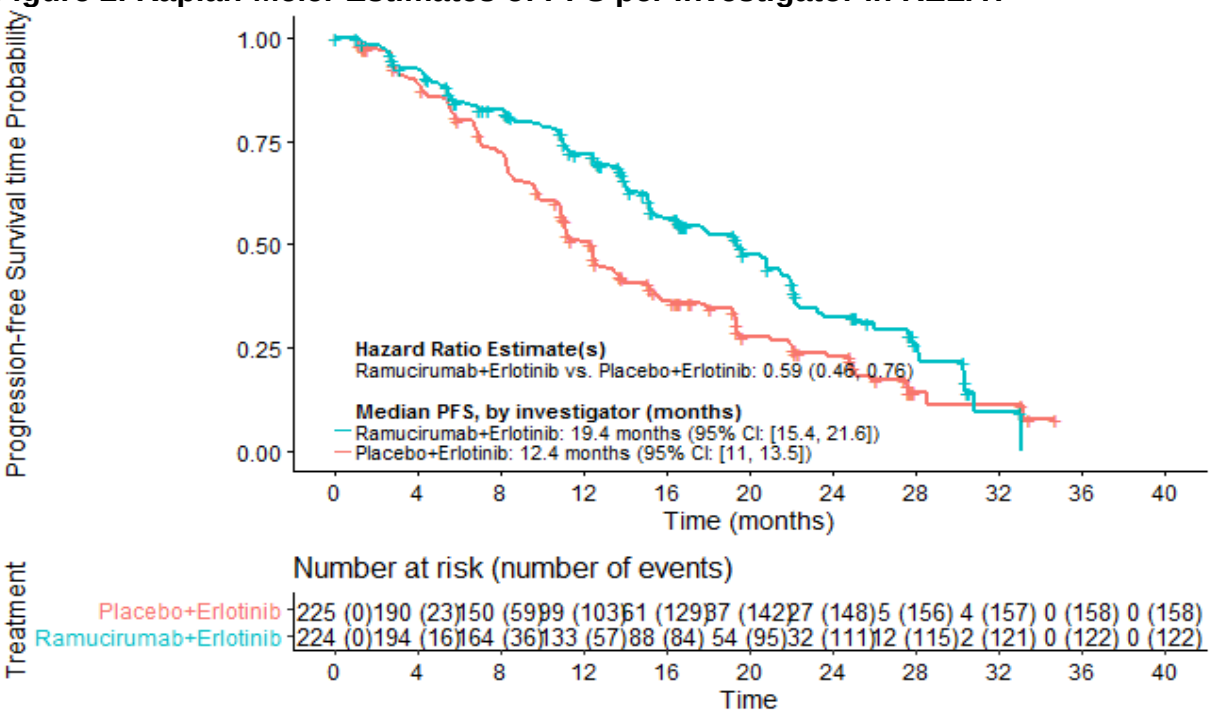
	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
PFS per investigator		
PFS events, n (%)	122 (54)	158 (70)
Median, months (95% CI)	19.4 (15.4, 21.6)	12.4 (11.0, 13.5)
Hazard ratio (95% CI)	0.59 (0.46, 0.76)	
p-value[1]	<0.0001	

CI = Confidence Interval

[1]Corresponding to stratified log-rank test

Source: FDA generated table – summarizing PFS using time to event analysis dataset (ADTTE, January 23, 2019 data cutoff date, submitted by Applicant)

Figure 2. Kaplan-Meier Estimates of PFS per Investigator in RELAY



Source: FDA generated figure – summarizing PFS using time to event analysis dataset (ADTTE, January 23, 2019 data cutoff date, submitted by Applicant)

As presented in Table 4,there was a 5.4-month difference in median PFS as presented per BICR. It is noteworthy that 9 patients (7 in ramucirumab plus erlotinib arm and 2 in the placebo plus erlotinib arm) were not able to obtain tumor assessment by BICR; therefore, the analysis is based on the remaining 440 patients. The concordance in assessment of progressive disease between investigator and BICR was 79%.

