FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Tuesday, April 12, 2016

8:30 a.m. to 12:25 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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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

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. ARMSTRONG: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices you have if you've not already done so. I'd also like to identify the FDA press contact, Angela Stark. If you're here, please stand up. There she is. Thank you, Angela.

Now, I'd like to have the members of the committee introduce themselves. We'll start with P.K. Morrow.

DR. MORROW: P.K. Morrow, Amgen.

DR. MAGER: Don Mager, associate professor at the University of Buffalo.

DR. SZABO: Eva Szabo, National Cancer Institute.

MS. GILLESPIE: Terry Gillespie, advocate.

DR. ORZA: Michelle Orza, Patient-Centered Outcomes Research Institute. I'm the acting

consumer representative today.

DR. FIGG: William Figg, National Cancer Institute.

DR. NOWAKOWSKI: Grzegorz Nowakowski, Mayo Clinic, Rochester.

DR. FOJO: Tito Fojo, medical oncology at Columbia University.

DR. ARMSTRONG: Deb Armstrong, medical oncology, Johns Hopkins and ODAC chair.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. ROTH: Bruce Roth, Washington University in St. Louis.

DR. MENEFEE: Michael Menefee, medical oncology, Mayo Clinic, Florida.

DR. RINI: Brian Rini. I'm a medical oncologist at Cleveland Clinic.

DR. COLE: Bernard Cole, biostatistics at University of Vermont.

DR. LIU: Chao Liu, pharmacometrics, FDA.

DR. FASHOYIN-AJE: Lola Fashoyin-Aje, the clinical reviewer for this application, FDA.

DR. BLUMENTHAL: Gideon Blumenthal, clinical, FDA.

DR. KEEGAN: Patricia Keegan, division director, Division of Oncology Products 2, FDA.

DR. PAZDUR: Richard Pazdur, director, Office of Hematology, Oncology Products.

DR. ARMSTRONG: Thank you. 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, and 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 also 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.

I'll now pass it on to Jennifer Shepherd, who is replacing Lauren Tesh, who's on jury duty today, who will read the Conflict of Interest Statement. Life goes on.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. 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, which the government may expect from the employee.

Related to the discussion of today's meetings, 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 primary employment.

Today's agenda involves new drug application 208542, rociletinib tablets, application submitted by Clovis Oncology Incorporated. The proposed indication for this product is for the treatment of patients with mutant epidermal growth factor receptor, or EGFRs, non-small cell lung cancer, who have been previously treated with an EGFR-targeted therapy and had the EGFR T790M mutation as detected by an FDA approved test. This is a particular matters meeting during which specific matters related to Clovis Oncology's NDA will be discussed.

Based on the agenda for today's meeting 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 Dr. P.K. Morrow is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

We would like to remind members and temporary voting members that if the 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. ARMSTRONG: Thank you. We'll now proceed with the opening remarks from Dr. Blumenthal.

Opening Remarks

DR. BLUMENTHAL: Good morning, Chairperson Armstrong, members of the ODAC. We are here to discuss the rociletinib New Drug Application 208542 for proposed indication for the treatment of patients with EGFR mutation positive metastatic non-small cell lung cancer, who have been previously treated with an EGFR tyrosine kinase inhibitor and whose tumors harbor an EGFR T790M mutation as detected by an FDA approved test.

The applicant, Clovis Oncology, has requested accelerated approval for rociletinib based on the results of two non-randomized studies conducted in patients with EGFR mutation positive metastatic non-small cell lung cancer. The

companion diagnostic test to detect EGFR T790M mutations is also under review.

EGFR T790M mutation positive non-small cell lung cancer is a serious and life-threatening disease with unmet medical need. Safe and effective therapies to treat this disease are needed for patients who have progressed on first-line EGFR TKI and often platinum doublet chemotherapy.

Treatment options include docetaxel with or without ramucirumab, pemetrexed, or nivolumab, with response rates roughly 10 to 20 percent and median survivals of 1 to 2 years. Recently, FDA granted osimertinib accelerated approval for patients with T790M mutation positive non-small cell lung cancer based on a confirmed objective response rate of 59 percent by independent radiologic review in 411 patients.

Responses appear to be durable with a median duration of response of 12 months. In addition, osimertinib was well tolerated with no grade 3 or 4 toxicities occurring in more than 3 percent of

patients.

During the review of the rociletinib application, a number of issues arose and several uncertainties remain. With respect to efficacy, FDA disagreed with the applicant's inclusion of unconfirmed responses when reporting ORR. FDA's pooled analysis revealed an ORR of 30 percent with a median duration of response of 9 months.

A key point to discuss is whether the ORR and durability observed with rociletinib is better than available therapies for second-line lung cancer, which have demonstrated survival benefits. Superiority to available therapy is necessary for accelerated approval.

The main uncertainties with respect to safety are the serious and life-threatening risks associated with rociletinib and its toxic metabolites M502 and M460. These toxicities include serious hyperglycemia, which occurred in a third of patients.

Furthermore, rociletinib is pro-arrhythmogenic with cases of ventricular

tachyarrhythmias and sudden deaths. The true incidence of deaths due to arrhythmia may be underestimated given that rociletinib was evaluated in single-arm trials.

A major source of variability and exposure to the metabolites M502 and M460 is a patient's NAT2 genotype. Patients who are NAT2 slow acetylators are at increased risk for serious hyperglycemia and QTc prolongation leading to ventricular arrhythmia, and uncertainty remains with respect to how best to risk stratify patients based on acetylator status.

With respect to dose, the applicant's proposed dose of 625 milligrams twice daily is not supported by the available clinical, clinical pharmacology, or pharmacometric data submitted in the application.

Today, we will discuss these issues and the residual uncertainties. The discussion will focus on the overall benefit-risk profile of rociletinib for the proposed patient population and whether more information is needed from the results of the

randomized control trial of rociletinib versus single-agent chemotherapy prior to making a regulatory decision on this application. Thank you.

DR. ARMSTRONG: 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 they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have 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'll now proceed with the applicant's presentation.

Applicant Presentation - Lindsey Rolfe

DR. ROLFE: Good morning. I am Lindsey Rolfe, chief medical officer at Clovis Oncology. We are pleased to be here to present our candidate, rociletinib, for accelerated approval for the treatment of T790M positive non-small cell lung cancer patients.

Lung cancer is the second most common serious cancer in the U.S. with over 200,000 new cases each year and is the leading cause of cancer-related death in the U.S. Non-small cell lung cancer accounts for almost 85 percent of lung cancers and is associated with high mortality. By the time of detection, most non-small cell lung cancer patients have metastatic disease for which there is no cure. Thus, treatment is focused on reducing tumor burden, controlling disease, and

managing symptoms.

Major recent advances in treating non-small cell lung cancer have come from understanding the underlying molecular abnormalities that drive the disease. We now know that approximately 15 percent of non-small cell lung cancer patients in the U.S. have epidermal growth factor receptor, or EGFR, activating mutations in their tumor, the majority of whom will respond to a first or second generation EGFR targeted tyrosine kinase inhibitor, or TKI. However, almost all patients will develop acquired resistance to therapy predominately due to a second EGFR mutation, T790M.

Rociletinib was specifically designed to inhibit T790M. Rociletinib is a novel, potent, third generation EGFR targeting TKI. It irreversibly inhibits both the initial activating EGFR mutations and the T790M resistance mutation without the dose limiting skin and GI effects that are clinically observed with the first and second generation inhibitors.

The proposed indication for rociletinib is

for the treatment of patients with mutant EGFR non-small cell lung cancer who have been previously treated with an EGFR targeted therapy and have the EGFR T790M mutation as detected by an FDA approved test.

We are seeking accelerated approval and will show that rociletinib meets the criteria outlined by FDA. First, rociletinib treats a serious condition in a subgroup of patients with advanced EGFR mutant non-small cell lung cancer.

Second, rociletinib provides an advantage over available therapy, which includes single agent chemotherapy and immunotherapy.

Third, objective response rate is an endpoint that reasonably predicts meaningful clinical benefit in lung cancer. In addition, our confirmatory randomized, controlled phase 3 study is ongoing.

I would like to take a moment to discuss why we are seeking approval for a different dose than the recommended dose in the NDA. We studied a number of doses in our phase 2 program, and all

doses were active. At the time of our NDA submission, we recommended 500 milligrams BID because we anticipated that the response rate at 500 milligrams BID would increase as the data matured.

As agreed previously with FDA, we submitted a more mature efficacy update following our initial submission, which also included a new analysis of the data at FDA's request. Based on these data, we revised our recommended dose to 625 milligrams as the objective response rate is higher at 625 milligrams than at 500 milligrams, with similar toxicity.

Due to the observed activity of both doses, however, we are studying both the 500-milligram and the 625-milligram doses in the randomized confirmatory study.

For our agenda for the rest of the presentation, Dr. David Carbone from the Ohio State University will present the need for new treatment options. Then, Dr. Sergey Yurasov from Clovis Oncology will review the rociletinib efficacy data.

I will return to the lectern to present the safety data and our dose selection rationale. And then Dr. Ross Camidge from the University of Colorado will provide his clinical perspective on the benefit-risk of rociletinib. I will then return to answer your questions.

Additionally, we have some external experts with us today to help answer your questions. All have been compensated for their time. And now I would like to invite Dr. Carbone to the lectern.

Applicant Presentation - David Carbone

DR. CARBONE: Good morning. I am David Carbone, professor of medicine and director of the James Thoracic Center at the Ohio State University. I also serve as the president of the International Association for the Study of Lung Cancer.

My research interests have been focused on the development of new targeted therapies on lung cancer genetics and immunotherapy of lung cancer. I'm pleased to be here to discuss the need for new effective treatments for patients with EGFR mutant non-small cell lung cancer.

Because we're not able to cure advanced EGFR mutant lung cancer, the goal of treatment is to achieve and maintain disease control while minimizing treatment related toxicities. The optimal therapy for newly diagnosed patients with advanced or metastatic EGFR mutant non-small cell lung cancer is to receive an EGFR targeted TKI as their first-line therapy.

The vast majority of these patients experience clinical benefit from this with an overall response rate of 50 to 70 percent and a duration of response that ranges between 6 and 12.5 months, with progression-free survival ranging from 10 to 14 months.

As patients can remain on treatment for many months, even low-grade treatment related toxicities that are present continuously can become important to patients. Particularly relevant to patients receiving EGFR inhibitors are skin effects, nail changes, and diarrhea. While they sound innocent, they can be difficult for patients to tolerate for long periods of time.

Regardless of treatment and toxicities, all patients will eventually progress. In approximately 60 percent of patients, progression is due to a second EGFR mutation T790M, which renders first and second generation EGFR inhibitors ineffective. So how do we treat these patients?

Since it is generally considered optimal to maintain well-tolerated oral TKI therapy for as long as possible before transitioning to chemotherapy, strategies include local therapy for oligoprogressive disease and third generation TKIs targeting the T790M resistance mechanism.

After exhaustion of TKI options, fit patients may be appropriate for a platinum-based doublet. There are now FDA approved second-line therapies for treatment of metastatic non-small cell. These include single agent chemotherapies pemetrexed and docetaxel, immunotherapy with nivolumab, and anti-VEGFR2 ramucirumab used in combination with docetaxel.

Let me describe what can be expected with the approved second-line agents. Single agent

chemotherapy offers little clinical benefit as second-line therapy with response rates in the single digits and a median duration of response between 4 and 9 months.

These patients also experience significant clinically evident toxicities, including nausea, fatigue, hair loss, and neuropathy. Neutropenia is frequent with these agents and increases the risk for symptomatic infection and may require hospitalization with a substantial negative impact on their lifestyle and can also lead to treatment discontinuation.

There are two other approved treatments for patients with non-small cell lung cancer. Immunotherapy has shown activity in unselected patients receiving second-line therapy. There's insufficient data in patients with EGFR mutant lung cancer.

It should be emphasized that all of these options are available to EGFR mutant patients after exhaustion of TKI options. In addition to having a low response rate in these patients, the side

effect profile of nivolumab is benign in the majority of patients, but a small number of patients do experience severe adverse events, like colitis, hepatitis, pneumonitis, and rash. The combination of ramucirumab plus docetaxel has all the side effects of single-agent docetaxel plus those associated with VEGFR2 inhibition.

While this is an exciting time for research and development in an area of high unmet need, there is still a need for more EGFR targeted treatment options. I've been treating patients with lung cancer throughout my career for the past 25 years, and it's hard to overemphasize how awful a disease lung cancer is.

With over 220,000 cases a year, the majority of these cases diagnosed at stage 4, where the global median survival is only 6 months from diagnosis to death. Thus, the goal of treatment is to control patient symptoms as effectively as possible for as long as possible, and I believe this is achieved by maximizing time on TKIs.

Each of the current therapies I discuss has

a unique risk-benefit profile enabling oncologists to tailor therapy to individual patients. As a clinical oncologist who has worked with lung cancer patients, what's absolutely clear to me is that no single therapy is appropriate for all patients. There is a clear clinical need for new therapeutic options for patients with EGFR T790M mutant non-small cell.

Now, I will turn the lectern over to Dr. Yurasov.

Applicant Presentation - Sergey Yurasov

DR. YURASOV: Thank you, Dr. Carbone. My name is Sergey Yurasov, and I will present the efficacy data for rociletinib. The evidence support an accelerated approval comes from two phase 2 trials, study 008 and study 019. Both studies were ongoing at the time of the data cutoff.

These studies have similar design and patient populations, and data that we'll present today is combined from the two studies. Results were similar across trials.

Study 008 was an open-label phase 1-2 study to assess safety and efficacy of rociletinib in patients with EGFR mutant non-small cell lung cancer who have progressive disease after one or more prior EGFR TKI therapies. Tumor responses were seen at several dose levels during dose escalation in phase 1.

In phase 2, T790M status was confirmed by central lab. We started with a 750 milligram twice daily dose, however investigators commented that lower doses might have better tolerability while maintaining the overall response rate. We expanded the study to include 500- and 625-milligram BID doses.

In study 008, tumor assessments were performed every 6 weeks. Treatment continued until disease progression or death. The end of study evaluation was conducted 28 days after the last dose. Patients were then followed every 2 months to capture subsequent therapy as well as survival data.

Based on the emergent data from study 008,

the 625-milligram dose was chosen for further evaluation in study 019. Study 019 was a phase 2, open-label, single-arm study to evaluate the safety and efficacy of rociletinib 625-milligram BID dose in patients with centrally confirmed T790M positive EGFR mutant lung cancer who had progression after one prior EGFR TKI therapy. Tumor assessments were performed every 8 weeks. Treatment continued until disease progression or death.

Overall, 457 patients were enrolled in study 008 and 019 across different dose levels. Free-base formulation was discontinued early in development and will not be presented. Our clinical analyses are based on hydrobromide formulation, which has a better PK profile. Overall, 400 patients received rociletinib at 500, 625-, 750-, and 1000-milligram doses. This is our safety population.

The T790M efficacy population contains only patients who were treated with rociletinib and had evidence of T790M positive tumors confirmed by central lab and who had scans submitted for

independent review; 325 patients matched these criteria. This is our efficacy population.

Key inclusion criteria was similar for both studies. Adult patients with ECOG performance status 0 or 1 with confirmed EGFR mutation positive lung cancer were enrolled. These were patients who had recurrent disease after prior therapy with an approved EGFR TKI. T790M mutation status was centrally confirmed using tumor tissue.

For study 008, patients could have received one or more prior lines of treatment. For study 019, only patients who received one prior EGFR TKI were enrolled. Key exclusion criteria were also similar and excluded use of medications that prolonged the QT interval, prior treatment with T790M targeted agents, and unstable CNS metastatic disease.

Demographics for the T790M positive patients was typical of EGFR mutant lung cancer and consistent across all doses. Most patients were recruited from the United States. At least two-thirds of patients had ECOG performance

status 1.

Disease characteristics were typical of patients with recurrent progressive lung cancer. Median time since initial diagnosis ranged from 23 to 33 months. The vast majority of these patients had distant metastases with two or more organs affected, including approximately one-third of patients with liver lesions or bone disease. More than 40 percent of patients had a history of CNS disease, which typically has a worse prognosis.

Patients progressed after multiple prior therapies with a median of 2 to 3 prior therapies for lung cancer. Fifty-seven to 73 percent of patients received more than two prior lines of therapy. Fifty-two to 68 percent of patients received at least one chemotherapy regimen with almost all of these patients having received a platinum-containing chemotherapy.

Approximately one-third of patients received two or more treatments with an EGFR TKI prior to rociletinib. Patient disposition was generally consistent across doses. Between 35 and 42 percent

of patients continued to receive therapy at the time of data cutoff.

The main reason for treatment discontinuation across all doses was disease progression followed by adverse events. Death as the reason for treatment discontinuation was a rare event.

Now, let's look at the efficacy results. The primary endpoint was objective response rate, or ORR, based on RECIST 1.1 criteria. While ORR was evaluated by both independent physiological review and investigator assessment, I will present the IRR results. Investigator assessment results are similar and included in your briefing book.

The key secondary endpoint was the duration of response measured from the first observation of response until radiographic evidence of disease progression.

Now, turning to the primary efficacy endpoint, consistent with the FDA approach of pooling data across all doses for efficacy analysis, the confirmed objective response rate

overall was 30 percent. The response rates were similar for 625- and 750-milligram doses. Confirmed ORR at 500-milligram dose was slightly below the lower boundary of 95 percentile confidence interval for overall ORR.

Now, on to the duration of response. Responses were durable for all rociletinib dose levels combined. The median duration of response was 8.9 months. At the 625-milligram dose, which represents 51 percent of patients and is shown on the graph in blue, the duration of response was 8.8 months.

