FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Morning Session

Thursday, September 22, 2022

9:00 a.m. to 1:10 p.m.

Meeting Roster

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P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. GARCIA: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is April Grant. Her email and phone number are currently displayed.

My name is Jorge Garcia, and I will be chairing today's meeting. I will now call the first session of the September 22-23 of 2022 meeting of the Oncology Drug Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting, and she will begin with introductions.

Introduction of Committee

DR. CHEN: Thank you, Dr. Garcia.

Good morning. My name is She-Chia Chen, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll first start with ODAC members.

Dr. Garcia?

DR. GARCIA: Jorge Garcia. I'm a GU medical oncologist and the chief of Solid Tumor Oncology at University Hospitals Seidman Cancer Center, at Case Western Reserve University in Cleveland, Ohio.

DR. CHEN: Dr. Kunz?

DR. KUNZ: Good morning. My name is Pamela Kunz. I'm a GI oncologist and director of the GI cancer program at Yale Cancer Center in New Haven Connecticut.

DR. CHEN: Dr. Lieu?

DR. LIEU: Good morning, everybody. My name is Chris Lieu. I'm a GI medical oncologist and associate director for clinical research at the University of Colorado Cancer Center.

DR. CHEN: Dr. Madan?

DR. MADAN: Good morning. My name is Ravi Madan. I'm a medical oncologist specializing in GU malignancies at the National Cancer Institute.

DR. CHEN: Mr. Mitchell?

MR. MITCHELL: Hi. I'm David Mitchell. I'm the consumer representative to ODAC. I am the

founder of Patients for Affordable Drugs, and I'm a cancer patient myself.

DR. CHEN: Dr. Rosko?

DR. ROSKO: Good morning. I'm Ashley Rosko. I'm an associate professor in the Division of Hematology at the Ohio State University, and medical director of the oncogeriatric program.

DR. CHEN: And Dr. Sung?

DR. SUNG: Good morning. My name is Anthony Sung. I'm an associate professor of medicine in the Division of Hematologic Malignancies and Cellular Therapy at Duke University.

DR. CHEN: Thank you.

Next, we'll move on to temporary voting members.

Dr. Halmos?

DR. HALMOS: Good morning. This is Balazs Halmos here. I'm a thoracic oncologist, and I'm also associate director for clinical science at the Montefiore Einstein Cancer Center in the Bronx, New York.

DR. CHEN: Dr. Harrington?

DR. HARRINGTON: Good morning. This is Dave Harrington. I am a biostatistician at Dana-Farber Cancer Institute and the Harvard School of Public Health.

DR. CHEN: Mr. Pantelas?

MR. PANTELAS: Good morning. I'm Jim Pantelas. I'm a patient representative, Navy veteran, and 17-year survivor of stage 3B non-small cell lung cancer.

DR. CHEN: Dr. Scilla?

DR. SCILLA: Good morning. I'm Katherine Scilla. I'm a thoracic medical oncologist at the University of Maryland Greenebaum Comprehensive Cancer Center in Baltimore, Maryland.

DR. CHEN: Dr. Thomas?

DR. THOMAS: Anish Thomas. I'm a clinical investigator/thoracic oncologist, focused on lung cancers mostly, at the National Cancer Institute.

DR. CHEN: And Dr. Waldman?

DR. WALDMAN: Good morning. I'm Scott Waldman. I am the chair of the Department of Pharmacology, Physiology & Cancer Biology. I'm an

internist with a subspecialty in clinical pharmacology, and my research focuses in GI malignancies.

DR. CHEN: Next is the acting industry representative to the committee, Dr. Kraus.

DR. KRAUS: Yes. Good morning, everyone. Albert Kraus. I work in cancer drug discovery and development. I'm currently with Pfizer Corporation.

DR. CHEN: Thank you.

Finally, I will like to introduce FDA participants.

Dr. Pazdur?

DR. PAZDUR: Hi. I'm Richard Pazdur, and I'm the director of the Oncology Center of Excellence here at the FDA.

DR. CHEN: Dr. Beaver?

DR. BEAVER: Hi. I'm Julia Beaver. I'm a medical oncologist and chief of medical oncology in the Oncology Center of Excellence at FDA.

DR. CHEN: Dr. Singh?

DR. SINGH: Hi. This is Harpreet Singh.

I'm the director of the Division of Oncology 2 here at the FDA, which houses thoracic cancer.

DR. CHEN: Dr. Drezner?

DR. DREZNER: Hi. This is Nicole Drezner. I am a cross-disciplinary team lead in the Division of Oncology 2 at the FDA.

DR. CHEN: Dr. Malinou?

DR. MALINOU: Hi. This is Justin Malinou. I am a medical oncologist and clinical reviewer in the Division of Oncology 2 at the FDA.

DR. CHEN: And Dr. Fourie Zirkelbach?

DR. ZIRKELBACH: Hi. I'm Jeanne Fourie Zirkelbach. I'm a clinical pharmacologist at FDA.

DR. CHEN: Thank you all.

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

Thus, a gentle reminder; individuals will be

allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

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

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

Dr. She-Chia Chen will now read the Conflict of Interest Statement.

Dr. Chen?

Conflict of Interest Statement

DR. CHEN: Thank you, Dr. Garcia.

The Food and Drug Administration, FDA, is

convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose 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 the discussion of new drug application, NDA, 215643 for poziotinib tablets, submitted by Spectrum Pharmaceuticals, Inc. The proposed indication, use, for this

product is for the treatment of patients with previously treated, locally advanced or metastatic non-small cell lung cancer, NSCLC, harboring HER2 exon 20 insertion mutations. Select patients with NSCLC for treatment with poziotinib based on the presence of HER2 exon 20 insertion mutations using an FDA-approved test. This is a particular matters meeting during which specific matters related to Spectrum Pharmaceuticals' 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, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 (b)(3) to Drs. Balazs Halmos and Ashley Rosko.

Dr. Halmos' waiver involves his employer's research contract for one study funded by competing firms. This study is funded by a competing firm, and Dr. Halmos' employer received between $0 and $50,000 per year. Dr. Rosko's waiver involves her employer's research contract for one study funded by a competing firm. This study is funded by

Innovent Biotherapeutics, and Dr. Rosko is not aware of the funding amounts being provided to her institution for the study.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. 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 will like to disclose that Dr. Albert Kraus is participating in this meeting

as a non-voting industry representative acting on behalf of a regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other product 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. GARCIA: Thank you, Dr. Chen.

We will now proceed with FDA introductory comments from Dr. Nicole Drezner.

Dr. Drezner?

FDA Introductory Comments – Nicole Drezner

DR. DREZNER: Good morning. I am Nicole

Drezner, an oncologist and cross-disciplinary team leader at the FDA. I will refer to Spectrum Pharmaceuticals as the applicant for the remainder of the presentation.

FDA is bringing this application to the Oncologic Drugs Advisory Committee to enable public discussion of the poziotinib drug development program and our significant concerns regarding the overall risk-benefit assessment. The applicant is seeking accelerated approval of poziotinib 16 milligrams once daily for the treatment of patients with previously treated, locally advanced or metastatic non-small cell lung cancer harboring HER2 exon 20 insertion mutations. Poziotinib is an oral inhibitor of pan-epidermal growth factor receptors, including HER2. As this application is being considered for accelerated approval, I will first discuss the provisions of the accelerated approval program.