Table 4. Results of Progression Free Survival as Assessed by BICR

	Ramucirumab + Erlotinib N=217	Placebo + Erlotinib N=223
PFS per BICR		
Events, n (%)[1]	116 (53)	138 (62)
Median, months (95% CI)	16.5 (13.7, 19.3)	11.1 (9.7, 12.7)
Hazard ratio (95% CI)	0.67 (0.52, 0.87)	

CI = Confidence Interval

[1]7 patients in ramucirumab arm and 2 patients in the placebo arm were not able to obtain tumor assessment by BICR;

Source: FDA generated table – summarizing PFS using time to event analysis dataset (ADTTEIR, January 23, 2019 data cutoff date, submitted by Applicant)

3.2.2.2. Results of Secondary Endpoints

The results of the secondary endpoints of RELAY are presented in Table 5. Secondary endpoints were to be tested hierarchically if the primary endpoint was statistically significant, beginning with OS as the key secondary endpoint. Due to the lack of statistical significance for the OS interim analysis, no other secondary or exploratory endpoints could be formally tested. Due to the lack of statistical significance of the OS interim analysis, no other secondary or exploratory endpoints could be formally tested.

At the time of the data cut-off for the final PFS analysis, a total of 79 deaths had occurred, resulting in an information fraction of 26% of the required events for the final OS analysis. Given the immature data, the median OS was not reached for either arm.

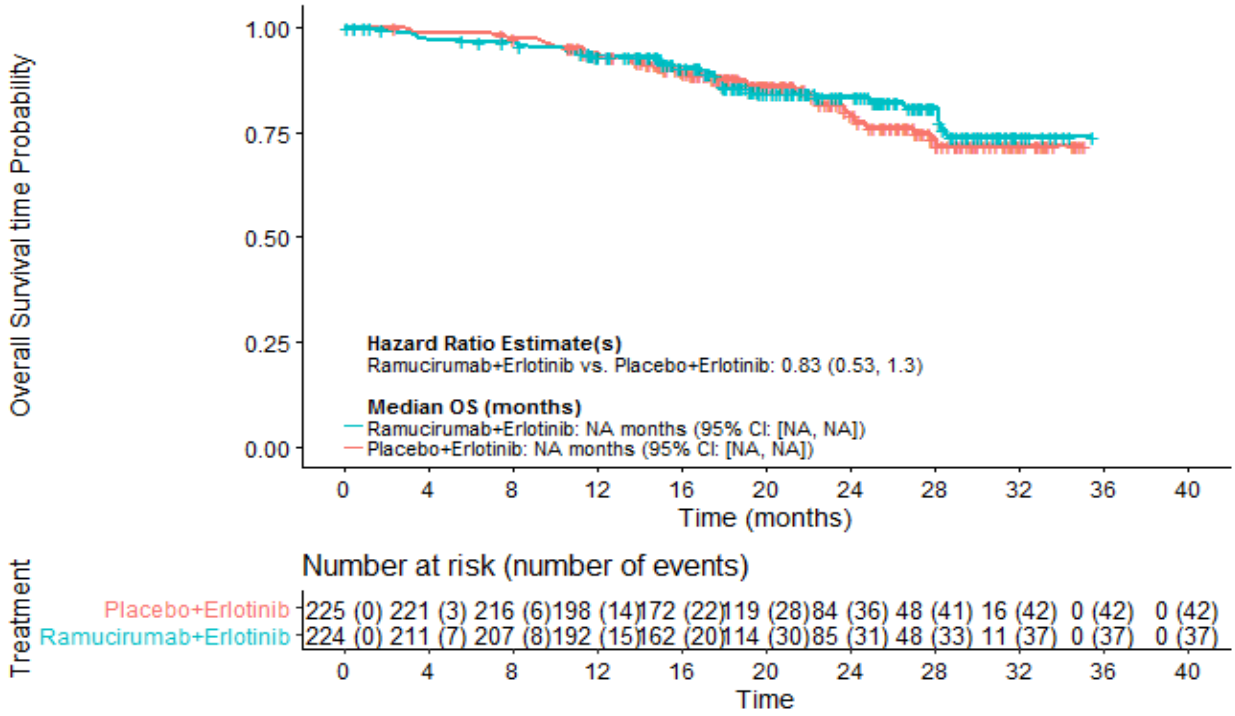
Figure 3 presents the Kaplan-Meier estimated survival curves for interim OS analysis in ITT population.