Let's look at the target lesion reduction in patients who have measurable disease at baseline. Clinically meaningful benefit in patients receiving rociletinib 625-milligram dose is supported by significant target lesion reduction as demonstrated on this waterfall plot with 93 percent of patients who experienced target lesion reduction when compared to baseline.

We also looked at efficacy across a number of subgroups. At the top of this graph, the

overall response rate of 30 percent seen across all doses combined is shown. Overall, the response rate was consistent across all major clinically relevant subgroups as shown on this forest plot.

For all doses combined, substantial tumor response was observed in patients with poor prognostic factors, such as age above 65, ECOG performance status 1, patients with liver and bone disease, and history of CNS disease.

For patients who received two prior lines of therapy, which is similar to the patient population in our confirmatory phase 3 study, the response rate was 33 percent.

In conclusion, rociletinib demonstrates clinically meaningful and durable responses in patients with T790M positive lung cancer. For all doses combined, the objective response rate is 30 percent with a median duration of response of approximately 9 months.

The 625-milligram BID dose with a response rate of 32 percent and duration of response close to 9 months is the appropriate dose to treat these

patients, especially when compared to approved chemotherapy-based regimens for recurrent lung cancer. Similar response rates were observed across all major clinical subgroups, including patients with poor prognostic factors.

Now, I will turn the lectern over to Dr. Lindsey Rolfe.

Applicant Presentation - Lindsey Rolfe

DR. ROLFE: Thank you, Dr. Yurasov.

Next, I will review the safety data set from the combined 008 and 019 studies. The safety population includes all patients treated at each dose, including patients with or without the T790M mutation.

The median duration of treatment ranged from 18 to 25 weeks across all three doses. Thirty-seven percent of patients on the 500-milligram and 625-milligram doses were treated for longer than 6 months with a higher percentage on the 750-milligram dose. The analysis we present is the most conservative, including events of disease progression. Almost all patients reported

one or more adverse events.

As we will show, AE frequencies tended to be very similar between the 500-milligram and 625-milligram doses and higher at the 750-milligram dose. Approximately 57 percent of patients had an AE of grade 3 or 4 severity at the 500-and 625-milligram dose, and 65 percent at 750 milligrams. More patients on the 750-milligram dose had an AE that led to dose modification.

Approximately 20 percent of patients had an AE that led to discontinuation across all the doses. About 46 percent of patients had a serious AE and approximately 15 percent of patients had a fatal AE.

Almost all of the deaths were related to disease progression in line with the advanced disease state under study. The most common adverse events were diarrhea, nausea, hyperglycemia, and fatigue across all doses.

Now, looking at grade 3 and 4 adverse events, the most common were hyperglycemia, QT prolongation, fatigue, and anemia. The large

majority of these were grade 3 events.

We investigated AE preferred terms related to diarrhea and cutaneous adverse events. These AEs were generally mild across all doses. While about half the patients experienced diarrhea, the majority of the diarrhea events were grade 1 or 2.

We see a low rate of rash. When looking at the combined terms of rash, the majority of events were grade 1 or 2. Notably, very few events were grade 3, and none was grade 4. This is important because for other EGFR TKIs, rash can lead to discontinuation.

The most common adverse events leading to dose modification were hyperglycemia, QT prolongation, nausea, diarrhea, and fatigue. I should note that the protocol required a dose interruption followed by a reduction for grades 3 QT prolongation. Almost all patients who had dose modifications remained on study.

Approximately 22 percent of patients discontinued treatment because of adverse events, of which approximately half were events of disease

progression. Discontinuation rates for other events were low and similar across doses.

Now, moving to serious adverse events. Approximately 46 percent of patients experienced a serious adverse event. The most common serious adverse event across all doses was tumor progression. Except for hyperglycemia on the 500-milligram dose, all other serious adverse events occurred in less than 10 percent of patients.

Although 13 to 17 percent of adverse events resulted in death, it is important to note that 86 percent of these events were events of disease progression and judged unrelated to rociletinib by the investigator. One patient died of pneumonia in each of the arms, and 2 patients died with no cause identified.

Now, I will review the adverse events of special interest, starting with QT prolongation. Using SMQ terms, approximately 34 percent of patients experienced an adverse event in the QTc prolongation category across all doses with

8 percent, 13 percent, and 16 percent reported as grade 3 or higher on the 500-, 625-and 750-milligram doses respectively. Approximately 12 percent of patients had dose modifications as was required by the protocol. Very few patients discontinued treatment.

Included in the serious adverse events were 3 events of ventricular tachyarrhythmia and 2 deaths where no cause of death was identified. Detailed information related to these 5 events is provided in the appendix of the briefing book.

A comprehensive ECG monitoring program was included in the clinical trials and all ECGs were collected and analyzed centrally by a specialist vendor. The database, which comprises more than 25,000 individual tracings, has enabled us to characterize the observed effect thoroughly.

This table shows the frequency of QTc prolongation. QTc was greater than 500 milliseconds in 12 percent of the patients on the 500-and 625-milligram doses and in 18 percent in the 750-milligram dose.

In the trials, we measured QTc on day 1, day 15, and on the first day of each subsequent cycle. No effect on QTc was observed on day 1. The increases were observed by day 15, and then remained stable throughout the duration of therapy.

While we recognize that QTc prolongation occurs frequently, we do believe that these events are manageable, and we have developed a comprehensive risk management program. The components and structure of the plan have been agreed with FDA.

The risk minimization strategy has three key elements. Firstly, a REMS program; secondly, a black box warning on the prescribing information; and thirdly, clear labeling statements on patient selection, patient monitoring, and dose modifications in case of QTc prolongation.

The goal of the REMS communication plan is to mitigate the risks of prescribing rociletinib and to inform the prescribers of the risk messages. The risk messages are that rociletinib prolongs QTc interval and that Torsades de pointes and sudden

death have occurred. Also, that ECG and electrolytes must be monitored, and rociletinib is not recommended in patients with prolonged QT at baseline.

Communication to healthcare professionals and professional societies will be by letter, by fact sheets, at congresses, and via a dedicated website with an assessment plan. All new prescribers will be identified on an ongoing basis by Clovis and contacted in a timely manner in order to receive documentation informing them of the risks and of the risk mitigation plan.

The black box warning on the label will provide clear information on which patients are not suitable for rociletinib therapy based on baseline risk factors that increase the risk of QT complications.

The proposed label will also inform about patient selection as well as provide information on ECG monitoring during therapy. The ECG effect is stable by day 15, and the proposed product labeling will recommend ECG monitoring at day 8, day 15 and

thereafter periodically.

There will also be a warning that electrolytes should be checked and normalized before starting therapy and if clinically indicated. There will be information that drugs causing QT prolongation should be avoided whilst taking rociletinib.

Lastly, the proposed label will contain clear guidance on when and how to dose reduce to manage QT prolongation, and when to interrupt rociletinib for prolonged QTc and when to restart.

Moving to hyperglycemia, as mentioned earlier, approximately 55 percent of patients at 500 milligrams and 625 milligrams, and 66 percent at 750 milligrams, reported an AE within the hyperglycemia category. Grade 3 or 4 events were similar between the 500-milligram and 625-milligram doses, and higher at 750 milligrams. Most occurred early in treatment. A similar number of patients on 500-and 625-milligram doses had dose modifications with substantially more on the 750-milligram dose. Overall, very few patients

discontinued for hyperglycemia as there are a number of measures to manage hyperglycemia.

Because most cases of grade 3 or higher hyperglycemia occur early in treatments, regular glucose monitoring in the initial weeks of therapy, followed by periodic monitoring, is appropriate.

We know that hyperglycemia is caused by rociletinib metabolites that inhibits insulin receptor pathways. Therefore, it is appropriate to manage the hyperglycemia using agents that target insulin resistance. Dose reductions may be used if hyperglycemia is not otherwise manageable. Finally, hyperglycemia can be detected and monitored by blood or urine testing, both of which are widely available.

Additionally, there are some other special interest AEs that we looked at. These include pancreatitis and cataracts. Acute pancreatitis was reported in 4 percent of patients. All patients recovered and continued on rociletinib therapy. After the data cutoff for the NDA, a report of pancreatitis was received in a patient treated at

625-milligrams BID with an outcome of death.

Cataract formation appears to be a late effect of rociletinib, therefore we performed an updated analysis of the NDA data set with a cutoff in January 2016. At this time, there were 41 patients with treatment emergent cataracts reported across all dose levels. We are continuing to monitor this evolving signal to provide optimal management guidance.

Overall, rociletinib has a well-defined, manageable, and differentiated safety profile. Thirty-seven percent of patients had treatment duration greater than 6 months. The starting dose of rociletinib may be reduced to manage adverse events. Prescriber education will help manage the events of QTc prolongation and hyperglycemia.

Awareness of these effects will enable appropriate patient selection and implementation of management strategies that reduce the risk of potentially serious sequelae.

Lastly, the AE profile differs from other AGFR TKIs in that it has higher rates of

hyperglycemia and QTc prolongation. However, cutaneous toxicities are minimal. These safety data, together with the efficacy results, informed our dosing recommendation.

An examination of the benefit-risk by dose justifies our recommendation to use rociletinib 625-milligrams BID as the best dose. The point estimate of the objective response rate was higher in patients taking 625 milligrams than 500 milligrams, with no incremental increase at 750 milligrams.

Additionally, the safety profile between rociletinib 625 milligrams and 500 milligrams are generally similar with higher frequency of grade 3 and 4 adverse events at 750 milligrams. Overall, we chose the most effective dose with an acceptable and manageable safety profile. As such, rociletinib 625 milligrams is the dose for which we are seeking accelerated approval.

I would like to briefly describe our confirmatory study. Our confirmatory study is a phase 3, randomized, controlled trial of

rociletinib compared to the investigators' choice of single agent cytotoxic chemotherapy. To be eligible patients, must have previously had at least one line of EGFR inhibitor therapy and cytotoxic chemotherapy comprising of platinum-containing doublet.

Patients' tumors will be assessed for T790M but the mutation is not a requirement for enrollment. The primary endpoint for this study is progression-free survival in T790M positive patients. Secondary endpoints include response rate, duration of response, and overall survival.

Let me describe the study design. It is important to note that this study began prior to determining 625 milligrams as the recommended dose. Thus, our confirmatory study currently randomizes patients to open-label treatment with rociletinib 500 milligrams or investigator choice of pemetrexed, gemcitabine, placlitaxel, or docetaxel. We amended the protocol to add a 625-milligram BID arm.

After randomization, treatment will be

continued until disease progression or death. Patients will be followed every 2 months to capture subsequent therapy as well as survival data. The confirmatory study is currently projected to complete in the second half of 2018.

The study has enrolled 137 patients as of April the 8th, 2016 and is tracking to enrollment projections. We are opening more centers outside of the U.S. to compensate for the availability of third generation EGFR TKIs. This is giving us confidence that the study will be completed in a timely manner.

Thank you, and I will now turn the lectern over to Dr. Ross Camidge to provide his clinical perspective on the benefit-risk of rociletinib.

Applicant Presentation - Ross Camidge

DR. CAMIDGE: Thank you. I'm Ross Camidge, the director of the thoracic oncology program at the University of Colorado. Over the past several years, I've treated many EGFR mutant lung cancer patients with both licensed and investigational agents, including rociletinib and osimertinib.

Today, I'll provide my clinical perspective on the benefit-risk profile of rociletinib 625 milligrams, and why I believe it should be granted accelerated approval.

With regard to dose, while there was no statistically significant difference in the response rate between 500, 625 and 750 milligrams, the highest point estimates occurred at 625 and 750 milligrams; and the lower confidence interval, the response rate at 500 milligrams, seems disparate from those at the higher doses.

Could these rates actually be the same? Of course. Equally, they may not truly be the same, so why would we not give our patients the best possible chance to respond?

While a 750-milligram dose was associated with the highest incidence of adverse events, there appears to be no significant difference in the side effect profile between 500 and 625. In addition, most side effects with this drug can be effectively managed either through additional supportive medications or through dose modification.

In my own experience, patients with symptomatic lung cancer feel better, often very rapidly, when their cancer responds to rociletinib. So aiming to get as many patients as possible to respond, together with a tolerable side effect profile, has to be the major goal of clinical practice.

Given that a higher proportion of patients responded at 625 than at 500, while the side effect profiles were comparable, I believe 625 milligrams should be the starting dose in order to give our patients the best benefit-risk ratio possible.

While at first sight, a grade 3 or 4 adverse event rate of 50 to 60 percent may seem worrisome, I'd like to discuss two of the most common side effects in detail to illustrate how all grade 3 or 4 events are not created equal in terms of their impact on patients' lives.

As discussed by Dr. Rolfe, most of the grade 3 and 4 adverse events were primarily related to hyperglycemia or QT prolongation. It is important to note that rociletinib associated

hyperglycemia is often only a laboratory observation.

Indeed, the grading system used focuses primarily on blood values and not symptoms, with grade 3 events representing glucose values between 251 to 500 milligrams per deciliter, and grade 4, values greater than 500.

As the frequency of hyperglycemia SAEs was significantly lower than the rate of grade 3 hyperglycemia, consistent with my own observations, this supports the idea that most, although admittedly not all, cases of rociletinib associated hyperglycemia can be managed without serious consequences, especially now that the underlying mechanism is understood.

With regard to QTc prolongation, note that the grading system doesn't specify symptoms until grade 4 events occur. Grade 3 QTc represents EKG values greater than 500 milliseconds. Grade 4 events use the same absolute QTc threshold but in association with life-threatening signs or symptoms. And such events occurred very rarely,

both by grading and by SMQ-grouped SAEs, which capture both unequivocal cardiac events and potential ones, such as loss of consciousness or sudden death.

While it is important not to minimize these rare clinically significant cardiac events when they do occur, it is also important to consider any QTc risk in the context of an already established, often heavily pretreated, life-threatening advanced lung cancer.

In the data set you have seen, the patients' treatment before rociletinib ranged from 1 to 13 prior lines of therapy with more than half of them having received platinum chemotherapy and a third having received at least two prior TKIs. Overall, when we look at the alternatives for patients with T790M positive tumors, rociletinib provides an important therapeutic option very different from the others currently available.

As you saw from Dr. Carbone, and from the FDA briefing document on the proposed comparator therapies, single agent docetaxel and pemetrexed

are associated with response rates below 10 percent, together with the common toxicities and inconveniences of intravenous chemotherapy.

The addition of ramucirumab to docetaxel can increase the response rate to 23 percent but at the expense of inflicting severe toxicities on nearly 80 percent of patients, and importantly these toxicities, including neutropenia, nausea, neuropathy, and hair loss, are not simple laboratory or asymptomatic EKG changes, but toxicities that often dramatically alter the quality of patients' lives.

With regard to immunotherapy, early data suggests that PD-1 inhibition may be less active in patients with EGFR mutant disease than in the general lung cancer population. Indeed, the latest insight publication from the NCCN states that currently immunotherapy in EGFR mutant lung cancer can neither be recommended for or against based on the available data.

To summarize, I believe the benefit-risk profile of rociletinib at 625 milligrams is

favorable. I have seen large masses shrink within days of starting rociletinib, together with a unique but manageable side effect profile, keeping many patients alive, some of whom are sitting in the audience today, when they had very few other options to pursue.

Rociletinib allows patients with EGFR mutant advanced lung cancer to maintain disease control through oral therapy for longer and put off the generally less effective, less proven, and/or less attractive options of cytotoxic chemotherapy or immunotherapy.

Beyond the fully approved options, there are of course other third generation drugs being developed, but rociletinib is not just a variant of these. Each differs in its side effect profile, and indeed we now know the common mechanisms of acquired resistance to third generation drugs seems to differ between these agents.

Consequently, the more options we have now, the greater the chance is that we will not have to deny patients access to safe and effective

treatments simply because one size is never going to fit all in the cancer therapy arena. Thus, I believe the results we've seen today merit giving patients immediate access to this drug via accelerated approval. Thank you.

DR. ARMSTRONG: Thank you. We'll now proceed with the presentation from FDA.

FDA Presentation - Lola Fashoyin-Aje

DR. FASHOYIN-AJE: Good morning. I'm Lola Fashoyin-Aje, the clinical reviewer for NDA 208542, rociletinib. I, along with Dr. Chao Liu, will present the results of the efficacy, safety, and clinical pharmacology evaluation of this application. I would like to acknowledge the other members of the review team whose collective effort is represented in today's presentation.

During the review of this application, several issues were identified. We will discuss these issues highlighting areas of disagreement with Clovis. The data demonstrate that rociletinib is an active drug in the indicated population. However, it is unclear whether the activity of this

drug, specifically as measured by an overall response rate of 30 percent and a median duration of response of 9 months, demonstrates improvement over available therapy.

The incidence of serious adverse reactions is substantial. Up to one-third of patients experienced grade 3 or grade 4 hyperglycemia. Eleven percent of patients experienced grade 3 or grade 4 QTc prolongation, and potentially fatal ventricular tachyarrhythmias, including Torsades de pointes, were observed. Two sudden and unexplained deaths were also reported.

Single-arm trials are inadequate to characterize the true extent of the incidence of these serious and life-threatening adverse reactions.

The clinical pharmacology evaluation indicates that there is considerable variability in the exposure to the rociletinib metabolites that can contribute to the increased risk of hyperglycemia and QTc prolongation. Factors independent of dose may explain this variability

and increased risk, including NAT2 acetylator genotype status.

However, there is uncertainty regarding whether and how to risk stratify patients according to the NAT2 acetylator status to mitigate the increased risks post by the rociletinib metabolites. Finally, the data submitted to the NDA do not support Clovis' proposed dose of 625 milligrams, and the uncertainty remains regarding the optimal dose.