The ZENITH20 study provides the primary efficacy and safety data in support of the application. After presenting the top-line

results, I will provide a high-level overview of the four major review issues contributing to the FDA's risk-benefit assessment.

The efficacy of poziotinib does not demonstrate a meaningful improvement over available therapy, given the low overall response rate and limited duration of response. The safety data for poziotinib demonstrates a high rate of toxicity with a substantial incidence of drug interruptions and dose reductions. The dose was not adequately optimized, and the confirmatory trial has yet to enroll any patients. Finally, I will present the discussion topics and voting questions for the ODAC committee.

As you will hear in the subsequent FDA presentations, the major review issues were discussed with the applicant prior to submission of the NDA and throughout poziotinib's development. Beginning in 2017, we informed the applicant that their plans for dose optimization were not adequate to support a registrational program. When the applicant presented their top-line data at a

pre-NDA meeting in late 2020, we requested that additional data on dose optimization be provided in the NDA but felt that the application was fillable [ph].

Given that one year elapsed between the pre-NDA meeting and submission of the NBA, our concerns were once again expressed in July 2021, and the applicant committed to providing additional data at the time of NDA submission. Our formal review began in November 2021, which has confirmed and magnified our several concerns.

According to the Code of Federal Regulations, accelerated approval may be granted to a drug that is intended to treat a life-threatening disease and has an effect on an intermediate endpoint that is reasonably likely to predict clinical benefit. Accelerated approval is available only for products that provide a meaningful therapeutic benefit over existing treatments, and further investigation of the drug to verify its clinical benefit is required.

FDA guidance interprets a meaningful

therapeutic benefit to be an improvement in efficacy and/or safety in the context of available therapy. Given the residual uncertainty associated with a drug approved under the accelerated approval pathway, for regulatory purposes, the Division of Oncology has considered available therapies to be marketed drugs with traditional or regular approval or those that are considered standard of care. FDA guidance also states that if postmarketing studies are required as part of the accelerated approval provision, it is anticipated that the confirmatory trial should be underway at the time of an accelerated approval action.

I will now review the ZENITH20 study design. ZENITH20 is an ongoing multicohort, dose-finding and activity-estimating study of poziotinib in patients with non-small cell lung cancer with EGFR or HER2 exon 20 insertion mutations. Patients enrolled in Cohort 2 provide the primary efficacy data for this application. The primary endpoint is overall response rate assessed by independent central review. Secondary endpoints included

duration of response. Data from Cohort 5 was also included in the NDA to provide supportive evidence for the adequacy of dose optimization, and included patients treated at a range of doses.

I will now describe the major risk-benefit considerations for this application. First, we assert that the efficacy of poziotinib, as demonstrated by the limited response rate with poor durability observed in the primary efficacy population, is not improved over available therapy.

For patients with non-small cell lung cancer who have received both prior platinum-based chemotherapy and an immune checkpoint inhibitor, available therapy includes docetaxel in combination with ramucirumab, with a benchmark ORR of 23 percent. Anti-PD-L1 therapies are considered available therapy if not previously received and are associated with lower ORRs with more substantial durability than what is observed with chemotherapy.

Trastuzumab deruxtecan, a HER2 targeting antibody drug conjugate, received accelerated

approval last month for the treatment of patients with HER2 mutated non-small cell lung cancer, an indication which would include the patients who comprised the primary efficacy population in this application. The drug demonstrated a response rate of 58 percent with a duration of response of 8.7 months, both considerably greater than what was observed with poziotinib. A randomized trial of trastuzumab deruxtecan to confirm its clinical benefit is well underway.

The ORR for poziotinib-treated patients in the primary efficacy population was low at 28 percent, with poor durability demonstrated by a median DOR of 5.1 months. Of the 25 responders, 24 percent had a response lasting more than 6 months. Similar results were observed in the subgroup of patients who had progressed on both prior platinum-based chemotherapy and an immune checkpoint inhibitor. Importantly, one-third of the patients did not receive prior treatment with an immune checkpoint inhibitor, which would be considered an available treatment option for these

patients.

The second key issue for discussion is the high rate of toxicity observed with poziotinib at the proposed dosage. In FDA's subsequent presentation, we will describe the highly toxic safety profile seen with the 16-milligram, once-daily dose reflected by approximately 80 percent of patients requiring treatment interruption and over half requiring dose reduction. The overall toxicity profile is driven by very high rates of diarrhea, mucositis, and rash, each occurring in over 70 percent of patients. In addition, our review details fatal events of pneumonitis observed at this dose level. It is still unclear whether alternative doses would improve the toxicity profile associated with poziotinib.

The third key issue for discussion is the inadequate optimization of the poziotinib dosage throughout the development program. You will hear from our clinical pharmacologist that the 16-milligram daily dose may not represent the

optimal regimen. The applicant studied other doses in very limited patient numbers, resulting in similar response rates with overlapping confidence intervals. Given the toxicity profile of the 16-milligram daily dose, further dose exploration is warranted.

The final key issue for discussion is the delay in confirmation of benefit. To verify the clinical benefit of poziotinib, the applicant has planned a randomized study of poziotinib 8 milligrams twice daily versus docetaxel in the second-line setting, the same population for which they are seeking accelerated approval. The primary endpoint is progression-free survival and the targeted benefit is 2.5 months.

However, despite ongoing discussions with the FDA about the need for a confirmatory trial beginning as early as 2020, enrollment was not opened until well after submission of the NDA, and no patients have been enrolled as of this month. Furthermore, the selection of poziotinib 8-milligram BID as the dosage to be tested in the

confirmatory trial is incongruent with the potential approval of a dosage of 16 milligrams once daily, and with the applicant's assertion of improved efficacy at 16 milligrams once daily. Finally, it may not be feasible for this planned study to be conducted given the recent approval of trastuzumab deruxtecan in the same space.

The risk of treatment with poziotinib at the proposed dosage must be considered in the context of its potential benefit in a rare patient population with few available therapies. FDA's risk-benefit assessment presents layers of uncertainties when the application is considered in its totality. The efficacy results from ZENITH20 are not improved over currently marketed second-line therapies. If granted accelerated approval, this would be the least effective targeted therapy for lung cancer approved to date.

In addition, there was a high rate of toxicity at the proposed dosage. The applicant failed to adequately explore various dosages throughout the development program, resulting in

disparate dosages being investigated in ZENITH20 versus the planned confirmatory trial. It is still unclear whether the 8-milligram twice daily dose is optimal.

Finally, given that the confirmatory trial is not yet under way, the risks of severe toxicities and marginal efficacy may be borne by patients for years, pending results of the randomized study.

I will now present the discussion topics and voting question for the advisory committee. We ask that the committee discuss the overall risk-benefit of poziotinib 16-milligram, once daily, given the following: its limited response rate with poor durability; high rate of toxicity; inadequate optimization of the currently proposed dose; and the delay in confirmation or refutation of benefit.