Table 5. Results of Secondary Efficacy Endpoints in RELAY

	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Overall Survival		
Deaths, n (%)	37 (17)	42 (19)
Median, months (95% CI)	NR (NE, NE)	NR (NE, NE)
Hazard ratio (95% CI)	0.83 (0.53, 1.30)	
Overall Response Rate[1]		
Complete Responses, n (%)	3 (1)	2 (1)
Partial Responses, n (%)	168 (75)	166 (74)
ORR, % (95% CI[2])	76 (70, 82)	75 (68, 80)
Median DOR, months (range)	18.0 (13.9, 19.8)	11.1 (9.7, 12.3)

CI = Confidence Interval, NR = Not reached, NE = Not estimable
[1]Tumor responses are not confirmed; [2]95% CI calculated using the Clopper-Pearson exact method
Source: FDA generated table – summarizing OS and ORR using time to event and response analysis datasets (ADTTE, ADRS, January 23, 2019 data cutoff date, submitted by Applicant)

Figure 3. Kaplan-Meier Estimates of Overall Survival in RELAY



Source: FDA generated figure – summarizing OS using time to event analysis dataset (ADTTE, January 23, 2019 data cutoff date, submitted by Applicant)

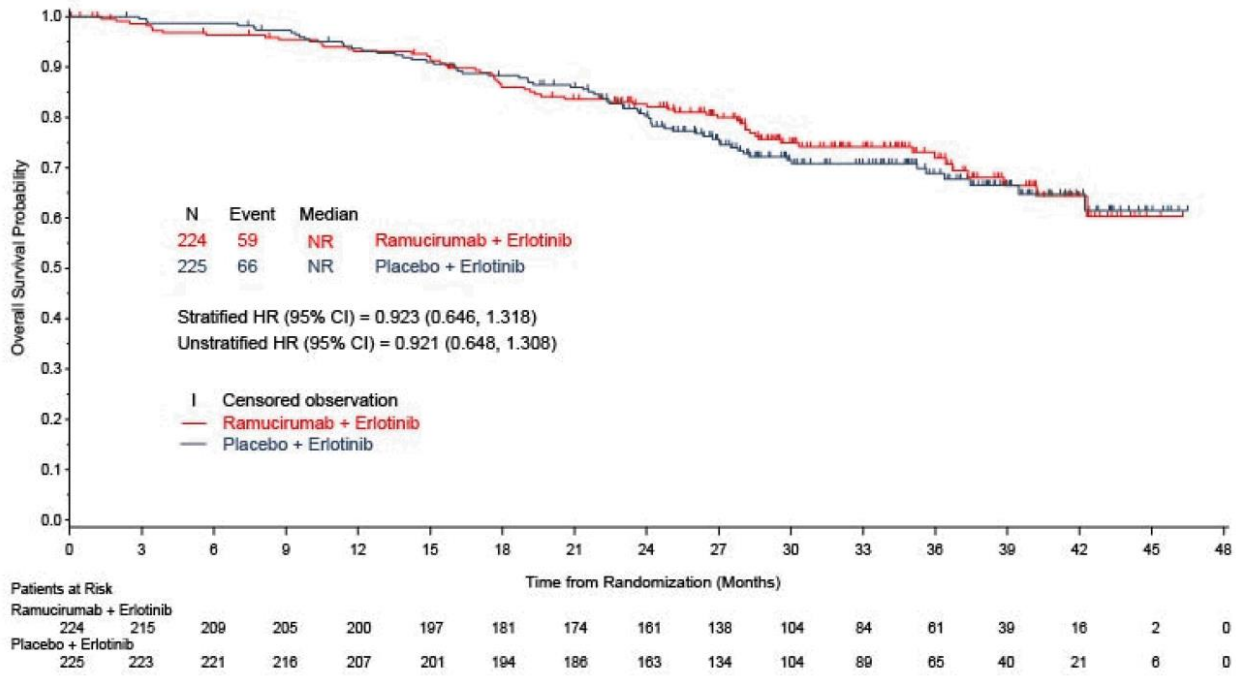
Per FDA's request, Lilly provided an updated analysis of OS with a cut-off date of December 31, 2019. At this data cut-off, 125 deaths were observed, corresponding to an information fraction of 42%. The medians for OS were still not reached in either arm. The results of the Lilly conducted analyses, including numerical estimates and Kaplan-Meier estimated survival curves are presented in Table 6 and Figure 4, respectively. FDA's independent review and confirmation of these results is pending receipt of the individual patient-level data from the December 2019 cut-off.