During the course of this presentation, I will introduce the application, focusing on the regulatory background and on the key issues in this application. Dr. Liu will discuss the pertinent clinical pharmacometric findings, focusing on whether the data submitted in the NDA support Clovis' proposed recommended dose.

I will then discuss the efficacy and safety results with emphasis on the major safety concerns and conclude the presentation by summarizing the key issues relevant to our meeting today.

Rociletinib is a small molecule tyrosine

kinase that irreversibly binds and inhibits the common activating mutations Exon 21 L858R substitution and Exon 19 deletion, and the EGFR resistance mutation T790M.

The proposed indication for rociletinib is for the treatment of patients with mutant epidermal growth factor receptor non-small cell lung cancer who have been previously treated with an EGFR targeted therapy and have the EGFR T790M resistance mutation as detected by an FDA approved test.

As described by Clovis, lung cancer is the leading cause of cancer related mortality in the United States and worldwide. Non-small cell lung cancer accounts for nearly 85 percent of all cases.

Current treatment of non-small cell lung cancer is guided by the presence of actionable mutations, such as driver mutations in the kinase domain of the EGFR gene, which occur in 10 to 15 percent of white patients, but more commonly in Asian patients. The presence of these EGFR mutations predicts for sensitivity to EGFR tyrosine kinase inhibitors and improved outcomes in patients

who receive these agents compared to patients who are treated with chemotherapy.

Most patients who are treated with EGFR tyrosine kinase inhibitors subsequently develop acquired resistance. The T790M mutation is the most common resistance mutation and is observed in approximately 60 percent of patients. This mutation renders the currently approved EGFR tyrosine kinase inhibitors erlotinib, gefitinib, and afatinib ineffective.

Following disease progression, patients are managed in a similar fashion to unselected patients with non-small cell lung cancer who have progressed following doublet chemotherapy.

Shown here are the FDA approved treatment options for these patients. These agents are considered available therapy for the purposes of this application. In the clinical trials that supported the approval of these agents, the overall response rate was not the primary efficacy endpoint, and in most cases, the overall response rate was assessed by the investigator. This is an

additional limitation to consider when comparing overall response rates between studies.

Available therapies for the treatment of metastatic EGFR mutation positive non-small cell lung cancer in the second-line setting have demonstrated response rates ranging from 6 to 23 percent. There are limited data on duration of response, however, nivolumab provides a 17-month median duration of response. Importantly, all available therapies have demonstrated definitive clinical benefit as measured by improvements in overall survival.

Another approved EGFR tyrosine kinase inhibitor is osimertinib. Osimertinib received accelerated approval in November 2015 for the treatment of patients with metastatic EGFR T790M mutation positive non-small cell lung cancer who have progressed on or after EGFR TKI therapy.

Since osimertinib was approved under accelerated approval, it is not considered available therapy as described in FDA guidance documents. However, given that the indication for

which it is approved is similar to the indication that is sought for rociletinib, I will briefly review the basis for its approval.

The key efficacy endpoint for the osimertinib application was overall response rate according to RECIST and as assessed by central independent radiology review. As highlighted in the red box, the overall response rate was 59 percent with a median duration of response of 12.4 months.

The most common adverse reactions in patients who received osimertinib were diarrhea, rash, and nail toxicity. These adverse reactions are similar to those caused by other EGFR targeted therapies. The most common grade 3 or grade 4 adverse reactions were pneumonia and venous thromboembolism. These adverse reactions occurred in less than 3 percent of patients.

Other clinically important adverse reactions are listed here. Relevant to our discussion today, QTc prolongation occurred in patients who received osimertinib. However, less than 3 percent of

patients had serious QTc prolongation.

This table lists the regulatory milestones for the rociletinib application. Rociletinib received breakthrough therapy designation in May 2014 on the basis of an overall response rate of 54.5 percent in 33 patients who received rociletinib across several doses.

In the NDA, Clovis has requested accelerated approval for rociletinib based on the results of two clinical studies, study 008 and study 019. Clovis has presented the key elements necessary to meet the requirement for accelerated approval, and as such, I will not review them again.

Listed here are the two studies that support the application. These have also been described in detail by Clovis. To reiterate, the overall response rate and duration of response were the main efficacy endpoints. These outcomes were assessed by the investigator and by an independent radiology review in both studies.

Also described in Clovis' presentation is the proposed confirmatory study, study 020. The

rociletinib dose to be evaluated has been amended several times, as you heard. In the most recent amendment, Clovis stated that the two doses of rociletinib, 500 milligrams and 625 milligrams, will be evaluated in two study arms comparing each rociletinib arm to the chemotherapy therapy arm.

FDA and Clovis held several meetings to discuss the approach to the efficacy evaluation, as well as to better understand our respective interpretations of the clinical and clinical pharmacology data. We disagree with Clovis' approach to selecting the recommended dose for rociletinib.

FDA's approach relies on the findings of the clinical pharmacology data analysis, which will be presented by my colleague. Another area of disagreement with Clovis was the interpretation of the efficacy results. I will discuss this in the upcoming slides.

To provide context for the basis of our disagreement with Clovis' proposed rociletinib dose, I will provide a brief history of FDA's

recent interactions with Clovis regarding this issue.

In July 2015, Clovis submitted the clinical component of the NDA, including draft labeling, which indicated that 500 milligrams administered twice daily was the dose for which Clovis sought approval.

In December 2015, Clovis stated their intention to amend the NDA to propose 625 milligrams. According to Clovis, this decision was based on the observation of a numerically higher point estimate for tumor response at that dose compared to the 500-milligram dose. Clovis submitted a revised draft label reflecting this change in January 2016.

In February, FDA informed Clovis that the available pharmacokinetic data submitted in the NDA did not appear to support their proposal to change the recommend dose to 625 milligrams. In March, Clovis submitted a formal amendment to the proposed confirmatory trial, study 020, to evaluate the 625 milligrams in a third study arm.

Dr. Liu will now present the clinical pharmacology findings as they pertain to the applicant's proposed dose.

FDA Presentation - Chao Liu

DR. LIU: Good morning. My name is Chao Liu, and I am the pharmacometric reviewer of this application. On behalf of the FDA review team, I'll be giving a brief summary of the pharmacological property of this drug, and then addressing if the rociletinib 625-milligram BID is adequately supported by the available data.

Rociletinib exposure at steady state is highly variable. When pH is greater than 2, rociletinib is practically insoluble. Food affects the drug absorption, and the rociletinib exposure increases with a high fat meal. Therefore, in the clinical trials, rociletinib was administered with food to boost absorption. Rociletinib is mainly metabolized by amide hydrolysis and N-acetylation.

The parent drug rociletinib is the moiety associated with anti-tumor activity. Via amide hydrolysis, rociletinib is converted to 2 major

metabolites, M502 and M460. These two metabolites are responsible for two major adverse reactions, hyperglycemia and QT prolongation. Hyperglycemia is primarily attributed to M502, and QT prolongation is attributed to M460.

Here is the in vitro evidence for the mechanism of action. The table shows the IC50 values of rociletinib M450 and M502 for different targets. Lower values indicate stronger binding to the receptors and a higher potency.

Rociletinib selectively binds to T790M EGF receptor contributing to the anti-tumor activity. Metabolites have limited activities against EGF receptor, and thus are not contributing to the efficacy.

M460 with high potency for hERG inhibition leads to QT prolongation by inhibiting hERG related potassium influx. M502 is primarily responsible for hyperglycemia by inhibiting insulin-like growth factor 1 receptor and insulin receptor.

Both M460 and M502 showed a similar potency for IGF1 receptor and insulin receptor inhibition,

but M502 exposure is 23-fold higher than M460 exposure. Therefore, M502 is mainly responsible for the hypoglycemic effect of rociletinib.

To assess the proper dose of rociletinib, we evaluated a dose exposure relationship over the dose range from 500- to 1000-milligram BID. The analysis was based on the intensive PK data collected from a subset of the subjects in the trial.

Non-compartmental analysis was employed to derive the individual Cmax and a steady state AUC on day 15 at cycle 1. Each dot represents one individual patient data. The regression lines for Cmax on the left and the steady state AUC on the right are both flat, suggesting similar exposure over the dose range from 500- to 1000-milligram BID.

This slide shows the dose exposure relationship based on the population PK analysis from over 300 patients. Each dot represents the steady state AUC from one individual patient. The box plot represents the distribution of individual

exposures.

Consistent with the results from intensive PK data, subjects with 500-, 625-, 750-, and 1000-milligram BID doses showed similar rociletinib exposure. Therefore, based on the intensive and the population PK analysis, we concluded that the dose exposure relationship is flat from 500-to 1000-milligram BID.

Exposure efficacy relationship between rociletinib steady state AUC and objective response rate was explored using data from patients who were treated at various dose levels. Rociletinib steady state AUC was derived from the population PK model. The relationship was characterized by a saturable model.

In the plot, the mean and a 95 percent confidence interval of the observed response rate of 4 quartiles based on the rociletinib exposure are represented by the stars and the black vertical bars.

The dashed black line and the green band represent the model predicted ORR at the 95 percent

confidence interval. The box plots at the bottom represent the distribution of rociletinib steady state AUC at each dose group. The vertical line within the box represents the median sample value, and the diamond represents the mean value. The end of the box represents the 25th and the 75th quartiles.

The plot shows that within the exposure range between 500- to 750-milligram BID doses the effect of drug exposure efficacy reaches a plateau. Using this model, the predicted ORRs for the 500-, 625-, and the 750-milligram BID dose cohorts were about 32 percent with overlapping 95 percent confidence intervals. Other covariates were screened, and no significant independent risk factors were identified. Based on the exposure efficacy analysis, the results predict comparable efficacies at 500-, 625- and at 750-milligram BID.

Metabolite M502 is primarily responsible for hyperglycemia. This slide represents exposure safety relationship between M502 steady state AUC and the incidence of grade 3 or 4 hyperglycemia

evaluated by the FDA. The mean and 95 percent confidence interval of the observed incidence of grade 3 or 4 hyperglycemia of 4 quartiles, based on M502 exposure, are represented by the stars and the black vertical bars.

The dashed black line and the green band represent the model predicted incidence of grade 3 or 4 hyperglycemia and its 95 percent confidence interval. The box plot at the bottom represents the distribution of M502 steady state AUC at each dose group.

According to the exposure safety analysis, there appeared to be a correlation between increasing M502 exposure and the incidence of grade 3 or 4 hyperglycemia suggesting that patients with higher M502 exposure are at greater risk of grades 3 or 4 hyperglycemia.

Metabolite M460 is responsible for QT prolongation. A model to describe the relationship between M460 exposure and a QT prolongation was developed. The X-axis is the concentration of M460, and the Y-axis is the change of QTcF from

baseline.

The solid red line in the blue band represent the predicted change from baseline in QTcF and its 95 percent confidence interval across the concentration ranges. The model showed a correlation between prolongation of QTc interval and the increasing M460 concentration.

Due to the similar exposure from 500- to 1000-milligram BID, the clinical pharmacological data do not support a 625-milligram BID, and the data could be pooled for efficacy and a safety evaluation. In addition, based on the identified exposure response relationship from 500- to 1000-milligram BID, patients with high rociletinib exposure are unlikely to have further benefit.

However, subjects with higher concentration of metabolite are at greater risk for QT prolongation and hyperglycemia. Therefore, 625-milligram BID is not adequately supported by the available data.

Next my clinical colleague, Dr. Fashoyin-Aje, will continue the efficacy and

the safety findings. Thank you.

FDA Presentation - Lola Fashoyin-Aje

DR. FASHOYIN-AJE: I will now discuss FDA's approach to defining the primary efficacy endpoint for this application. To reiterate, the clinical pharmacology review concluded the following. The dose exposure relationship appears to be flat across doses ranging 500 to 1000 milligrams. The exposure efficacy relationship also appears to be flat.

On the basis of these findings, FDA performed a pooled analysis of the efficacy data across several dose groups. This approach may provide a reasonable estimate of the effect of rociletinib on tumor response. FDA discussed this approach with Clovis.

You may recall from Clovis' presentation that patients enrolled in the two clinical studies that support this NDA received two different formulations of rociletinib and were T790M mutation positive or negative.

Shown here are the criteria upon which FDA

based its selection of the efficacy analysis population. The assessment of efficacy is based on patients who received rociletinib hydrobromide salt formulation, who were T790M mutation positive by central testing, and whose scans were reviewed by independent radiologic review. The table shows the contribution of each of the 2 clinical studies to the efficacy and safety populations by dose cohort.

I will now discuss the efficacy results. These are the primary efficacy results as presented by Clovis during the application orientation meeting and in the NDA submission. Clovis claimed that the overall response rate by investigator in patients who received rociletinib 500 milligrams was 42 percent as shown here.

This is the corresponding overall response rate by central independent radiology review. Clovis submitted an update to the efficacy results as agreed upon during the pre-NDA meeting. The main purpose of the update was to provide additional data on durability of response. The update was submitted to FDA in October 2015.

During the review of the application, FDA noted the following. The overall response rates included patients with unconfirmed responses. The denominator in the independent radiology review assessment of the overall response rate did not include all patients in the intent-to-treat population. And, Clovis proposed investigator assessed overall response rate as the primary efficacy endpoint and the basis for the request for rociletinib's approval.

FDA's position on these issues is as follows. The assessment of overall response rates will be based only on confirmed responses, consistent with RECIST and as specified in the study protocols for studies 008 and 019.

The denominator in the independent radiologic review assessment should include all patients in the intent-to-treat population also consistent with RECIST. And, the overall response rate as assessed by independent radiology review will be the primary efficacy endpoint upon which a regulatory decision is based.

This position was conveyed to Clovis at the time of the mid-cycle meeting in November 2015. Subsequent amendments to the efficacy data was submitted to the NDA and are the basis for FDA's analysis of efficacy.

The overall response rates shown here are based on the data submitted at the time of the efficacy update with additional amendments as I noted earlier. These are the overall response rates by the assessment of the independent radiology review. The following observations are noteworthy.

The overall response rate for the 500-milligram dose cohort is 22.8 percent, which represents a 15 percentage point decrement in the overall response rate compared to the initial submission.

Secondly, while the point estimates for overall response rate differ across dose cohorts, the confidence intervals are wide and they overlap. Please note that the assignment to a particular dose cohort was not random and, thus, important

differences in patient characteristics between dose cohorts may account for the numerically different overall response rates seen here.

Notwithstanding this limitation, based upon the analysis of the PK data, which were described earlier by Dr. Liu, FDA conducted an analysis pooling data across doses in an attempt to get a more precise estimate of the effect of rociletinib on overall response rate.

The overall response rate using this approach is 30 percent, as shown in the red box. The 95 percent confidence interval for this estimate is narrower than that seen at the 500- and 625-milligram dose groups. The median duration of response in the pooled analysis is 8.9 months.

I will now discuss the key safety findings. Of note, single-arm studies are limited in providing reliable information regarding the incidence of fatal adverse reactions as these could be erroneously attributed to disease progression, particularly in patient population with advanced cancer. Randomized controlled studies are much

more reliable in providing this information.

As the applicant showed, overall, there were no notable differences in the incidence of adverse reactions in patients who received rociletinib 500 milligrams or 625 milligrams.

The information in this table has been presented by Clovis. Almost all patients who received rociletinib experienced one or more adverse reaction, as highlighted in the pooled safety population. Adverse reactions that occurred in 30 percent or more or patients are listed here.

The salient points from this slide are the following. The incidence of common adverse reactions is similar between the 500-milligram and 625-milligram dose groups. The incidence in the pooled population is shown in the red box.

Hyperglycemia and QTc prolongation are the most common adverse reactions observed in patients who received rociletinib, and a considerable proportion of patients experienced these two adverse reactions had grade 3 or grade 4 events.

This table provides an overview of the

incidence of treatment interruptions, dose reductions, and treatment discontinuations due to adverse reactions. Over half of the patients who received rociletinib had one or more dose interruption or dose reduction.

Consistent with the incidence of common adverse reactions, hyperglycemia and QTc prolongation were the most common adverse reactions leading to dose interruptions. A similar pattern is observed with regards to adverse reactions leading to dose reductions.

The previous two slides described the incidence of adverse reactions leading to treatment interruptions and dose reductions. FDA conducted an analysis to determine the number of inter-patient dose modifications. The results of this analysis conducted for dose reductions is shown here.

Overall, the proportion of patients in each dose cohort who had dose reductions is shown in the red box. The proportion of patients requiring dose reductions and those requiring multiple dose

reductions increased with increasing dose.

FDA postulates that patients who received the higher doses of rociletinib likely had more dose reductions because dose reductions to doses of 500 milligrams and above were unlikely to lead to a decrease in exposure. This may indicate that the applicant's proposed strategy to mitigate toxicity at the proposed dose of 625 milligrams may not be effective.

I will now discuss some adverse reactions of special interest. Listed here are serious toxicities that were observed in high frequency in patients who received rociletinib. Also included are other toxicities that have been observed in patients who are treated with EGFR directed therapies.

Before I describe the incidence of adverse reactions of special interest, I would like to review the role of NAT2 acetylation status on the occurrence of toxicity in patients who received rociletinib. As you heard previously, M502 and M460, the major metabolites of rociletinib, are

primarily responsible for hyperglycemia and QTc prolongation.

These two metabolites undergo N-acetylation by the enzyme N-acetyltransferase 2, or NAT2, to form other metabolites. The NAT2 polymorphism results in variable activity in the NAT2 enzyme with individual patients classified as slow, intermediate, or rapid acetylators.