We would like the advisory committee to vote on the following question. Do the current benefits of poziotinib outweigh its risks for the treatment of patients with non-small cell lung cancer with HER2 exon 20 insertion mutations? Thank you.

DR. GARCIA: Thank you, Dr. Drezner.

Both the FDA 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 Spectrum Pharmaceuticals LLC's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with presentations from Spectrum Pharmaceuticals, Inc.

Applicant Presentation – Francois Lebel

DR. LEBEL: Good morning. Mr. Chairman, members of the committee, FDA representatives, and members of the public, I'm Francois Lebel, the executive vice president of R&D at Spectrum Pharmaceuticals. I first would like to thank you for the opportunity to share the data supporting our application for an accelerated approval of poziotinib for the treatment of patients with non-small cell lung cancer, harboring HER2 exon 20 insertion mutations. I would also like to thank patients and their families, investigators and their staff, who have supported our efforts to develop this drug and made it possible for us to be here today.

Poziotinib is an oral, irreversible, tyrosine kinase inhibitor or TKI. Patients with HER2 exon 20 insertion mutations urgently need effective and safe therapy. Our presentation today will demonstrate that poziotinib is clinically

effective and safe in a patient population who currently has no approved oral treatment options.

In early 2021, the FDA granted fast-track designation for poziotinib in our proposed indication shown here. Our clinical development program consists of 22 studies in more than 1300 patients, representing the largest data set in this rare disease. We extensively evaluated doses in seven studies at multiple dose levels, from 0.5 to 32 milligrams per day. In addition, we conducted our positive pivotal study at 16 milligrams QD.

For our presentation today, we will focus primarily on our ongoing Study 202, also known as ZENITH20, which is a global, open-label, multicohort phase 2 trial. Pivotal efficacy data comes from Cohort 2 in previously treated patients. This is the largest study ever conducted in patients with HER2 exon 20 insertion mutations. The study met its prespecified endpoint.

Supportive efficacy data in the second-line setting comes from Study 202, Cohort 5, in an

investigator initiated study conducted at MD Anderson Cancer Center. Supportive efficacy data in the first-line setting comes from Cohort 4, which also met its prespecified primary endpoint. Taken together, the clinical data supports approval of poziotinib under the accelerated approval pathway.

Our clinical program was designed in accordance with FDA guidance and meets the criteria for accelerated approval. First, non-small cell lung cancer, HER2 exon 20 insertion, is recognized as a rare and life-threatening disease. Second, poziotinib provides a meaningful advantage over available therapies with an overall response rate of 28 percent, exceeding all available therapies. Please note that as highlighted in the FDA's briefing document, trastuzumab deruxtecan is not considered available therapy.

Third, pozi [ph] demonstrated substantial evidence of efficacy in the pivotal Cohort 2, exceeding the prespecified ORR, which is likely to predict clinical benefit. And finally, a

randomized confirmatory trial, Study 301, is currently underway to confirm the clinical benefit demonstrated in this patient population, with a futility analysis in 2024.

There are four key points for discussion today. Patients need new treatment options now. Poziotinib addresses the unmet need, and the ORR exceeded available therapies and met the prespecified primary endpoint. The safety profile is typical of the TKI class with high rates of diarrhea and rash, with a low rate of permanent discontinuation. These AEs are familiar and handled routinely by the medical oncology community. In addition, poziotinib shows a low rate of fatal pneumonitis.

We must point out that extensive dosing study has already been done for this rare disease, including seven studies comprising over 404 patients. The 16-milligram QD dose met the primary endpoint with protocol allowed dose modification. Finally, the confirmatory study is actively underway with 8-milligram BID dosing, as

agreed with the FDA. We remain committed to working with the FDA if an alternate dose warrants further evaluation. A futility analysis will be conducted within two years.

With that background, let me take you through the agenda for today's presentation. Dr. John Heymach, head of Thoracic Head and Neck Medical Oncology department at MD Anderson, will present the unmet need and the mechanism of action of poziotinib. Dr. Gajanan Bhat from Spectrum will review the efficacy data.

I will then return to present our safety data, and Dr. Mark Socinski from the AdventHealth Cancer Institute will provide a clinical perspective as an experienced thoracic medical oncologist and investigator in our program. We have additional experts here with us today to help answer your questions. All external experts have been compensated for their time.

Thank you. I will now turn the presentation over to Dr. Heymach.

John?

Applicant Presentation – John Heymach

DR. HEYMACH: Well, thank you, and good morning. I'm John Heymach, and I'm professor and chair of Thoracic Head and Neck Medical Oncology at MD Anderson. Over the past two decades, I focused my career on caring for lung cancer patients, conducting clinical trials, and running a laboratory that studies new targeted therapies for HER2 mutations and other subgroups. I'm here today as a clinician and an investigator with first-hand experience using poziotinib to treat these patients with a high unmet need.

ErbB-2 exon 20 insertions are a targetable oncogenic driver, and there are therapeutic targets in non-small cell lung cancer. HER2 mutations as a whole comprise 2 to 3 percent of non-small cell lung cancer cases. Among these, the majority -- up to 86 percent or about 2300 cases per year in the U.S. -- are specifically exon 20 insertions, which is the population we're discussing today. Importantly, this is the only major tyrosine kinase subgroup for which there is no oral tyrosine kinase

inhibitor currently FDA approved. This is due to the structural challenge in developing inhibitors of this particular mutated kinase domain. I'll briefly describe the challenge in developing TKIs for these patients.

The ribbon diagram shows the crystal structure of the HER2 kinase domain. HER2 exon 20 insertions cause the P-loop of the protein, shown here in green, as well as the alpha C helix in turquoise, to be pushed inward, reducing the volume of the binding pocket and resulting in steric hindrance, making it hard for most TKIs available in the clinic to bind. For this reason, TKIs active for tumors with amplification of wild-type HER2, like neratinib or lapatinib, are not effective here. Poziotinib is able to overcome this steric hindrance largely because of two features: the small halogenated terminal group and the flexible amine linker that enables the molecule to fit into the binding pocket. Because of this structure, the molecule is able to more potently inhibit these insertions.

Here we show viability curves for the six most common HER2 exon 20 insertions. The further to the left, the greater the potency of inhibition. As you can see, poziotinib is an order of magnitude or more potent than other HER2 TKIs currently in the clinic, such as neratinib or lapatinib. All of these drugs also have some activity against wild-type EGFR, which leads to the predictable, reversible class effects, such as rash and diarrhea.

Other TKIs have been tested in the clinic for this population, and the clinical data is consistent with the preclinical observations. In the first four rows are trials that specifically tested TKIs for HER2 exon 20 insertions, and as you can see in the highlighted text, response rates are quite low, ranging from 0 to 12 percent. This really highlights that TKIs currently available in the clinic for other purposes are not effective against HER2 exon 20 insertions.

Given the lack of efficacy of the current HER2 TKIs, what are the treatment options to these

patients after first-line, platinum-doublet therapy? This data here is from the FDA briefing document. As you see, docetaxel has a low response rate and a median PFS of about 3 months. While this is not highly active, it is the most relevant standard, and for this reason has been used as the standard comparator for phase 3 studies in platinum refractory, non-small cell lung cancer patients. Docetaxel has also been combined with ramucirumab, and a narrow response rate of 23 percent was observed in a median PFS of 4.5 months. Given its toxicities and the comorbidities of the non-small cell population, ramucirumab is only used in a minority of cases.