Table 6. Updated Results of OS Analysis in RELAY

	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Overall Survival		
Deaths, n (%)	59 (26)	66 (29)
Median, months (95% CI)	NR (NE, NE)	NR (NE, NE)
Hazard ratio (95% CI)	0.92 (0.65, 1.32)	

CI = Confidence Interval, NR = Not reached, NE = Not estimable
Source: Regulatory Response to FDA Information Request submitted January 27, 2020 (Table 4.1, December 31, 2019 data cutoff date)

Figure 4. Updated Kaplan-Meier Estimates of Overall Survival in RELAY (December 31, 2019 data cutoff date)



Source: Regulatory Response to FDA Information Request submitted January 27, 2020 (Figure 4.1, December 31, 2019 data cutoff date)

3.2.2.3. Results of Exploratory Endpoints

Results of exploratory efficacy endpoints, including PFS2, are not presented here. PFS2 is defined as the time from randomization to second disease progression. FDA does not consider PFS2 a valid endpoint for regulatory consideration. FDA has not determined that PFS2 is clinically meaningful. Specifically, this exploratory endpoint is

subject to measurement bias, due to the lack of consistent and structured radiological follow-up for progression. Additionally, there is differential use of various post-progression anti-cancer therapies, confounding the estimation of treatment effect of the experimental agent.

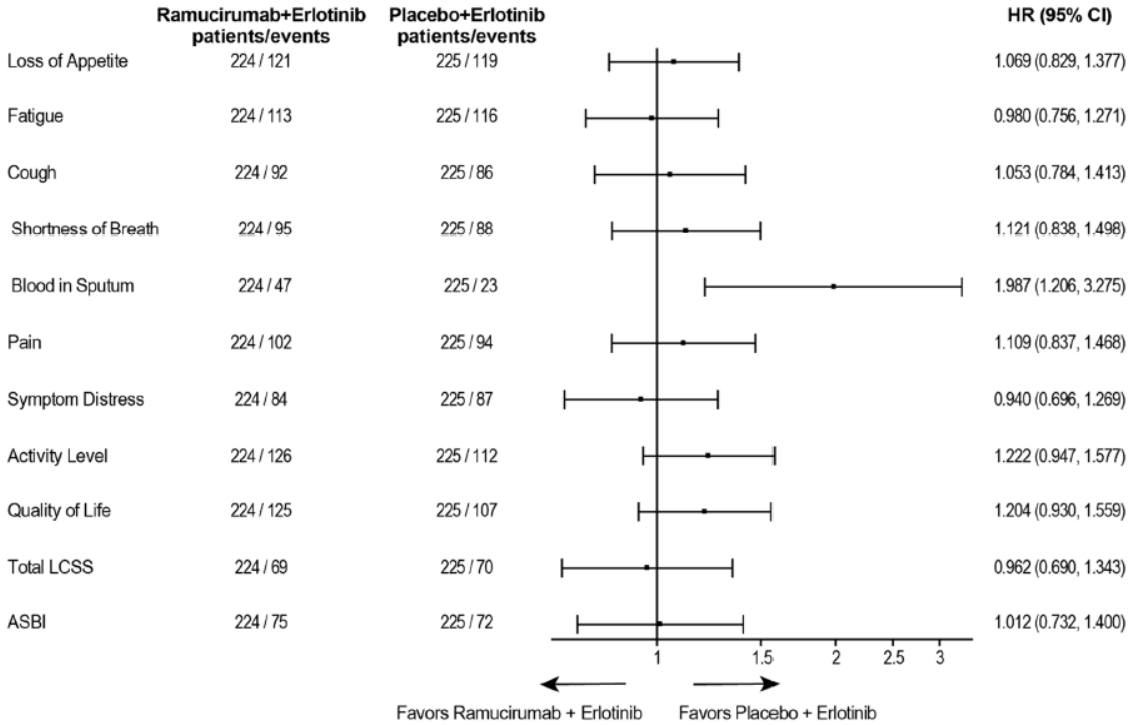
3.2.2.4. Results of Clinical Outcome Assessments