Patients who are slow acetylators have a high exposure to M502 and M460 metabolites compared to intermediate or rapid acetylators. In the United States approximately 40 to 60 percent of white and black patients are slow acetylators.

Data on the NAT2 genotype and the inferred acetylator status were available for 303 patients who received rociletinib at doses ranging from 500 to 1000 milligrams. The X-axis on each box shown here represents increasing exposure from left to right of rociletinib, so the parent drug, and the metabolites M502 and M460.

The exposure to parent drug, rociletinib, was similar across the phenotypes as shown in the

first box. However, NAT2 slow acetylators had higher M502 and M460 exposures compared to intermediate or rapid acetylators indicating that slow acetylators are at greater risk for hyperglycemia and QTc prolongation.

QTc prolongation was a common adverse reaction in patients who received rociletinib. Prolonged QTc interval can lead to serious and potentially fatal cardiac arrhythmias, such as the polymorphic ventricular tachyarrhythmia termed Torsades de pointes. Torsades de pointes can degenerate into ventricular fibrillation and lead to sudden death.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, or ICH, has published the E14 document, which is a guideline for the clinical evaluation of QT interval prolongation and pro-arrhythmic potential for non-anti-arrhythmic drugs.

The correlation between a specific change in QTc interval and the risk of fatal arrhythmias has not been clearly established. However, increases

in the QTc interval do appear to identify drugs with a high risk of Torsades de pointes.

The ICH E14 document states that drugs that prolong the mean QTc interval by greater than 20 milliseconds have a substantially increased likelihood of being pro-arrhythmic. In addition, marked QTc increase is defined as QT interval greater than 500 milliseconds or a change in QTc of greater than 60 milliseconds.

The NCI-CTCAE relies on QTc interval of greater than 500 milliseconds, and increase in QTc over baseline of 60 milliseconds or more, as criteria for severe or life threatening QTc prolongation in individual patients.

Please note the NCI-CTCAE definitions for grade 3 and grade 4 QTc prolongation shown here. FDA's QT interdisciplinary review team has identified a population mean increase in QTc over baseline of 30 milliseconds as likely to identify drugs with an increased risk. As will be shown on the next slide, based on any of these measures, rociletinib is a drug with pro-arrhythmogenic

potential.

This table provides a summary of the change in the QTc interval from baseline following initiation of rociletinib. Focusing on the red box, in patients who received rociletinib, the mean change in QTc is 36 milliseconds.

Seventy-six percent of patients had a mean QTc increase over baseline of greater than 30 milliseconds, and for 34 percent of patients, the change was greater than 60 milliseconds.

Three patients experienced ventricular tachyarrhythmias, including one patient who experienced Torsades de pointes. There were two sudden deaths. The review of each of these patients' case report forms yielded no identifiable cause of death.

Please note that Torsades de pointes is very infrequently captured in clinical databases, even for those drugs known to have significant pro-arrhythmic effects. Therefore, the observation of even one case of Torsades de pointes, and the occurrence of other clinical arrhythmias, indicates

the substantial risk of treatment with rociletinib.

Furthermore, single-arm trials inadequately characterize the true incidence of fatal adverse reactions such as fatal ventricular tachyarrhythmias, as death may be attributed to progressive disease.

Recall that M460 is the rociletinib metabolite responsible for QTc prolongation and that slow acetylators have the highest exposure to M460. This slide shows the incidence of QTc prolongation by NAT2 acetylator status.

The top half of the table shows the incidence as reported by the investigator while the bottom half shows it by central ECG measurement. In both assessments, the incidence of QTc prolongation is highest in the slow acetylators compared to the intermediate or rapid acetylators.

This is a listing of drugs that are approved for oncology indications and that are known to cause QTc prolongation. Rociletinib is listed in red for the purposes of comparison. Overall, patients who receive the approved drugs in clinical

trials had a mean increase in QTc interval ranging from 10 to 35 milliseconds.

Patients who received rociletinib had a mean increase of 36 milliseconds. One to 4 percent of patients receiving the approved drugs had a QTc interval greater than 500 milliseconds. The corresponding incidence is 13 percent for patients who received rociletinib.

Hyperglycemia is another adverse reaction of special interest in this application. As a reference, the definitions for hyperglycemia severity, according to the NCI-CTCAE, are listed here. Grade 3 hyperglycemia is defined as fasting glucose greater than 250 milligrams per deciliter up to 500 milligrams per deciliter. Grade 4 hyperglycemia is defined as fasting glucose greater than 500 milligrams per deciliter.

This slide summarizes the incidence of hyperglycemia as shown earlier and provides additional information regarding important clinical factors. Over half of the patients who received rociletinib had hyperglycemia, and a third had

grade 3 or grade 4 events.

Forty-nine percent of patients required anti-hyperglycemia medication following initiation of rociletinib. Insulin was required for the management of hyperglycemia in 23 percent of those patients who required treatment for hyperglycemia.

Importantly, metformin was initiated prophylactically in the absence of grade 2 to grade 4 hyperglycemia in 9 percent of patients who received anti-hyperglycemia treatment. This was not consistent with protocol specified guidelines.

This slide shows the incidence of hyperglycemia by NAT2 acetylator status. Patients who were slow acetylators had a high incidence of hyperglycemia and a higher incidence of grade 3 and grade 4 events.

Other noteworthy adverse reactions include pancreatitis, which occurred in 4 percent of patients, and pneumonitis, which occurred in 3 percent of patients. The incidence of cataracts was 10 percent, and the majority of patients who developed cataracts required surgical management.

To summarize, treatment with rociletinib resulted in the following, an overall response rate of 30.2 percent in a pooled analysis of patients who received rociletinib 500, 625 or 750 milligrams administered twice daily. The median duration of response is 8.9 months.

These results must be compared to available therapies for the treatment of second-line non-small cell lung cancer. Treatment with docetaxel and ramucirumab confers an overall response rate of 23 percent, and this treatment regimen has demonstrated improvement on overall survival.

Nivolumab was also approved on the basis of improvement on overall survival. This treatment resulted in an overall response rate of 19 percent and a median duration of response of 17 months. If approved, patients may forgo these treatments to receive rociletinib.

To summarize the safety, common adverse reactions in patients who received rociletinib included hyperglycemia, diarrhea, nausea, QTc prolongation, and vomiting. Common grade 3 or

higher adverse reactions included hyperglycemia, QTc prolongation, and cataracts.

Other serious adverse reactions were pancreatitis, ventricular tachyarrhythmias such as Torsades de pointes, and two sudden unexplained deaths. Treatment modifications were frequent with over half of patients experiencing treatment interruptions or dose reductions.

Overall, there remain considerable uncertainties regarding the efficacy, safety, and the appropriate dose for rociletinib. With respect to the benefit of treatment with this drug, the key question is whether an overall response rate of 30 percent and a median duration of 9 months is better than available therapy. An affirmative response to this question is a requirement for accelerated approval.

With respect to safety, key issues include considerable risks of serious adverse reactions such as serious hyperglycemia, which occurred in a third of patients who received rociletinib. Another key safety concern is that by most

standards used to assess the risk of potential fatal cardiac arrhythmias, rociletinib is an arrhythmogenic drug, and the risk of death from arrhythmias may be underestimated in single-arm trials.

Thirdly, the risk of increased exposure to toxic metabolites may be explained by NAT2 acetylator status. However, uncertainty remains regarding the measures that may be necessary to address this risk.

With respect to the dose, the available data do not support a dose of 625 milligrams administered twice daily. At this dose, Clovis' proposed dose reduction strategy to reduce to 500 milligrams is unlikely to lead to a decreased exposure to the rociletinib toxic metabolites, and thus may not be an effective risk mitigation strategy.

Ultimately, the benefit of rociletinib must be weighed against the serious and life-threatening toxicities observed in patients who received rociletinib and the considerable uncertainties that

remain at this time. The FDA requests the advice of the ODAC on the questions listed here. Thank you very much for your attention.

DR. ARMSTRONG: Thank you. Before we move on to clarifying questions, I'd like for the audience to know that we've opened up Room 1504 as an overflow room. It's down the hall back there, so for those of you who are standing, there's some extra space. Also, committee member, Dr. Rajan, could you introduce yourself?

DR. RAJAN: I'm Arun Rajan, a staff clinician in the thoracic oncology branch at the NCI.

Clarifying Questions to the Presenters

DR. ARMSTRONG: Thank you. So we'll now taking clarifying questions for the presenters. Please remember to state your name for the record before you speak. And if you can, please direct your questions to a specific presenter, whether from FDA or from the applicant. And you can let Jennifer know about a question.

Dr. Menefee?

DR. MENEFEE: Michael Menefee, Mayo Clinic, Florida. I had two questions for the applicant. The first is regarding the sequencing of T790M inhibitors.

There are some published data that have looked at -- or have demonstrated activity of osimertinib after patients have received rociletinib, and I wanted to know, do we have the converse? Do we have any data, either published or unpublished, where rociletinib has been used?

I know 008 and 019 did not study that population, but outside of those studies, do you have any data?

DR. ROLFE: So, no we don't.

DR. MENEFEE: Okay. So then, the extension of that question -- and this may be better suited to Dr. Camidge -- when I think about this drug, I start thinking about how could we potentially -- is it going to be used in the clinic, should approval be granted. And it's just not very clear to me how it's going to be used because we already have a drug in this space that has at least equivalent

activity, if not greater. We have a drug that is perhaps less toxic.

So it's hard to see where you would use this drug in the first-line setting for a patient with a T790M mutation. Then, are we using this drug as a second-line agent? And if so, the studies that currently being evaluated weren't really designed to evaluate it in that setting.

So I'm just curious if the drug was available today, how would you envision using it in exception of a patient that might have cardiomyopathy, which might not be a good candidate for the other available agent.

DR. CAMIDGE: Ross Camidge, medical oncologist. Hi. Thank you for that question. I can imagine three possible scenarios where you might want to reach for this drug as opposed to osimertinib. I'm assuming that's your question as opposed to this versus chemotherapy or immunotherapy.

The first, as you've kindly volunteered, there are some people who have preexisting risk

factors that you might say that the risk of osimertinib, which has a proven anti-HER2 activity, and people with preexisting cardiac failure, might make you reach for the rociletinib first. The second is people who you try osimertinib with the best possible intentions, but they just don't tolerate it, and that does happen every day in the clinic.

Then, the third one, which is perhaps your first question is, is there going to be a population who might initially benefit from osimertinib, progress, and then might they benefit from this drug?

There's some very interesting data coming out in terms of the mechanisms of acquired resistance to these drugs, and I hinted at that, but they do appear to be a different spectrum of resistance mechanisms, so they may not be cross-resistant.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: I had a couple of questions, and before I appear to be somewhat critical, I commend

the company for conducting the trial in the United States in U.S. patients because that's always helpful in approving a drug for U.S. patients.

Could we see CO-37? And where I'm going to go with this is what makes me feel uncomfortable that I don't understand everything about this drug. This is a really nice waterfall plot, and the back-of-the-envelope calculation says that 60 percent of the patients had greater than 30 percent reduction, and yet the overall response rate is 30 percent, basically, which to me says that half -- of these 60 percent, 30 percent of these 60 percent, had a response that was not durable.

That to me says one of two things, either the drug's not very good and it can't hold the response, or the drug is toxic, and it gets discontinued after the response has been achieved, and then the response is quickly lost, and you can't maintain it.

So that it's toxic I think is clear. You know, 20 percent dose discontinuation, 50 to 70 percent dose reduction or dose interruption,

that's a drug with a fair amount of toxicity. And it's not in the grade 3-4 toxicities, it's not in the QTc prolongation. Nobody walks in and says, "Doc, this QT prolongation is just -- I can't take this any longer." The hyperglycemia, the same thing, which is why you looked at dose toxicities, and you say, look, no dose reduction.

So when I try to find out here why is this drug being discontinued or reduced, I just don't see it; a little bit of nausea, a little bit of fatigue, no diarrhea, no skin rash. So there's something here that's missing as far as I'm concerned, and I wonder if you could tell me what that is. Or is it just I'm sick and tired of this drug, and that's why I'm discontinuing it?

Then the other thing, which is what the FDA is getting at, is the dose of 500 and 625. Not to be trivial, but by way of a note to self, if in January you say to the FDA that we're going to go to 625, and in February the FDA says, no, don't do that, in March, a month before the ODAC, you don't do that. And that's what you did.

But I actually think that you've got data of sorts that tells you that, in fact, the FDA is right, that 500 and 625 are not different because when you've added this extra dose level to the study, and you've now got 300, 300 and 300 -- so you've got 300 patients in the 625 and 300 in the 500, and you're telling us the study's not powered to tell the difference between 500 and 625, you're telling us that a 600 patient study embedded in this, with 300 in each arm, won't be able to tell the difference, which to me means that there's actually no difference, or very, very small difference.

So number one, what causes these dose reductions? What is in the dose discontinuations, since it's not the grade 3, 4 toxicities? And number two, really, what is the data that 625 is better than 500, and why can't we see it with a 300-patient-in-each-arm study?

DR. ROLFE: So to answer the first part of your question regarding lack of confirmation of responses, I'll show you the data. But what it

shows is that it's predominately due to disease progression between the first restaging and the second restaging scan rather than to discontinuation for toxicity or other reasons.

So here's the data on a slide. For 500-milligram, 625-milligram doses, I'm showing the reasons that an initial PR was not confirmed. I mean, you can see that, by far, the commonest reason is development of progressive disease between the two scans. This was progressive disease either in CNS only or below the neck, plus or minus above the neck.

DR. FOJO: That can't be all the data because you showed data for 625, and that was 100 and some odd patients. And 30 percent of those patients are not confirmed, so that can't be that then you have 11 and 1 and 1, so this is missing data.

DR. ROLFE: So let me clarify. The waterfall plot shows one element of RECIST, so that's the change in the size of the target lesions. RECIST has two other elements, which is

progression or non-progression of non-target lesions as well as development of new lesions between restaging scans.

So the waterfall plot is a very objective measure that can be displayed easily on a graph, but it just shows one of the RECIST components. So every person who developed the 30 percent shrinkage on the waterfall plot does not necessarily have a RECIST response.

DR. FOJO: Okay. I still don't understand it. There were 170 patients, which is what I suspect is in the waterfall plot. Thirty percent of them, or 51 roughly, would have had a response that then wasn't confirmed, and you showed us what happened with 13.

DR. ROLFE: Well, the 13 patients were the patients who had a RECIST response based on one restaging scan, so a response according to all the 3 components of RECIST, and 13 patients did not confirm that response subsequently.

DR. FOJO: So then I'm assuming the other 38 had the drug discontinued and had progression for

that reason?

Do you follow? I mean, 60 percent of the patients, or about 60 times 170, about 102 patients, had greater than 30 percent reduction. And then only 30, 32 percent, or about 51 patients, have a confirmed response. So there's 50 some odd patients -- there's somebody who seems to get it in the group that wants to answer and maybe --

DR. FIGG: While he's getting ready to answer that, do we have the 500, the waterfall for 500?

DR. FOJO: Yes. Go ahead.

DR. YURASOV: Sergey Yurasov, oncology. If I can have the table that shows response rates. So the response rates, as Dr. Lindsey Rolfe pointed out, are based on RECIST .1, 1.1, so 3 components, the waterfall plot showing only the target lesion reduction.

So for 170 patients at 625 that you're referring to, 32 percent of patients actually had confirmed response. So out of those 32 percent, the data that Dr. Rolfe showed shows that

12 percent -- 12 patients that had an initial partial response didn't make it to those 32 percent, but not from a target lesion on the waterfall plot.

DR. FOJO: No, no, no, no. So I won't belabor this if I'm the only one who's lost, but the numbers just aren't adding up. So these would be 32 percent who had a confirmed --

DR. ARMSTRONG: Perhaps, for more clarification, is how many patients does this represent on slide CO-37? You don't actually say how many patients this is.

DR. ROLFE: So one patient is represented by one of the bars. We can get back to you on that after the break with the precise number.

DR. ARMSTRONG: And then the second part of your question, Dr. Fojo?

DR. FOJO: Yes. So the second part of the question is, what is the data that makes you so confident that 625, not -- what is shown here, the FDA has I think appropriately raised concerns that there's no difference. And what is that data that

you don't even think that a 600-patient trial with 300 in each arm is going to show a difference?

So it can't be so robust data. If you really had robust data you only need 100 patients in each arm, and you'd get the difference. You're enrolling 600 patients essentially in a sub-study within the large study, and you're not going to be able to tell us that 625 is better than 500.

Again, to me that says the FDA is right, 625 is no better. And since toxicity is what's going to be important, I think in this discussion, you want to go to where there's less toxicity.

DR. ROLFE: So I'll answer the first part of the question, then I'll ask my statistician colleague to specifically address the statistical assumptions in the confirmatory study.

So we agree with FDA that you cannot distinguish between 500 and 625 milligrams based on PK data. Our concern is that the lower bound of the confidence interval for response rate at 500 milligrams is 14 percent. And I think the 500-milligram data set taken alone does not provide

an accurate representation of the activity of rociletinib.

In the phase 1 part of the study, we studied lower doses than 500 milligrams, but they were with a different form of the drug, the free-base form. At the next lowest dose, we studied 7 patients T790M positive in phase 1, and of those 7 patients, none responded. So taken together we believe that 625 milligrams BID is a more accurate representation of the drug's activity.

To answer the second part of your question, Dr. Isaacson, please take us through the statistics.

DR. ISAACSON: Jeff Isaacson, senior director of biostatistics and data management with Clovis. I think it's fair to say we agree, the difference in response rate, about maybe 10 percent between the two groups is going to take a lot of patients to show that, probably in the order of 400 patients per arm. So yes, the phase 3 trial, as it stands, isn't powered to pick up that small a difference.