Finally, I'll point out that trastuzumab deruxtecan received accelerated approval last month. However, as noted in the FDA briefing document, it is not considered available therapy from a regulatory standpoint because it is approved under the provisions of accelerated approval.

Now, what about immunotherapy? Checkpoint inhibitor plus platinum-doublet chemotherapy is now

the approved first-line treatment and the NCCN recommendation for patients with wild-type EGFR and ALK, including those with HER2 exon 20 insertions. Furthermore, it's worth nothing that EGFR and ALK mutant tumors -- HER2 mutant tumors like them typically are poorly responsive to checkpoint inhibitors likely due to their low PD-L1 and TMB levels.

This is illustrated by the data from the three largest cohorts reported for checkpoint inhibitor monotherapy for HER2 mutant tumors. In all three cohorts, checkpoint inhibitors provide a very short PFS, ranging from 1.9 to 3 months, and objective response rates from 7 to 8 percent when given as monotherapy. For patients who didn't receive checkpoint inhibitors in the first-line setting, this table shows the efficacy of the overall population and the HER2 mutant population, where lower response rate and median PFS were observed.

To summarize, docetaxel, and not checkpoint inhibitors, is the relevant comparator for

second-line therapy both because checkpoint inhibitors are used as first-line treatment now with platinum doublets, and because they are not effective as second-line monotherapy in this population.

I mentioned before that in addition to oral TKIs, the other targeted approach our HER2 antibody drug conjugates like trastuzumab deruxtecan. These drugs have distinct mechanisms and distinct toxicities that are relevant for selecting the most appropriate therapy. The TKIs are oral, they inhibit the kinase directly, and toxicities are predictable related to inhibiting wild-type EGFR. HER2 ADCs are intravenous in their toxicities like neutropenia are related to their chemotherapy payload.

Now, ILD/pneumonitis has been a concern with trastuzumab deruxtecan with a rate of 26 percent ILD/pneumonitis seen in the DESTINY 01 lung study, published in the New England Journal, at the 6.4-milligram per kilogram dose. After modification of the dose to 5.4 milligrams per

kilogram, and limiting patients with certain pulmonary risk factors such as history of severe COPD, asthma, pulmonary embolism, pleural effusion, pneumonectomy or pneumonitis, a rate of 12 percent was observed in the package insert, but it highlights that patients with certain pulmonary risk factors, common in lung cancer patients, may not be suitable for the drug. Resistance occurs through distinct mechanisms, which likely explains why poziotinib appears to retain its activity after HER2 ADCs.

The benefits of having mechanistically distinct drugs such as these recently has been seen with the approval of amivantamab, a bispecific antibody for EGFR exon 20 insertions, as well as mobocertinib, an oral TKI for the same population that was recently approved with an objective response rate of 28 percent.

To summarize, what is the current treatment landscape? First-line therapy typically consists of platinum doublets with or without checkpoint inhibitors, and as per NCCN recommendations, or

HER2 ADC, such as trastuzumab emtansine, there's an option, but some patients may not be suitable due to pulmonary risk factors. For these patients, the standard option would be a docetaxel regimen with the low response rates in chemotherapy associated toxicities.

Given these available options, as a clinician who treats lung cancer patients for a living, I would consider an objective response rate of 15 percent and a median PFS of greater than 4 months to be clinically meaningful in the second- or third-line setting for these patients, given the available options. With this in mind, you can see that there is an important unmet need for more effective second-line therapies after platinum doublets, particularly for patients who are not suitable for trastuzumab deruxtecan or who prefer an oral regimen. There's also a need for a third-line option after a HER2 ADC for a docetaxel regimen.

As you'll hear from Dr. Bhat, poziotinib is an effective oral treatment option with a favorable

benefit-risk profile that addresses these unmet needs. I will now turn the presentation over to Dr. Bhat.

Applicant Presentation – Gajanan Bhat

DR. BHAT: Thank you, Dr. Heymach, and good morning. I'm Gajanan Bhat, senior vice president of clinical science at Spectrum. I'm pleased to review the efficacy data that demonstrates the clinically meaningful benefit of poziotinib.

Data from Study 202 provide the primary efficacy to support poziotinib in the proposed indication. I'll focus on the pivotal Cohort 2 first, and then supportive evidence from Cohort 5. Additionally, I'll share supportive data from an investigator initiated trial at MD Anderson Cancer Center, which also investigated poziotinib in the refractory setting.

Cohort 2 was an independent study with a prespecified primary endpoint and patient population. Patients were required to have NSCLC harboring HER2 exon 20 insertion mutations and be previously treated for locally advanced or

metastatic NSCLC with at least one systemic therapy. Patients were required to have at least one target lesion per local investigator using the RECIST 1.1 criteria. All patients received poziotinib 16 milligram once daily for up to 24 months. The dose could be reduced in 2-milligram increments if necessary in the presence of toxicity.

Now let me talk about the study endpoints. The primary efficacy endpoint was the objective response rate defined as the proportion of patients with a confirmed complete response or partial response. Response assessment was based on the central radiographic review by an independent review committee.

Dr. Heymach has just summarized the literature for efficacy for the currently available therapy in second-line NSCLC HER2 mutations. Based on the literature and for the FDA discussion, and observed ORR of 30 percent, with 17 percent at the lower bound for 95 percent confidence interval, was considered to represent clinically meaningful

efficacy in this study. The ORR was evaluated in the as-treated population. Secondary endpoints included disease control rate, duration of response, and PFS.

Next, let's look at the patient disposition. A total of 90 patients were treated, and one patient was ongoing at the time of the November NDA 120-day safety data update. The primary reason for discontinuations was disease progression reported in 58 percent of the patients. Demographics and other baseline characteristics were representative of the published literature for this patient population. The mean age was 60 years old, and two-thirds of the patients were younger than 65 years. The majority of the patients were female, white, and non-smokers, with an ECOG status of 1.

Next, let's look at the prior therapy data. Patients in this study were heavily pretreated with a median of two prior lines of therapy: 39 percent of patients received at least three prior lines of systemic therapy at study entry; 68 percent had

received prior immune checkpoint inhibitors therapy; and 28 percent had received at least prior HER2 targeted therapy, including trastuzumab and T-DM1.

I will now present the summary of efficacy. Cohort 2 met the prespecified primary endpoint of ORR in the as-treated population. Based on the independent central imaging review using RECIST 1.1 criteria, the ORR was 27.8 percent, the lower bound of the 95 percent confidence interval was 18.9 percent, and that exceeded the prespecified criteria of 17 percent. This ORR demonstrates clinically meaningful efficacy compared to the reported literature of available therapies. The disease control rate was 70 percent in this study.

In this slide, a waterfall plot shows the tumor reduction due to poziotinib in Cohort 2. Poziotinib demonstrated anti-tumor activity with 74 percent experiencing tumor reduction during the treatment. This Kaplan-Meier plot shows the duration of response in the 25 responders. The median DOR from the initial response to disease

progression or death was 5.1 months. The duration of response at 6 months was 24 percent. The Kaplan-Meier plot in this slide shows the PFS. The median PFS was 5.5 months and the PFS at 6 months was 38 percent.