LCSS was completed by 96% of patients randomized to ramucirumab and erlotinib and 97% of patients randomized to placebo and erlotinib at baseline. On treatment, over the first 12 months of therapy completion rates remained above 94% for ramucirumab and erlotinib arm and 96% for placebo and erlotinib arm.

Generally, the hazard ratios in the time to deterioration (TtD) analysis for the LCSS items, total score and ASBI do not favor ramucirumab and erlotinib arm, however most confidence intervals cross 1 (see
Figure 5). The symptoms observed in the LCSS single items are corroborated by the clinician reported events (blood in sputum, pain, shortness of breath).

The conclusion of these findings presented by Lilly in the clinical study report was "These findings suggest no evidence that overall QoL and average symptom burden were negatively impacted by treatment with ramucirumab and erlotinib relative to placebo and erlotinib." The FDA does not agree with this conclusion. Lilly performed a TtD analysis, which is focused on efficacy (delaying tumor progression-related symptoms) rather than tolerability. Additionally, patients who came off the therapy due to AEs are likely to have been censored (i.e., and therefore their QoL was not captured), and this issue is magnified in a time to event analysis. Regardless of the PRO endpoint selected, the absence of a clinically meaningful superiority result in the investigational arm over the control arm is not evidence of equivalence between the arms, and it is notable that several scores, including quality of life and activity levels, trend toward favoring the placebo arm.

Figure 5. Forest Plot for Time to Deterioration for Lung Cancer Symptom Scale, ITT Population.



Abbreviations: ASBI = Average Symptom Burden Index; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat, LCSS = Lung Cancer Symptom Score.
Data cutoff date: 23 January 2019
Source: b_f_forest_ttlcss.png

Source: Applicant Clinical Study Report

Conclusions from the Patient-Reported Outcomes data from RELAY Trial

- Completion rates were high among patients remaining on study drug.
- PRO data in from RELAY is considered descriptive, as the trial was not designed to compare differences in patient-reported symptoms and QoL, nor were these patient-reported endpoints prospectively identified and included in the statistical testing plan.
- FDA disagrees with Lilly's conclusion that there was no evidence that QoL and average symptom burden were negatively impacted by treatment with ramucirumab and erlotinib relative to placebo and erlotinib given trends in QOL and activity level results favoring the placebo arm.
- The LCSS focuses primarily on patients' symptoms and QoL and does not capture tolerability of therapy. Therefore, conclusions about tolerability cannot be meaningfully drawn from this data.

4.2.4 Safety Results

The RELAY study provides the primary evidence of clinical safety for ramucirumab in combination with erlotinib in patients with EGFR-mutation positive NSCLC. The safety population excluded three patients who did not receive study drug, all on the ramucirumab plus erlotinib arm.