DR. ROLFE: And can I further clarify that the phase 3 study enrolls T790M positive and T790M negative patients. Therefore, we do not expect to get 300 T790M positive patients per arm; more like 150.

DR. FOJO: Okay.

DR. ARMSTRONG: Dr. Roth?

DR. ROTH: I would dispute the contention about picking the lower end of the confidence interval. I mean, you have half as many patients treated at 500 as you do at 625, so you're going to have a wider confidence interval.

But to build on what Tito was saying, if you really believe that 625 is better, why don't you replace the 500 arm in the phase 3 trial? Why add a third arm and then have it powered such that you can't compare 500 and 625? My concern is that we will know no more about what the right dose is for this drug after 900 more patients than we do now.

DR. ROLFE: Well, we were fortunate to be able to study relatively large numbers of patients in our phase 2 program at each of the doses, but I

don't think we can say definitively which is the best dose at the moment. Therefore, we are intending to pursue both doses in a randomized, controlled phase 3 study and to compare each one of those doses against standard of care just to confirm superiority.

DR. ROTH: So at the end of that trial, and if both those doses are superior to standard single agent chemotherapy, and you don't have enough patients to compare the two doses, how are you going to tell me what dose is correct?

DR. ROLFE: Well, assuming the risk and benefit looks similar in each treatment arm, we would assume that 500 milligrams was the best dose as demonstrated in the randomized phase 3 study.

DR. ARMSTRONG: Did that answer your questions? Yes.

Dr. Rini?

DR. RINI: So I have a question. I think it's at a couple points about accelerated approval. One is that there has to be an advantage over standard therapy, so I think what we've heard is

that there's probably a 10 percent response rate advantage of this drug over say nivo and the other drugs that are available, not including the drug just approved under accelerated approval.

The other part of accelerated approval is meaningful clinical benefit. So I guess the real question, the crux of the question is, is that delta, a 10 percent increase response rate, does that represent meaningful clinical benefit?

My real question is, do you have data about symptom control, quality of life, narcotic use, something in this population that I imagine is very advanced in refractory, right, and I assume has a lot of symptoms that would support that delta of 10 percent as being clinically beneficial?

DR. ROLFE: So we don't have quality-of-life data available.

Could Dr. Carbone comment on symptomatic changes in the patients that he's treated, please?

DR. CARBONE: David Carbone, medical oncologist. First of all, the assumption of a delta in the response of 10 percent is not a solid

one because the response rates in single-arm studies are not really comparable across studies. For example, when carboplatin and paclitaxel first came out, the first 2 or 3 phase 2 studies showed a 60 percent response rate, and the real value is more like 25.

My clinical experience with this drug is more in line with the waterfall plot than with the objective response rate. I've treated in our clinic 18 patients with this drug. Virtually, every one experienced substantial and immediate clinical benefit with often a decrease in side effects from first or second-line agents, such as afatinib, which, by the way, is very often started at the dose below recommended by the FDA for toxicity reasons as well.

Does that answer your question?

DR. RINI: My question was, are there objective data, though? I believe you, and I think the waterfall is impressive, but I'm just wondering about some objective measure of that.

DR. CARBONE: That's a company question.

DR. ROLFE: So no, we don't have a quality-of-life readout from this study, however, in the randomized phase 3 study, there are quality-of-life measures built in to that as is appropriate in a randomized setting.

Just to be completely clear, we did do quality-of-life questionnaires in the single-arm studies, however the NDA was submitted based on an interim data cut while the studies were still enrolling, and we have not got that readout yet.

DR. ARMSTRONG: Dr. Figg?

DR. FIGG: I have three broad questions, and I'm going to let you answer after each one. So on page 44 of the document you provided, you stated that the Cmax and AUC of the parent compound, the metabolite 502, 544, were reduced by 69 percent to 72 percent when co-administered with omeprazole. Of the last sentence of that paragraph, you go on to say that there is no drug interaction with omeprazole.

How could you conclude that? Furthermore, what about the metabolite 460? And did you test

other agents that altered GI pH, such as H2 antagonists? And why did you not include these in the proposed label?

DR. ROLFE: Dr. Jaw-Tsai?

DR. FIGG: Pardon?

DR. JAW-TSAI: Sarah Jaw-Tsai, Clovis Oncology. The rociletinib solubility is pH dependent. So therefore, when you increase the pH in the presence of PPI, you tend to see this decrease in exposure.

We have results from the clinical pharmacology study conducted in healthy subject. We saw a 70 percent reduction in the Cmax and AUC. However, in the population PK analysis, where we have a bigger number of patient population, they took the PPI as we recorded in their concomitant medicine list. In that patient population, we did not see a decrease in the rociletinib, either Cmax or AUC, as compared to the patients that did not take the PPI.

DR. FIGG: Well, I'm not sure, then, I would agree with your assessment. I mean, if the PK data

shows that it changes the AUC so significantly, it seems like you should call that a drug interaction. Furthermore, did you see that those individuals in the clinical trial actually had responses?

Nonetheless, let's move on to the next one. We know that the M460 is responsible for the QTc changes. You also know that it has a long half-life, 50 some hours. You also know that the PK exposure by NAT2 genotyping showed that slow acetylators status is associated with higher levels of M460.

We also know that 51 percent of the slow acetylators have a QTc of greater than 60 milliseconds, which is only 22 and 23 percent for those that are rapid and intermediate. Why would you not want to, a priori, genotype for NAT2?

DR. ROLFE: Well I'll answer from the sponsor perspective, and then I'll ask Dr. Kowey to comment from an expert cardiology perspective. The NAT2 slow acetylators comprise half the patients. We believe that thorough QT monitoring and management strategies should be required for all

patients that are treated with rociletinib, and that patients who are intermediate or the small number who are rapid acetylators would not require any less thorough risk management for this effect.

We have done the NAT2 genotyping in a subgroup of patients within these two single-arm studies, and we're continuing to study the signal in the randomized phase 3 study in order to obtain a larger amount of data to get a more definitive analysis.

Does that answer your question?

DR. FIGG: Okay. My last one is just a general one. Have you run the drug against a panel of transporters to figure out movement both in and out of cells?

DR. ROLFE: Sorry. Can you repeat the last phrase?

DR. FIGG: To understand which transporters are involved in the movement of the drug.

DR. ROLFE: So we've done hERG testing, and it has an inhibitory effect on the potassium channel, but nothing more than that.

DR. FIGG: No, I'm referring to the ABC transporters, the OATP transporters, et cetera, which is important in also predicting drug interactions. It sounds like you probably haven't done it yet.

DR. ROLFE: Dr. Jaw-Tsai.

DR. JAW-TSAI: Yes, we have evaluated the potential effect of the rociletinib, the inhibitor of the transporters. OATP1B1 and 1B3, under the criteria as set up by the FDA's DDI guidance, rociletinib does not meet the threshold to do a drug-drug interaction.

However, under the guidance, P-gp, that's the only transporters that rociletinib is required to do a DDI study, and we have conducted a study with digoxin as a probe substrate of P-gp. In that study, we saw about 30 percent increase in the exposure, which was measured by Cmax and AUC, in the presence of the rociletinib. So it's a weak inhibitor of P-gp in vivo.

DR. SONG: This is Pengfei Song, a clinical pharmacology reviewer at FDA. Rociletinib is a

substrate and inhibitor of P-gp and BCRP, but is not a substrate of hepatic uptake transporter OATP1B1 or 1B3. Rociletinib is an inhibitor of OATP1B1, 1B3, OCT1 and OCT2, weakly interact with OAT1 but not always with OAT3.

The sponsor conducted in vitro studies evaluating the DDI potential and conducted an in vivo study with P-gp substrate. The interaction is generally mild. Thank you.

DR. ARMSTRONG: Dr. Pazdur?

DR. PAZDUR: I just wanted to follow up on something that Dr. Figg mentioned because it is something that we want thoroughly discussed in the discussion phase, and that is the role of NAT2 acetylator status, and we think that that is a very important issue for the committee to focus on.

Here again, between the rapid acetylators and the slow acetylators, you see significant differences in toxicity, not only with regard to QT status, but also with regard to hyperglycemia. And we believe that the risk-benefit really differs between these two populations.

So this is something we really want the committee to hone in on. We don't have an available test at this time marketed, I don't believe, to look at this. And the other issue is, for the ongoing phase 3 study -- and this is my question to the sponsor -- are they looking at acetylator status prospectively in the phase 3 study?

DR. ROLFE: Yes, we are.

DR. PAZDUR: And how are you doing that?

DR. ROLFE: Patients have to provide additional consent because it's a genomic test, and we're using the same laboratory that we used for the two studies you see here. So it's using the CLIA test that's available in the U.S. by Genelex.

DR. FIGG: And you're using germline DNA, right?

DR. ROLFE: Correct.

DR. ARMSTRONG: Thanks. Dr. Szabo?

DR. SZABO: Eva Szabo, medical oncology, NCI. I have two questions. Since it appears that almost half the people, 40 to 47 percent of the two

doses, actually had one or more dose reductions, do you have any data about the response rates and the duration of response in those people who were at lower doses, since a lot of them wind up being at less than 500 milligrams BID? That's one question.

The other question is something that we never focus on, are all the other drugs that people take to support taking the drug that we're focusing on. In this case, about half of them received a variety of anti-diabetic agents, and those don't act similarly.

You had some people taking insulin, others taking insulin sensitizers would drop down your levels of insulin. Do you have any data about those who had the various types or classes of drugs, insulin lowering, insulin raising, and how they did in terms of responses and duration of response?

DR. ROLFE: Dr. Yurasov?

DR. YURASOV: Let me start with your first question about the effect that dose reductions have on the relationship between the dose reductions and

efficacy, and I will bring up the slide for both patients at 500 and 625.

So starting from the top, 470 patients that were treated with 625 milligram dose, 93 patients, as you pointed out, experienced a dose reduction. And then we show the confirmed overall response rate for those patients actually is comparable to what we're seeing overall with durable responses, the duration of response 8.8 months. And for 500 milligram, the data follows a similar trend.

Your second question, in terms of usage of anti-hyperglycemia medications and relationship to efficacy, you're correct, a number of patients used different types of medications, metformin as was already brought up previously used fairly commonly in this patient population. And we actually didn't see a significant relationship between metformin responses.

Now of course -- and I bring up this slide with the data that shows you broken out by dose, and we can just focus on overall response rate in the right column. So patients who received

metformin while on study versus patients who did not receive metformin in the lower part of the table.

So response rates are comparable. Now, of course there is a caveat to this that metformin is a variable that is introduced during the treatment, so these patients, the duration of observation is different for the two subgroups.

DR. ARMSTRONG: Did that answer your question? Great.

Dr. Orza? I'm sorry, we're going to push the break back a little bit just so we can continue to ask questions, so it will probably be at 11:00.

DR. ORZA: Michelle Orza. I have requests for additional data to help me make the two comparisons I think we're being asked to make. The first is with approved available therapies, and we've seen the data on the objective response rate for the approved therapies and this drug, and this drug has a higher ORR than the approved ones. But we don't know anything about the overall survival, and apparently we don't know anything about the

quality of life or the clinical outcomes.

But is there anything that shows us side-by-side the side effect profiles on that comparison? I didn't see anything in either the sponsor's materials or FDA's that would help sort of make that comparison directly.

Then the second comparison seems to be between this drug and the other -- I'm going to pronounce it wrong -- osimertinib, that has accelerated approval where the ORR is not as good, and we don't know anything about overall survival for either. But I'd also like to see the side effect profiles and the experience of the patient side-by-side for both of those.

DR. ARMSTRONG: Maybe I can ask the agency to address that.

DR. BLUMENTHAL: Yes, just to clarify, first of all on your second point, actually the ORR for osimertinib is double that of rociletinib, so about 59 percent versus 30 percent. And the duration of response is about 12 months at the medians with osimertinib versus about 9 months with rociletinib.

With respect to side-by-side comparisons for toxicities, I think Drs. Carbone and Camidge alluded to it earlier. From our perspective, we did have a slide comparing the QTc risk with rociletinib versus other approved oncology agents that also have warnings or boxed warnings or even REMS programs.

At least if you look at the proportion of patients with QTc prolongation of 500 or greater, it was about 3 times that of vandetanib, which is another drug considered to be highly pro-arrhythmogenic.

As far as other toxicities with nivolumab, I think Dr. Carbone alluded to it. Nivolumab is generally well tolerated. There are a fraction of patients who get serious autoimmune type adverse events, which can be pretty serious. Docetaxel and ramucirumab/docetaxel, there are chemotherapy type toxicities, and then ramucirumab, a VEGF type agent, so not a lot of additive toxicity there, some hypertension, some proteinuria, and then some serious toxicities as well.

DR. ARMSTRONG: But I will point out this is the problem when you're looking at a single-arm phase 2 and trying to figure out whether or not -- then you're doing cross-trial comparisons, and those are fraught with problems. But I didn't know if --

DR. ROLFE: I'd like Dr. Kowey to comment specifically on the cardiovascular risk from his expert perspective.

DR. KOWEY: Peter Kowey, cardiologist and electrophysiologist in Philadelphia. I wanted to comment on this vandetanib issue because I think it's extraordinarily important. It is a precedent setting drug in that it did have a central tendency effect on QT interval, which is very similar to what we're seeing here, almost identical.

I would not use the outlier analysis, the categorical analysis, in that study to compare to this; that that is the number of people who went over 500 milliseconds in the vandetanib experience versus this application, for lots of reasons.

First of all, cross-trial comparisons, as

several people have already said, are very, very hazardous. How you define it and how frequently you sample, and who's reading, and what time points is really very, very critical to this categorical analysis issue.

So what I would focus on if I were the committee in that table is the central tendency effect, because I believe that that has the most robust reflection of the true repolarization changes. And as you know, vandetanib was approved, and it was labeled, and it has been used successfully for patients with medullary thyroid cancer, with I think fairly good clinical success to this point.

DR. PAZDUR: Could I just jump in here? The vandetanib trial was a randomized trial, so we had a random -- I mean, we had a comparator arm really to look at here. This is the major question that we're focusing on, is what this QT prolongation means in a single-arm trial where you don't have a comparator, you have very sick patients here. And we look at attribution of death is a very, how

should I say it, ambiguous area here.

Here again, we don't know what's going on with this drug in a sense with QT, and that's one of the uncertainties that we're trying to highlight here. But we did have a randomized trial that led to the approval of vandetanib, so we were able to really to characterize this.

DR. ARMSTRONG: And with two unexplained sudden deaths, you do add those and almost double the rate or not. That's certainly an issue.

DR. FIGG: Do we know the NAT2 status on those two deaths?

DR. ROLFE: They were both slow acetylators.

DR. ARMSTRONG: Thank you. Dr. Rajan?

DR. RAJAN: Thank you. My question was actually very closely related to what Dr. Szabo just asked, and it was specifically about metformin. And I think you answered my question about the response rates and those who did and did not receive metformin. If I remember correctly, the numbers were 40 some percent and 23 percent or so.

So I'll just make a comment at this time, and I'd just say there was a letter written in response to the original rociletinib paper in August of last year. And in that they had this waterfall plot of T790M positive patients who had responses. I think there were a bunch of responses, 27 partial responses among whom 38 -- about 38 percent of patients got metformin.

For the doses that we are talking about, the 625 milligram dose, 4 out of 5 patients got metformin. So it's just something to keep in mind, and I just wanted to highlight that. Thank you.

DR. ARMSTRONG: Thank you. Dr. Nowakowski?

DR. NOWAKOWSKI: Good afternoon. Nowakowski, Mayo Clinic. A question to the sponsor. In your presentation, you alluded that early on, it was decided, from the feedback from investigators, that the dose 750 milligrams is not the way to go. I just want to clarify if all the toxicity has been captured in the slides 43 to 45, or was there any other feedback from the investigators why the 750 milligrams was not the

way to develop it.

DR. ROLFE: Dr. Camidge, could you take that?

DR. CAMIDGE: Ross Camidge, medical oncology. So let me see if I've got your question right. So your question was what was the clinical experience with 750 milligrams?

DR. NOWAKOWSKI: Right. In the presentation, it was alluded that there was an early feedback from the investigators that 750 milligrams was toxic. And I just would like to understand, was there any additional feedback apart from what's being presented as far as toxicity is concerned about 750 milligrams, which you decided this is not a feasible dose to develop?

DR. CAMIDGE: I mean, we're looking at it in a group of patients, and some people did tolerate it. But the overall impression was that the hyperglycemia, the fatigue, tended to be more prominent. It's interesting that the modeling of the PK didn't suggest a difference in exposure, yet the clinical experience was that there was a

difference. So there may be some questions about the validity of the model because that's very different from my own experience and that of the other investigators.

DR. NOWAKOWSKI: Okay. The other question relates to the protocol amendments. This protocol had a number of amendments during its course, and the one on April 17, 2014 specified that the patients who are not eligible, based on the potassium or magnesium levels, were eligible for replacement. Then, if they were meeting the values, then they could enter the protocol.

Do you have a sense, or the data, how many patients actually required replacement of potassium or magnesium to enter the protocol? And if you do, do you have any sense if the cardiac toxicity was higher in the patients who required replacement to enter the protocol, since we know that the patients who are hypokalemic or have hypomagnesemic at baseline are at the risk of recurrent electrolyte abnormalities later on?

DR. ROLFE: So we don't have that data

available, but in the risk mitigation plan moving forward, we will recommend that patients have normal potassium, magnesium, and that it's maintained within the normal range throughout the duration of rociletinib therapy.

DR. NOWAKOWSKI: So in the mitigation plan, if the patients were hypokalemic, you would not allow them to be replaced to normal level to enter, to be treated?

