FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUG ADVISORY COMMITTEE (ODAC)

Wednesday, February 26, 2020

1:15 p.m. to 4:48 p.m.

Afternoon Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:15 p.m.)

Call to Order

Introduction of Committee

DR. HOFFMAN: Good afternoon and welcome back to some. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I'd also like to identify the FDA press contact, Brittney Manchester. Thank you.

My name is Philip Hoffman. I'm the chairperson for this meeting. I will now call the afternoon session of today's meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introduce ourselves, starting with the FDA to my left and go around the table.

DR. PAZDUR: Richard Pazdur, director, Oncology Center of Excellence.

DR. SINGH: Harpeet Singh, acting director, Division of Oncology 2.

CDR LARKINS: Erin Larkins, the thoracic

head and neck team lead.

MS. SCEPURA: Barbara Scepura, clinical reviewer.

DR. LI: Xiaoxue Li, statistics.

DR. HALABI: Susan Halabi, statistician, Duke University.

DR. HINRICHS: Christian Hinrichs, investigator, NCI.

DR. KLEPIN: Heidi Klepin, geriatric oncologist, Wake Forest.

DR. HOTAKI: Lauren Tesh Hotaki, designated federal officer.

DR. HOFFMAN: Philip Hoffman, medical oncologist, University of Chicago.

DR. CRISTOFANILLI: Massimo Cristofanilli, medical oncology, Northwestern University.

DR. GARCIA: Jorge Garcia, GU medical oncologist, formerly at the Cleveland Clinic and now transitioning as a division chair of oncology at Simon Cancer Center, Case Western Reserve.

DR. HAWKINS: Randy Hawkins, internal medicine and pulmonary medicine, Charles Drew

University, Los Angeles.

MR. MATSON: Tracy Matson, patient representative, Little Rock.

DR. MALIK: Shakun Malik, NCI, CTEP.

DR. DEEKEN: John Deeken, medical oncologist from the INOVA Health System.

DR. SZABO: Eva Szabo, medical oncologist, NCI.

DR. CHENG: Jon Cheng, medical oncology. I'm the industry rep, and I'm with Merck Research Labs.

DR. HOFFMAN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass to Dr. Lauren Hotaki who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting

members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not

so substantial as to be deemed likely to affect the integrity of the services at which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and their primary employment.

The afternoon session of today's agenda involves discussion of supplemental biologics license application 125477, supplement 34, for Cyramza, ramucirumab, injection for intravenous use submitted by Eli Lilly and Company. The proposed indication used for this product is in combination with erlotinib, for first-line treatment of patients with metastatic non-small cell lung cancer

whose tumors have epidermal growth factor receptor exon 19 deletions or exon 21 L858R substitution mutations.

This is a particular matters meeting during which specific matters related to Eli Lilly's supplemental BLA will be discussed. Based on the agenda for today's meeting and afternoon session, and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Jonathan Cheng is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is

employed by Merck Research Laboratories.

We would like to remind members and temporary voting members that if discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. HOFFMAN: We will now proceed with the FDA's opening remarks from Dr. Erin Larkins.

FDA Opening Remarks - Erin Larkins

CDR LARKINS: Good afternoon. My name is Commander Erin Larkins. I'm a medical oncologist and team leader for the thoracic and head and neck cancers team in the Division of Oncology 2, in the Office of Oncologic Diseases. I'd like to extend my thanks to the members of the advisory committee,

the Eli Lilly team, invited guests, visitors, and FDA colleagues for attending and participating in today's discussion of the supplemental application for ramucirumab BLA 125477.

In my introductory comments, I will provide a brief background on the application, FDA's reasons for requesting input from the committee, and the issues that FDA has identified for consideration during today's discussion.

Ramucirumab is a vascular endothelial growth factor receptor 2, VEGFR2, inhibitor, approved for several indications, including 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.

Eli Lilly seeks approval of ramucirumab for use in combination with erlotinib for first-line treatment of patients with metastatic non-small cell lung cancer with epidermal growth factor receptor, EGFR, exon 19 deletions, or exon 21 L858R mutation, hereafter referred to as EGFR

mutation-positive non-small cell lung cancer.

Oncogenic driver mutations in EGFR are present in approximately 15 to 30 percent of non-small cell lung cancers of adenocarcinoma histology with EGFR exon 19 deletions and exon 21 L858R substitution mutations the most common. Recommended first-line treatment for patients with EGFR mutation-positive non-small cell lung cancer is single-agent therapy with an EGFR tyrosine kinase inhibitor.

Over the past decade, one of the major advancements in the treatment of non-small cell lung cancer has been the identification and targeting of genomic tumor aberrations such as EGFR mutations. The development of drugs targeting these genomic tumor aberrations has changed the treatment landscape for non-small cell lung cancer and is believed to be one of the factors which has led to the recently reported improvements in lung cancer survival rates.

For EGFR mutation-positive non-small cell lung cancer, this path forward started with the

development of EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib and progressed to more effective, later generation EGFR tyrosine kinase inhibitors. For example, osimertinib, the EGFR tyrosine kinase inhibitor most recently approved for the first-line treatment of EGFR mutation-positive non-small cell lung cancer, demonstrated an improvement in overall survival when compared to investigator's choice of erlotinib or gefitinib. Ramucirumab is a VEGFR2 inhibitor that does not specifically target an oncogenic driver mutation.

Results of the RELAY trial provide the primary evidence to support the safety and effectiveness of ramucirumab administered in combination with erlotinib for the proposed indication. As depicted in this slide, RELAY is a double-blind, randomized, placebo-controlled multicenter trial. They randomized 449 patients with metastatic EGFR mutation-positive non-small cell lung cancer to receive either ramucirumab in combination with erlotinib or placebo in

combination with erlotinib until disease progression or intolerable toxicity.

The primary efficacy outcome measure for the RELAY trial was progression-free survival, or PFS, according to investigator assessment using Response Evaluation Criteria for Solid Tumors, Version 1.1.

The primary analysis of RELAY demonstrated a statistically significant improvement in PFS as assessed by investigator in patients randomized to receive ramucirumab plus erlotinib compared to patients randomized to placebo plus erlotinib. The hazard ratio for PFS was 0.59 with a 95 percent confidence interval of 0.46 to 0.76, corresponding to a median improvement in PFS of 7 months.

Results for PFS, as assessed by a blinded independent central review, demonstrated the difference in median PFS of 5.4 months with a hazard ratio of 0.67 and a 95 percent confidence interval of 0.52 to 0.87, favoring the ramucirumab plus erlotinib arm.

Overall survival is the key secondary

endpoint for the RELAY trial. The statistical analysis plan specified an interim analysis of overall survival to be conducted at the time of the final PFS analysis, with the final analysis of overall survival plan to occur after approximately 300 deaths are observed. However, the study did not prespecify effect size assumptions for the overall survival analysis.

At the time of the interim analysis, overall survival results were immature. A total of 79 deaths had occurred, 26 percent of the required events for the final overall survival analysis. Median overall survival was not reached in either arm, and the hazard ratio was 0.83 with a 95 percent confidence interval of 0.53 to 1.30.

At FDA's request, Lily provided an updated analysis of overall survival with a data cutoff date of December 31, 2019. At the time of this updated analysis, a total of 125 deaths had occurred corresponding to 42 percent of the required events for the overall survival analysis. Median overall survival was still not reached in

either arm and the hazard ratio was 0.92 with a 95 percent confidence interval of 0.65 to 1.32.

In general, the safety profile of ramucirumab plus erlotinib observed in RELAY was consistent with the known adverse reaction profiles of ramucirumab and erlotinib. Patients receiving ramucirumab plus erlotinib experienced a higher incidence of grade 3 or higher adverse events and serious adverse events. Events of interest occurring at a higher incidence in patients receiving ramucirumab plus erlotinib included hypertension, bleeding, proteinuria, and severe infections.

Over the last decade, for the first-line treatment of metastatic non-small cell lung cancer, FDA approvals of therapies which do not specifically target oncogenic driver mutations have been based on demonstration of an improvement in overall survival. Progression-free survival has been used by FDA as the primary endpoint to support approval for the first-line treatment of metastatic non-small cell lung cancer for drugs that

specifically target oncogenic driver mutations.

In studies of earlier generation EGFR TKIs, crossover was an issue confounding the interpretation of overall survival results. In more recent studies comparing third generation EGFR tyrosine kinase inhibitors to first generation EGFR tyrosine kinase inhibitors, improvement in overall survival has been observed.

FDA has identified two issues related to the benefit-risk assessment of ramucirumab administered in combination with erlotinib in this application, which will be described in the next two slides.

As previously mentioned, ramucirumab is a VEGFR2 inhibitor that does not specifically target an oncogenic driver mutation. While the RELAY study enrolled patients with EGFR mutation-positive non-small cell lung cancer, all patients in the study received the EGFR tyrosine kinase inhibitor erlotinib, and ramucirumab is considered the investigational agent in this study. Post-progression use of ramucirumab is not an issue for the RELAY study, as only 4 percent of patients

in the control arm received ramucirumab as subsequent treatment.

FDA acknowledges that a difference in progression-free survival favoring the ramucirumab plus erlotinib arm has been demonstrated in the RELAY trial. However, based on the results of the updated analysis of overall survival requested by FDA, with 42 percent of the events required for the final analysis, the hazard ratio for overall survival is 0.92 with a 95 percent confidence interval of 0.65 to 1.32.

Given the upper limit of the 95 percent confidence interval of 1.3, the results suggest uncertainty regarding the effect of treatment with ramucirumab plus erlotinib on overall survival, including the possibility of a detrimental effect on survival. In the context of an add-on therapy associated with increased toxicity, FDA considers this a potential safety concern.

The second issue relates to the increased toxicity associated with the addition of ramucirumab to erlotinib. In the RELAY study, the

incidence of grade 3 or higher adverse events was almost 20 percent higher in patients receiving ramucirumab plus erlotinib than in those receiving placebo plus erlotinib. The incidence of serious adverse reactions was also higher in patients treated with ramucirumab plus erlotinib.

Events of interest occurring at a higher incidence in patients receiving ramucirumab plus erlotinib included hypertension, bleeding, proteinuria, and severe infections. The incidences of both all-grade and grade 3 hypertension were approximately 4 times higher in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm.

Notably, almost a quarter of patients receiving ramucirumab plus erlotinib experienced hypertension requiring 3 or more antihypertensives versus 2 percent of patients receiving placebo plus erlotinib.

As part of the benefit-risk assessment for ramucirumab administered in combination with erlotinib for the first-line treatment of patients

with EGFR mutation-positive non-small cell lung cancer, FDA considers the totality of information, including the observed improvement in PFS in the RELAY study; available results for the key secondary endpoints, including overall survival; and the increased toxicity associated with an add-on therapy.

FDA referred this application to the advisory committee due to uncertainty regarding the potential benefit provided to patients given the absence of mature overall survival data and the increased toxicity associated with the addition of ramucirumab to erlotinib.

While the treatment of patients with EGFR mutation-positive non-small cell lung cancer remains an unmet medical need, there are therapies currently approved for which an improvement in overall survival has been observed when compared to first-generation EGFR tyrosine kinase inhibitors.

FDA is seeking the committee's opinion on whether the benefit-risk profile of ramucirumab plus erlotinib is favorable for the first-line

treatment of patients with EGFR mutation-positive non-small cell lung cancer. This concludes my remarks. Thank you for your attention.

DR. HOFFMAN: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the applicant's presentations.

Applicant Presentation - Allen Melemed

DR. MELEMED: Good afternoon. I am Allen Melemed, senior director of global regulatory affairs for Eli Lilly and company. I'm a pediatric oncologist by training. I'd like to thank the FDA and the Oncologic Drugs Advisory Committee for the opportunity to present data from the RELAY study.

For more than five years, Cyramza, also known as ramucirumab, has been approved in the United States. In 2014, Cyramza was approved in combination with docetaxel for second-line treatment of metastatic non-small cell lung cancer based on improvements of both progression-free and overall survival. In addition, Cyramza is also approved for the treatment of patients who have second-line gastric cancer, colorectal cancer, and

hepatocellular carcinoma either as a single agent or in combination with chemotherapy.

To date, more than 125,000 patients have been treated with Cyramza worldwide. Lilly is seeking a new indication for Cyramza in combination with erlotinib for the first-line treatment of patients with metastatic non-small cell lung cancer with activating EGFR mutations.

Cyramza is a recombinant human monoclonal antibody antagonist of vascular endothelial growth factor receptor 2 developed for the treatment of solid tumors. Cyramza specifically binds to the vascular endothelial growth factor receptor 2, which blocks the binding of three ligands: VEGF-A, VEGF-C, and VEGF-D. This is unique from other molecules that specifically inhibit the VEGF-A ligand such as Avastin.

The rationale for the combination therapy was supported by preclinical data, indicating that dual blockade of VEGF and EGFR pathways would be more effective than either approach alone. This is a similar approach to other synergistic

combinations of targeted agents, for example, BRAF and MEK inhibition, where one agent inhibits the oncogenic driver and the other inhibits a downstream target.

Let me explain. It is known that the VEGF secreted by tumor cells act in a paracrine manner to promote angiogenesis, however, the autocrine activity of VEGF triggers intratumor kinase pathways. This is where VEGF and EGFR are interconnected.

In addition to EGFR activation increasing VEGF expression, both VEGFR and EGFR activation induces intratumor kinase pathways, which results in promotion of tumor growth and proliferation. In our study, erlotinib inhibits the oncogenic driver while Cyramza targets the downstream effects inhibiting VEGFR, therefore the dual blockade presents a viable strategy to improve efficacy outcomes.

Historically, approvals for non-small cell lung cancer have been based on significant improvement in overall survival, as a median

survival was relatively short, less than a year. In scenarios were overall survival is long, FDA has recognized in guidance that a clinically meaningful primary endpoint to assess benefit is progression-free survival. Our reason for this is that assessment of drug effect can be affected by subsequent cancer therapies.

In the metastatic EGFR-mutated patient population, overall survival is long and confounded by multiple lines of subsequent therapies. As such, PFS is the best assessment of treatment effect, and PFS has been used as the basis for approval for all current first-line treatments for EGFR non-small cell lung cancer.

As shown, FDA approvals for early generation treatments have had median progression-free survival around 10 to 15 months with overall survival around 2 years. We approached the design of the RELAY recognizing the evolution of this disease with new therapies and increase in durations of the overall survival. We continue to see this trend with newer generation treatments

showing median PFS up to 19 months and overall survival exceeding 3 years. Additionally, no study has demonstrated statistically significant improvement of overall survival at the time of approval.

We sought FDA's advice on RELAY's design in a 2014 meeting and aligned that PFS would support a regulatory application for approval. As the trial was powered to show a large magnitude of improvement in progression-free survival, the sample size limited the power to assess benefit in overall survival.

Lilly submitted their protocol to FDA in 2014. In June 2019, during the sBLA meeting, FDA informed us that while therapies specifically targeting oncogenic drivers have received regular approval based on clinically meaningful improvements of PFS, ramucirumab didn't specifically target these driver mutations. Additionally, FDA had safety concerns and recommended we wait to submit.

Given the high unmet medical need and

clinically meaningful benefits observed in the RELAY study, we submitted the application in July. The clinically meaningful benefits are further supported by recent approval in Europe and inclusion in updated NCCN guidelines. The data demonstrate a positive benefit-risk profile for Cyramza as first-line treatment. The combination of erlotinib shows statistically significant and clinically meaningful improvements in progression-free survival with no detriment in overall survival.