Here is a forest plot presenting ORR in subgroups. The vertical line in the center denotes the overall study ORR. Across patient subgroups of demographics, baseline characteristics, and other subgroups, we observed mostly similar efficacy. Now let's look at a few of these in more detail.

Poziotinib shows activity in patient subgroups regardless of prior lines of therapy. Although the study was not a statistically powerful stratified subgroup analysis, it's noteworthy that for patients who had received three or more lines of prior therapy, the ORR was higher at 37 percent and the median DOR and PFS was similar to that of the overall study.

Now, this slide shows the summary of efficacy by types of prior therapy. ORR scored generally similar between subgroups regardless of

types of prior therapy, including patients previously treated with checkpoint inhibitor or HER2 targeted therapy, except for TKIs where the ORR was 50 percent. Efficacy analysis was also performed for the 14 patients with stable brain lesions that were identified at baseline. In this subgroup, the ORR was 28.6 percent and the median DOR and PFS were 5.1 in 7.4 months, respectively, suggesting poziotinib activity in the brain.

Here we have the quality-of-life data from Cohort 2 showing a mean change from baseline in symptom scores. Note that in this analysis, the decreasing mean symptoms score reflects improvement in symptoms. Lung cancer related symptoms like cough, pain, and dyspnea all showed a trend towards improvement over time, while diarrhea wasn't initially but stabilized over time.

Let me move to the first of two supportive efficacy studies, which is Cohort 5. Cohort 5 includes 95 patients previously treated with HER2 exon 20 mutations across dosing schedules. I will now focus on the efficacy data for the

10 previously treated HER2 exon 20 patients who received 16-milligram QD.

This slide shows the Cohort 2 on the left as a reference, and Cohort 5 results are shown on the right. In Cohort 5, the ORR was 40 percent, median DOR was 6.5 months, and median PFS was 7.3 months. Although the number of patients is small, results of ORR, DOR, and PFS in 16-milligram QD is supportive of the primary efficacy from Cohort 2.

Next, I'll review the second supportive efficacy study. This was a prospective investigator-large study conducted at MD Anderson in 27 patients previously treated with a platinum-based therapy. This waterfall plot shows the best change from baseline in tumor reduction in 30 patients out of which 27 were in second line. A majority of patients showed tumor reduction consistent with the results from Cohorts 2 and 5.

Here, I am showing the overall survival data from Cohort 2 in the MD Anderson study. Cohort 2 was not designed for the OS follow-up, and there was high censoring since patients were not followed

once disease progressed. However, the median OS ranged from 15 to 17 months, which compares favorably to the historical standard in platinum refractory treated with docetaxel that range between 6 to 10 months.

In addition to the studies I just reviewed, Spectrum has also conducted a phase 2 study of poziotinib in treatment-naive patients with NSCLC HER2 exon 20 mutations. The primary endpoint of ORR in Cohort 4 provides additional poziotinib efficacy as first-line treatment in patients with HER2 exon 20 mutations. The ORR in the as-treated population by independent central review was 45 percent treated with 16-milligram QD. Median duration of response was 5.7 months and median PFS was five.6 months, and 74 percent patients achieved disease control rate.

Next, let's look at the waterfall plot. As you can see here on this slide, there was again tumor reduction in the majority of patients. In summary, in pivotal Study 202, Cohort 2, poziotinib with 16-milligram QD dose met the prespecified

primary endpoint and demonstrated clinically meaningful efficacy in heavily pretreated patients of NSCLC HER2 exon 20 insertion mutations. The efficacy was seen across all subgroups.

These results were further supported by Cohort 5, where poziotinib demonstrated consistent response observed in 16-milligram QD dosing arm. Further support comes from the MD Anderson Cancer Center study, where poziotinib demonstrated anti-tumor activity in refractory patients, supporting the finding of pivotal study in this heavily pretreated population. In Cohort 4, first-line patients who received 16-milligram QD poziotinib showed a high response rate of 45 percent, meeting the prespecified primary endpoint. In conclusion, poziotinib showed consistent and reproducible efficacy in the proposed patient population.

Thank you very much. Now I'll turn the presentation over to Dr. Lebel.

Applicant Presentation – Francois Lebel

DR. LEBEL: Thank you.

Poziotinib is a second-generation TKI, and like other drugs in this class has toxicities related to wild-type EGFR receptor, and as a result, on-target adverse events are expected. Although these AEs are typical of this class and managed by clinicians every day, one should not minimize the burden on patients. The proposed labeling will allow clinicians to inform and guide their patients on what to expect and what measures can be taken to mitigate adverse events, allowing patients to derive benefit from this drug. Let's review the data.

We studied poziotinib in more than 1336 patients in our clinical program. Our primary safety data supporting the proposed indication was Group 1 from our briefing document, which included 482 patients treated with poziotinib 16-milligram QD or 8 BID, regardless of EGFR, or HER2 receptor, or line of therapy. I should point out that in the FDA briefing book, the safety population is restricted to patients treated with 16-milligram QD, a group of 368 patients. In spite of this

difference, the safety results are similar.

Today I will present safety data from Group 1, as well as Cohort 2, which is the basis of our NDA. Cohort 2 patients were dosed with 16-milligram QD, and therefore are included in Group 1. This table shows poziotinib exposures based on dosing data recorded in patient diaries. The duration of treatment showed a large range with a median of 113 days. The relative dosed intensity was 72 percent of the planned dose to be received. Any day without a reported dosing level, or with a missing dose diary, entry was counted as a dose interruption.

Median time to first dose reduction was 36 days and first dose interruption was 16 days. The most commonly reported adverse events were generally on target in our typical class effect of second-generation TKI. The most frequent AEs included diarrhea, rash, stomatitis, and paronychia.

Adverse events were predominantly associated with either skin and subcutaneous tissue or GI

disorders. Similarly, grade 3 events were on target, with rash, diarrhea, and stomatitis occurring most often. Grade 4 adverse events were uncommon. Generally, events were manageable by following study protocol, prophylactic recommendation and management plan or site-specific institutional protocols.

Now turning to serious adverse events, as expected, serious adverse events of dyspnea and pneumonia were observed most often in these advanced lung cancer patients. Importantly, SAEs for rash and diarrhea were relatively low, occurring in 3 percent of patients or less. There were no serious events of pneumonitis or ILD in Cohort 2. Individual adverse events leading to treatment discontinuation occurred at low rates. Rash was the most common cause in 4 percent or less of patients. Treatment-related AEs leading to permanent discontinuation was 12 percent.

Pneumonitis, or ILD, of any grade was seen at a frequency of 1.1 percent in Cohort 2 and 3.3 percent in Group 1. There were 16 patients in

Group 1 who experienced an event of pneumonitis, or ILD, and most events were a set as related to poziotinib. There were 4 fatal events on pneumonitis at a rate of 0.8 percent in 3- and 16-milligram QD and one at 8-milligram BID. Importantly, there were no fatal ILD cases in Cohort 2.