DR. ROLFE: Patients who had potassium below the lower limits of the reference range in screening were able to be enrolled if, following supplementation, that took their potassium into the normal range.

DR. NOWAKOWSKI: Right. And then moving forward, would you still allow it, or would you say that just the patients with normal electrolytes should be treated in the future with this?

DR. ROLFE: So we would still allow it. Supplemented patients could go in as per normal practice.

Dr. Kowey, could you add to that?

DR. KOWEY: Peter Kowey again. You're absolutely correct, that maintenance of potassium, magnesium, are extraordinarily important in managing patients with drugs that have the potential to prolong the QT interval.

I don't have an answer to your question about the pro-arrhythmic rates, but I can tell you that repleting potassium and magnesium, as has been put into place in this protocol and in the randomized trial, is more than adequate. And there are monitoring parameters that have been put into place that the investigators need to adhere to. So it's very, very important.

DR. ARMSTRONG: Okay, question answered. Dr. Fojo?

DR. FOJO: So you were going to tell us in the waterfall plot, because actually as I look at today's thing where you can see the lines a little better, I couldn't see it on my printout. It begins to appear that maybe not all the 625-milligram patients are in that waterfall plot. How many of the 170 are in that waterfall plot?

DR. ROLFE: So we will get back to you with the specific number right after the break.

DR. FOJO: Right after the break. Okay.

DR. ROLFE: But can I just explain one limitation of a waterfall plot is that it can only include patients who have a measurable target lesion at baseline that is subsequently scanned and measured again. So it does not include patients who don't have a secondary staging scan for whatever reason.

DR. FOJO: Yes, what is going to emerge is that this is not representative of the population at large, which is worrisome because you start off with -- I mean, you have 400 percent -- 400 percent -- 400 patients in the safety, you've got 325 in the efficacy. Boom. We lost 20 percent for whatever reason. Even within that 325, there were 10 percent that didn't have -- where you said missing data, we don't have anything. It starts a subset.

Then, I had another question. When was the last patient enrolled in these two trials that

we're looking at, the 008 and the 019?

DR. ROLFE: Dr. Yurasov, could you explain the difference between the safety and efficacy? And while he's preparing, I'll answer the question about enrollment.

DR. FOJO: Right.

DR. ROLFE: The enrollment cutoffs were different according to each dose. As FDA mentioned, we did not enroll the doses in parallel, they were enrolled sequentially.

DR. FOJO: Right.

DR. ROLFE: So the 750-milligram data set is the most mature.

DR. FOJO: Right.

DR. ROLFE: And the enrollment cutoff for 750 milligrams was 31st of December 2014, and it's the same date for 625 milligrams. Five hundred milligram cohort was the last cohort to enroll, so the enrollment cutoff is slightly later. I think it's March 2015, something like that, for the 500-milligram cohort.

DR. FOJO: Yes. So then, let me follow up

on that because that's what I thought. I mean, somewhere in here, those were the numbers I came up with.

What bothers me is, with the duration of response, there's a ton of patients that are censored for the duration of response. Actually, the numbers that we're seeing for median are not real numbers, they're Kaplan-Meier estimates of the median duration of response.

Why is it that a year ago, when we enrolled the last patient, you tell us that most of the responses occur quickly, within the first assessment, which appears to be the case. So even the last patient that was enrolled would have at least 10 months of follow-up by the time we come here today, and probably 9 months when you were getting this ready for us.

Why is it that the past 6 months, there's hardly any patients? I mean, you can see in the 750, it drops off dramatically. So when you look today, the number at risk and the number of events past 6 months, you can see that the majority of

patients are censored, and the FDA thing that was submitted to us, you can see the tick marks.

Why don't we have longer follow-up on these patients, all of whom have now been on study 13 months? And that would be -- you know, it starts to get a little bit concerning that this data is incomplete. Now, we're going to find out that the waterfall plot is incomplete. We already had incomplete data from before.

It just leaves a lot of gaps in the data, in a single-arm trial where we really want to know what's going on, especially practically all of them were and the United States. It shouldn't be so difficult to get this data and gather it for the committee.

DR. ARMSTRONG: Let's go ahead and give them some time to answer.

DR. ROLFE: We did perform an updated duration of response analysis based on a later data cut applied to all patients. We updated the duration of response analysis with a September 2015 data cut. The duration of response rates are very

stable, and I will be able to show you them right here. This slide shows 500- and 625-milligram doses only with a September 2015 data cut for the NDA data set. And you can see that the duration of response is very comparable with the duration of the response in the original NDA. I could get back to you after the break with 750 milligrams if that will be useful.

DR. FOJO: This is good enough.

DR. FASHOYIN-AJE: May I ask what the number of patients is in that figure, in each of the dose groups?

DR. ROLFE: So in the Kaplan-Meier curve that I just put up?

DR. FOJO: Yes.

DR. FASHOYIN-AJE: Yes.

DR. ROLFE: It is virtually identical to the number of patients in the NDA. There may have been 1 or 2 additional responders since the NDA data cut who would be included. But again, I can get back to you with those precise numbers after the break.

I would like to ask Dr. Yurasov to clarify

the question around efficacy and safety data sets because it's an important one.

DR. YURASOV: So let me go back to the slide that we had in our core presentation. As you pointed out, 400 patients, this is our safety population, 325 patients is our efficacy population.

Now, the efficacy population has all patients who received rociletinib who had T790M status confirmed and who had a scan submitted for IR. Out of those 325 patients, there were patients who did not have measurable disease, but based on the approach, we agreed with the FDA they are included in the efficacy population.

So when we go to the waterfall plot that I showed, in that waterfall plot, you will see less than 170 patients at 625 because some of them did not have a measurable disease. That's the reason for discrepancy.

DR. ROLFE: And please, would you display the slide that has the flow chart regarding T790M positive and negative?

DR. ARMSTRONG: We have a ton of people who want to ask questions.

DR. ROLFE: Okay.

DR. ARMSTRONG: We can show this later if you need to.

DR. ROLFE: Sure.

DR. ARMSTRONG: So we can get to break.

Dr. Cole?

DR. COLE: I would like to ask about the representativeness of the sample. Any time you pool multiple studies together, you run the risk of getting a total population as representative of neither original target population.

I was wondering, the epidemiologist part of me would take these data and kind of compare with other studies to make sure that the demographics and all the prognostic indicators line up with the general population, and possibly do some analysis, sensitivity kind of analysis, to see how my confidence intervals and my estimates might move around a bit when doing that.

I think it's important here because the

response rate of 30 percent that was observed seems to be improved over historical controls, but the gap is not really very large when you factor in the possibility that there could be some selection bias or there could be variability in the estimates.

I'm just wondering if you did any kinds of additional analyses in the epidemiologist kind of realm to look at the sensitivity of the results to differences in the population compared to general.

DR. ROLFE: Well, I'll answer from the sponsor's perspective, and I will ask Dr. Camidge to comment from the wider population perspective. We did a number of subgroup analyses within the studies, and we showed that within all the subgroups we looked at, the response rate was very consistent.

So those were the sensitivity approaches that we took. Dr. Camidge, could you comment on the overall population similarities?

DR. CAMIDGE: So there were certain clinical and demographic factors associated with having an EGFR mutation, which will make it look somewhat

different than a standard lung cancer population. There's a higher incidence of those of East Asian origin, a higher incidence of never smokers, a slight female bias. So it's never going to look exactly the same as an unselected lung cancer population.

I think one thing just to factor in when you're talking about not a big difference in the objective response rate is a very significant difference in what delivering the therapy means. One is an oral therapy with most of the adverse events made up of potentially asymptomatic abnormalities, the other standard comparator to intravenous with a lot more in the way of symptomatic toxicities, as I'm sure you're aware.

DR. ARMSTRONG: A final question from Dr. Mager. And I just will remind all the panel members that during the questions to the committee and committee discussions, if there are other burning questions, we can ask at that time.

DR. MAGER: Just a quick question regarding risk management strategy. It follows on, actually,

Dr. Figg's question earlier. Given the extreme variability in the M460 concentrations, the lack of a priori genotyping, and the relatively strong relationships between the concentrations and the adverse events, why therapeutic drug monitoring wasn't at least considered as part of the risk management strategy.

DR. ROLFE: We believe that frequent ECG monitoring is a better strategy because it actually reads out on the event.

DR. ARMSTRONG: Is that it?

So we'll now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume in 10 minutes at 11:17.

(Whereupon, at 11:07 a.m., a recess was taken).

Open Public Hearing

DR. ARMSTRONG: I'll ask everybody to take your seats, and we'll move to the open public hearing section.

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, 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 the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have 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 a great importance on the open public hearing process. The insights and the comments provided can help the agency and this committee in their 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 consideration.

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

DR. GOTTSCHALK: Hi. Thank you for the opportunity to speak today. My name is Dr. Lauren Gottschalk. I received my PhD in cellular and molecular medicine from Johns Hopkins School of

Medicine and previously worked as a cancer researcher. I'm speaking today on behalf of the National Center for Health Research.

Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from pharmaceutical companies, and therefore I have no conflicts of interest.

We understand that patients who have T790M positive lung cancer are tired and frustrated because time after time, they're given a cancer therapy only to be told it is not working to treat their cancer. So the promise of a new drug that will successfully treat their specific form of cancer, even down to the exact mutation, can sound very promising. However, based on the data presented today, we think you'll agree that rociletinib does not meet FDA's standards of proven safety or effectiveness.

First, we're concerned with the efficacy of rociletinib. The objective response rate of about

30 percent does seem promising, but several important caveats need to be kept in mind. Accelerated approvals can often lead to more lenient clinical trials, including the single-arm studies used here.

We believe that without proper controls an accurate assessment this drug's efficacy and safety cannot be made. The surrogate endpoint used for the studies, objective response rate, has in the past been shown to be a poor indicator of cancer drug efficacy.

A study from December of last year looked at cancer drugs that were approved by the FDA over a recent five years based on surrogate endpoints. In postmarket studies, only 14 percent of these approved cancer drugs were found to improve patient survival, and yet our center found that all of the unproven cancer drugs were still on the market, many costing more than $100,000 per year. These results show that surrogate endpoints such as objective response rate too often provide false hope while costing patients more than they can

afford.

In this study, there's also a possible red flag warning. Only one patient had a complete response out of the 98 patients who actually had an observed response to the drug. This makes it seem unlikely that the drug will be found to be effective in controlled clinical trials.

The ongoing randomized phase 3 trials comparing this drug to chemotherapy should give a better idea of overall survival in patients. Until those results are available, the FDA should not approve yet another drug that could easily fail to be effective for T790M patients.

In addition to questioning the efficacy, we are also very concerned with the safety profile. The drug had numerous side effects that would directly decrease a person's quality of life, diarrhea, fatigue, nausea and vomiting in approximately half of the patients. Meanwhile most patients suffered for almost two months before learning that the drug wasn't working for them. Even more troubling were the high incidences of

serious adverse effects, such as hyperglycemia and QT prolongation.

As a result, the side effects resulted in most patients reducing, interrupting, or stopping their dosing completely. Since there was no standardized method for reducing dosage in patients, this makes it difficult to accurately assess the efficacy of this drug.

In conclusion, we realize that there is currently an unmet need for a drug to treat patients whose NSCLC has become resistant to first-line TKI therapies via the T790M mutation. However, this does not warrant the approval of yet another drug that will not significantly improve outcomes for these patients.

Fortunately, there's hope on the horizon, as mentioned here before, because of the preliminary results for osimertinib for the same patients and appears to be more effective with fewer serious side effects.

For rociletinib to be worthy of FDA approval, studies are needed to determine which

subgroups of patients are most likely to benefit from treatment and determine how to reduce the number of adverse events experienced by these patients, perhaps by looking at NAT2 status again as mentioned here today.

Additionally, these studies should have the proper control group and outcome measures to demonstrate effectiveness as measured to clinically relevant endpoints, such as overall survival. Thank you for your time.

DR. ARMSTRONG: Thank you.

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

MS. PENA: Good morning. My name is Glenda Pena, and I've been an oncology nurse for 22 years. I'd like to thank each of you for giving me the opportunity to honor my dad's memory by telling his story. I know he would be proud of me today if he knew that my being here today to tell his story could make a difference in the lives of many. I'd also like to express my gratitude to Clovis

Oncology for supporting my travel here today and making this possible.

My dad, Mickey Mutter, was one of the bravest, wisest, Godliest men that I've ever known. He was in the army, and he served his country in Vietnam where he was exposed to Agent Orange. When he retired from the army as lieutenant colonel after 20 years of service, he went to work at Kennedy Space Center for safety.

He retired at 57 so he could volunteer his time for his church, community, and family, and I always joked to him and my mom that they should go back to work to rest. He babysat his grandchildren, volunteered his time working for hospice, he worked at his church as handyman, fixing anything and everything, and he mentored and helped people through Stephen ministry.

In December of 2011, our family was blindsided when scans revealed that he had stage 4 lung cancer. How dare they tell us that my dad, my hero, was dying? Dad was started on cabazitaxel and Avastin before he had his EGFR status back

because we wanted him started on treatment as soon as possible. One of the hardest things I've ever had to do in my life was see my dad sitting in that chemo chair for the first time.

He completed six cycles and stayed on Avastin maintenance until he showed progression in August 2012. His treatment was changed to Tarceva since he had tested positive for the EGFR mutation.

In February 2013, his PET scan showed increased activity in his lung lesions, so Alimta was added, and he had stable disease for 13 cycles, but unfortunately in October, we learned that the cancer had outsmarted the chemo and progressed.

He was referred to Moffitt Cancer Center and was put into a phase 1 clinical trial with afatinib and dasatinib, but after a few months, a bone scan revealed lesions in his back and ribs. He got radiation and was able to go back on trial, but shortly after that, in May, a brain scan was done, and the results were devastating.

The cancer had gone to his brain. He got more radiation, and the symptoms were controlled,

but other scans soon revealed that he had lesions in his adrenals, pancreas, and liver. The cancer was out of control, but he wasn't willing to give up the fight.

I heard about a clinical trial for PD1 and PDL1 for lung cancer at Florida Hospital, but when Dr. Mekhail looked at his case after the referral, he said, "I think I might have something better for you," and a biopsy of an enlarged lymph node revealed the T790 mutation.

He was placed into the clinical trial CO1686, which we now know is rociletinib. When he went in for the first results of his CAT scan at five weeks, Dad and Mom sat there crying while they were being told that the target lesions in his lungs had decreased significantly, and the lesions in his liver, pancreas, as well as some of the smaller lesions in his lungs, were completely gone. Finally, we had some hope.

He tolerated the rociletinib very well. His medical team at Florida Hospital monitored him closely for glucose and heart issues. He never

experienced any issues with his blood sugar, and although he did have some subtle changes in his EKG readings a couple of times, it was nothing that prevented him from staying on trial. His GI symptoms were mild and tolerable. And because the medication helped palliate his symptoms from his cancer, he was able to scratch off several items from his bucket list.

He went to the Grand Canyon with my mom and their best friends. He traveled to Georgia to see family. And he was able to continue doing the things that he loved to do, like working in the yard, fishing, and taking walks to the beach with my mom.

He did well with stable disease for five months, but unfortunately in February 2015, he developed neurological symptoms again, and the cancer had returned to his brain. He was taken off the medication while he went through a second round of whole brain radiation and was able to return to study for a short time, but then he developed obstructive pneumonia.

He was placed on steroids and antibiotics and had to have another CAT scan to determine if he could be put back on the trial. Before we could get the results, on April 25, 2015, Michael Dean Mutter, devoted husband, dad, and friend, went home to heaven to be with his best friend, Jesus.

I was so grateful that I could be there with him on his journey, and I know that if even one person could be helped by the use of rociletinib, he'd be willing to fight his battle again. I know how much quality-of-life matters, and I know that this medication gave him the opportunity to do things that he wouldn't have otherwise been able to do.

My dad had five more months to create memories with my mom, his children, and his grandchildren, and that wouldn't have been possible without this medicine.

I know that there is another medicine currently approved for the T790 mutation, but the more options available for people like my dad, the better. I truly believe that if we had known about

this medicine sooner, it is possible he would be with us today. And although there are no guarantees, I want to be a part of spreading the word that there is hope with rociletinib. Thank you.

DR. ARMSTRONG: Thank you.

Will speaker number 3 step up to the podium, introduce yourself? Please state your name and organization that you're representing for the record.

MS. TOMLINSON: My name is Celia Ruiz Tomlinson. I am a 75-year-old lung cancer patient. I'm representing myself. First of all, I thank the board for allowing me to share my experience with lung cancer and Clovis Oncology for making my trip possible.

I am a retired engineer entrepreneur, a published author, and a professional motivational speaker. Growing up in a Manila slum, awash with rotten trash and human waste, I transcended numbing poverty and became a civil engineer in the mid-1960s when female engineers were unheard of.

Buoyed by that success, I came to the United States in 1968 legally, alone with only $300 and my diploma.

To my rude awakening, the American engineers confronted me with fierce resistance. Through sheer tenacity, I gained acceptance. In 1983, I founded an engineering company with $2000 from my own pocket. As its own president and CEO, I grew the firm and received national entrepreneurial leadership awards. Twenty-five years later, in 2008, I sold the business and retired.

Four years into retirement, in the summer of 2012, I had a cough that didn't seem to go away. A visit to my doctor led to an image of a golf ball-sized tumor at the bottom of my left lung, and tiny nodules, too many to count, in both lungs.

Biopsy followed. The diagnosis, non-small cell lung cancer, stage 4. Prognosis, eight months to live, a year at most. True to character, I faced the dire prognosis with aplomb, but spunk alone can't fight cancer. Drugs are needed.