The combination of ramucirumab plus erlotinib is associated with increased toxicity compared to placebo plus erlotinib. There was a higher incidence of Grade ≥3 adverse events (72% vs. 54%) and serious adverse events (29% vs 21%) in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm. Adverse events of special interest occurring at a higher incidence in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm in the RELAY study included bleeding/hemorrhage, hypertension, and proteinuria. There was also a higher incidence of severe infections in the ramucirumab plus erlotinib arm.

There were more deaths due to adverse events on study or within 30 days of treatment discontinuation reported in the ramucirumab plus erlotinib arm (n=6) compared to the erlotinib plus placebo arm (none). Of these six deaths in the ramucirumab plus erlotinib arm, FDA considers one death (attributed to hemothorax) related to treatment with the combination and one (attributed to encephalitis influenza) possibly related / cannot be ruled out. FDA agrees with Lilly's assessment of the other four deaths due to adverse events as unrelated to treatment with ramucirumab plus erlotinib.

Table 7 provides a safety overview of the RELAY study.
Table 8 summarizes the treatment-emergent adverse events in RELAY occurring in ≥ 20% of patients. Table 9 presents selected adverse events which occurred at a higher incidence in the ramucirumab plus erlotinib arm. Table 10 shows laboratory abnormalities worsened from baseline in ≥20% (All Grades) of patients receiving ramucirumab with erlotinib with a difference between arms of ≥2%.

Table 7. RELAY Study Safety Overview (Safety Analysis Set)

	Ramucirumab plus Erlotinib N= 221 n (%)	Placebo plus Erlotinib N=225 n (%)
Duration of Therapy, median in months		
Ramucirumab or Placebo	11.0	9.7
Erlotinib	14.1	11.2
Ramucirumab or Placebo Infusions received, median	21	19
Patient with ≥1 AE	221 (100)	225 (100)
Patients with Grade≥ 3 AE	159 (72)	121 (54)
Patients with ≥ SAE	65 (29)	47 (21)
Treatment discontinuation due to AE	29 (13)	24 (11)
With at least one dose reduction	23 (10)	4 (1.8)
Erlotinib with at least one dose reduction	99 (45)	96 (43)

AE = adverse events; SAE = serious adverse events
Source: FDA generated table – summarizing safety using adverse event analysis datasets (ADAE, ADSL, ADDS, January 23, 2019 data cutoff date, submitted by Applicant)

Table 8. RELAY Study Treatment Emergent Adverse Reactions in ≥20% of patients

	Ramucirumab plus Erlotinib N= 221 n (%)		Placebo plus Erlotinib N=225 n (%)	
	All Grades (%)	Grades 3-5 (%)	All Grades (%)	Grades 3-5 (%)
Diarrhea	155 (70)	16 (7)	160 (71)	3 (1.3)
Dermatitis acneiform	149 (67)	33 (15)	153 (68)	20 (9)
Paronychia	118 (53)	9 (4.1)	114 (51)	7 (3.1)
Hypertension	100 (45)	52 (24)	27 (12)	12 (5)
Stomatitis	92 (42)	4 (1.8)	82 (36)	3 (1.3)
Dry skin	83 (38)	1 (0.5)	91 (40)	5 (2.2)
Alopecia	75 (34)	NA	44 (20)	NA
Proteinuria	75 (34)	6 (2.7)	19 (8)	0
Epistaxis	74 (33)	0	27 (12)	0
Decreased appetite	57 (26)	6 (2.7)	47 (21)	4 (1.8)
Nausea	57 (26)	2 (0.9)	44 (20)	2 (0.9)
Pruritis	51 (23)	2 (0.9)	66 (29)	2 (0.9)
Peripheral Edema	50 (23)	2 (0.9)	10 (4.4)	0
Cough	48 (22)	1 (0.5)	35 (16)	0
Pyrexia	47 (21)	0	28 (12)	1 (0.4)

Source: FDA generated table – summarizing safety using adverse event analysis dataset (ADAE, January 23, 2019 data cutoff date, submitted by Applicant)