The magnitude of difference in PFS was 7 months. Results were consistent across sensitivity analysis and subgroups. This outcome was also supported by secondary and exploratory analysis. Importantly, the safety profile was well characterized and the toxicity observed was manageable. Having another first-line option would give oncologists a dual targeted therapeutic strategy to treat their patients.

With this information in mind, here's the agenda for our presentation. All outside experts

have been compensated for their time and travel for today's meeting. Thank you. I'd like to turn the lectern now to Dr. Vokes.

Applicant Presentation - Everett Vokes

DR. VOKES: Thank you.

I'm Dr. Everett Vokes, physician and chief at the University of Chicago. I'm a medical oncologist focusing on patients with lung cancer. Metastatic EGFR-mutated non-small cell lung cancer is a serious and life-threatening disease. There's an ongoing need for new targeted approaches to prolonged PFS and optimized patient outcomes.

Globally, more than 32 percent of non-small cell lung cancers are EGFR mutation positive, and about 60 percent of patients present with advanced or metastatic disease at diagnosis. Median survival is around 25 months and 5-year survival rates are around 14 percent. Treatment is focused on extending life and delaying disease progression while allowing patients to maintain their quality of life by using chemotherapy later in their overall treatment sequence.

The EGFR pathway is a frequent driver in the development and progression of non-small cell lung cancer. Activating EGFR mutations are found in about 10 to 20 percent of Caucasian patients and up to 40 to 60 percent of Asian patients. Regardless of ethnicity, these mutations are commonly found in females, non-smokers, or those who have adenocarcinoma histology. As a result, patients have fewer comorbidities.

The most common activating mutations in EGFR are deletions with an exon 19 or a substitution in exon 21. The presence of these activating EGFR mutations in advanced non-small cell lung cancer is associated with sensitivity to small molecule EGFR TKIs. To date, three generations of TKIs have been approved.

The first targeted agents were gefitinib and erlotinib, followed by second generation afatinib and dacomitinib, and the most recent generation TKI, osimertinib, was originally approved in 2017 as second line specifically to target the dominant resistance mutation T790M. Osimertinib was later

approved for first-line treatment regardless of the T790M mutation. All targeted treatments remained current first-line options based on international guidelines and practices. Only monotherapy regimens are currently approved in the United States.

Despite the initial benefit of the earlier generation EGFR TKIs, they are associated with inevitable development of treatment resistance, and patients would eventually experience loss of clinical benefit.

Osimertinib has demonstrated efficacy and tolerability advantages over early generation TKIs, however, the mechanisms of resistance after first-line osimertinib are heterogeneous and are mostly non-targeted. Thus, patients currently have no options other than chemotherapy-based regimens once they progress on osimertinib. Furthermore, immunotherapy options for this population are rarely successful.

Let me present this treatment sequence visually. Our goal is to delay progression and the

use of chemotherapy as long as possible. The early generation treatments offer 9 to 15 months of progression-free survival, however, about 50 percent of patients will develop a T790M mutation, and since 2017, these patients can receive osimertinib, adding 10 months of PFS before needing chemotherapy. Patients who are T790M negative proceed immediately to chemotherapy.

Since 2018, osimertinib can be given to all patients with EGFR-mutated non-small cell lung cancer resulting in a median PFS of 19 months and eliminating T790M as a resistance mechanism. No additional targeted therapy options are available for patients once tumors progress.

A combination therapy has the potential to further improve outcomes by offering patients an alternative mechanistic option. In fact, there is preclinical rationale for such a combination based on numerous publications. It's well understood that EGFR-mutant tumors are more VEGF dependent than EGFR wild-type tumors, and dual VEGF EGFR pathway blockade enhances efficacy.

EGFR mutations result in constitutive upregulation of VEGF and HIF-1 alpha in EGFR-mutant lung cancers, and EGFR inhibition lowers VEGF levels via HIF-1 alpha, resulting in anti-angiogenic effects. Additionally, acquired EGFR inhibitor resistance is associated with an increase in VEGF.

EGFR-mutant tumor cells have higher levels of VEGF than EGFR wild-type cells, and VEGF is markedly reduced in these cells by erlotinib. We know that resistance to EGFR inhibitors is associated with a rise in VEGF levels. This may explain why VEGF inhibition can delay the emergence of EGFR inhibitor resistance. The combination of VEGF and EGFR inhibitors is particularly effective for EGFR-mutant tumors.

In summary, there is an ongoing need for additional first-line treatment options that provide clinically meaningful benefits, including delaying disease progression and use of chemotherapy. There's also a need for new mechanistic approaches to further advance the

field, as well as offer the potential for improved patient outcomes.

Having a choice of therapy is not to be minimized. When patients come to my office, I discuss their options, and they want to have informed choices in their medical health. Expanding the selection of first-line options available would allow oncologists greater strategic choices in shared decision making with our patients. Thank you. I'll now turn the presentation to Dr. Abada.

Applicant Presentation - Paolo Abada

DR. ABADA: Thank you. I'm Paolo Abada, senior medical director and lead for the Cyramza global product development at Eli Lilly, and currently a practicing oncologist. Let me start by describing the RELAY design.

The phase 3 portion of the RELAY study was a global, multicenter, randomized, placebo-controlled, double-blind study. 449 patients were randomized one-to-one to receive either 10 milligrams per kilogram Cyramza every

2 weeks in combination with erlotinib 150 milligrams per day or to placebo plus erlotinib.

Patients underwent imaging every 6 weeks for 72 weeks and every 12 weeks thereafter until disease progression. For patients who discontinued treatment prior to documented progression, tumor assessments were continued until objective evidence of progressive disease, death, or study completion. Following discontinuation of study treatment, patients and investigators remained blinded, and the choice of post-discontinuation therapy was at the discretion of the investigator. Currently, the study is ongoing and blinding will be maintained until the final overall survival analysis.

The primary endpoint was progression-free survival. This was defined as the time from the date of randomization until the date of documented radiographic progression or death. The study was powered to show a clinically meaningful improvement of at least 4 and a half months for the combination. Secondary efficacy endpoints are listed here. Overall survival was the only

secondary endpoint in the hierarchical scheme of error-controlled endpoints. Other secondary endpoints were evaluated independently of PFS and overall survival.

Key inclusion criteria specified enrollment of patients with cytologically or histologically confirmed diagnosis of stage 4 non-small cell lung cancer; patients who were eligible for first-line treatment with erlotinib based on documented evidence of tumor with EGFR exon 19 deletion or exon 21 substitution mutation; and patients with an ECOG performance status of 0 or 1 and adequate organ function.

The study specified exclusion of patients with a known T790M EGFR mutation, CNS metastases, clinically active interstitial lung disease, or any prior anticancer therapy for advanced disease.

Moving to patient demographics, the enrolled population reflects that expected of an EGFR-mutant non-small cell lung cancer population in clinical practice. Demographics were well balanced between treatment arms. Most patients in either group were

female, around 65 years of age, and Asian.

Disease characteristics were also well balanced. The majority of patients had primary metastatic disease. Most were non-smokers and had good performance status at baseline. Consistent with eligibility criteria, all patients were EGFR mutation positive and equally divided between exon 19 deletion and exon 21 EGFR mutation.

449 patients were randomized, which constitutes the intent-to-treat population, 224 patients to the Cyramza plus erlotinib and 225 to placebo plus erlotinib. Three patients in the Cyramza plus erlotinib group were not treated, and the safety population consisted of 221 patients for Cyramza plus erlotinib and 225 for placebo plus erlotinib.

The primary reasons for treatment discontinuation in either group were progressive disease and adverse events; 64 Cyramza patients and 43 placebo patients remained on study treatment at the time of data cutoff in January 2019.

Now turning to the primary results, RELAY

met its primary endpoint demonstrating a statistically significant and clinically meaningful improvement in progression-free survival compared to an approved standard of care. With a median follow-up time of 20.7 months, the investigator-assessed median progression-free survival was 19.4 months in the Cyramza plus erlotinib arm compared to 12.4 months in the placebo plus erlotinib arm, representing a 7-month longer median PFS for Cyramza.

Treatment with Cyramza reduced hazard of disease progression or death by 41 percent with a stratified hazard ratio of 0.591 and a highly significant p-value of less than 0.0001. The Kaplan-Meier curves show an early separation at 3 months that was sustained through about 30 months of follow-up.

The primary results are supported by multiple and prespecified sensitivity analyses, including an analysis conducted by a blinded independent radiological review committee. All analyses demonstrated a hazard ratio between 0.58

and 0.67, consistent with the primary analysis. A consistent PFS benefit was also observed across prespecified subgroups. As you can see, all point estimates fall below a hazard ratio of 1.

Moving now to secondary efficacy endpoints, the objective response rate was high and similar between arms. Disease control rate was close to 100 percent in both treatments. Thus, it's difficult to appreciate the treatment benefit based on objective response alone. Rather than improvement in response rate, the benefit of this therapy is clearly demonstrated by the more durable response for patients in the Cyramza arm.

The median duration of response was significantly longer in the Cyramza arm than in the placebo plus erlotinib arm. The median duration in the Cyramza arm was 18 months versus 11.1 months in the placebo arm. The significant improvement in the duration of response demonstrates the durability of response that Cyramza contributes.

We also assessed patient-reported outcomes. Patients rated their symptoms and quality of life

utilizing the Lung Cancer Symptom Scale, or LCSS, where lower scores represent fewer symptoms. Patient completion was more than 95 percent in both arms. Consistent with the enrolled patient population, patients reported relatively good overall quality of life and low symptom burden at baseline with summary scores of 22 or less.

Hence, we would not anticipate significant improvements in the LCSS. We do observe mean LCSS total scores remained similar between arms over the course of treatment with no significant changes from baseline.

Time to deterioration in the LCSS total score and the average symptom burden index did not differ between treatment arms. The time to deterioration by individual components of the LCSS shows no differences by treatment arm for all scores except blood in sputum. The blood in sputum finding is consistent with symptoms associated with non-small cell lung cancer and the known bleeding risk for hemoptysis and epistaxis with VEGF inhibitors.

Moving now to the secondary endpoint of overall survival, according to the protocol, interim overall survival was assessed at the time of the primary PFS assessment in January of 2019. Interim overall survival was immature with a censoring rate of more than 80 percent. Fewer deaths were observed in the Cyramza plus erlotinib arm with 37 compared to 42 in the placebo plus erlotinib arm. The stratified hazard ratio for interim overall survival was 0.83.

At FDA's request, an additional unplanned interim overall survival analysis was performed using a more recent data cutoff from December 2019. This showed similar results with a hazard ratio of 0.92. Some variability in the overall survival hazard ratio is expected as the OS data are maturing with the updated analysis subject to more than 70 percent censoring. Fewer deaths continued to be observed in the Cyramza arm.

Median survival is not yet reached, and of note, it's projected to be more than 50 months. For our prespecified statistical analysis plan,

Lilly plans to submit final overall survival data when 300 events are reached, which is estimated to be some time in 2023.

As we discussed earlier, the development of T790M potentially impacts subsequent therapy. We assessed the frequency of this mutation at the time of progression on study treatment. Circulating tumor DNA was assessed in plasma collected at the time of progression.

In patients for whom EGFR activating mutations were detectable in the post-progression sample, the rates of post-progression EGFR T790M mutation were similar between treatment arms, at 43 percent in the Cyramza arm and 47 percent in the placebo arm. The addition of Cyramza to erlotinib does not appear to alter the proportion of patients with T790M mutation at the time of progression on first generation TKIs.

We also looked at post discontinuation anticancer therapy use. This table shows a summary across all subsequent lines of therapy. The addition of Cyramza did not preclude use of

subsequent therapy. More than 75 percent of patients who progressed have received subsequent anticancer treatments, and patients continued to receive additional lines.

EGFR TKIs were the most common post discontinuation therapy with around 40 percent of patients receiving osimertinib. Please keep in mind that these percentages may underrepresent current practice, as osimertinib was not globally approved until part way through the study.

Chemotherapy was the second most common. Additionally, 15 percent of Cyramza patients and 24 percent of placebo patients received a VEGF inhibitor post-progression. The number, types, and potential differences in sequencing of various post-progression anticancer therapies likely confounds and attenuates effects on overall survival.

Looking specifically at first subsequent post-discontinuation anticancer therapy, we see that investigators chose to sequence an EGFR TKI first in more than 70 percent of patients, with

only about 24 percent of patients receiving chemotherapy first. Due to this finding, we performed a post hoc analysis evaluating time to chemotherapy or death, which revealed a median time of 34 months for patients on Cyramza and erlotinib.

In conclusion, results from the RELAY study demonstrated statistically significant, clinically meaningful, and durable benefits in patients who received Cyramza plus erlotinib compared with placebo plus erlotinib. The primary endpoint was met, demonstrating a 7-month improvement in median progression-free survival and reduced the hazard ratio of disease progression or death by 41 percent with Cyramza compared to placebo. This result was consistent across sensitivity analyses and consistent across subgroups.

Importantly, improvements in secondary and exploratory endpoints support the meaningful delay in disease progression. This included improvements in PFS2, time to chemotherapy, and a significant improvement in the duration of response with 18 months in the Cyramza plus erlotinib arm versus

11 months in the placebo plus erlotinib arm, and no evidence of detriment on overall survival. The demonstrated efficacy results reinforce the benefit of targeting the EGFR and VEGF pathways with this treatment regimen.

Thank you. I would now like to turn the podium to Dr. Carla Visseren.

Applicant Presentation - Carla Visseren

DR. VISSEREN-GRUL: Thank you, Dr. Abada.

I'm Carla Visseren-Grul, the global medical lead for the RELAY study. I'll now review the safety data of RELAY, demonstrating that adverse events were manageable, and the safety profile of Cyramza plus erlotinib was consistent with expectations based on the established safety profile of the individual treatment components.

The safety profile of Cyramza is well established. As of September 2019, more than 6,400 patients have received Cyramza in the clinical trial program, and more than 125,000 patients have been treated with Cyramza worldwide, across five licensed indications in the postmarketing setting.

In RELAY, the median duration of each study treatment was longer among patients in the Cyramza plus erlotinib arm. The median duration of Cyramza therapy was 11 months compared to 9.7 months for placebo. The median relative dose intensities of each study drug was high, comparable between treatment arms and consistent with the targeted dose. The longer duration of study treatments in the Cyramza plus erlotinib arm and similar relative dose intensities of the study drugs between treatment arms attest to the tolerability of the combination regimen.

Turning to an overview of the safety profile, all patients reported at least one treatment-emergent adverse event, and this would be expected for combination treatments. The incidence of grade 3 or higher treatment-emergent adverse events and serious adverse events was higher in the Cyramza plus erlotinib arm compared to placebo plus erlotinib. Of note, the grade 3 or higher events were predominantly grade 3 in severity. Despite the increases in these events, the percentage of

patients who discontinued off study treatment due to an adverse event was similar between arms.

Adverse events leading to death on study treatments or within 30 days of treatment discontinuation were reported in the Cyramza plus erlotinib arm with 6 patients in total. One of these events was assessed to be related to Cyramza by the investigator, and I'll review this case in greater detail shortly.

Here are the most commonly reported any grade adverse events occurring in greater than or equal to 20 percent in the Cyramza plus erlotinib ARM. These events are consistent with the known safety profile of these approved agents and what is expected to occur within this disease setting, and for infection we showed a composite term.

The majority of the differences in the incidences between arms were observed in grade 1 and 2 events with the exception of hypertension. A grade 3 or higher adverse events occurred with a 2 percent or higher rate in the Cyramza plus erlotinib arm for hypertension, dermatitis

acneiform, and diarrhea. None of these were grade 4 or 5.