We have proposed language in the warnings and precautions section of the label to address common drug-related toxicity. Based on event severity, we are recommending to whittle dose, reduce dose, or permanently discontinue. A detailed plan is outlined in the briefing document. Off-target adverse events were uncommon. There were no clinically significant abnormal ECG in Cohort 2, and no patient had QTc prolongation. There was no clinically meaningful change in cardiac parameters.

In summary, the safety profile of poziotinib is similar to second-generation EGFR TKI. The most common adverse events were on target, and included rash, diarrhea, and stomatitis. Most AEs were

reversible following study protocol and recommended measures. Importantly, pneumonitis/ILD, a potentially life-threatening adverse event, was rarely observed in the total data set; of note, our previously treated patients and population with HER2 exon 20 insertion with only one patient with grade 1 pneumonitis in Cohort 2.

Now let me briefly review the dosing rationale for 60-milligram QD. The FDA briefing document mentioned that various doses needed to be adequately explored. However, we have conducted seven studies with 404 patients, concluding that 16-milligram QD is the appropriate starting dose. Preclinical allometric scaling in mice projected 15-milligram QD as the safe and effective dose in humans.

We then explored continuous and intermittent dosing, ranging from 0.5 to 32 milligrams per day. Our phase 1 study determined the maximum tolerated dose of poziotinib to be 18 milligrams continuous daily or 24-milligram QD 2 weeks/1 week off dosing. As a result, 16-milligram QD was selected for an

investigator-led study at MD Anderson and for our pivotal trial. In addition, we conducted the randomized dose-ranging study in Cohort 5 that confirmed 16-milligram QD as the appropriate starting dose. Recently, we have communicated to the agency our willingness to consider conducting additional dose optimization post-approval.

When we look at efficacy and safety across dose in Cohort 5 for HER2 exon 20 patients only, we can see that the 16-milligram QD arm has the highest proportion of responses compared to the other dosing arms. We also investigated 10-milligram QD and 6-milligram BID dose, however, they were deemed to have lower performance.

Now let's examine the tolerance of various dosing arms. Grade 3 or higher related AEs were higher in the 16-milligram QD arm, especially the on-target side effects of rash, in line with the higher efficacy of 16-milligram QD. The proportion of patients who needed to reduce or enter other dosing was not much different across dose levels. Overall, the efficacy and safety data support

16-milligram once daily continuous dosing for poziotinib. Following extensive dose exploration in this rare patient population, 16-milligram QD is a safe and effective starting dose to address an urgent medical need in patients who need therapeutic options.

Now let me turn to our confirmatory study. The study has been initiated to confirm the clinical benefits seen in Cohort 2 as required for an accelerated approval. The study is designed to enroll 268 patients with previously treated non-small cell lung cancer harboring HER2 exon 20 mutations in up to 150 sites globally. Patients are being randomized 2 to 1 to 8 milligrams of poziotinib orally, administered twice daily, versus docetaxel. Based on data available at the time of discussion with the agency and on the evolving PFS data from Cohort 5, 8-milligram BID was chosen as the poziotinib starting dose. The primary endpoint is PFS, and the study includes a futility analysis planned for 2024.

The study was originally designed based on

the results from Cohort 2 and the stage 1 of Cohort 5 dose-ranging study. Stage 1 analysis of Cohort 5 showed 8-milligram BID had a similar efficacy and possibly better tolerance. The dose for the PMR was determined after discussion with the agency. Given the urgency to start the confirmatory trial, the agency and Spectrum decided to initiate the trial at 8-milligram BID; 16-milligram QD remains safe and effective, but the 8-milligram BID shows a trend to slightly better tolerability. We remain committed to working with the FDA to amend the protocol if necessary.

Here is the current snapshot of the study status. Spectrum has targeted 448 sites across 29 countries. A total of 97 sites have been qualified as of August '22. Based on the enrollment projection, we expect the futility analysis to be completed in 2024 and final analysis in 2026.

In our presentation today, we've addressed the key points raised by the FDA and show that the benefit of poziotinib outweighs the risk in a

patient population who currently has no approved oral treatment options. Thank you very much for your attention, and let me turn the podium to Dr. Socinski.

Mark?

Applicant Presentation – Mark Socinski

DR. SOCINSKI: Thank you, Dr. Lebel.

I'm Dr. Mark Socinski, and I'm a thoracic medical oncologist and the executive medical director of the AdventHealth Cancer Institute. I have 30 years of experience treating patients with lung cancer and was an investigator in Study 202.

Patients with lung cancer harboring HER2 exon 20 insertion mutations are in desperate need for additional treatment options, and poziotinib would be a welcomed addition for these patients. Treating these patients has become increasingly complex, and I am here to share my clinical experience.

Let me begin by sharing an example of the anti-tumor activity of poziotinib in a patient from Cohort 2. As you can see on the screening CT scan,

the patient had a liver metastases, as well as abdominal wall metastases. On the bottom row, after receiving poziotinib, there is a clear and significant reduction in measurable tumor with durability of the response lasting 9-plus months or 11 cycles. There isn't a patient in my clinic that wouldn't welcome access to a drug that would potentially induce a similar response.

Lung cancer consists of multiple molecular subgroups, some of which are harder to drug than others. Patients have benefited from having multiple targeted options available for these subgroups, especially if they are mechanistically distinct. As an example, as Dr. Heymach pointed out, amivantamab, a bispecific antibody, was approved for EGFR exon 20 insertion mutations. Shortly thereafter, mobocertinib, an oral TKI, was also approved with a 28 percent overall response rate in the pivotal study similar to poziotinib.

Likewise, for KRAS G12C mutations, in the randomized confirmatory study presented last week at ESMO, sotorasib demonstrated a 28 percent

overall response rate and a median progression-free survival of 5.6 months. Keep in mind poziotinib had an overall response rate of 28 percent in the heavily pretreated group and 45 percent in the treatment-naive group.

These are different molecular subgroups, so results shouldn't be compared to one another, but it illustrates that for hard-to-treat subgroups such as these, the response rates are not only higher than docetaxel, but also demonstrate meaningful clinical benefit.

In terms of risk, EGFR TKI adverse events have been routinely managed for well over a decade or so as part of the day-to-day supportive care carried out by our oncology nurses and oncologists in practice. We can see that poziotinib's safety profile, shown in blue, is in line with a number of these TKI agents, including the recently approved mobocertinib and dacomitinib.

Based on the data here and my clinical experience with this drug, the on-target adverse events are both predictable and manageable.

Compared to the other options of chemotherapy in HER2 ADC treatments, the lack of myelosuppression and its consequences, absence of cardiac toxicity, and a very low rate of ILD provide an option that may make it a treatment of choice in selected patients.

As I reflect on what I've heard today, these data are particularly important to me. Poziotinib showed a meaningful advantage over available therapies in the second and beyond lines of treatment. Let me remind you that there are no currently approved drugs for third-line patients who have exhausted all options, including docetaxel. Note that in this heavily pretreated setting, poziotinib showed an overall response rate of 37 percent with a median progression-free survival of 5.5 months. I believe that for these heavily pretreated patients with no other approved options, the benefit of pozi is clear. Let me illustrate this in the context of the treatment landscapes.