At the time, FDA had just approved Tarceva

for the first-line treatment of my type of cancer. My oncologist put me on Tarceva, 150 milligrams daily. No immediate side effects for one week. On the eighth day, rash blanketed my face and my chest. We cut the dosage in half, and the rash went away. After 100 days on Tarceva, the main tumor shrank 80 percent. Subsequent CAT scans showed a stability. My quality of life was good.

After 20 months, my oncologist suspected resistance and suggested that I participate in the rociletinib clinical trials. Having qualified, I was accepted. I took 1500 milligrams of rociletinib daily. For four months, no side effects. My quality of life was great.

On the fifth month, my blood sugar elevated. My oncologists and I worked with metformin to control the hyperglycemia. Later, we reduced the rociletinib dosage to 1000 milligrams. One day, I went on a three-day drug vacation. When I resumed medication, the hyperglycemia mysteriously disappeared.

I have been on rociletinib now for two

years. It's stable with zero side effects the last 12 months. My awesome quality of life allows me to blog, inform, and inspire other cancer patients.

Today is a far cry from the summer day of 2012 when the first oncologist sort of declared me a dead woman walking. I implore the board to please remember my story when deciding on the fate of rociletinib. A cancer drug affects each patient differently. It has been very good to me, therefore having more approved drugs is better than having less. Thank you.

DR. ARMSTRONG: Thank you.

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

MS. FIGUERAS: Distinguished members of the Oncology Drug Advisory Committee and other guests, my name is Anita Figueras, and I am 64 years old. I come to you from Russell, New York, a tiny rural township in the Adirondack foothills. Clovis Oncology supported my travel here today. Clovis

has not reviewed my statement. My words are my own.

I am married and have been with my husband for more than 40 years. He can't be with me today because he is town supervisor of our little town, and he has a board meeting tonight. I have a stepson, three grandchildren, and a daughter who is here with me today. She is a biostatistician and a post-doctoral fellow at the NCI.

At the time of my diagnosis with lung cancer, I was finance and personnel manager, plus farm business management educator, for a non-profit that is part of New York State's Cooperative Extension Network. It was a big job that required more than full-time effort from me, and the first decision I made the day I learned that I have advanced cancer was to retire.

I was diagnosed with stage 4 adenocarcinoma of the lung in June 2014. I had one 3-centimeter tumor in my upper left lobe, a pleural effusion on my left lung, and metastases to lymph nodes. My oncologist at the Community Cancer Center advised

basing treatment on a genetic analysis of the cancer, and the biopsy results were EGFR Exon 19 deletion. I began treatment with erlotinib in mid-August 2014.

Initially, I had an excellent response, but by February 2015, my cancer started showing signs of resistance. I was aware from research I had done that two drugs were being tested in clinical trials that could be my best second line of treatment.

A web search led me to the Clovis clinical trial navigation service, which matched me to an open phase 2 trial being conducted at Roswell Park Cancer Institute. This trial was logistically feasible, and I enrolled in the trial in April 2015. A new biopsy came back positive for the T790M mutation, and I took my first dose of rociletinib on June 11, 2015, taking 500 milligrams twice daily.

I had a very good response to rociletinib with 43 percent reduction in cancer across all sites over the first 12 weeks of treatment, and

stability after that. I also experienced side effects, including hyperglycemia.

My blood sugar levels rose dramatically about two weeks after beginning treatment with spikes in the 400s, and I started losing weight. After little success with metformin, glimepiride, and diet changes, my trial oncologist collaborated with my general practitioner, who has much experience with controlling diabetes.

We added Jardiance to my drug regime. Blood sugar levels stabilized in short order, and we were able to discontinue metformin after a few weeks. This led to a big increase in my feelings of wellbeing, and I stopped losing weight.

Twice we had to reduce my dose of rociletinib due to QT interval prolongation. My CT scans remain stable at a three-quarter's dose, but my cancer started to progress at a half dose, and I left the clinical trial on February 18th.

My quality of life on rociletinib was excellent overall. I was able to lead my life with no restrictions, to travel, exercise, shovel snow,

to walk the dog, be a volunteer income tax preparer, and to help my husband put up the firewood that we depend upon for heat in the winter. There were days when I almost forgot that I have a serious and incurable disease.

I am here today because even though my run on rociletinib was cut short by QT interval prolongation, I had eight very good months on this drug. As you consider your recommendation about this drug, please keep in mind the preciousness of quality of life to people in my situation.

Please also consider the individuality of cancer, that different patients with similar biopsies can have different responses to treatments. Both patients like me and our doctors need options because one drug will not suit all. Thank you.

DR. ARMSTRONG: Thank you. Is speaker number 5 here?

(No response.)

DR. ARMSTRONG: If not, we'll move to speaker number 6. Please step up to the podium and

introduce yourself. State your name and any organization you're representing for the record.

DR. SPIRA: Good morning. Thank you for having me here. My name is Dr. Alex Spira. I am board certified medical oncologist, just across the river, with Virginia Cancer Specialists, whom I represent. I'm here as an investigator who treated about 20 to 30 patients on the study. We were active investigators and our organization, but not myself, received compensation from them. I did previously do some consulting work, but Clovis did not pay for any time or travel today.

I appreciate you giving me an opportunity to speak at this open hearing today. I have used rociletinib and have seen many of my patients benefit. As I have said, we have put about 20 or 30 patients on the studies presented here today. These patients are mainly from the Virginia, Maryland, but also throughout the entire East Coast. And it's safe to say that without these treatments, these patients would not have lived nearly as long or as well as they did.

Although there is another third generation EGFR TKI, osimertinib, from my perspective, there is still an unmet need for another treatment for these patients with EGFR mutated T790M positive non-small cell lung cancer. Adding new options to a clinician's treatment regimen and armamentarium is always beneficial, especially for patients who may not respond or may not tolerate current therapies.

As you've heard with the data today, platinum-based cytotoxic chemotherapy is rarely a good option for these patients. They do not tend to respond, and they do not tend to tolerate it very well. These also adversely affect the patient's quality of life, in my opinion, far more than rociletinib. Furthermore, the other TKIs are associated with rash and other toxicities that may compromise the tolerability, and it's always nice to have a different option for patients.

In my clinical experience treating patients on these studies, I believe it clearly has a favorable risk-benefit profile, especially as

related to any of the current standard of care treatments. It's also important to have options to sequence patients, and we may very well learn that some drugs work where others fail.

From my perspective as an investigator and physician, there is clearly value in granting accelerated approval under the provisions of the 21 CFR to very promising molecules, especially those that are indicated for patients who have very limited treatment options.

Following accelerated approval, clinical benefit will obviously need to be confirmed in the phase 3 randomized study as you've heard, although again, based upon experience, chemotherapy we know is very toxic and very unlikely to work.

In closing, I would like to ask the committee to consider making a very positive recommendation to approve rociletinib for the treatment of advanced EGFR mutated T790M positive non-small cell lung cancer. And if approved, based upon my clinical experience and seeing tons of patients, there is no doubt that these patients

will benefit where they have otherwise very limited treatment options. Thank you.

DR. ARMSTRONG: Thank you.

Will speaker number 7 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. PACE: Madam Chairman and members of the Committee, I appreciate the opportunity to be here today, and I want to thank Clovis Oncology for helping to support my travel, but I have no financial interest whatsoever in the company.

My name is Russell Pace. I'm 87 years old, going on 57. I live in Midlothian, Virginia with my wife, Margaret, who is with me here today, and I have six kids, age 28 to 61, so I've had a long and fruitful life and a very lucky man.

After graduating from college, I volunteered for the Air Force. I served three years during the Korean War, part of the time as assistant director of intelligence for 315th Air Division in the Far East.

After that, I went to law school and later practiced law with a firm here in Washington, DC, and then left the practice to co-found a large financial service company, which was very innovative in putting stockbrokers in the New York Wall Street firms into the annuity business. And we licensed and trained about 40,000 of them, and they sold over $2 billion worth of business for us in just a couple of years.

So it was a very exciting interesting time, and I've been very fortunate in all the challenges and opportunities that have been presented to me in my life.

I never thought about my mortality or about the fact that I was getting old, even at 81, until I was diagnosed with small cell lung cancer in December in 2010. My pulmonologist told me, and my family, that with good luck, I might have nine months to live, and I better get my house in order.

But he didn't know that my new cancer doctor, the doctor that just testified here a moment ago, Dr. Alex Spira, what he had in mind for

me. So I went on chemo for about four months, and then he put me on Tarceva, which saved my life for over four years, a full four years.

I guess when it appeared that it might no longer be effective to me, Dr. Spira talked to me and was instrumental in getting me enrolled in this clinical trial. And I started taking this drug in July of last year, and been on it 9 months. And the results appear to have been very successful. As a matter of fact, Dr. Spira has indicated that from the CAT scans that I've had over the last several months, that he can't see any cancer anymore. It's almost as it I don't have -- haven't had it.

I also would like to say to you that I've had no side effects. The only one possible one that I could relate was a little bit of fatigue, which I've been complained to Dr. Spira that why in the heck can't I get strong and do the things that I used to do. And he said, "Hell, Russell. You're 87 years old. What do you expect me to do -- what else for you to do with me?"

(Laughter).

MR. PACE: But I did develop a little curly hair with Tarceva, and I was hoping this drug would help to continue it, but it seems to be gradually disappearing, but I have no complaints about that.

I'm very grateful to Dr. Spira and Clovis for helping to extend my life. My family, my friends, and my business associates thank you. It has allowed me to continue to be active in business and to innovate in a number of new business ventures with my children and others.

Dr. Spira and Clovis are performing a great public service in their fight against cancer. I know that you members of the Committee have a job to do, but I must tell you that in my opinion this drug should be approved so that many others like me may benefit from its use. I appreciate your thoughtful consideration and thank you.

DR. ARMSTRONG: Thank you. Will speaker number 8 step to the podium, introduce yourself? Please state your name and organization you're representing for the record.

MR. CAUGHRAN: Yes, good morning. My name is Scott Caughran. I'm 43 years old, and I live with my family in Bend, Oregon. I would like to thank Clovis Oncology for supporting my travel so that I could be here today.

My wife and caregiver, Darcy, is here with me today. We've been together for over 20 years. We have three children, two daughters age 16 and 13, and a terror of a 3-year-old son. I'm an active duty lieutenant colonel in the Oregon National Guard where I proudly served as an infantry officer.

Prior to my diagnosis, I was an incredibly driven and busy person. I spent a lot of time away from home working, professional travel, and attending training courses. I deployed four times in service to our country. I filled my free time with family activities, achieving a high level of fitness, and completing college degrees that would give me a professional edge and prepare me for life after the military.

I served my state and community through

involvement in various special committees and coalitions, leading to national recognition at both the Pentagon and the White House. I no longer work. I would have retired from the military this coming January. I now focus on making up lost time and making the most of the time I have left.

Eighteen months ago, I was about six months into a deployment in Afghanistan. I was the task force commander responsible for security throughout the entire city of Kabul and the surrounding areas, an area populated by almost 4 million residents that were conducting their first democratic presidential election. I was entrusted with the lives of over 800 soldiers from several countries to accomplish my mission.

For six months, I had been fighting increasing pain in my side and was having difficulty improving my fitness. One night the pain got bad. I couldn't sleep. I got up to shower thinking maybe it would help. I ended up passing out from a standing position and landing on my face on a tile floor. I laid there for about

30 minutes before I came to and crawled to get help.

I received an x-ray shortly thereafter at the local military hospital, and all at once I was told I had stage 4 lung cancer, that I would be medically evacuated out of Afghanistan in a matter of hours, with no opportunity to say goodbye to my soldiers, and that I had two to six months left to live.

I was told I probably had cancer in excess of two years, and that my right lung was full of fluid from a pleural effusion and probably had been for months. That night, I made several tough phone calls to my family to let them know I was coming home early and why.

My biopsy showed that I had the EGFR mutation so I was prescribed Tarceva. The Tarceva worked for me for eight months, but I fought hair loss and severe rashes on my upper body and face, and continuously open sores on my head. Once Tarceva quit working, a second biopsy showed the T790M mutation. I then went through six chemo

treatments with no positive effect in order to become eligible for the rociletinib drug trial.

Prior to the trial I also lost my ability to walk due to a cancer tumor on my spine. I was taking 240 milligrams of extended release morphine daily, plus wearing a fentanyl patch in order to control severe pain. I had lost almost 30 pounds from my previously healthy weight.

Rociletinib quickly improved my physical condition. The cancer in my lung decreased significantly in size, and the fluid in my lung dried up. With the help of back surgery, I became able to walk again. I've gained back 20 of my 30 lost pounds. My pain medication has been decreased by over 75 percent, and I'm largely pain free.

My original 625-milligram dose of rociletinib was reduced to 500 milligrams as a result of increasing glucose levels. I was prescribed metformin to take as needed, and my glucose has remained fairly stable. I have not suffered from rashes or any other major side effects, and I've now been on rociletinib for six

months.

Rociletinib has given me more energy than I've had during any other treatment or since I was diagnosed. I've been able to work around the house, do yard work, play with my kids, attend sports competitions and school performances, visit with family and friends, and travel.

I traveled here today because rociletinib has made a tremendous difference in my life. I'd like to see the FDA approve this drug so it can be available to others to benefit them as it has benefited me. It's given me the gift of life, months of quality time with my family, the opportunity to watch my kids compete, perform, and grow, to achieve a greater level of financial stability for those I'll leave behind, and the energy to complete those last few bucket lists.

I don't believe I would be alive today without rociletinib. When you're fighting a disease that strikes randomly and harshly, any drug or treatment that stops or slows the spread of cancer is a blessing. Thank you.

Questions to the Committee and Discussion

DR. ARMSTRONG: 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 turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We'll now proceed with the questions to the committee and panel discussions.

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. I'll ask the FDA to review the questions.

DR. FASHOYIN-AJE: Thank you. The FDA requests the advice of the ODAC to discuss whether the benefit-risk profile of rociletinib is favorable in the proposed indicated population. Thank you.

DR. ARMSTRONG: Are there any questions or comments regarding the wording of the question?

(No response.)

DR. ARMSTRONG: If not, we'll open the question to discussion. So the issue is the benefit-risk profile of rociletinib in the population. Discussion? Go ahead.

MS. GILLESPIE: As a lung cancer advocate, or survivor, I understand the importance of new and innovative drugs to give everyone a little more time for the next possible drug. However, I feel that we need to have more responsibility on the safety and efficacy of drugs that come to the FDA. I am still on the fence on this one because I'm not real sure how much risk there is as opposed to benefit.

DR. ARMSTRONG: Thank you very much.

Maybe I'll take chair's prerogative here and just to -- and honestly, in spite of the very positive comments from the speakers from the audience who are a group that's done well with this drug, I think it's very difficult for us to look at a single-arm study in a subgroup of non-small cell lung cancer and try to look particularly at the

toxicities in relation to the benefits.

We have certainly heard that, compared to historic controls, that there's a better response to this drug, but those historic controls are actually in a broader population of non-small cell lung cancer patients and don't include -- and are not enriched for the EGFR mutation carriers who do better. Thus, that 10 percent or so difference in outcome may or may not really be significant. And unfortunately in a non-randomized trial and a single-arm phase 2, it's really difficult to know that.

The second is that we see that, based on the metabolism of this agent, that about half the population are at risk for excess toxicities, both the cardiac toxicities and potentially arrhythmias and sudden cardiac death, as well as hyperglycemia, which certainly can be dealt with, but it still is a significant issue and is high grade in about a third of the patients.

My feeling would be that some sort of risk stratification in terms of looking at this agent

with regard to the metabolism, I think, is certainly in order; not necessarily saying that you have to limit the population that can get this, but that really trying to better understand. And I know we've mentioned it several times, but I think just looking at QT prolongation is probably not sufficient.

We might end up with actually a much better risk-benefit ratio if we were really looking at this in the population that doesn't have the toxicities and the side effect.

I'm also concerned about the dosing issue. I think we've heard the issue between the 500 and the 625 that there potentially is very little difference. And yet, we still have this very large 900-patient study that's going to look at both doses. And the statistician says there's still not going to be enough patients on the 300 milligrams of each of those doses to really probably be able to give a difference.

I think the dosing is going to be an important issue and potentially is going to be an

important issue with regard to the toxicity and the risk-benefit. That's my feeling.

Dr. Orza?

DR. ORZA: I have another question actually for the FDA, but it goes to trying to understand the proposed population and if there is a population that we can define narrowly enough that really needs this as an option or not.

I thought Dr. -- I'm going to say your name wrong -- Fashoyin-Aje, on one of your last slides when you were doing the efficacy summary, I thought you said there was a concern that people might choose this over available therapies known to be effective and improve survival.

Is that what you said? Can you say a little more about that?

DR. FASHOYIN-AJE: Yes. So if approved, rociletinib would be approved to be used in the same space as the available therapy we discussed; so second-line treatment of non-small cell lung cancer following progression on an EGFR TKI therapy, and sometimes after chemotherapy, doublet

chemotherapy.

DR. ORZA: And this drug does not compare favorably with those other drugs, and so we wouldn't want it to be -- we want it to be maybe a third choice or a last resort?

DR. FASHOYIN-AJE: I think that's our question to the committee. We are concerned about the serious and life-threatening risks in patients who receive rociletinib.

So while the numeric overall response rate may be better when you compare to available therapies -- notwithstanding all the limitations we've discussed about comparing overall response rate across several studies, but if you're just looking at the number, there are serious risks associated with the use of this drug, which may not confer an improvement over the therapies that are already approved. That is our question to the committee.