A higher rate of infection grade 3 or higher was observed with Cyramza plus erlotinib at 17 percent compared to 7 percent. The majority of these infections occurred in 1 to 2 patients each. Three events were associated with grade 3 or higher neutropenia. The only grade 3 or higher event occurring at a higher rate in Cyramza plus erlotinib treated patients was pneumonia.

A higher percentage of Cyramza plus erlotinib treated patients reported serious adverse events compared to placebo. Most of the serious adverse events occurred in single patients each, and the analysis of serious adverse events did not reveal any notable findings.

During study treatment, or within 30 days of treatment discontinuation, 8 deaths occurred in the Cyramza plus erlotinib arm and 2 occurred on placebo plus erlotinib. Two patients in each group died due to study disease. Six patients on Cyramza plus erlotinib died due to adverse events. No

additional deaths due to adverse events have been reported based on the unplanned data cutoff for overall survival re quested by the FDA from December 2019, which includes an additional 8.4 months of patient follow-up.

Of the 6 events just noted, one event of hemothorax was assessed by the investigator as related to study treatments. The event began on day 74, 28 days after the last dose of Cyramza and 5 days following insertion of thoracic drainage for pleural empyema. The remaining 5 events were assessed as not related to Cyramza or erlotinib by the investigator. Three of these deaths occurred several months after discontinuation of Cyramza treatments and while on erlotinib.

Moving to discontinuations, the overall incidence of adverse events leading to discontinuation of all study treatments were similar between treatment arms, demonstrating that the adverse event profile is manageable, allowing the majority of patients to remain on study treatments. Few adverse events leading to

discontinuation of all study treatments were reported in more than one patient with no predominant adverse event identified leading to discontinuation of Cyramza plus erlotinib.

Here are the adverse events leading to discontinuation of one study treatment, Cyramza or placebo, while patients continued erlotinib treatments. The most common adverse events leading to discontinuation of Cyramza were predominantly low grade, grade 1 or 2 events. Events leading to discontinuations with at least a 2 percent difference were proteinuria, platelet count decreased, and neutropenia.

Moving on to adverse events of special interest, adverse events of special interest are prespecified, selected adverse events of clinical interests that have been associated with other antiangiogenic agents in a similar pharmacological class of Cyramza that inhibits the VEGF signaling pathway. The combination treatment resulted in an overall higher rate of adverse events of special interest, but the majority of events were of low

grade severity and manageable.

Grade 3 or higher events are shown in darker blue for Cyramza plus erlotinib and darker gray for placebo and erlotinib. Hepatic events were the most predominant in both arms. The high rate of hepatic events in the Cyramza-erlotinib arm was due to lab abnormalities of grade 1 and 2 ALT and AST increases. Bleeding or hemorrhage events were primarily driven by low grade epistaxis.

Let's discuss how these adverse events commonly associated with a class of VEGF pathway inhibitors were managed. Hypertension is easily detected through routine monitoring and managed with antihypertensive therapy and dose adjustments. Of the patients who had an event of hypertension, no grade 4 or 5 adverse events occurred and 2 patients experienced a serious adverse event.

Eighty-seven percent of patients experienced a single event with no study treatment change and 13 percent required Cyramza dose adjustments, which were mainly dose delays. Antihypertensive therapy and dose adjustments were effective with only one

patient discontinuing Cyramza alone, and overall, hypertension did not impact the patient's ability to continue treatments.

Adverse events of bleeding or hemorrhage were tolerable and manageable with dose adjustments and pharmacological therapy. Of the patients with bleeding or hemorrhage, 7 experienced a series of adverse events; 90 percent did not require change in study treatments; 9 percent were managed with dose adjustments, which included delays or omissions; and one patient had a blood transfusion. Importantly, management strategies were effective and didn't impact the patient's ability to continue study treatments, as only one patient require discontinuation from all study treatments and 4 patients discontinued Cyramza alone.

Proteinuria is easily detected through routine monitoring and managed with dose adjustments. The majority of the events that occurred were grade 1 or 2. One patient experienced serious adverse events. Sixty-two percent of patients who experienced proteinuria did

not require change in treatments. Cyramza dose adjustments involving dose delays, reductions, or omissions occurred in about 20 percent each. Dose adjustments allowed most patients to continue on therapy with two patients requiring discontinuation of all study treatments and 90 patients discontinuing Cyramza alone.

In conclusion, the safety profile of Cyramza is well characterized based on extensive postmarketing experience over almost 6 years across 5 approved indications. The safety profile in RELAY was consistent with the safety profile of the individual treatment components or events in the disease setting. Importantly, adverse events were manageable.

Overall, the combination of Cyramza plus erlotinib was well tolerated, as it's supported by the longer duration of study treatments in the Cyramza plus erlotinib arm and the high median relative dose intensities of each study drug. Cyramza plus erlotinib resulted in greater toxicity as compared to erlotinib alone. The additional

toxicities were easily detected through routine monitoring and managed through dose adjustments and supportive care.

Thank you. I'd now like to invite Dr. Heymach to the podium to share his clinical perspective.

Applicant Presentation - John Heymach

DR. HEYMACH: Thank you. I'm Dr. John Heymach. I'm the chair of thoracic and head and neck medical oncology at MD Anderson Cancer Center. I've been treating patients with lung cancer for 20 years, and during that time I've been involved in clinical trials of VEGFR and EGFR inhibitors, and my laboratory focuses specifically on mechanisms of resistance to these drugs.

The potential efficacy of blocking these two pathways has been reported in the literature for more than a decade, and having devoted a large part of my career to researching this dual blockade treatment strategy, it's truly gratifying to see results from RELAY that are fully consistent with these earlier reports.

These results are both exciting for the future of the field and for our patients, and as my colleagues noted, the treatment of EGFR-mutant non-small cell lung cancer remains a major challenge. There's been clear progress, but resistance inevitably develops to EGFR inhibitors, leaving patients with few options beyond chemotherapy based regimens.

The Cyramza-erlotinib combination offers a new mechanistic approach that fills this important unmet need. The combination expands first-line options for patients. The addition of new options is increasingly important in the medical community and is exemplified by the updated NCCN guidelines, which now recommend this combination as well as the EMA approval based on the data from RELAY.

This combination also enables patients to receive additional EGFR TKIs, particularly osimertinib as second-line therapy, potentially delaying the time to chemotherapy-based regimens and the use of PD-1 or PD-L1 one inhibitors.

Now, let me return to our treatment

landscape presented earlier by Dr. Vokes and show where the Cyramza-erlotinib combination may fit in as a first-line option. The dual targeted strategy gives us an option to start with the highly effective targeted regimen, and for the roughly 50 percent of patients who develop T790M resistance, osimertinib would remain a treatment option.

Therefore, this approach would maximize the time on EGFR-targeted therapies and potentially delay the time to platinum doublet chemotherapy, which not only carries substantial toxicity but is relatively ineffective in this population with the median PFS of 4 to 5 months.

In fact, in the RELAY trial, 74 percent of patients went on to EGFR TKIs and only 23 percent of patients went on to chemotherapy as the first subsequent therapy. By contrast, there are no targeted agents approved for patients who progress on osimertinib; therefore, it's unsurprising that in the FLAURA study, 68 percent of patients who progressed went on to chemotherapy as their first subsequent therapy.

Perhaps most impressive to me is the magnitude of the Cyramza plus erlotinib effect on PFS. As noted earlier, the study was designed to show at least a 4.5 month difference in PFS, a difference deemed clinically meaningful based on the ASCO guidelines and prior clinical results in this space. These RELAY results far exceeded these expectations with the 7-month difference in PFS.

Now, to put these findings into context, here's a figure showing the difference observed in median PFS for RELAY and the prior approved first-line treatments in this indication.

As a reminder, PFS was the basis for approval for all of these prior treatments. The Cyramza-erlotinib data show a magnitude of effect in PFS in line or above its predecessors while being compared to a proven standard of care, erlotinib. Additionally, the use of the combination did not preclude the subsequent use of osimertinib.

Cyramza in combination with erlotinib demonstrated statistically and, more importantly,

clinically significant improvements in PFS. Again, I stress that the magnitude of difference in PFS between Cyramza and placebo is particularly meaningful in this setting.

The primary endpoint of PFS is supported by the duration of response, which further demonstrates meaningful improvement in patient outcomes, and no detriment was observed in overall survival analyses. The RELAY study was well conducted and far exceeded the benefit it was designed to show.

Now, if overall survival becomes the standard for approval in disease settings with long survival as we observe here, we'll have to change how the trials are designed and enrollment will be challenging, as sample sizes will have to be greatly increased, and we'll be asking patients to wait unreasonable durations for drug approvals.

When patients come into my office, they want to know their disease is not progressing and they're comforted by knowing they can maintain response over time while potentially retaining

targeted therapy options in the future and delaying the time until chemotherapy may be needed.

Now, turning our attention to safety, the safety profile was consistent with the known safety profiles of each of the individual treatments and the underlying disease. While Cyramza plus erlotinib resulted in more toxicity than erlotinib alone, the adverse events were manageable with dose adjustments and routine supportive care. Also, patients on Cyramza were able to receive subsequent targeted therapy, including osimertinib post-progression.

To conclude, the Cyramza-erlotinib combination demonstrated a positive benefit-risk profile. There's a strong scientific rationale for the combination of a VEGF and EGFR inhibitor, and data from the RELAY study support this understanding. Cyramza plus erlotinib demonstrated statistically significant and clinically meaningful improvement in PFS. The safety profile is as expected, well understood, and manageable.

So why approve this combination now? Why

not wait until the final OS data is reported in three years? Well, in agreement with the statement from the FDA's briefing book, "First-line treatment of patients with EGFR-positive non-small cell lung cancer remains an unmet need," in this context, an additional three years is too long for patients to wait.

Expanding this selection of effective first-line options provides oncologists a dual-targeted therapeutic strategy to treat our patients, provides patients with more choices, and may delay the time to chemotherapy-based regimens, which provide limited benefit for patients with EGFR mutations. More so, the data from RELAY support a positive benefit-risk for the combination.

It would be unfortunate to deny approval of this new targeted therapeutic strategy to give patients an effective alternative first-line treatment. Thank you.

DR. HOFFMAN: Okay. We'll now proceed with the presentation from the FDA.

FDA Presentation - Barbara Scepura

MS. SCEPURA: Good afternoon. My name is Barbara Scepura, and I am a nurse practitioner and a clinical reviewer for the supplemental biologics licensing application 125477, for ramucirumab plus erlotinib, submitted by Eli Lilly, referred to as the applicant for the remainder of the presentation.

These are the names of the members of the FDA team for this application, and my presentation reflects their collective input. The FDA review issue for this application is as follows: Is the benefit-risk profile of ramucirumab plus erlotinib favorable for patients with untreated, metastatic, EGFR-positive non-small cell lung cancer?

The RELAY study shows an improvement in progression-free survival, however, there is uncertainty regarding the potential impact on overall survival, and there is increased toxicity associated with the addition of ramucirumab to erlotinib. During my presentation, I will begin with a brief overview of the results of the RELAY

study; I will then present the review issues that serve as the basis for referring this application to the advisory committee; and finally, I will provide a summary followed by the discussion topic and question for the committee.

Before we review the study design, here is a brief description of the regulatory history. In November 2014, a meeting was held between the applicant and FDA to discuss the design of the RELAY study.

During this meeting, FDA informed the applicant that, in general, a clinically meaningful and statistically persuasive improvement in progression-free survival, with a favorable benefit-risk profile and consistent effects in key secondary endpoints, including no evidence of a decrement in overall survival, would support a regulatory application for marketing.

In December 2014, the applicant submitted the RELAY study protocol. There were no further interactions between FDA and the applicant related to this study until June 2019, when a meeting was

held to discuss top-line results of the RELAY study. FDA recommended that the applicant wait for the mature prespecified analysis of overall survival in the RELAY study before filing an application for the proposed indication, and stated that if filed before mature survival data is available, FDA may seek the advice of the advisory committee. The supplemental BLA was submitted on July 29, 2019.

In the next few slides, I will provide a brief overview of the RELAY study. As a reminder, the RELAY study provides the primary evidence to support the evaluation of safety and efficacy for this application. The design of RELAY is shown here.

RELAY is a randomized, placebo-controlled, blinded study to evaluate the benefit of adding ramucirumab to erlotinib compared to single-agent erlotinib in patients with previously untreated metastatic EGFR mutation-positive non-small cell lung cancer. The primary endpoint of the RELAY study was investigator-assessed, progression-free

survival. The study had 80 percent power to detect a hazard ratio of 0.71 with 270 progression-free survival events.

The key secondary endpoint of RELAY was overall survival. The final analysis of overall survival was planned to occur after 300 deaths are observed, but the statistical analysis plan did not prespecify effect size assumptions or power for the overall survival analysis.

FDA agrees with the applicant's presentation of the final analysis of the primary endpoint of investigator-assessed progression-free survival. The RELAY study demonstrated a statistically significant improvement in progression-free survival per investigator assessment for patients in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm. This difference in median progression-free survival as assessed by investigator was 7 months with a hazard ratio of 0.59.

This is the plot of the Kaplan-Meier estimates of progression-free survival. Presented

here are the results for progression-free survival as assessed by blinded, independent central review. These results are relevant given the possibility of unintentional loss of blinding due to differential toxicity between treatment arms.

The difference in median progression-free survival as assessed by blinded independent review was 5.4 months with a hazard ratio of 0.67. The concordance and assessment of progressive disease between investigator and blinded independent central review was 79 percent, which is considered an acceptable range for oncology studies.

At the time of final progression-free survival analysis, a prespecified interim analysis of overall survival was performed. Seventy-nine deaths had occurred and the median follow-up was 20.7 months. Median overall survival had not been reached in either arm. The hazard ratio was 0.83 with a 95 percent confidence interval of 0.53 to 1.30.

Due to the immaturity of the overall survival data provided in the submission, FDA

requested updated survival data. The updated data cutoff provided an additional 8.4 months of median follow-up time. A total of 125 deaths had occurred, corresponding to 42 percent of the information needed for the final analysis. The median survival was not reached in either arm and the hazard ratio was 0.92 with a 95 percent confidence interval of 0.65 to 1.32.

This is the plot of the Kaplan-Meier estimates of overall survival from the December 31, 2019 cutoff. FDA agrees with the applicant's presentation of overall response rate. The overall response rate was similar between study arms. The median duration of response was 7 months longer for patients treated with the combination of ramucirumab plus erlotinib compared to those treated with placebo plus erlotinib.

Progression-free survival 2, or PFS2, was an exploratory endpoint in RELAY. It is defined as the time from randomization to second disease progression. Issues such as measurement bias due to inconsistent post-progression scan schedules and

confounding by post-progression therapies make estimation of the treatment effect on PFS2 difficult, therefore, FDA does not use PFS2 as the basis for regulatory decisions.

Two additional exploratory endpoints in RELAY were patient-reported outcome measures. Specifically, the Lung Cancer Symptom Scale and EQ-5D-5L were collected. The quality of the data collection was high with good completion rates, however, the trial was not designed to make comparative claims, and there was no prespecified statistical analysis plan controlling for type 1 error for PRO endpoints.

The applicant claims that the patient-reported data suggested overall quality of life and average symptom burden were not negatively impacted by the addition of ramucirumab to erlotinib compared to placebo plus erlotinib. The FDA disagrees with the applicant's position for the following reasons.

First, the hazard ratios generally do not favor the ramucirumab plus erlotinib arm. Second,

the patient-reported symptoms corroborate with clinician-reported adverse events. Lastly, the Lung Cancer Symptom Scale measures symptoms and quality of life but does not allow for a direct assessment of the tolerability of therapy.