Earlier in the presentation, Dr. Heymach

shared the current treatment landscape, an unmet need for patients diagnosed with advanced HER2-positive exon 20 insertion disease. Patients need more options and more time. With the data that you've seen today, poziotinib would be an option at many points in the journey of the patient. This could be an option after HER2 ADC treatment, or as a second-line option in patients who prefer oral treatment, or who have pulmonary risk factors that make them not suitable for trastuzumab deruxtecan; and it even has activity after docetaxel, as demonstrated. In all of these cases, the approval of poziotinib would give my patients more options, and potentially thus more time.

In conclusion, poziotinib represents an important advance for patients with HER2 exon 20 insertion mutations. The data you've seen today demonstrated poziotinib has clear efficacy in this molecularly defined population of patients with an urgent unmet need. It has manageable safety profiles similar to a number of other currently

approved FDA EGFR TKIs. Lastly, poziotinib would fit into a number of different treatment scenarios we face in the lung cancer clinic every week, either immediately after first-line chemo or after the other subsequent lines of therapy. I would welcome poziotinib as an option for patients with this disease. Thank you.

DR. GARCIA: Thank you.

We will now proceed with the FDA presentations from Dr. Justin Malinou and Dr. Jeanne Fourie Zirkelbach.

FDA Presentation – Justin Malinou

DR. MALINOU: Good morning. I am Justin Malinou, medical oncologist at the FDA. I would like to acknowledge all the members of the multidisciplinary review team.

The applicant is seeking accelerated approval of poziotinib for the treatment of patients with previously treated advanced non-small cell lung cancer harboring HER2 exon 20 insertion mutations. As you have heard, there are several major review issues for this application. The

efficacy, as demonstrated by the low overall response rate and poor duration of response, does not represent an advantage to patients over current therapies. The safety profile for poziotinib demonstrates a high level of toxicity, requiring a large number of dose reductions and drug interruptions.

You will hear from clinical pharmacology that the applicant did not adequately justify their dose selection and prematurely moved forward with the 16-milligram daily dose. The confirmatory trial has not yet enrolled any patients, which will significantly delay confirmation or refutation of the drug's benefit.

I will describe the FDA's risk-benefit assessment based on the major review issue. The discussion and voting question for the committee will follow. The first key review issue is the limited response rate with poor durability observed in the primary efficacy population. Patients with HER2 mutated non-small cell lung cancer who progressed after first-line therapy may be treated

with either chemotherapy or docetaxel plus ramucirumab, which offers a response rate of 23 percent. Single-agent immunotherapy yields response rates of up to 20 percent, with substantial duration of response of at least 16 months. This is an option available to patients who did not receive immunotherapy in the front-line setting.

Trastuzumab deruxtecan was recently granted accelerated approval specifically for patients with HER2 mutated non-small cell lung cancer. The approval was based on single-arm data with a response rate of 58 percent and a median duration of response of over 8 months.

The demographic information for ZENITH20 is shown. We would like to highlight that roughly one-third of patients were not treated with immunotherapy prior to enrollment, therefore, immunotherapy is considered an available treatment for these patients, as discussed on the previous slide.

As you have heard, poziotinib yielded an

overall response rate of 28 percent with a lower limit of the confidence interval at 19 percent. For patients who received both platinum chemotherapy and immunotherapy, the overall response rate is unchanged. The median duration of response was 5.1 month, and of the patients that responded, only 24 percent had a durable response lasting 6 months or longer.

Poziotinib's duration of response is considerably lower than all other recent targeted therapy approvals. We do not consider these efficacy results demonstrate a meaningful benefit over currently marketed therapies. To put this in context of current therapies, this slide shows that poziotinib yields a similar response rate to docetaxel plus ramucirumab. The durability of response to poziotinib is similar to that of single-agent chemotherapy.

For the one-third of patients enrolled in the primary efficacy population who did not receive immunotherapy, single-agent pembrolizumab or nivolumab offers a modest response rate and up to

17 months of durability. Thus, the FDA asserts that the efficacy of poziotinib does not represent a clinically meaningful benefit over current therapies.

Patients experienced high rates of toxicity with poziotinib at the 16-milligram daily dose. The applicant states that the safety profile of poziotinib is similar to other drugs in class, however, in our assessment, poziotinib is more toxic than other tyrosine kinase inhibitors for lung cancer, especially at the 16-milligram dose. Eight of 10 patients experienced grade 3 to 4 adverse events. Similarly, over 80 percent of patients required a drug interruption, and almost 60 percent of patients needed a dose reduction. You will hear from Dr. Fourie Zirkelbach that these frequent treatment modifications may impact the overall efficacy of poziotinib.

The applicant states that poziotinib may provide an alternative for patients who cannot tolerate antibody drug conjugates such as trastuzumab deruxtecan, in part, due to the known

risk of pneumonitis associated with these therapies. However, there were serious pulmonary events, including severe cases of dyspnea, pneumonia, and 8 cases of pneumonitis in patients treated with poziotinib. Patients also experienced serious events of diarrhea and acute kidney injury.

In the overall 16-milligram daily population, 26 patients, or 7 percent, had fatal adverse events. Included in the 7 percent are 3 patients who died from pneumonitis. There were other fatal respiratory events, including respiratory failure and pneumonia. Given the rate of severity of pneumonitis and other pulmonary toxicity, poziotinib's safety profile does not represent an advantage over other treatment regimens.

Our FDA analyses show that the rate of fatal adverse events seen in patients who received poziotinib are 3 to 5 times higher than those seen in recently approved targeted therapies. Patients treated with poziotinib experienced high rates of rash, diarrhea, and mucositis. Almost 50 percent

of patients with rash experienced severe symptoms and required drug interruption. A quarter of patients experienced grade 3 or 4 diarrhea. Almost one-third of patients with diarrhea required drug interruption, and 1 out of 5 patients with diarrhea needed a dose reduction.

While it is known that TKIs cause both rash and diarrhea, in the next few slides I will show you how poziotinib compared to other recently approved drugs in class. For example, the incidence of rash in patients treated with poziotinib was 92 percent, substantially higher than most other approved therapies. Similarly, rates of diarrhea with poziotinib are also high relative to other targeted therapies for non-small cell lung cancer. I would like to point out that the applicant has brought up mobocertinib a few times, though this drug, although with similar ORR, had a substantially longer DOR and ongoing confirmatory trial, and did not have the dosing issue seen with poziotinib.

In multiple analyses of cancer and

therapy-associated symptoms, diarrhea has been found to be highly associated with decreased healthcare-related quality of life and with social functioning. It is important to note that according to the CTCAE grading scale, grade 2 diarrhea is defined as an increase of up to 6 stools per day over baseline, and grade 3 indicates hospitalization.

Patients with cancer often cite low-grade chronic diarrhea as having a negative impact on their quality of life. In ZENITH20, 82 percent of patients experienced grade 1 to 2 events of diarrhea, with one quarter of patients requiring hospitalization due to grade 3 to 4 diarrhea. Almost one-third of patients interrupted treatment, despite treatment interruption not being recommended in the management algorithm until grade 3 diarrhea occurred. This may indicate that lower grade diarrhea may have been considered intolerable by the patients, resulting in therapy modification.