Table 9. RELAY Selected Adverse Events

	Ramucirumab plus Erlotinib N= 221 (%)		Placebo plus Erlotinib N=225 (%)	
	All Grades n (%)	Grades 3-5 n (%)	All Grades n (%)	Grades 3-5 n (%)
Infections	178 (81)	39 (17)	171 (76)	15 (7)
Bleeding /Hemorrhage	121 (55)	4 (1.8)	59 (26)	4 (1.8)
Hypertension*	100 (45)	52 (24)	27 (12)	12 (5)
Proteinuria	75 (34)	6 (2.7)	19 (8)	0
*Patients requiring ≥3 antihypertensives for TEAE of HTN 22% vs. 2%				

Source: FDA generated table – summarizing safety using adverse event analysis dataset (ADAE, January 23, 2019 data cutoff date, submitted by Applicant)

Of the patients with a treatment-emergent adverse event of hypertension, 22% of such patients on ramucirumab plus erlotinib required treatment with three or more antihypertensives vs 2% of such patients on the placebo plus erlotinib arm.

Table 10. RELAY Laboratory Abnormalities Worsening from Baseline in ≥20% (All Grades) of Patients Receiving Ramucirumab with Erlotinib with a Difference Between Arms of ≥2%

	Ramucirumab plus Erlotinib		Placebo plus Erlotinib	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Increased ALT	74	11	60	13
Increased AST	71	6	47	4
Increased alkaline phosphatase	25	<1	16	1
Hypokalemia	24	5	18	2
Anemia	42	5	25	2
Thrombocytopenia	41	3	12	3
Neutropenia	33	7	21	4

Source: FDA generated table – summarizing safety using laboratory results analysis dataset (ADLB, January 23, 2019 data cutoff date, submitted by Applicant)

5 Summary of FDA Review Issues

Over the last decade, demonstrated improvements in OS have formed the basis for first-line approvals for metastatic NSCLC therapies which do not specifically target oncogenic driver mutations. PFS has been used as the primary endpoint to support regular approval of therapies targeting oncogenic driver mutations for the first-line treatment of NSCLC harboring oncogenic driver mutations, such as EGFR-positive NSCLC. In studies of first- and second-generation EGFR TKIs, the control arm consisted of platinum-based chemotherapy, and a large proportion of patients who received chemotherapy as the study treatment went on to receive an EGFR-TKI as subsequent anti-cancer therapy. Therefore, OS results were potentially confounded by subsequent treatment of patients in the control arms. In more recent studies comparing third-generation EGFR TKIs to first-generation EGFR TKIs, improvement in OS has been observed[1,2] Several approvals in other tumors types in the first-line metastatic setting have been based on a statistically significant and clinically meaningful benefit in PFS.

Ramucirumab is a human VEGFR2 antagonist and does not specifically target the EGFR oncogenic driver mutation. Potential confounding of OS results due to post-progression receipt of ramucirumab is not an issue for the RELAY study, as only 4% of patients in the control arm received ramucirumab as subsequent treatment. While the RELAY study met its primary endpoint of improved PFS favoring the ramucirumab plus erlotinib arm, the OS data was immature with 26% information fraction as of the January 23, 2019 (final PFS analysis) data cut-off. With further follow-up (42% information as of December 31, 2019), the updated OS HR is 0.92 (95% CI: 0.65, 1.32).

The combination of ramucirumab plus erlotinib is associated with increased toxicity compared to placebo plus erlotinib. There was a higher incidence of Grade ≥3 adverse events (72% vs. 54%) and serious adverse events (29% vs 21%) in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm. Adverse events of special interest occurring at a higher incidence in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm in the RELAY study included bleeding/hemorrhage (55% vs. 26%), hypertension (All Grades 45% vs 12%, Grade 3 24% vs. 5%), and proteinuria (34% vs 8%). Of the patients a treatment-emergent adverse event of hypertension, 22% of such patients on the ramucirumab plus erlotinib arm required three or more antihypertensives vs 2% of such patients on the placebo plus erlotinib

arm. There was also a higher incidence of severe infections in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm (17% vs 7%).