The combination of ramucirumab plus erlotinib resulted in increased toxicity compared to placebo plus erlotinib, including an increased incidence of grade 3 or higher adverse events and serious adverse events. Specific adverse events of interest occurring at a higher incidence on the ramucirumab plus erlotinib arm included hypertension, bleeding, proteinuria, and severe infections.

These will be discussed in more detail later in the presentation. There were 6 deaths due to adverse events on the ramucirumab plus erlotinib arm, with two considered possibly related to treatment with the combination.

I will now present the FDA review issues starting with the historical context of drug approvals for the first-line treatment of

metastatic EGFR- positive non-small cell lung cancer.

Over the last decade, approvals for first-line treatments for metastatic non-small cell lung cancer therapies, not targeting oncogenic driver mutations, have been based on demonstration of an improvement in overall survival. During this time period, there was a shift in the approach to treatment of non-small cell lung cancer focused on the development of therapies targeting specific genomic aberrations present in cancer cells such as EGFR mutations.

Approvals of first-line treatments for metastatic non-small cell lung cancer therapies that specifically target oncogenic driver mutations have been based on the demonstration of an improvement in progression-free survival. In studies investigating earlier generation EGFR TKIs, where the magnitude of overall response rate with EGFR TKIs was high compared to chemotherapy, the majority of patients in the chemotherapy arm received an EGFR TKI following disease progression.

The high rate of EGFR TKI used post-progression confounded assessments of overall survival. The RELAY study enrolled patients with non-small cell lung cancer with an oncogenic driver mutation, and all patients received erlotinib. Ramucirumab is the experimental agent in the study. Ramucirumab is a VEGF-R2 inhibitor that does not target an oncogenic driver mutation.

These are the agents currently approved specifically for the first-line treatment of metastatic EGFR mutation-positive non-small cell lung cancer. All are EGFR tyrosine kinase inhibitors. As previously stated, approvals of these targeted agents have been based on improvements in progression-free survival.

In trials of earlier generation EGFR TKIs, shown at the top of the table in white, the majority of patients who were randomized to chemotherapy and experienced disease progression subsequently received treatment with an EGFR TKI, confounding the analysis of overall survival in these trials.

In most recent studies of third generation EGFR TKIs that used a comparator of first generation EGFR TKI, shown at the bottom of the table in gray, improvements in overall survival have been observed. Potential confounding of overall survival due to subsequent therapy is not an issue for the RELAY study, as only 4 percent of patients in the control arm received ramucirumab as post-discontinuation anticancer therapy at any time.

As a reminder of the results presented earlier, the left side of the table shows overall survival results from the RELAY study at the time of primary progression-free survival analysis, and updated overall survival results are presented on the right. With an information fraction of 42 percent, the updated analysis of overall survival shows a hazard ratio of 0.92 with a 95 percent confidence interval of 0.65 to 1.32.

Given the results at the updated data cutoff were still immature and the confidence interval of the hazard ratio is wide, the treatment effect on

overall survival is unclear given observed data. Additional follow-up is the only reliable way to assess effect on overall survival.

I will now present the toxicity data. In the RELAY study, there was an almost 20 percent higher incidence of grade 3 or higher adverse events and an increased incidence of serious adverse events in the ramucirumab plus erlotinib arm compared to placebo plus ramucirumab.

There were more deaths due to adverse events on study or within 30 days of treatment discontinuation in the ramucirumab plus erlotinib arm, 6 compared to none in the placebo plus erlotinib arm. Of these deaths, FDA considers two to be possibly related to treatment with ramucirumab plus erlotinib, one death due to hemothorax and one due to encephalitis influenza.

These are the adverse events selected by FDA due to notable increase in incidence of events on the ramucirumab plus erlotinib arm. Eighteen percent of patients treated with ramucirumab plus erlotinib experienced grade 3 or higher infections

compared to 7 percent of patients treated with placebo plus erlotinib. Twice as many patients treated with ramucirumab plus erlotinib had all-grade bleeding or hemorrhage events with an incidence of more than 50 percent in the ramucirumab plus erlotinib arm.

Most of the bleeding events were low grade with only 4 patients treated with the ramucirumab plus erlotinib experiencing grade 3 or higher bleeding events, however, one of these 4 events resulted in death due to hemothorax.

There were no grade 3 or higher bleeding events on the placebo plus erlotinib arm. There was nearly 5 times more grade 3 hypertension on ramucirumab plus erlotinib compared to placebo plus erlotinib. Grade 3 hypertension by CTCAE definition is systolic blood pressure of 160 or higher and diastolic blood pressure of 100 or higher, and requires more than one drug or more intensive therapy than previously used.

Of the patients treated with ramucirumab plus erlotinib, 22 percent required 3 or more

antihypertensives compared with only 2 percent of patients on the placebo plus erlotinib arm. All-grade proteinuria occurred at 4 times higher incidence on the ramucirumab plus erlotinib arm as compared to placebo plus erlotinib.

The incidence of any grade treatment-emergent laboratory abnormalities was higher for patients treated with ramucirumab plus erlotinib as compared to placebo plus erlotinib, but the incidence of grade 3 or higher incidence laboratory abnormalities was similar between study arms.

I will now summarize the review issues related to the first-line treatment of metastatic EGFR mutation-positive non-small cell lung cancer with ramucirumab plus erlotinib. The RELAY study demonstrated an improvement in median progression-free survival for patients treated with the combination of ramucirumab plus erlotinib as compared to patients treated with placebo plus erlotinib, however, there are uncertainties regarding the effect on overall survival.

There is increased toxicity with the addition of ramucirumab to erlotinib. Of particular concern are the increased incidences of grade 3 or higher adverse events, serious adverse events, severe infections, and hypertension. Given the upper limit of the confidence interval of 1.3, the overall survival results suggest a possibility of a detrimental effect on survival for patients treated with the combination of ramucirumab plus 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 metastatic EGFR-positive non-small cell lung cancer remains an unmet medical need, there are therapies currently approved for which an overall survival improvement has been observed when compared to first-generation EGFR TKI.

I will now present the discussion topic and question for the advisory committee. Please discuss whether the results of the RELAY trial, with a demonstrated improvement in progression-free

survival, support a positive benefit-risk assessment given the uncertain effect on overall survival and increased toxicity with combination therapy.

The voting question is as follows. Is the benefit-risk profile of ramucirumab plus erlotinib favorable for patients with untreated metastatic EGFR-positive non-small cell lung cancer? This concludes the FDA's presentation. Thank you for your attention.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you. We'll now take clarifying questions for the presenters, and please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter.

Dr. Cristofanilli?

DR. CRISTOFANILLI: Yes. I have a question for the sponsor. You have a lot of data you showed, data that is certainly positive. I'm still puzzled trying to understand why your overall survival outside the toxicity is not improved. You

showed that progression-free survival has a significant improvement and that the progression-free survival 2 has improved.

This is not associated with an improved response but with a delay of progression, and it seems like the rate of T790M mutations is the same. So obviously I think about the possibility that you are selecting a more aggressive disease that is outside this particular mutation.

Are you looking at cell-free DNA in order to understand the disease at first progression, second progression, and if this is not due to toxicity but other reasons that compromise the additional response to other treatments? Have you looked at overall lung specific overall survival?

If you have 6 deaths to the combination, this may be a confounding factor, so you don't know if the treatment has modified the natural history of the disease or deaths are simply due to the combination of specific lung progression versus toxicity.

I think we need to try to understand, before

we can say that this progression-free survival is meaningful and that you can propose this as alternative first-line therapy, in particular where the toxicity is similar, in some respect, to chemotherapy.

DR. MELEMED: That was a lot of questions, so I'm going to try hit a couple of them first. I first would like to have Dr. Abada discuss where you mentioned progression-free survival 2. That was an endpoint that EMA recommended that we add to the trial, as they knew survival was long, and this was an endpoint in between survival to get an intermediate to see if you had maybe a worsening post-progression of effect to see; and then I want Dr. Abada to discuss overall survival. I'll get those two questions first.

Dr. Abada?

DR. ABADA: Paolo Abada, clinical development. Within the briefing book, we did have the PFS2, and that's shown here. As Dr. Melemed mentioned, this assesses the second progression-free survival event following the first

progression, so it's sort of an intermediate endpoint between progression-free survival and overall survival. We do see in this analysis that the benefit of adding erlotinib appears to be maintained into at least the second progression based on this analysis.

Now, moving on to overall survival, that analysis has also been shared. Currently, this is a very, still, immature analysis with still only around 30 percent of events. With this, we see a hazard ratio that still is on the side of favoring at 0.92, but still no clear difference between the arms. But I would also add, though, that in this setting, post-progression treatments are very different than what you may have seen with osimertinib, whereas, as has been mentioned earlier by Dr. Heymach, the majority of patients post-osi got chemotherapy, and whereas here we see a high proportion of patients getting additional TKIs.

So there's a higher risk here of seeing potential confounding, both from the number of additional therapies as well as, again, the very

long overall survivals that we're seeing here in excess of approaching 4 years.

DR. MELEMED: Can I ask Dr. Heymach to address your last question, which was modes of resistance from that aspect?

DR. HEYMACH: To address the first part, for example, is there an acceleration of the disease after progression that's a differential between the two? You could imagine a couple of reasons why OS may not be significant given the PFS difference. First of all, the study wasn't powered for that. The data is very immature. Only a third of patients have been seen, and the survival here is getting longer and longer, which is a good thing for the field.

In the FLAURA study, for example, the overall survival is 38.6 months. Back with the IPASS study, it was 18.6 months. Now we're over 50 months, so that means the results will be more and more confounded by subsequent therapies over time. So two possibilities; one is that it's chance. A second possibility is a shortening of

post-progression survival.

If we could put up the PFS2 data here, as Dr. Abada mentioned, there's no evidence that PFS2 is shortening. So if we thought that subsequently you had more aggressive disease, we would expect the difference to disappear here.

Now, if I could go to core side 42, a third possibility is that there is crossover to VEGF inhibitors that's confounding it in the control arm. If you look here, there actually is an imbalance. If you look at VEGF therapies in the placebo arm, 24 percent go on to receive VEGF therapies. In the Cyramza arm, only 15 percent do. So that's a 9 percent difference in those that received the VEGF therapies.

Among those, I think the data, while we can't know for sure, does not support an acceleration of the disease and does point more towards additional VEGF therapy in the control arm.

Let me just use the opportunity to mention one other thing. The idea was raised that this isn't a targeted therapy for EGFR-mutant disease.

We know that therapies can have benefit even if they're not directly targeting the mutation in defined populations.

For example, PARP inhibitors aren't targeting PARP mutants; they're targeting BRCA mutant patients often, patients who have a defect in homologous repair and you're targeting a downstream pathway. VEGF inhibitors are effective in kidney cancer that have this constituent of upregulation of the HIF-1 pathway through VHL mutations.

Here, we know that EGFRs mutants have constitutive upregulation of the HIF pathway, so in that sense they're renal cell-like with this constitutive upregulation, and we believe that's why this mechanistically is a targeted therapy, particularly for this subgroup. I'll mention here that this subgroup analysis from earlier studies -- and I'm happy to discuss in more detail to support -- this group is particularly sensitive to VEGF inhibitors compared to other subgroups of lung cancer patients.

DR. HOFFMAN: Dr. Hindrichs?

DR. HINDRICHS: I would like to ask a question from Dr. Heymach regarding CO-64. Can you put up that slide, please?

To me, in many ways, this is kind of the crux of the question because we're looking at how this combination therapy might add a useful treatment option to our toolbox that we have for patients. Given that there's already osimertinib available and it has a better toxicity profile, it leads one to think about what is the role, then, for this combination, and what is the intended niche for this. As far as I could tell from the presentations from the applicant, this looks like the explanation for that.

To add to that, my question then would be, for this slide, how much of this slide is a representation of clinical data and how much it of it is made up to illustrate what you hope is going to happen?

DR. HEYMACH: Well, thank you for that question. First, if I could have the pie chart

with osimertinib resistance. This is data now taken from several studies that have been published, and I'll mention in addition to the pie chart that's shown here, our group, MGH, a study led by Zosia Piotrowska and Geoff Oxnard at Dana-Farber, as well as the Memorial Sloan Kettering group, have all published similar results. So there's at least 4 independent studies that all show the same thing.

Because osimertinib targets T790M, the mechanisms become largely EGFR independent. If you look here in the pie chart, you see a variety of EGFR mutations, that light blue 6 to 10 percent. This includes the 718Q, the 797 mutations, and the 724. We don't have any approved agents for any of these. The S768I is the only one that has afatinib approved for that 1 percent.

We don't have any approved agents for MET amplification to this subgroup, and we don't have any approved agents in this setting for any of the other alterations. So there are no approved targeted therapies for osimertinib resistance

mechanisms.

This is actual data from the FLAURA study. The expected impact then would be -- unlike a treatment with the first generation where you typically get a T790M in 50 to 60 percent, here you don't have another EGFR TKI to go to.

If I could go to CC-25, please? Here is the actual data from the FLAURA, the New England Journal of Medicine publication, and they looked at the first subsequent therapy. Here, the first subsequent therapy was chemotherapy in 68 percent of the cases. In the comparator EGFR TKI arm, it was an EGFR TKI in 74 percent of cases. You look at the Cyramza and erlotinib arm, it is superimposable at 74 percent.

So this tells you that real data, patients who start with osimertinib can go on to additional EGFR TKIs. Now, in the case of FLAURA, it was a less effective regimen. Obviously, with Cyramza plus erlotinib, that's a more effective regimen. Only 23 percent went on to chemotherapy.

Finally, if we could have the time to

chemotherapy curve? Let me just show the last data, and this was mentioned by Dr. Abada, but we didn't show this data. This is the actual data about time to chemotherapy in this study or death between the two arms. You can see there's a significant difference in the time to chemotherapy. Now, this is an exploratory analysis post hoc, but this is just addressing this specific question.

This is real data saying it isn't theoretical. Patients who start with osimertinib, the majority go on -- 68 percent go to chemotherapy next. The patients who start with erlotinib plus Cyramza, the vast majority go on to EGFR TKI next. The time to chemotherapy is delayed in this study as well.

DR. HINRICHS: I just have a follow-up question then, because you've presented data to support what the sequence of drugs is, but really what's not important -- what's less important is the sequence and what's more important is the overall time until you get to chemotherapy.

DR. HEYMACH: Right.

DR. HINRICHS: Do you have any data to support the graph that you showed in CO-64?

DR. HEYMACH: Well, if we could back to the previous one here, this is the actual time to chemotherapy. Also, if we can show the two Kaplan-Meier plots from patients treated with osimertinib?

DR. MELEMED: That would be SU-7.

DR. HEYMACH: Again, at the EMA, they collected PFS2 data, which really is helpful for us understanding the impact of subsequent therapies.

This is, I think, the best one to address your question. This is the overall survival for patients who received osimertinib as their next subsequent therapy, and this addresses the earlier questions as well. Patients with Cyramza plus erlotinib who then went on to osimertinib had longer benefit than those who didn't go on to osimertinib.

Now, if you look over at the placebo arm, you see that the patients who went on to osimertinib still trended toward better than those

who didn't go on to osimertinib, but actually those under the Cyramza arm certainly didn't do worse as a result. There are no signs of acceleration. If anything, it actually looks more favorable in that. This is real data about patients who then went on to osimertinib, and this shows you that their survival is better. This is the actual data.

One last point; the overall outcomes for these patients one would expect would get better over time as osimertinib becomes more widely available. So a lot of the benefits we're talking about could not be fully realized because osimertinib was not globally available at the time the majority of the study was being run.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Susan Halabi, Duke university. I have several questions for the sponsor. The first one is how long will it take to reach the target of 175 deaths?