DR. ORZA: So is there any way to put parameters on a population that would use this as a last resort but would nonetheless need to have that

as an option? Is there a way to do that with the labeling or with the indications?

DR. FASHOYIN-AJE: I think Clovis would have to define a population in which the benefit outweighs the risks with the use of rociletinib. That's the job of the applicant.

DR. BLUMENTHAL: I agree completely. The other important caveat to note is that this drug wasn't studied in patients who progressed on nivolumab or on docetaxel plus ramucirumab. Furthermore, we don't know what the benefits would be in that patient population.

So the proposed indication is for T790M positive patients who have progressed on an EGFR TKI. The other studies, although they were conducted in broader populations like nivolumab versus docetaxel, was an all-comers and has a survival advantage.

So the question we are raising is, given that there are known survival advantages for some of these agents, they would be foregoing those agents to potentially go on rociletinib.

DR. ARMSTRONG: Does that answer your question?

DR. ORZA: Yes.

DR. ARMSTRONG: Great. Dr. Figg?

DR. FIGG: So I'm going to give you my take on the drug. I would like to see the company in their phase 3 actually stratify for NAT2. I think that you're going to find that those that are NAT2 slow metabolizers are going to be those that have a higher risk of side effects, and thus you need to actually monitor EKGs and blood glucose more closely. So to me, that would be the first thing.

I also think that 500 is probably the correct dose, especially if you consider that there is no increasing AUC with increasing dose, so it's hard to say that you're going to have a higher response. The only thing you're going to end up doing is have a higher side effect at some level probably.

I'm also very, very concerned about the variability in the pharmacokinetics, which is based upon the GI pH, and there are changes in GI pH that

could alter the plasma concentration substantially. So thus, I really believe that the 500 is better for that.

DR. ARMSTRONG: Any other discussion about the risk and benefit? Tito?

DR. FOJO: I think we have some trouble with the benefit. It's not clear. To me, it's not as clear as I would like it to be. And it's certainly not clear whether 625 is any better than 500. As I stated before, I think the overwhelming inclination in that is that there's no difference to that. And whether 625 is more toxic than 500, I don't think we know that either, but one would tend to think that it might be.

I think we have difficulties with the toxicity, and to be honest, is what I said, which is I don't understand why this drug is being discontinued. I actually think we've focused on QTc prolongation and hyperglycemia, and those are probably not going to be major issues.

I mean, even if you look at the sudden deaths, it occurred at 4 and 13 days, not quite

when you would expect, certainly the 4 day, to be a complication of the drug or the metabolite, which had probably not yet accumulated to any great level. And we know, as Dr. Carbone pointed out, that these are generally patients that have complicated diseases and have a lot of other reasons why they might experience a sudden death.

So I personally -- the QTc I think is manageable. The consultant was talking about managing potassium and magnesium and all of that, and I think it will be. I think Dr. Figg is right, when we look at the acetylator status, we'll even get a better handle on that.

So I think all of that eventually is manageable, but at the present time, we just don't have the data that we would like to have to know really what the risk is and for absolute sure we don't know the difference between 500 and 625.

Then maybe the FDA can comment. There seemed to be a suggestion in one of the slides that maybe even less than 500 might be effective. In the data that you showed, it seems to start to drop

off beneath 500, but then there's also the concern that Dr. Carbone pointed out, afatinib is given at a lower dose. I don't think we need to approve another drug at a dose that then gets reduced and where we don't know efficacy.

So I think we're missing a lot of information here. I don't know if the FDA wants to comment on the lower dose might even be something that might be --

DR. LIU: So this is Chao Liu from pharmacometrics. If we can go to the FDA presentation, the backup slide number 91. We do have some data showing if we lower exposure from the level at 500-milligram BID, we're probably going to lose efficacy.

DR. FOJO: Below 500?

DR. LIU: From 500 to the next dose level, say --

DR. FOJO: Which would be 375 maybe.

DR. LIU: 375, yes.

DR. FOJO: Yes, right.

DR. LIU: So this plot is showing the ER

analysis relationship based on the investigator assessed ORR. And in here, there is another formulation, a free-base formulation, where the exposure is lower than the proposed 625 milligram in the HBR formulation, where we could get some information to see if we decreased exposure to lower range, whether or not we have adverse response rates.

According to this plot, it seems like if we decreased exposure from the level at 500-milligram BID to lower ranges, we probably are going to lose efficacy.

DR. FOJO: But you also start to see how, if we get the acetylator status, you might find that there's a difference there, maybe at 375 in a low acetylator -- I mean a high acetylator would make a difference. A lot of things start to come into play. To their credit, they're doing all of that in this phase 3 trial, so I think we're going to have a lot of answers.

DR. LIU: Right.

DR. KEEGAN: So I want to make something

clear that's probably difficult to grasp. The acetylator status has no effect on the exposure of the parent compound, which is responsible for all the efficacy.

DR. FOJO: Right.

DR. KEEGAN: So there's no reason to modify the dose based on the acetylator status if you're trying to preserve the efficacy. The real issue is --

DR. FOJO: Toxicity.

DR. KEEGAN: -- is that the toxicity will be increased in the slow acetylators. There's a basal level of toxicity regardless across all patients, rapid, intermediate and slow, but that there's a higher risk in the rapid acetylators. But this is not a risk that can be mitigated by dose modifying the slow acetylators because you're eliminate the efficacy.

DR. FOJO: Yes, I understand that the toxicity plays into ability to continue these type of therapies, which I think all of us would agree is a drug therapy that has to be continued to be

effective and to have that long duration of response.

I think the randomized phase 3 trial is good. It's going to give a lot of information that we don't have today that we wish we had today, is my take on all of this.

DR. ARMSTRONG: Any other discussion regarding the risk-benefit analysis? Sure.

DR. MENEFEE: Yes, Michael Menefee, Mayo Clinic. I echo the comments that have already been made. I think when we talk about benefit-risk ratio, it really comes down to somewhat of timing issues. I think the landscape of the management of non-small cell lung cancer has changed a little bit since the drug application would have been submitted, and that has an impact on how I perceive benefit-risk for this particular patient population.

DR. FOJO: Yes, can I just --

DR. ARMSTRONG: Go ahead.

DR. FOJO: They were going to tell us after the break how many patients were in that waterfall

plot, which I think is probably about two-thirds of the patients.

DR. ARMSTRONG: Do you have the numbers for the waterfall plot? Thank you.

DR. ROLFE: So of the 170 patients in the 625-milligram efficacy dosing group, 145 were in the waterfall plot. The 25 who were not in the waterfall plot either had no non-target lesion at baseline, as measured by the independent reviewers, or no subsequent restaging scans, so they discontinued before the next scan.

Eighty-seven patients in that waterfall plot had a best target lesion reduction of 30 percent or more, and of those, 55 had a confirmed response. Dr. Camidge is going to give some additional clinical context here.

DR. CAMIDGE: So I think what you correctly pointed out is that a waterfall is that first snapshot, the best response. It doesn't have to include a confirmed response, and so a lot of what we're seeing here is the ones that weren't confirmed. Most of them were due to progression,

sometimes within the central nervous system, which was some aspect that hasn't been brought up in terms of the penetration of this drug into the brain.

A very high proportion of patients had a history of CNS metastases. But what we weren't really seeing was people coming off because of adverse events. So I hope that clarifies your question.

DR. FOJO: Yes, it does.

DR. ARMSTRONG: Thank you for the extra information.

If there's no other discussion regarding the risk-benefit, then I think we'll move to the vote. Do you want to go ahead and read the vote question?

DR. FASHOYIN-AJE: The FDA seeks the committee's advice on whether the results of the randomized clinical trial, TIGER-3, should be submitted before FDA renders a regulatory decision on the application. Please vote.

DR. ARMSTRONG: If there isn't any further discussion about this question, we'll begin the

voting process.

DR. ORZA: Just a point of information.

DR. ARMSTRONG: Sure.

DR. ORZA: The results of this study are due in 2018. Is that correct?

DR. ROLFE: Enrollment is scheduled to complete in the second half of 2018, probably the last quarter of 2018. The analysis is driven by number of events observed, and that time point will most probably occur right at the end of 2018 or in the first half of 2019.

DR. FOJO: And just to clarify, a yes will mean FDA should get this data before it makes a decision.

DR. ARMSTRONG: Correct.

DR. FOJO: Okay.

DR. PAZDUR: Yes, means delay it.

DR. FOJO: Yes means delay.

DR. ARMSTRONG: Okay? I'm going to read the question verbatim, and then go over the directions. The question we're asking to vote on is, should the results of the randomized clinical trial, TIGER-3,

be submitted before the FDA makes a regulatory decision on this application?

We'll be using electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please 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. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to.

Any questions?

(No response).

DR. ARMSTRONG: If not, please press the button on your microphone that corresponds to your

vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote, or you wish to change your vote, please press the corresponding button again before the vote is closed. No questions?

(Vote taken.)

LCDR SHEPHERD: For the record, the vote is 12 yes; 1 no; no abstain; no no voting.

DR. ARMSTRONG: 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. MAGER: Don Mager, the University of Buffalo. I voted yes. I think it's quite clear from the discussion today that the high variability and overlapping exposures really makes any attempt at a dose response an illusion.

I think the FDA has done a remarkable job at examining the exposure response relationship, and

that the dose that's proposed is really not supported by the data. The lower bounds of a single point estimate from a single-arm non-randomized study really doesn't justify the dose that's been chosen.

In my question earlier about risk management, again, I don't feel that they quite have it. But given that we won't have NAT2 genotyping, we have to have minimally that or some sort of therapeutic drug monitoring I think to assess given the very tight relationship, actually, between some of the exposure response in terms of the adverse events.

I don't think the confirmatory trial will necessarily give us any further information about the dose. I think that's pretty well answered, but I do think that it will provide additional efficacy data that would be very useful in assessing the risk-benefit.

DR. ARMSTRONG: Thank you. Dr. Orza? Dr. Szabo?

DR. SZABO: Eva Szabo, NCI. So I voted yes.

Though benefit-risk to me was not as clear as I would like it at this stage, there are multiple other drugs in the space currently. So how this drug would be used currently was not clear to me, and there are some very definite risks associated with it. So I just felt that we need some more information.

DR. ARMSTRONG: Thank you. Ms. Gillespie?

MS. GILLESPIE: Terry Gillespie. I voted yes, and I'm going to abstain.

DR. ARMSTRONG: Save your voice.

DR. ORZA: Michele Orza. I voted no, which is unusual for me because I'm a big fan of outcomes. I would like to see the results of the study, but I felt that -- I also voted very narrowly on the question.

I think that 2018, 2019 is a long time to wait, which is not to say that I would vote to approve it today for accelerated approval. I think there are a lot of questions that have to be worked out.

I'm not confident that the study, even when

it's done, will give us a lot of the answers we're looking for. I'm concerned that there is a population that could be benefiting from this in the meantime and we need to do some more work to identify that group and consider accelerated approval for them.

DR. FIGG: William Figg, National Cancer Institute. First, let me say that the public comments from the individuals that had received the drug, or are receiving the drug, was very compelling. With that said, I did vote yes. And I think it's just simply there are too many unanswered questions that need to be addressed. I am also concerned that the current phase 3 that is ongoing doesn't answer all the necessary questions.

DR. NOWAKOWSKI: Grzegorz Nowakowski, Mayo Clinic. I voted yes for the reasons, which were already mentioned here. I think that the degree of benefit over the standard therapy was not clear for the data presented and the quality of the data were not fully supporting it. More so though, I was more concerned about the safety profile with the

cardiac toxicity and the hyperglycemia. Also, the fact that the dose was not well defined, it is difficult to move this compound to move forward with 500 or 625.

I think there's also an elephant in the room, which is osimertinib. Although it was going to accelerated approval, so we should not consider this to be available, per FDA standards, it appears to be less toxic in this space. So for this reason, I think more data is needed on this very promising compound, and that's why I voted yes.

DR. FOJO: Tito Fojo. I voted yes, and I've stated my opinion. I do think that this is a drug that has activity, yes. This is a drug whose toxicity will be manageable, yes. I would say that I'm concerned, with you, that it goes to 2018, though that will be here unfortunately sooner than we realize.

But maybe the company ought to go back to the FDA and say, you know what, you were right; 500 is the same, why don't we just get rid of that third arm and do a 600 patient trial, 300 with

getting 500 or the few that have gotten 625 now against 300 with chemotherapy, and you'll get done sooner, and go forward with 500. Worry about 625 later. Get it approved sooner at 500.

DR. ARMSTRONG: Deb Armstrong. I voted yes as well. I think we have the well-documented and discussed issues about toxicity, dosing, and the metabolism issue that I think has not been completely addressed. But I guess, primarily, the requirement for accelerated approval to have superiority to current treatment I don't think has been shown by the data that we have at this point in time.

DR. ROTH: Bruce Roth from Wash U. I'd agree with Deb. I did not think it met the criteria to be accepted as superior to existing therapy. And as Dr. Nowakowski also said, I think that while we have the luxury of not considering the osimertinib data, if this was approved today, the same is not true of a practicing physician.

If you were going to prescribe a drug in a T790 patient, would you pick the drug that had a

59 percent response rate, a duration of response at 12.8 months, and a 2.7 percent incidence of QT prolongation beyond 60 milliseconds, or would you pick the 30 percent response rate with a median duration of response of 9 months, where you have to have a risk mitigation strategy for the QTc prolongation, and half your patients are going to be on an anti-hyperglycemic agent as well?

So I think, for me, it just did not meet the criteria for accelerated approval.

DR. MENEFEE: I voted yes for many of the reasons that have already been mentioned. I've actually kind of seen the scenario that Dr. Roth has just mentioned in clinical practice with medullary thyroid cancer, where we have vandetanib and cabozantinib, two drugs that were similar and in the same space, and we don't know exactly how best to use them, and it's not a good situation to be in.

So it would be helpful to have studies that were better designed that are going to help the practitioner know exactly how to use the drug. And

I share Dr. Figg's concern that TIGER-3 is unfortunately not going to answer those questions in terms of how to best use the drug in clinical practice.

But I do think it's a good drug. I think it's active. It's clearly helping some patients. And I think a lot of the issues in terms of dosing and toxicity can be managed, but we need better study designs that are going to be useful for practitioners.

DR. RINI: Brian Rini, Cleveland Clinic. I voted yes. Similar to others, it's clearly an active drug. Noting the response rate, the waterfall shows activity, notwithstanding the limitations that have been pointed out, and I think a number of compelling patient and clinical anecdotes from the treating physicians in the room that, clearly, there's activity to this drug.

For me, it didn't pass the standard of being clearly superior to the standard therapy at present, noting all the limitations of cross-trial comparisons, which are flawed, but which we've been

doing all day because they're necessary.

Again, there wasn't really objective evidence of clinical benefit, and that's what I struggled with. I don't doubt there was. Again, we heard it from the anecdotes that were mentioned, but we weren't presented any data of that, of quality of life, of narcotic use, of symptom control, or something that would convince us that this response rate, whatever the estimate ends up being, is beneficial to patients. And again, I don't doubt that it is, I just don't think that evidence was presented.

With regard to dose, again, I agree with the others it's a hugely complex issue. I think the major problem, and this is not a problem just for Clovis but for all of us who develop drugs, is we really don't individualize dose. We pick an average dose based on a small number of patients, and then we try to shoehorn people into that dose. And for some, it's probably too low, and for others, it's too high. And we just sort of hope for the best as we develop these drugs, and it's

really not a smart way to do it. And again, that's not a comment to this particular company but for anybody in the room who develops drugs.

Having said that, I think the comments about the ongoing phase 3 are very pertinent. So I would either pick one dose, and you can pick 625 or 500, just pick one dose and adequately test it, or power the study for each of the doses. Power it to compare.

This is not just from a regulatory standpoint, but you want people to use your drug at the end of the day, right, if it ultimately gets approved. So you want data to say that the benefit-risk is more favorable with one or the other, and otherwise, you're going to end up just with some underpowered data that won't really be informative. And I think that's a shame to waste those resources.

DR. RAJAN: Arun Rajan. So I voted yes. I do believe, like all clinicians in the room, that we should have multiple options at our disposal. It's always better. And clearly, we have heard

from patients and physicians that this drug does benefit patients clinically. But having said that, I think the risk-benefit ratio is informed by other options that are available. And had there been no option for T790M positive non-small cell lung cancer, maybe I would have voted differently.

So I think there are unanswered questions. There is an ongoing study. I really hope the sponsor can work with the FDA to try and at least attempt to amend the ongoing study to answer some of these questions, so that in two years from now, we're not in the same position where some of these questions have to be debated.

But I think the main crux for answering yes was that there is an alternative at the moment, which, at least on the face of it, appears to be safer and has a higher response rate. Thank you.

DR. COLE: Bernard Cole, University of Vermont. I voted yes largely for the same reasons that have been mentioned around the table. As a biostatistician, member of the committee, I focus my attention primarily on the statistical evidence.

Of course, here we are trying to make two bridges.

The first is the bridge from a single-arm study to a benefit, and the second is the bridge from a surrogate endpoint to a clinically meaningful outcome, such as progression-free survival or overall survival advantage. And unfortunately, the statistical evidence along these lines was rather weak and just simply not able to make that bridge.

I was very moved by the statements from the audience and the patients who have undergone the therapy, and I'm very hopeful that the phase 3 study will show a benefit that is a provable benefit.

Adjournment

DR. ARMSTRONG: Thank you. I'd just like to echo that the statements from the audience really are quite moving. And this is a drug that I think we would like to know where the right place is to use this drug, and I don't think we have that information yet.

We'll now adjourn the meeting. Panel

members, please remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thank you to everyone.

(Whereupon, at 12:25 p.m., the meeting was adjourned.)