There were more deaths due to adverse events on study or within 30 days of treatment discontinuation reported in the ramucirumab plus erlotinib arm (n=6 compared to none in the erlotinib plus placebo arm). Of these six deaths in the ramucirumab plus erlotinib arm, FDA considers one death (attributed to hemothorax) related to treatment with the combination and one (attributed to encephalitis influenza) possibly related / cannot be ruled out.

Given the upper limit of the confidence interval of 1.3, the results suggest a possible detrimental effect on survival for patients treated with the combination of ramucirumab and erlotinib. In the context of an add-on therapy associated with increased toxicity, FDA considers this a safety concern. While the first-line treatment of patients with EGFR-positive NSCLC remains an unmet medical need, there are therapies currently approved for which an improvement in OS has been observed when compared to first generation EGFR TKI.

6 Issues for the Committee

- Can the risk benefit profile of this combination be adequately assessed in the absence of mature overall survival data?

- What is the clinical meaningfulness of the observed effect on PFS in the context of additive toxicity associated with the combination of ramucirumab and erlotinib?

7 References

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4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 2.2020) https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf Accessed January 14, 2020.
5. GILOTRIF- afatinib tablet, film coated. Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc Revised October 2019.
6. IRESSA- gefitinib tablet, coated. Prescribing Information. AstraZeneca Pharmaceuticals LP. Revised May 2019.
7. TARCEVA- erlotinib hydrochloride tablet. Prescribing Information. Genentech, Inc. Revised October 2016.
8. TAGRISSO- osimertinib tablet, film coated. Prescribing Information. AstraZeneca Pharmaceuticals. Revised December 2019.

8 Appendix

Table 11. RELAY PFS Subgroup Analysis

		Ramucirumab + Erlotinib		Placebo + Erlotinib		Hazard Ratio (95% CI)
		n	Events	n	Events	
Sex	Male	83	43	83	64	0.51 (0.34, 0.75)
	Female	141	79	142	94	0.73 (0.54, 0.99)
Age	<65	102	57	114	92	0.53 (0.38, 0.75)
	>=65	122	65	111	66	0.77 (0.55, 1.09)
Geographical Region	East Asia	166	94	170	124	0.64 (0.49, 0.83)
	Other	58	28	55	34	0.61 (0.36, 1.01)
Race[1]	Asian	172	97	174	127	0.64 (0.49, 0.83)
	Non-Asian	52	25	51	31	0.60 (0.35, 1.03)
ECOG PS at Baseline	0	116	51	119	77	0.58 (0.41, 0.83)
	1	108	71	106	81	0.67 (0.49, 0.93)
Smoking History	Ever	64	32	73	55	0.58 (0.37, 0.90)
	Never	134	74	139	91	0.69 (0.51, 0.95)
	Unknown	26	16	13	12	0.24 (0.10, 0.57)
Liver Metastases	Yes	21	12	24	17	0.48 (0.23, 1.02)
	No	203	110	201	141	0.65 (0.51, 0.84)
EGFR Mutation[2]	Exon 19 del.	123	64	120	84	0.65 (0.47, 0.90)
	Exon 21 mut.	99	58	105	74	0.62 (0.44, 0.87)
EGFR Test[3]	Qiagen/Roche	96	46	101	74	0.40 (0.27, 0.58)
	Other	128	76	124	84	0.87 (0.64, 1.19)

[1]Of those patients who are categorized as non-Asian, 103 were White, 1 patient was Black/African American, and 1 patient was American Indian/Alaskan Native; and 1 patient did not have information on race collected and was excluded from the subgroup analysis; [2]Two patients are excluded from this subgroup analysis due to an EGFR mutation other than L858R as a protocol deviation or missing data; [3]One patient in the "other" category had missing information for EGFR testing method

Source: Reviewer generated table – summarizing patient characteristics using analysis datasets (ADSL and ADPTDC, January 23, 2019 data cutoff date, submitted by Applicant)