DR. MELEMED: I'd like to have Dr. Sashegyi address the target for our final survival analysis.

DR. SASHEGYI: Andreas Sashegyi, Lilly

statistics. We have observed 125 deaths in the study right now. We are looking for a subsequent 175 for a total of 300, and our projected date for achieving that outcome is some time in 2023.

DR. HALABI: The follow-up question, I wonder if the sponsor had computed conditional probability. While I agree with the FDA that the only way that we can estimate the benefit on overall survival is to have complete data on 300 deaths, for the non-statisticians in the audience, a conditional probability is the probability that the results are going to be positive given the interim data.

So I'm struggling with this because looking at the data from REVEL and the slide SU-12, it seems to me that the OS, the upper confidence interval is always way above 1 or around 1.

DR. MELEMED: I'm going to have Dr. Sashegyi specifically address your question, but I do want to reiterate that when we met with FDA to discuss the trial, we specifically powered this for progression-free survival and not for survival. We

didn't have conditional power on what the planned overall survival would be.

Dr. Sashegyi, can you address her question on a conditional probability, specifically?

DR. SASHEGYI: Andreas Sashegyi, Lilly statistics. The question around the conditional probability of OS outcomes at the final analysis was examined, and we have a summary here based on statistical modeling, where we projected, based on the information we have now, where we would be at 300 events.

This gives you -- I know there are a lot of numbers on this slide -- some indication of both the likelihood that the hazard ratio point estimate would fall below certain thresholds; for instance, below 1.0, and that probability is 84 percent; and also the likelihood that the upper confidence limit would fall below certain thresholds. And we can see that there was a very high probability, the last number on the right, on the bottom row -- a high likelihood that the upper confidence limit will be less than 1.3 at 300 events.

The take-away message here is when we think about fluctuations in the hazard ratio that are being estimated first at the interim analysis and now at this updated analysis, we see a 99 percent chance that this hazard ratio is going to be certainly less than this threshold of 1.3.

DR. MELEMED: Dr. Sashegyi, before you sit down, could you kind of give an estimate of what you'd have to power the trial for if you're even assuming a 7-month improvement of PFS to translate to survival?

DR. SASHEGYI: Yes, this really speaks to the challenge that we have in this disease setting, where survival now, as we have observed in the RELAY study, is in fact longer than in previous studies in this setting, exceeding even without statistical modeling, a projected 50 months in both treatment arms.

If we step back and think about a situation where the clinically meaningful difference in median PFS would translate directly to a benefit in overall survival, that would require powering a

study under the assumptions of medians of, let's say, approximately 50 versus 57 months, which translates to an assumed hazard ratio of 0.88. If you make that kind of an assumption, you would require approximately 2,700 patients and a trial that could take potentially as long as 10 years to complete.

DR. HALABI: Thank you. I still have more questions, so you may decide to be at the podium.

(Laughter.)

DR. MELEMED: I'm not going to answer them.

Andreas?

DR. HALABI: Considering the subsequent therapies as presented in slide CO-42, have you explored or done some rank preserve of structural failure time modeling?

DR. MELEMED: Dr. Andreas?

DR. SASHEGYI: We have not conducted those models. This is a good suggestion of course. In this trial, it's important to note there wasn't any particular pattern of crossover by design that we would be looking forward to make those kinds of

adjustments. The reality and the challenge that we face is that there were multiple lines of subsequent therapy, and it's not clear how an adjusted model for overall survival, or such an adjusted model, how that would even be conducted and whether that would indeed provide us with more convincing results.

The fact is that we have a significant benefit in progression-free survival, which has translated into a benefit of progression-free survival 2, which is an intermediary between PFS and OS. Currently, we see a lower rate of death on the experimental arm versus the control. And finally, the modeling that I talked about earlier also suggests a low likelihood of an OS detriment at the final analysis.

DR. HALABI: Then the final question to the sponsor -- although I have one question for the FDA -- is can you show the durability of hypertension? I did not see that presented.

DR. MELEMED: Dr. Nirodi, can you discuss hypertension, please?

DR. NIRODI: Sandhya Nirodi, Lilly, drug safety. Yes, we looked at the duration of specifically the hypertension events because of the higher incidence in the Cyramza arm. There was no particular trend, so the duration of events were anything from 1 day to 700 days just because of the way adverse events are collected in study and reported as being recovered or resolved by the investigator. So the data are a little bit spurious in the way that it was collected or reported by the investigator as an endpoint for each adverse event.

DR. MELEMED: Can you discuss how many patients discontinued due to hypertension?

DR. NIRODI: Yes. Overall, there were 100 patients who had hypertension in the Cyramza arm, and only one patient actually had to discontinue Cyramza alone because of hypertension, and there were no patients who discontinued study treatment because of hypertension.

DR. HALABI: Do you have any data, like a slide, that you could share with us on that?

DR. NIRODI: If they can put up the core slide for the discontinuation rates, just the core hypertension slide, please?

Here is just a presentation of the core slide, again, on hypertension. As I explained, the hypertension was really a very manageable event, and hypertension is a very commonly associated adverse event with all VEGF inhibitors, including Cyramza. It didn't lead to discontinuation of study treatment in any patient, and only one patient discontinued Cyramza alone, but that patient was obviously able to continue erlotinib treatment and derive benefit from that.

DR. HALABI: That's not exactly what I was imagining, but that's ok. I don't want to monopolize the podium here.

I have a question for the FDA. Since we're always looking at targeted therapy, as a statistician I'm a little bit struggling because if Cyramza is to be approved based on PFS, are we setting the stage for a new paradigm?

DR. SINGH: I think certainly in non-small

cell lung cancer, as both the presenters at the FDA, as well as the sponsor, alluded to, certainly there is a precedent within non-small cell lung cancer to use survival as an endpoint for non-targeted therapies and using PFS for targeted therapies.

I do think, though, that there was also reference to approvals in both breast cancer, renal cell cancer, and several hematologic malignancies, for example, in which they are approved based on progression-free survival in add-on trials such as this one with uncertain survival benefit at the time of approval, in a setting, in a therapeutic landscape where there are therapies available with have demonstrated survival benefit.

So in answer to your question, yes, this would be somewhat precedent setting for this particular tumor type, but certainly not in the broader scope of other therapeutic areas within oncology.

DR. HOFFMAN: Dr. Szabo?

DR. SZABO: Eva Szabo, NCI. This question

is to the sponsor and is regarding the dose, which is different from what has been used in other settings, including for non-small cell. It was referred to in the briefing document, but can you give me a little bit more insight as to why you went with this rather high dose?

DR. MELEMED: Yes. I'm going to have Dr. Abada address it, but while he's walking up, I'll let you know that our current approved dosing is 8 milligrams every 2 weeks for most malignancies, but in lung cancer, it's 10 milligrams every 3 weeks.

Dr. Abada, can you explain our dose rationale for this?

DR. ABADA: Yes. Paolo Abada, clinical development. In RELAY, we did use the dose of 10 milligrams per kilogram Cyramza every 2 weeks, and that was to achieve a higher exposure. The selection of this dose was based on exposure-response analyses that were done in the initial phase 3 Cyramza trials, where it was observed that in patients who are able to achieve

higher exposure, higher drug levels, they appeared to have better PFS and OS compared to patients who had lower exposure levels.

So based on that, the decision was made to try to push exposure by increasing dose with this particular regimen. And I should say in those same analyses for exposure response, where a potential benefit was seen with higher exposure, there was not any concerns over increased toxicity. So based on that, this was the dose selected for this trial.

DR. HOFFMAN: Dr. Malik?

DR. MALIK: Shakun Malik from NCI. I would like to go back to this hypothetical understanding that this should be approved because then the patients have other options of EGFR therapy that they could then go to osimertinib after they have progressed on this drug that we saw this graph.

My question is, as a second-line therapy, I'm not really surprised, but a large number of the patients got their EGFR therapy again, including erlotinib, where they had already received erlotinib. So I'm sure that the physicians

continued with the patients on erlotinib because they were receiving clinical benefit. On the other hand, I don't see that anyone continued with ramucirumab, so that's a different question.

My question is that out of the people -- so as we are saying, this is a better way to do this, and then the patient receives osimertinib when we know that the osimertinib by itself as the first line has improved overall survival. Now, if we are taking away the overall survival benefit and thinking that we will do it in this sequential manner and maybe we will get a better PFS, it is very important to understand what that will mean.

These patients did not have any improvement in response rate. They do not have any improvement in quality of life or symptoms. If there was any clinical benefit, that was a delay in chemotherapy or subsequent therapy that we're talking about because that's the only clinical benefit we have.

If we are moving the thought processes that we should move osimertinib in the second line, I would like to know of this subsequent therapy, how

many of the patients received osimertinib, because they had T790 mutation, because it is approved for T790, which will mean that we are taking the survival benefit away from the patients if it didn't help another 50 percent. So only 50 percent of the patients will develop this mutation and 50 percent will not.

So did it benefit both patients who developed T790 and who did not develop or did it help across the board? That this is my question.

DR. MELEMED: I'm going to address your last question first and then hopefully address your initial questions. When we looked at patients who got osimertinib as a second, third, or odd-line therapy, no patients received it when they had documented T790M mutations. I'm sorry. That's not correct. I'm going to go back to the first question because I'm mixing this up. Let me go to the first question. I got a little bit confused there; sorry about that.

Dr. Heymach, can you first address the

question about what the approved options are, and that erlotinib is an approved option and is utilized from that aspect, and how we'd use it? Then I'll go back to the T790M question.

DR. HEYMACH: That's right. So first to the question would you be removing the survival benefit from osimertinib, now keep in mind the results of the AURA 3 study that was published recently in the New England Journal, that showed that here, for T790M-positive patients, osimertinib did have a survival benefit compared to chemotherapy. So osimertinib has a survival benefit in both the first-line setting and the second line. And I think osimertinib is an excellent drug here, but it does have a survival benefit in both settings.

So you would say, well, if you only got to use one drug, given the toxicity and the inconvenience of getting an infusion, you'd pick osimertinib over Cyramza plus erlotinib. But the key is that the drugs are not all interchangeable. You can do Cyramza plus erlotinib followed by osimertinib, but you can't do them in the reverse

order. The PFS for osimertinib in the second-line setting is 10.3 months, so that's really a substantial benefit that one couldn't recognize if you did it in the opposite order.

Now, the second question, we have outcome for the T790M positive and negative. I believe we have PFS curves for those here.

DR. MALIK: That is really my question; did it differ in who had developed T790 or not? I know it works in T790 as a second line, but first line, it works for everybody.

DR. MELEMED: So are you talking about how many patients got T790M? Is that what your question is? I'm not following.

DR. MALIK: Yes. Actually, you had in your briefing package suggested that it was same, which is about 50 percent of the patients.

DR. HEYMACH: First of all, if we could go back to the PFS curves to the patients who got osimertinib, let me explain to people that don't treat lung cancer here the practice for assessing T790M. This was done using plasma T790M because,

of course, patients were being treated on the study here. Plasma is readily available.

Standard practice when we're treating these patients is to check plasma first. Plasma is specific but it's not sensitive. Plasma typically picks up about 80 to 86 percent, depending on what study you're looking for. Earlier studies with Cobis actually said as low as 60 to 70 percent of the T790M is detected. So if a patient progresses, if the plasma is positive, you move to osimertinib. If it's negative, you typically obtain a biopsy. In studies we and others have reported, you pick up T790M in an extra 15 percent or more.

In this study, the reported T790M frequencies were 43 and 47 percent. The rate of detection is proportional to tumor volume, so there could have been differences in tumor volume or shedding rates there. But again, this is an underestimate given that standard practice would be if plasma is negative, you would obtain a biopsy afterwards. So we expect that the true ultimate rate is going to be in the high 50's, which is

consistent with prior studies for T790M, and it's indistinguishable between the two arms there.

Again, the data we have, again, of course there are limitations to assessment of second-line osimertinib outcome data and the fact that not equal numbers of patients have progressed on the two arms. So that's why there are differences in the total number of patients on the Cyramza-erlotinib versus the placebo-erlotinib arm. But there's no detectable difference in how you did with osimertinib once you got there, and the rates of detection were not appreciably different between them either.

So insofar as the data can tell us in an exploratory post doc analysis, supports outcomes are comparable or better with patients treated with osimertinib after this regimen.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Thank you. Heidi Klepin. I wanted to just ask if you could provide us some additional data, hopefully via a slide, on the adverse events, particularly by subgroup. So I'm

particularly interested, for example, in how the older adult patients may have fared with respect to increased rates of toxicity compared to the younger patients. Then if you have any data on those with comorbid conditions, that would also be really interesting as we're thinking about the risk profile and the added risk potentially to patients on a combination.

DR. MELEMED: We don't have a specific slide on the comorbidities, but we do have one -- and Dr. Nirodi can discuss -- based on age less than and greater than 65.

DR. NIRODI: Yes. Sandhya Nirodi, drug safety. We looked at two age thresholds, 65 and above and 17 above. This is the overview of adverse events in patients 65 and above compared to younger than 65. What we noticed here was independent of treatment arm, actually, patients above the age of 65 had a higher rate of grade 3 adverse events and SAEs compared to those under the age of 65.

Looking at the specific trend in grade 3

events, really, only hypertension was the grade 3 event that occurred at a 5 percent higher rate in patients above the age of 65 treated with Cyramza plus erlotinib compared to those treated with placebo.

We didn't identify any specific pattern in SAEs, and I think of interest, there was equal number of patients in the Cyramza plus erlotinib arm under 65 and over 65 years of age who had deaths due to AEs on study treatment, and discontinuation rates were fairly similar between age groups.

DR. KLEPIN: Just a quick follow-up, you said you also looked at a different age cutoff of those data?

DR. NIRODI: Yes.

DR. KLEPIN: Did you say 70 or 75?

DR. NIRODI: Just from a clinical perspective, we looked also at the 70-year cutoff because of, really, more critical relevance as for an elderly population. Here we saw a slightly -- bear in mind the number of patients

over the age of 70 only made up a relatively small proportion compared to those under 70, as reflected in the overall demographics for this indication. In the Cyramza plus erlotinib arm, we saw a higher rate of grade 3 adverse events in the older population compared to patients under 70. Independent of treatment arms, the SAE rate was higher in patients 70 years or older compared to under 70.

Interestingly, the deaths due to AEs, 5 or 6 deaths occurred in patients under 70. When we look at the specific trends in the grade 3 events, similar to the overall population, we saw a higher incidence of hypertension and diarrhea at a higher rate of 5 percent in the Cyramza treated patients above the age of 70 compared to those under 70. Really, most of the differences that we observed were in low-grade events between treatment arms, so grades 1 and 2.

DR. HOFFMAN: Dr. Hindrichs?

DR. HINDRICHS: Thank you. I'm still really struggling to understand the unmet clinical need,

and I just want to try to reiterate and clarify the question.

There are five approvals in this space now. One of them is osimertinib, which actually seems to be supported as well, or better, than the current treatment that's being proposed. Also, it doesn't require an every 2-week IV infusion, so it's less convenient for patients.

So it seems like the unmet clinical need is not really in the indication that's being sought, but the unmet clinical need the applicant seems to be inferring is the need to delay the time to chemotherapy. That is the purported benefit of this treatment, is to use it in a strategy where it's sequenced before osimertinib to delay the time to chemotherapy.

I would say that if the benefit is in the delay of time to chemotherapy, then shouldn't that be the primary endpoint of the clinical trial; and the question being asked and the data that's being generated is for us to evaluate whether there's a benefit to the drug? I'd like to ask if maybe

Dr. Vokes could address that, please?

DR. MELEMED: Before Dr. Vokes goes, when we designed the trial, osimertinib was not approved. Still currently, erlotinib is an approved and utilized regimen that's done.

But, Dr. Vokes, can you address the question?

DR. VOKES: Yes. I would maintain first that PFS was the primary endpoint, and it was met. So you do have with this trial, and with this combination, a very specific prolongation of progression-free survival that I think is very meaningful to patients.

Now, we don't have a direct comparison to osimertinib. That was not available at the time, so that is correct, so we have to say how would we use this in clinical practice? I think that that is correct. The way I would go is to tell a patient there is osimertinib. It is a terrific drug, and it has a good progression-free survival. But patients will always come and ask what is plan B?

Progression-free survival when it ends is a shock to the patient, as we all know. It disturbs their understanding that the disease is under control and it leads to a next discussion with the patient. So a patient will ask "What is your plan B when I have progressive disease?"

The idea is that we will be able to answer, well, there is another treatment option where you get 2 drugs. It does require you coming here every 2 weeks -- some patients find that reassuring to get a drug intravenously -- but then there is a 50 percent chance that we will be able to follow that up with a non-chemotherapy option subsequently. I think that from a treating-physician point of view, very positive.

DR. PAZDUR: If I could just jump in here, I'd like to put this in some kind of regulatory framework. We're talking about a regular approval for this drug. Basically, the drug has to show that it's safe and effective, not that it meets some unmet medical need; not that it's better than a comparator drug so to speak. It doesn't have to

be better than the next available drug. It just has to, on its face value, show that it's safe and effective. So I just want people to understand that.

DR. HOFFMAN: Okay. Dr. Deeken?

DR. DEEKEN: John Deeken, from Inova Health System, a clarifying question about the timeline to getting mature overall survival data. You said you need another 175 events, and that would take until 2023. Is that January '23? December '23?

I'm just curious by the math on that. If you had 46 events in 2019, I would expect an accelerating rate of events given the expected survival of these patients. How is the calculation of either the end or beginning of '23? What's that based on? What's the numbers of events per year you think you'll get to over the next four years?

DR. MELEMED: Dr. Sashegyi, Can you address our projections regarding overall survival?

DR. SASHEGYI: Andreas Sashegyi. Yes, there's of course some inherent uncertainty in terms of estimating when we will arrive at 300

events. Our best guess right now is some time in the first half of 2023. While you're right that one might assume that the rate of deaths ought to increase over time, what's of course also happening is that the risk, the number of patients remaining at risk to die, is also getting smaller. But this is our projection right now, first half of 2023.

DR. HOFFMAN: Dr. Pazdur, just so I clarify what you meant by your comment, the decision that we make --

DR. PAZDUR: It's a regulatory perspective here --

DR. HOFFMAN: Well, right. But I mean if we approve this request because we think it's safe and efficacious, it's not up to us how the company may market it and so on, even though it may be number 5 or number --

DR. PAZDUR: It may not even be marketed; I don't know. But here again, the determination is safe and effective. There is no legal imperative that they have to demonstrate the drug meets an unmet medical need, nor do they have to show that

it's better than an available therapy.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: Jorge Garcia. A question and a comment. I don't think there is any doubt that you guys have met your primary endpoint of PFS. I think in 2020, most medical oncologists are quite familiar with how to identify and how to manage side effects from vascular disrupting agents, so I'm not that bothered about the side effects profile with the exception of those 6 patients who have died on trial.

One question is, what is the utilization or the use of doce and rami in the United States right now as a second-line therapy for non-small cell lung cancer?

My comment relates to what Dr. Hinrichs has alluded to. I don't want to recycle the comments, but I think in slide CO-64, for me, what has been misleading is the flow of receiving rami and erlotinib, and upon progression, if you have mutation T90, then you get osimertinib.

I would argue that this is misleading simply

because that data that you guys are putting, this slide reflects the data from second-line therapy after EGFR-failure patients. So that 10.1 months, at least how I interpret this, is not reflective of osi in the post-erlotinib in combination with rami because that data doesn't exist.

So I think that is what I'm sort of struggling with because if the argument is you can get erlotinib and rami and then follow up progression, and you get osi if you have a T90 mutation, it's no different than what you saw in your first progression, where 66 percent of patients who got the combination went on to receive erlotinib and osi, and 57 percent who received placebo and erlotinib went on to stay and/or receive an EGFR inhibitor.

DR. MELEMED: I'm going to have Dr. Heymach discuss this. But, in general, you're correct. We don't have specific data on this trial and what the sequencing is. I think that's a question for future study design. When Dr. Vokes presented initially, it was what we had seen with the current

design, but right now we don't have the data specifically in this trial.

Dr. Heymach, can you discuss what the options are and what you'd use for chemotherapy, specifically?

DR. HEYMACH: Just to clarify and I guess put us all on the same page, it's the AURA 3 study, and the eligibility for AURA 3 is that you had to have failed an EGFR TKI and have T790M positivity in the setting of a sensitizing mutation, which is what was here.

Now, it is a theoretical possibility that patients who progressed on a TKI would do better than patients who progressed on a TKI plus a VEGF inhibitor. That's absolutely a theoretical possibility. Unless you did an entire study of just patients treated with Cyramza and erlotinib, there would be no way to formally address it.

The best we can do to address that with the data we have is, first of all, to look at did patients then go onto EGFR TKIs? In here, if we go to a CC-25, the answer is absolutely yes; they went

onto EGFR TKIs. We have the breakdown on a different slide, but where available, they went onto osimertinib. So this absolutely showed they could go on osimertinib here.

Now, I'll mention also, standard of care for patients with EGFR mutations nowadays -- and you may wonder when we had a number of drugs approved with just PFS advantages, how has survival gotten so good?

Well, the way it's gotten so good is we'll often in the case of oligoprogression radiate a single lesion. Let's say you've just got a bone met or a brain met, radiate that, and then continue the TKI. So that's why patients on the Cyramza plus erlotinib arm, consistent with the NCCN recommendations, might have oligoprogression, local treatment, and continue on erlotinib, then go to osimertinib later.

So the TKIs after the first-line regimen consist of patients who had oligoprogression and then continued on a TKI, and those who had T790M, and then crossed over to osimertinib.

Now, if I could have the two Kaplan-Meiers again? And I apologize for showing this, but to the question -- which is a legitimate question and a possibility that one would have to consider -- does prior treatment with Cyramza lead to you doing worse on subsequent osimertinib, the best data we have is here.

This is the PFS2 for patients treated with osimertinib, and you can see that in the Cyramza plus erlotinib -- and again, this is a post hoc analysis just with the best data we have -- actually, if anything, do better than patients on the control arm, who then crossed over to osimertinib. Perhaps it's because they have a smaller disease burden because they have a deeper, longer response.

Obviously, it's speculation, but there's no evidence, that we have in hand, that Cyramza plus erlotinib shortens how you do on osimertinib. This is fully consistent with the data we see in the real world.

DR. HOFFMAN: Dr. Malik?

DR. MALIK: I have a follow-up question on that graph, please. My question is the graph is about patients who have developed T790. Maybe I was not clear the first time. I wanted to know if you have any data on patients who did not have T790, who just progressed on EGFR. I see that the graph shows that if you have T790, that you could on this drug -- they still respond to osimertinib.

So my question is, of the 50 percent of the patients who did not develop T790 -- you are taking the first-line therapy from them, which has survival, and giving them this combination. So my question is how did they do?

DR. HEYMACH: Right. I believe we had a supplemental slide -- I don't remember the number -- for the outcomes of patients with T790M positivity versus T790M negativity.

DR. MALIK: That really was my question from the first time.

DR. HEYMACH: Do we --

DR. MELEMED: I don't believe we have that slide.

DR. HEYMACH: We may not.

DR. MELEMED: I think if you request, we can try to get that at the break. But how you're specifically looking at it, I don't think we have that analysis right now.

DR. HEYMACH: And I'll point out, in general, patients that develop T790M negative resistance do worse overall, but the first-line PFS -- so the question is, are you giving up -- are you now putting them on a less effective treatment and losing osimertinib? Well again, the efficacy is measured by response rate, and PFS is 19.4 months for Cyramza plus erlotinib, and 18.9 months for osimertinib.

So I think you can say, well, you've subjected them to more visits and the additional toxicity, but there are no signs they've received a less effective first-line therapy if they don't develop T790M subsequently.

DR. MALIK: Yes. But then what treatment will they get? They will still get the chemotherapy, which is the question.

DR. HEYMACH: Right.

DR. MALIK: So these are not just small numbers; these are 50 percent of the patients who will not develop T790.

DR. HEYMACH: T790M negative patients in general, immunotherapy is not indicated. Immunotherapy is not approved until it's after platinum-free EGFR mutants. So the standard of care for a T790M-negative patient would be chemotherapy unless they continue to TKI with oligoprogression. That's correct, regardless of what the first-line treatment is.

DR. MALIK: Right. So I understand that, but then you take these patients who do not have T790, the activated mutations, and you give them osimertinib in the first line, so they have a survival advantage. So are we taking 50 percent of the patients and giving them this combination, and then subsequently they have nothing but chemotherapy is really the question.

DR. HEYMACH: Right. Unfortunately, right now we don't have a way to predict who's likely to

develop T790M or not at the end of subsequent therapy --

DR. MALIK: Correct.

DR. HEYMACH: -- so in both cases, if you're T790M negative, in the case of osimertinib, you don't develop T790M-negative resistance ever. That's a smattering of different resistance mechanisms we showed --

DR. MALIK: Correct.

DR. HEYMACH: -- and chemotherapy is the standard.

Here, after a comparable period of time, if you don't develop T790M, chemotherapy is indicated.

DR. MALIK: Correct.

DR. MELEMED: Can I make a quick comment here? We don't specifically have the answer, and we'll look to see if we can get that. We do have progression-free survival 2, which we did show, and we didn't see any worsening in the second progression. That captures all patients. So we can also look to see specifically in T790M negative, but we don't have that, and we'll see if

we can get that after the break.

DR. MALIK: Okay. Thank you.

DR. HOFFMAN: Okay. Let's take a 15-minute break and reconvene at 3:45. Thank you. And I remind the panel not to speak about the matters at hand during the break.

(Whereupon, at 3:32 p.m., a recess was taken.)

DR. HOFFMAN: Dr. Melemed informed me that he has an answer for the question that Dr. Malik raised at the end of our discussion, so please go ahead, and then we'll have our open public session.

DR. MELEMED: Can you pull up slide AA-2? Slide up.

We did just do an analysis looking to see, in T790M-negative patients at progression, whether they had a worsening of survival from that. Again, this is very long, but we are not seeing any evidence that there's a worsening survival in that aspect. The hazard ratio at this point is 0.66 in favor of patients receiving Cyramza in the T790M-negative patients.

Open Public Hearing

DR. HOFFMAN: Okay. Thank you. We're going to now go to the open public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial

relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in its consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

I'll now ask speaker number 1 to step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman.

I'm president of the National Center for Health Research. We do not accept funding from pharmaceutical or medical device companies, so I have no conflicts of interest.

Our center analyzes scientific and medical data and information, and we use that to provide objective health information to patients, health professionals, and policy makers. We have a particularly large program on cancer issues, cancer prevention, and treatment, and we also have a help line for cancer patients and their families. We do a lot of communication with patients that's relevant to today's meeting, but I also should just say my training is as an epidemiologist previously on the faculty at Yale and a researcher at Harvard.

As you know and as you've heard, there's not long-term data to make conclusions about overall survival, but the results aren't promising so far. The longer the study continued, there was a reduction in the apparent benefit, or possible benefit, for overall survival, but in fact the survival rates are almost identical.

We agree with the FDA and their analysis that based on the confidence intervals, there could be a benefit of about 30 percent or it could be worse, about 30 percent, in terms of overall survival. So we have to look at both sides of the confidence intervals.

As you also know, we should look at the number of deaths, and within 30 days of the 221 patients taking Cyramza, 6 died from adverse events. And there was a conclusion that at least one of those was from the drug, one other one might be from the drug, and the other 4 didn't seem to be from the drug. But we didn't really have enough data for the rest of us to look at that and draw conclusions.

The bottom line here is that we know that Cyramza can be fatal, and based on the data provided so far, there's no evidence that it increases overall survival, on average, for the patients in the indication. If it does benefit any specific types of patients in terms of overall survival, that group hasn't been identified yet.

I want to talk about progression-free survival because we talk to a lot of patients at our center. As I said, we have a help line and we also provide a lot of user-friendly information to patients. They specifically want to live longer and they want to have a better quality of life for the days, weeks, and months they have left.

The only patients I've ever talked to that really wanted or really cared particularly about progression-free survival, I have to tell you, they didn't actually know what it meant. So when you talk to patients, they know what they want, and progression-free survival matters only if the quality of life is good; otherwise, it's not what they want. It's not what they are looking for. It's hard to explain that to them, and unfortunately not all doctors are able to do that.

I guess the only other thing I want to say in the time I have left is that the adverse events are really very important to look at, and they're very serious. I will also say heart disease is the number one killer, and high blood pressure is the

silent killer. So implying that that's not a serious adverse event is really a problem, and we shouldn't be looking at it that way, in addition to all the other adverse events that we know about.

So given the situation and the fact that FDA did say they wanted longer term data, the company decided to go ahead anyway. And I just want to say that I hope that you will urge the FDA to continue to demand longer term data to find out if there really is a benefit for overall survival because that's what really matters to patients, and that's what, as a scientific agency, FDA needs to focus on. Thank you very much.

DR. HOFFMAN: Thank you.

Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MS. MIXON: Hi. My name is Samantha Mixon. I was diagnosed with -- I'm here on behalf of Eli Lilly. They paid for my travel and lodging, but that's it. They didn't pay for my time. And my

time is very important because I have stage 4 lung cancer, and I have a daughter at home. So I'm taking my time away from her to come up here to talk about this.

I have deletion exon 19, and I'm here to talk about the benefits of this drug. I was very nervous coming up here with the flu, and coronavirus, and everything else. I bought the most expensive mask. It was $52; ridiculous. I'm a single mother. I've been living 7 years with stage 4 lung cancer with my daughter. I didn't think that I would see her go from 7 years old to 15, so she's driving now.

I was only given 12 to 18 months to live. The quality of life that I've had on this TKI has been amazing. I don't think that I could ask for a better quality of life. I had to go to three different places in order to get the kind of treatment that has helped me live this long. Each place had a different idea about what treatment I should go on. One of them happened to be chemotherapy, which I am totally against. As a

mother, you don't want your child to watch you wither away from chemotherapy, so therefore I just want to take these TKIs and go and try to have as many options as I possibly can.

I've had bumps in the road, radiation, pulmonary embolisms, strokes, but I've been blessed. I've had those even with the drug that I'm on, but I'm still here. It may not be the norm.

I know recently we lost quite a few long-term EGFR survivors, and I did hear a lot about people passing away. I lost 3 friends in 3 days at the beginning of this month, and they were at 6 years, 11 years, and 5 years. I'm not surrounded by family, so if I had to go on chemotherapy, I have to move away from my daughter. I have to move in with my sister in North Carolina -- and I live in south Georgia; that's where the accent comes from. I have to move with my sister in North Carolina so she can help take care of me.

Lung cancer patients like me, they want to

push off chemo as long as possible. We want more targeted therapies. Each one offering more and more is what we want. I don't want to ever run out of options. I want to see my daughter graduate. I want to see her play volleyball. I want to see her have children. I want to see all that, and right now we don't have the options.

Even if it is scary, you know, whatever could happen, we have stage 4 lung cancer and we've accepted that. Life isn't fair. I learned that 7 years ago, and it's very hard for me to realize that I may not be here for all those times with my daughter. I mean, I was only 33 when I was diagnosed. I'm 40 now, which is great, but I want more. I want more of life.

So I think that the quality of life is really what matters. I've already informed my parents that if I have to go into chemotherapy, I would probably just stay at home and be with my daughter as long as possible. That's mainly what I have to say. Thanks.

DR. HOFFMAN: Thank you.

Will speaker number 3 step up to the podium and introduce yourself? State your name and any organization that you may be representing. Thank you.

MS. PHILLIPS: Good afternoon. My name is Anne Phillips, and I'm here to share my story. While Eli Lilly is paying my travel expenses, they are not paying me for my time or dictating what I say. Since so many non-small cell lung cancer patients are diagnosed at a late stage without symptoms or cause, I'm going to give you a brief summary of my diagnosis.

Three days before diagnosis, I was on a trip away with my husband. I was clumsy and somewhat tired during the trip. The following Tuesday as I was getting my kids ready for preschool and first grade, I began shaking and collapsed to the floor. By the end of the day, I had had a CT, an MRI, and the oncology residents suspected that I had lung cancer. That's it; no other symptoms; no coughing; no pain; no family history; and no history of smoking. On Monday, I was healthy, and on Tuesday

I had a seizure and a terminal diagnosis.

After brain surgery and 2 rounds of gamma knife radiation surgery to treat my 16 brain mets, I started taking the targeted therapy erlotinib. The targeted therapies have side effects like the rash on my face. This picture doesn't show the heat radiating from my face and the painful itchiness going on, but this was short-lived. And after a dose adjustment, the symptoms all but went away. For most of us, the side effects are annoying but only a minor inconvenience on the treatment path.

Two and a half years later, one of lymph nodes lit up, and a biopsy showed that the new tumor had progression mutation T790M. It was time to switch medication. This time the targeted therapy I needed for both mutations was approved only 10 weeks earlier. I switched to osimertinib. I'm 2 years in on the second line of treatment with only a few radiation tune-up sessions.

Last night as I was eating dinner at the hotel, I wrote a post on Facebook about this

speech. My friend Peggy commented immediately, saying, and I quote, "I had 29 consecutive Cyramza infusions, 16 in combo with Taxotere and 13 as maintenance. This was my miracle drug for a long time."

While Peggy has an EGFR mutation, it is an extremely rare one that doesn't respond to TKI inhibitors. Peggy was on the Taxotere-Cyramza combo for a year. She took Cyramza for 18 months with no progression. She ended our conversation with, "I'm just thrilled you're here doing this. No one has been talking about Cyramza for 3 and a half years, and it was such a miracle drug for me." She definitely had a favorable result from this drug.

I have a bachelor's of science, but it's engineering, not in medicine. I can't hope to stay on top of the intricate mechanisms of inhibition and mutation expression being investigated in today's research arena, but I also do not choose to make understanding my cancer a full-time job. I want to live my life and make memories with my

kids. I depend on scientists like the ones in this room to work with the policy makers to approve the drugs and procedures that will keep me alive.

I have many other friends currently in trials because they have unique cancer expressions, no other treatment and no other treatment options. Research matters, and it matters to me. Research is not some attenuated abstract idea. PFS and treatment options are extending patients' lives right now.

I'm here to convey the sense of urgency that those of us who advocate for lung cancer feel. Lung cancer is the most deadly cancer for both men and women, and yet receives just a fraction of research funding of other cancers. In 2018, I visited my state senators and representatives in Washington D.C. with the American Lung Association to advocate for more research funding. Later that year, I raised more than $8,000 for research.

In 2 months, I'll be a 5-year survivor. As I tell my oncologist at every appointment, I just need 10 more years. Drugs like Cyramza are

stepping stones on the path to make lung cancer a chronically-managed disease instead of a death sentence. Thank you for doing your part. I'm here doing mine. Thank you for your time.

DR. HOFFMAN: Thank you.

Will speaker number 4 step up to the podium and introduce yourself? State your name and any organization that you're representing for the record.

MS. DIETZER: Hi. My name is Gina Dietzer. I am a wife, a mom, a nurse, and a lung cancer survivor of 4 years. Advocating for lung cancer is so important to me that I traveled 2000 miles yesterday just to speak here today and will jump back on a plane in a few hours to travel 2000 miles home. Eli Lilly covered my travel expenses but not my time, and I am not speaking on their behalf. I'm here on behalf of patients and their families.

In 2015, I was diagnosed in the emergency room with lung cancer without any lung cancer symptoms. I went to the ER due to lower back pain, which I believed were kidney stones. A CT scan

showed kidney stones, as well as a mass in my left lung and lesions all along my spine. I was shocked, and I didn't know what to do. I was 51 years old and a non-smoker my whole life. Then fear hit me as I realized my father died of cancer when he was 51 due to a brain tumor.

My community oncologist was not supportive of clinical trials. He didn't want to talk to me and gave me about 6 months to live. He chose to treat me with 3 chemotherapy drugs. These 3 chemos were harsh on my body and having a delicate stomach made it almost unbearable. I lost 30 pounds in 5 weeks. I was sick, and with treatment, I felt sick.

I fell into a depression, lost my straight long hair within weeks, couldn't do my job as a nurse, and felt sad that I would miss main-life events such as high school graduation or marriages of my daughters who were 16 and 19. When I felt well enough to go back to church, my pastor, who had lost his wife after a 6-year battle, recommended that I get a second opinion and that I

needed to be my own advocate. After all, I was a nurse, and that's what I tell my patients all the time. Advocate for yourself.

I began my research that day and discovered a National Cancer Institute right in my own city. Not only that, but there were 5 oncologists that specialized in lung cancer alone there. My liver lung cancer oncologist shared with me that my original biopsy results meant I was eligible for targeted therapy. In addition, and so importantly, I did not have to continue with chemo.

Life completely changed for me. I felt better, and my disease was not progressing. I found LUNGevity, a great advocacy organization with many resources and signed up for its LifeLine program. I also became a mentor for fellow patients.

Later, I sat on a patient advisory board and met face to face 7 other lung cancer patients and heard their stories. I attended a LUNGevity conference and met so many lung cancer patients, including my LifeLine program friend.

Unfortunately, she ran out of treatments and has since passed away.

Because of the effective medications for my cancer, I was able to see my oldest daughter get married and my youngest daughter graduate from high school. In addition, I recently became a grandma, and my youngest daughter has chosen pre-med as her major in college.

You see, each year and each month is so important. The medications can keep the cancer stable until the cancer finds a way to figure out the drug and grow again. Some treatments are harsher than others, but they all give us extra time. Too many of my lung cancer friends have lost the battle when there's no more treatments for them. We need more treatments.

Last year, I faced progression. Radiation helped, but my targeted therapy stopped working. My treatment was switched back to IV chemotherapy. I hate chemo, but I am glad and I thank God that my cancer's responsive and I'm stable again because every month matters. I am a wife, a mom, a grandma

now, an advocate, and a survivor. Thank you for listening to what's important to me. Now I have a flight to catch home, so thank you for your time.

Questions to the Committee and Discussion

DR. HOFFMAN: Thank you.

The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

I'd like to proceed with the questions to the committee and the panel discussions, and I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

The question to the committee is for us to discuss whether the results of the RELAY trial, with a demonstrated improvement in PFS, support a positive benefit-risk assessment, given the uncertain effect on overall survival and the

increased toxicity associated with the addition of ramucirumab to erlotinib.

Are there any issues or questions regarding the wording of our question? Yes?

DR. HALABI: Susan Halabi. I had a question but not regarding the wording, so can I ask my question or should I wait until later?

DR. HOFFMAN: Is your comment about the wording of the question?

(Dr. Halabi gestures no.)

DR. HOFFMAN: Okay. Before we get to the discussion, can we agree on the question?

(Panel members gesture yes.)

DR. HOFFMAN: Okay. Now we'll open the question to discussion. Dr. Halabi?

DR. HALABI: Thank you. Susan Halabi, Duke University. My question is more to the FDA first. What will happen if this committee approves PFS and the OS result in 2023 comes back with an upper confidence interval of 1.2. I'm going to be generous. I'm not going to say 1.3.

DR. PAZDUR: For a confidence interval?

DR. HALABI: For OS.

DR. PAZDUR: Well, I'd like to refer you to slide 20, where we have approved 3 drugs where the upper limit of the confidence interval is -- oh, above 1? Okay. So there's obviously a variability in overall survival. We'll have to take a look at what is the reason for that and do we really think that there is an adverse effect on overall survival. I think we'd be far more concerned if the point estimate was, so to speak --

DR. HALABI: Yes.

DR. PAZDUR: -- not the 95 percent confidence interval surrounding that evidence.

Here again, take a look at slide 20. There are 3 drugs that we've approved where the upper limit of normal has been above 1; then we have to understand why that happened. Was there an imbalance in patient characteristics; an imbalance in subsequent therapies? If it isn't, then we have to have a discussion with the company probably about withdrawing the drug.

I will make a public statement on this.

We've had these conversations with Eli Lilly, this exact same sponsor, a year ago on the withdrawal of a drug for sarcomas, and I will say publicly about this, they were very amicable and very helpful in removing that drug because they realized that it needed to be removed from the market.

We look at that as a safety finding that has emerged; not so much an efficacy finding, but this is a safety finding that must be addressed to remove the drug from the market. But here again, I think the important thing is to understand why because, here again, there are many drugs that have the probability, when one takes a look at the upper limit, to have a detrimental effect, but are we actually seeing a detrimental effect? We've had these discussions before with sponsors.

DR. HALABI: Thank you.

DR. HOFFMAN: Okay. I think the floor is open to discussion among us, and I would request that in the course of the discussion that we not indicate our specific vote. We'll put that off until the actual voting time.

Please, Dr. Szabo?

DR. SZABO: Eva Szabo, NCI. Can I just follow up on that? If OS is 1, so no evidence of -- with survival, drug stays on the market, or the drugs?

DR. PAZDUR: Yes. This is a discussion question I think we have, and this is the, the essential question here. And that is, this 7-month difference in progression-free survival, does this represent a benefit to patients?

I was thinking about this as I was sitting here, and it drew me to the discussion that we had in 2008. There was a big meeting in this room about Avastin plus Taxol, versus Taxol, and our public statement at that time -- and this was a hearing to withdraw the drug, and we were quite clear on our position on this, which is not that different from what we're talking about here. There are some differences, but not that different.

We were not expecting an improvement in overall survival. We were not demanding an improvement in overall survival. But what we were

asking for was an improvement in progression-free survival of more than 5 months. Guess what these show? Just bringing that up, because we have to put this, obviously, in the context of other approvals and other discussions that we have. If we decide not to approve this drug or approve it, we have to put it in the context of other drug approvals.

But I just wanted to give that historical perspective because there was a great deal of notoriety around that and the discussion of progression-free survival as an independent endpoint irrespective of an improvement in overall survival.

Again, if you take a look at slide 20, which I think is a very telling slide here, we have many drugs that were approved without a survival advantage. But I think any lung cancer expert, or anybody that treats this disease with EGFR mutations, will recognize that even though all of these drugs were approved on the basis of a non-survival endpoint, survival has definitely been

increased for patients with this disease.

We have seen this in multiple other diseases such as multiple myeloma, where we have almost 10 drugs approved, where the overall survival are based on progression-free survival and where the improvement in overall survival has dramatically been improved in that disease, from 2 years to almost 10 years. So I think we have to be realistic of where we are with other disease approvals, and that's the point I want to make through these comments.

DR. SZABO: So just so that I understand a little bit better, if we had the mature OS data today and it was a hazard ratio of 1, we do have osimertinib, which compared to erlotinib was better, we'd be having a different conversation today then. Is that correct or would we still say PFS improved?

If we, let's say, assume that we think that the benefit-risk ratio is okay, but it's not better --

DR. PAZDUR: We have to judge each

application on its own basis. As I said before, for full approval of a drug, you have to demonstrate safety and efficacy of that drug --

DR. SZABO: Okay.

DR. PAZDUR: -- not that it's better than a previously approved drug or something that wasn't even approved. In other therapeutic areas where you could use placebos, they just do placebo-controlled trials. For example, in the study of headaches, et cetera. This would not be ethical in, obviously, life-threatening diseases.

DR. HOFFMAN: Dr. Cheng?

DR. CHENG: John Cheng, industry rep. I do appreciate the FDA framing the discussion of a study where there's a PFS advantage, but the OS is probably underpowered because at the time of this study, the standard of care, it keeps evolving. So this is an important discussion, and I appreciate the FDA framing it on PFS and the mutation.

I guess my question, just in general, is that the FDA has approved a number of agents with PFS as the primary endpoint, particularly when the

first-line metastatic OS is very difficult or very long. In this situation with first-line EGFR-mutant patients, where the overall survival seems well over 4 years and might be even longer, is it that different from the other kind of first-line indications that have been approved with PFS, whether it's renal, or breast cancer, or other things like that?

Regardless of a mutation or not, is the disease longevity, where you have a long overall survival, where you're not easily able to power it and you have subsequent therapy that confounds OS, are they not more similar than dissimilar?

DR. PAZDUR: I think that's one of the reasons why we brought this forward for discussion because there was some disagreement among the staff on this, to be honest. There are many reasons why you cannot demonstrate overall survival, and we have written extensively about this, one being the long natural history of the disease; for example, CLL diseases where you have long histories because of therapeutic advances such as multiple myeloma

where there isn't equipoise. That was present when we first saw these TKIs because they had such higher response rates than conventional chemotherapy. You couldn't not allow crossover, which would confound overall survival, so we were forced to really accept PFS in this setting.

Then in situations, basically, where you just have very small numbers of patients, we're seeing that, obviously, in increasing numbers in lung cancer with the segmentation of disease, and to ROS1 mutations, and to BRAF mutations, MET mutations, and RET mutations, et cetera, where randomized studies probably cannot be done, certainly not randomized survival studies.

So there are many reasons not to look at overall survival. Here again, we want to make sure we're not having a detriment in overall survival. We always take a look at overall survival. Even in single-arm trials, we'll take a look and try to compare it, cognizant of the effect of cross-study comparisons to make sure we're not having a loss in overall survival.

DR. HOFFMAN: Dr. Malik?

DR. MALIK: I think that one of the things, we had a slide from the FDA where you have all first-line therapies, and out of all the therapies that have shown PFS improvement for which they were approved, the OS was not shown to be improved, but there was no detrimental effect. Most of them, the patients did receive second-line targeted therapy, and that's why it was thought why they did not show an OS benefit.

But in this trial, that's not the case. In this trial, that is not a benefit that you can see later on with subsequent therapy. So really, I'm still struggling with whether these patients will do better with osimertinib as a first line or this combination.

My other thought process is that when you are looking at the targeted therapies, I don't recall, but please remind me if I forgot, that most of these trials -- none of these trials had increased toxicity when you used targeted therapy compared to either placebo or chemotherapy.

Compared to this trial, where we are seeing not only an increase in toxicity, having to use 3 drugs for hypertension control in 22 percent of the cases and 6 patients who we can't be sure whether they die from the therapy, it is of concern to me.

Really, the osimertinib would be the drug that you could compare this to, but having that and not knowing that -- and none of the drugs that were approved by the FDA, that I remember, showed no improvement in quality of life. In this drug, although FDA says that the quality of life was not tested the way that it should have been, still there was no difference in quality of life, so there was no improvement.

What we know clinically, if the patient has EGFR mutation and you give them the drug, they actually improve in their shortness of breath and they improve their coughing, but none of that was noted in this trial. So that's what I remember, that none of them had a detrimental effect on either quality of life or in the OS at the time of approval. So I'm assuming that that was correct.

Yes?

DR. PAZDUR: I believe so [off mic].

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: This is just something to discuss among the committee. This is a little bit more complicated than it seems. We're being directed to answer the supposedly simple question of whether the drug is safe and effective. The issue, though, is not just whether the drug is safe and effective in terms of the impact on patients, but whether it's going to be used in a way that's safe and effective and will benefit patients.

It's clear from the applicant's presentation that the intent is for this to be given as a first-line therapy that's not clearly more effective than osimertinib and that actually may be less effective. Also, it may well be more toxic and more difficult to administer than osimertinib, so that we can then give osimertinib later to an unknown fraction of the patients who emerge with T790M-positive tumors, where the other half of the patients then actually never get the osimertinib

and only experience the more toxic -- well, we don't have these things compared head to head, but the possibly more toxic and the possibly less effective combination of Cyramza and erlotinib.

Does that make sense? I'm concerned that an approval will set up a pattern of practice that actually is not supported by the data that's presented and will do harm to the patients.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Thanks. Heidi Klepin. I have a question that is probably difficult to answer and then a comment. I think the question is we're following up on this issue of how concerned should we be about the potential detrimental effect on survival based on what we know so far, looking at the available survival data.

I'm looking at Susan because I'm trying to figure out if our statistician on the committee could provide any additional input around --

DR. PAZDUR: We have additional survival analysis.

DR. SINGH: We do. We can look at backup

slide 11. The FDA conducted our own modeling predictions in terms of survival, and certainly they do vary widely from the sponsor's predictions, based on the estimates that were used.

I'll invite our statistical colleagues to comment on this. You can use conservative versus liberal assumptions, and ultimately, as it shows on the bottom of the slide, the only really reliable way to assess the effect on overall survival is additional follow-up. But as mentioned, certainly if the ultimate survival results do show a detriment in survival, we would be compelled to review that data and possibly pull the indication, and likely pull the indication.

DR. KLEPIN: But my interpretation of the top bulleted point there is that the point estimates could range from 30 percent to 63 percent, coin flip --

DR. SINGH: Correct.

DR. KLEPIN: -- kind of, somewhere. Okay. Thank you.

So that addresses that question, and then my

comment is just around the quality-of-life data that we've talked about. There are limitations, of course, to the quality-of-life data, as has already been mentioned, and we don't see a clear signal of improvement in quality of life for reasons that were discussed.

I think the other comment that I just wanted to make that throws another complicating factor into that is if you look at the study design, and we think about comparing quality of life across arms, both arms of the trial, because of the placebo design, were coming in every 2 weeks getting IV infusions for over a year.

So you're comparing a strategy that would not really be the alternate. The alternate strategy is being on an oral medication and not coming in and getting an infusion every 2 weeks.

So understanding what the real quality-of-life difference is, given all the limitations of just surveys and PROs, the study design complicates that. So potentially it would be, potentially, a bigger detriment in quality of

life than what we could ever assess from this study design.

DR. HOFFMAN: Dr. Deeken?

DR. DEEKEN: Thank you. John Deeken from Inova Health. I'm struggling with a couple of questions, one of which is the difference between molecular-targeted agents and activated mutation targeting. Ramucirumab has a targeted VEGF, and we know from previous trials that erlotinib plus another VEGF inhibitor might show progression-free but not overall survival at the end of the day.

I'm also sympathetic, though, that this trial was designed in 2014, and PFS was a meaningful target at that point. The world has changed since 6 years. If I could ask for a hypothetical, if you had this conversation today for a planned phase 3 targeted therapy, maybe not activating mutation, is PFS still a meaningful primary endpoint that you'd encourage a sponsor to go after, or is overall survival now what you really encourage them to have as their primary endpoint?

DR. SINGH: I think we're flexible. We've, again, demonstrated in multiple tumor types, including breast, GU, hematologic malignancies, that we accept progression-free survival as a meaningful clinical endpoint. I think depending on the agents used in this proposed trial, we would consider PFS as an endpoint certainly for targeted therapies.

Now, I take your point that we have said that ramucirumab is not a targeted agent, but to the sponsor's point, there is this synergistic activity, and there is a great deal of study combining VEGF with targeted therapy. So I think it really depends on the agents used in the trial design, but in a broader scope, certainly PFS is an acceptable endpoint.

DR. DEEKEN: What about for non-small cell lung cancer in 2020; would that be a meaningful --

DR. SINGH: So as of today, all of the approvals in first-line non-small cell lung cancer that are not targeted therapies, which have been immunotherapy, ramucirumab-docetaxel in the second

line, and necitumumab, those trials were conducted with OS as a primary endpoint. That is unique to non-small cell lung cancer and, again, certainly this has been broached in other tumor types.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: So I appreciate FDA, again, how you guys frame the hazard ratio, specifically to slide 20. I initially was not that concerned about PFS and the hazard ratio for survival, but hearing you right now, it makes me wonder if, with the data that we have seen today, I can discern if the hazard ratio on the upper confidence interval is related to toxicity, and therefore causing detriment.

That is what I'm struggling right now; is it those patients who die on therapy or perhaps with longer follow-up, we're going to see more deaths? If indeed, if there was data that we can use to discern that, I think, obviously, it would be easier. But I don't think we have that data, and that's what I'm trying to figure out.

Obviously, it's an unfair comparison

compared with the EGFR TKIs from the past. When you have hazard ratios that can go up to 1.17 1.68 [indiscernible], and 1.35, clearly there was no detrimental outcome because the side effect profile was quite different. So to some extent, I think it's unfair to compare an antibody against KDR compared with an EGFR inhibitor in that context. But I still haven't seen the data as to whether or not the toxicity profile has really actually been the cause of the detrimental effect and we may be seeing with survival.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: Massimo Cristofanilli. I share some of the concern, but I want to make sure that we don't compare cross-studies in terms of progression-free survival improvement. The reality is the patients have changed. We can see, if you were to do this comparison, that the progression-free survival for this group just on the control is approximately 11 months, and that's pretty significant.

So if that's the case, 7 months improvement

in a population that is very well screened, monitored, et cetera, with all the data that we've seen, I think is relevant.

The other issue regarding the survival, if we're talking about toxicity -- and we look at survival affected by this, 6 deaths, 2 of them probably related to drug, from now on technically we should start to see death related to the disease progression. So that will be the true reading of what the overall survival impact will be on the treatment.

So maybe this is an earlier reading for a disease that has a long overall survival and for which we just see some of the patients, for which the toxicity is and what's going to happen no matter what, and being related to the disease.

So I just want to make sure we put it in the right context as we look at this study because maybe having another option for these patients, as every treatment is not for everyone, could be something that might allow for prolongation of survival. I think it would be important to see, at

some point, what osimertinib, after this first line, will look like to see if, really, we can put this in the context of a sequence. Unfortunately, the way we develop drugs is not in an sequence; it's one point at a time.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, internal medicine. I appreciate the conversation around the table. I do believe that the quality-of-life question is done well or very, very important.

One conclusion I've come to after coming to the meetings as a consumer rep, and one of my other jobs on the medical board of California and a consumer rep in California, is that although there's a bias towards folks who tend to come to the meetings and represent a product that they want to have available to them, although I'd like to feel that I could put myself in their place relative to toxicity and tolerance, I really can't.

It appears that many of the people, although there's a bias, want to have an option, want to have the ability to have something that makes a

difference to them while something else didn't, or something didn't work for someone they know or that they've talked to, whoever, with a similar diagnosis.

So I'm just making a statement that I think that it's important to focus on the question and realize that we may not be able to answer all the nuances as it relates to the product [indiscernible]. And I hope I'm not too confusing, but I'm going to stop there.

DR. HOFFMAN: I think we're ready to move on to the vote process. I think we've heard many comments and concerns about the fact that, again, we're dealing with progression-free survival rather than overall survival, though I think we've addressed that in some detail.

Concerns about the toxicities have been raised, the concerns about the sequence of where this would fit, though I don't think that's particularly our purview necessarily. I think our charge is to look at this data and decide if we believe that the benefits and the risk profile here

warrant approval.

We'll be using an electronic voting system for this meeting, and once we have the votes, the buttons will flash. You'll enter your vote and press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record, and next we'll go around the room, and each individual who voted will state their name and their vote into the record. You may also state the reason why you voted as you did if you want to.

For the record, I'll just read the question that is before us. Is the benefit-risk profile of ramucirumab plus erlotinib favorable for patients with untreated metastatic EGFR-positive non-small cell lung cancer?

Please press the button on your microphone

that corresponds to your vote. You'll have approximately 20 seconds. Press the button firmly.

(Voting.)

DR. HOTAKI: For the record, the vote is 6 yes; 5 no; and zero abstentions.

DR. HOFFMAN: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

Dr. Szabo?

DR. SZABO: Evan Szabo, NCI. I voted yes. The reason I voted yes was that although the side effect profile I think is more severe than erlotinib alone, and maybe other TKIs -- probably other TKIs -- I was convinced by Dr. Pazdur's framing of the question as not a comparison but as an independent drug strategy.

I think it is a feasible drug strategy. Now, many people may choose to use it or not use it, but it's another option. The 7-month PFS is fairly impressive, so I think it's an option that

some people could potentially take.

DR. DEEKEN: John Deeken, medical oncology. I voted no. I think in 2020, it's hard to argue for this disease that occurs -- I know it wasn't the primary endpoint, but an overlapping, completely overlapping, overall survival curve is hard to argue given the toxicity that we saw. I'm hopeful that the company will -- not that I'm hoping the events happen more sooner, but that we'll have overall survival final results sooner than 2023 so that that application can be based on that solid endpoint.

DR. MALIK: Shakun Malik, NCI. I voted no for the same reasons, that there was no improvement in quality of life and there was increased toxicity. Although the PFS was improved, my concern was also that the OS was not going in the right direction. It's possible that with the time and the events that it might, and I am hoping that the company can come back sooner than 2023 if that is the case. Thank you.

MR. MATSON: Tracy Matson, patient

representative. Earlier today, one of the presenters mentioned a plan B, and when I was a cancer patient, my poor oncologist, I was a plan D, E, and F guy. While I'm not sure that this is a massive breakthrough, I do feel that it could be an important weapon in the arsenal for doctors and patients to discuss.

I'd also like to commend the patients for traveling. It's tough to fight for what you believe in under these circumstances and can be intimidating when you feel great. But to come across the country when you're battling this serious of a disease is worthy of my admiration. Thanks.

DR. HAWKINS: Randy Hawkins. I voted yes. Similar to Dr. Szabo and Mr. Matson, I agree with what they said. I also thought about complication and adverse events. Many of our specialists are able to manage these adverse events, and patients tolerate them or they don't, and they withdraw.

I thought about the hypertension. I take care of -- probably 40 percent of my hypertensives

are on 3 drugs or more. But I voted yes, and I thought that this deserved to be in the toolkit of the oncologist who I trust and the patients who I trust.

DR. GARCIA: Jorge Garcia. I voted no. I think that with the question in mind, there is a presence of already a poor survival benefit in this patient population. I think moving to a proven agent or a combination like this, based upon PFS with immature survival data and with the AE profile, I'm not sure that that's the most logical step at this time.

DR. CRISTOFANILLI: Cristofanilli. I voted yes. I think looking specifically at the study, without comparing, the progression-free survival endpoint was met. There is still immature data for a number of other endpoints. I think this study will give us a lot of information for subsequent therapies and better strategies.

DR. HOFFMAN: Philip Hoffman. I voted yes. I struggled with it, but I ultimately came down on the side of yes for the strictest definition of the

question, which was did I believe that this was safe and effective? I am a lung cancer doctor. For many years, we used bevacizumab, another VEGF inhibitor, which caused hypertension and we sort of dealt with it. There were issues, and sometimes we had to adjust.

I would like to hope that the proposed sequence of having erlotinib and ramucirumab for a period of time, and then upon progression, that patients would then be able to get another substantial period of benefit from osimertinib. I realize we don't have that information, and that's something that I hope might come along.

I share the concerns of many of my colleagues that the hassle of coming in every 2 weeks and getting an infusion is not inconsequential, so I don't actually know whether I'll use this or not, or whether I'll use it in some patients, and discuss it with patients, and so on. But I do think it's reasonable to have it available as an option. As others have said, it's not up to me how this gets marketed, if you will.

DR. KLEPIN: Heidi Klepin. I voted no. This was a difficult decision. As everyone pointed out, the progression-free survival, it looks good but, to me, that matters if we have good evidence and the data that we're looking at, and that that would likely translate to either improved overall survival or at least not result in potential detriment in survival.

So that's where I'm hung up with the data that we have and the immature survival data, and that we have some concerns, still, based on where we are now, that there could potentially be an overall survival detriment. So in that setting, progression-free survival in my opinion is not enough.

DR. HINRICHS: Christian Hinrichs. I voted no. I agree with what Dr. Klepin said, and that is that if there is an improvement in PFS but also an increase in toxicity and no improvement in overall survival, there are several possible explanations for that, and one of them is that the drug's not beneficial, and I'm not convinced that the drug is

beneficial.

The other issues I've mentioned before is that I think that the thinking around whether the drug is safe and effective should include consideration of how the drug is actually going to be employed in the clinic and whether it's going to be employed in a treatment paradigm that's safe and effective. We really don't have data for the treatment paradigm that will be used for treating patients with this combination of drugs, and then in some cases followed by another drug. That just simply wasn't studied.

Along those lines, I would encourage the FDA, in designing trials with applicants, to consider how the drug is actually going to be deployed in the clinic, in clinical practice, and make sure to design the trials in a way where we can assess if the drug is actually going to be useful.

DR. HALABI: Susan Halabi, statistician. I voted yes, and the reason why I voted yes is because PFS is a legitimate endpoint. I think it's

very difficult to do an OS trial, a trial with a primary endpoint of OS. Even though the projected probability did show that it's likely, the hazard ratio with a 95 percent confidence interval even higher than 1, as a statistician, we can never underplay the role of chance, so it may be or it may not. At the end of the day, it will be the task for the FDA, if worst things happen, to pull the drug off the market.

DR. HOFFMAN: I appreciate everyone's comments. I think the people that voted yes, to summarize, felt that this was a feasible combination to add to our armamentarium, that the progression-free survival was indeed a worthwhile difference. Again, it's another weapon to have available, and the safety appears to be tolerable.

The people that voted no are concerned about the lack, at this point, of overall survival information, and particularly the possibility that overall survival might be reduced with this combination yet to be determined; that there does not appear to be an improvement in quality of life;

that there is significant toxicity for some patients; and that that made it not something that they could approve.

Dr. Pazdur, do you have any other comments, now that we've made your decision so simple?

DR. PAZDUR: This reflects our own internal discussions here. I had to laugh because we had many of these same discussions internally, and I guess hearing them from an external committee just shows that we're in tune with the outside world, so to speak --

(Laughter.)

DR. PAZDUR: -- in our own little cocoon here. Thank you.

Adjournment

DR. HOFFMAN: Okay. I apologize that we're a few minutes early --

(Laughter.)

DR. HOFFMAN: -- but we will now adjourn this meeting. Panel members, please leave your name badges on the table so that they can be recycled, and be sure to take all your personal

belongings as the room is going be cleaned at the end of the day. You may leave your meeting materials on the table if you want them to be disposed of. Thank you.

(Whereupon, at 4:48 p.m., the afternoon session was adjourned.)