Patient-reported outcomes, which may have

assessed patients' perception of the tolerability of the adverse events observed, were inadequately collected in ZENITH20. The applicant used fixed questionnaires to collect patient-reported quality-of-life and lung cancer symptoms in a sparse schedule, as listed on this slide. Because of the infrequent and incomplete collection of patient-reported symptoms, tolerability of poziotinib is not clear. Specifically, the severity, duration, and trajectory of notable side effects, such as diarrhea, stomatitis, and rash, were not adequately captured.

In terms of efficacy, no meaningful conclusions can be made as there was no prespecified PRO hypothesis and the majority of patients did not provide a PRO response after cycle 3 due to attrition. Overall, the applicant did not assess patient-reported outcomes in a frequent and comprehensive way to better characterize the tolerability of poziotinib.

The third key issue is the inadequate dosage optimization throughout the poziotinib development

program. You will now hear from Dr. Jeanne Fourie Zirkelbach, FDA clinical pharmacology team leader, for further discussion of this topic.

FDA Presentation – Jeanne Fourie Zirkelbach

DR. ZIRKELBACH: Good morning. I am Dr. Jeanne Fourie Zirkelbach, a clinical pharmacologist at FDA. FDA's concerns regarding dose optimization date back to 2017 when the trial was initiated. We recommended studying a lower daily dose within the efficacious range of 12 to 16 milligrams daily due to the lack of information differentiating the 16-milligrams once daily dosage from alternative dosages.

When FDA reviewed the top-line data in 2020 and 2021, we reiterated our concerns regarding efficacy, safety, dose selection, and the delay of confirmation of benefit. In an effort to accelerate the confirmatory trial, the applicant moves forward with a different dosage of 8 milligrams twice daily for their randomized trial, however, FDA continued to reiterate the need for additional data to support the proposed dosage.

Initiating the trial absent these data was at the applicant's risk.

Clinical data at the proposed dosage show that poziotinib has marginal activity with a high rate of toxicity. Limited data available are available for other dosages, and it is uncertain if alternative dosages can maintain effectiveness and improve tolerability, therefore, additional dosage optimization is still warranted. As of today, FDA's clinical pharmacology team does not have sufficient information to determine the optimal poziotinib dosage.

In a preliminary study in patients with advanced tumors, dose selection was based on a maximum tolerated dose approach. Dose escalation occurred at doses of 12, 16, 18, and 24 milligrams administered once daily. Sixteen milligrams once daily, as shown in the highlighted box, was selected as the applicant's recommended dosage. Because the patient cohorts were so small -- for example, only 3 patients were enrolled in the 12-milligram cohort -- there were very limited

safety and preliminary activity data available. These insufficient data were not adequate to identify differences in safety or activity within this dosage range. Thus, the available clinical data did not support selection of 16 milligrams once daily for the registrational trial.

The applicant's recommended dosage of 16 milligrams once daily was investigated in Cohort 2 to support the proposed indication. Based on FDA feedback, alternative dosages, including once-daily and twice-daily regimens, were later explored in Cohort 5. The evaluation of safety and effectiveness for these alternatives dosages is still ongoing.

In the next few slides, I will summarize the available data from these alternative dosages, along with the exposure-response analyses for safety and effectiveness. You are aware that the ORR of poziotinib, at 16 milligrams once daily, in the proposed patient population was 28 percent. In looking at the ORRs and the confidence intervals for the alternative dosages being investigated, the

response rates again appear similar to that of 16 milligrams once daily. The confidence intervals are wide and overlapping, presumably due to small patient numbers. Though the applicant did provide additional data at alternative dosages as requested, the patient numbers remain insufficient to make a determination regarding the optimal dosage.

Preliminary exposure-response analyses do not support a dosage of 16 milligrams once daily compared to the alternative dosages. Exposure-response relationships for efficacy are inconclusive due to the limited data at dosages other than 16 milligrams once daily. However, when we look at safety, we see that higher average concentrations are associated with a higher risk of grade 3 or higher treatment-emergent adverse events and adverse events leading to dose reduction and treatment discontinuation. Thus, while we know that higher dosages do yield greater toxicity, it is not known if alternative dosages will yield comparable efficacy to the 16-milligram daily dose.

Given the high rates of interruption and dose reduction at 16 milligrams once daily, the relative dose intensity was only about 12 milligrams per day. This means that the average patient only receives 12 milligrams once daily or 75 percent of their prescribed dose, largely due to toxicity.

The first dose interruption occurred at approximately 29 days following treatment initiation and lasted about 8 days. Given the elimination half-life of poziotinib is approximately 6 hours, no drug would be found in this systemic circulation within 2 days after withholding poziotinib. It is uncertain whether these prolonged interruptions to manage toxicity have an impact on efficacy.

Most patients enrolled in Cohort 2 received a reduced dose within the first month, as illustrated by this graph. The dark blue shaded area shows the relatively short treatment duration at the proposed dosage. The black dashed line shown here marks the 6-week point after initiation

of poziotinib.

As shown by the dark blue shaded area, at this point less than 50 percent of patients remained on 16 milligrams once daily. The black dotted line shown here marks 24 weeks, or 6 months, after initiation of poziotinib. As shown by the lighter blue and orange shaded areas at this point, most patients received dosages of 12 milligrams daily or less. The red shaded area shows the fraction of patients who did not receive poziotinib due to treatment interruption.

In FDA's review of the applicant's clinical pharmacology package, we identified significant areas of concern regarding the lack of dosage optimization. Given that the applicant has provided insufficient data over the clinically relevant dose range, we cannot determine if alternative dosages may provide acceptable efficacy and an improved toxicity profile. Therefore, we continue to assert that the applicant failed to adequately justify their proposed dosage of 16 milligrams once daily.

I will now turn your attention back to Dr. Malinou to complete FDA's presentation.

FDA Presentation – Justin Malinou

DR. MALINOU: The file review issue is a significant delay in confirmation or refutation of clinical benefit. As a reminder, in the applicant's planned confirmatory trial, patients will be randomized to either poziotinib 8 milligrams twice daily or single-agent docetaxel, with progression-free survival as the primary endpoint. They are targeting a 2.5-month PFS event benefit, which may not be clinically meaningful. The trial has not enrolled any patients as of this month, and is not slated to read out until 2026 at the earliest. Patients could be exposed to a highly toxic drug with unverified clinical benefit for at least four years.

Now let's consider this application within the framework of the FDA's risk-benefit assessment. The FDA considers the totality of evidence when making risk-benefit determinations. We recognize that this is a rare population with limited

therapeutic options, however, given the marginal ORR and limited DOR, FDA asserts that poziotinib does not represent a meaningful therapeutic benefit when compared to current therapies.

Poziotinib has a high level of toxicity with high rates of grade 3 to 4 AEs, serious AEs, fatal AEs, dose reductions, and drug interruptions. The dose proposed for marketing is not currently optimized. In addition, there are no definitive plans for alternate dose exploration beyond 8 milligrams twice daily. The selection of the 8-milligram twice daily dose for the confirmatory trial is incongruent with the approval of a 16-milligram daily dose.

Finally, initiation of the confirmatory trial is significantly delayed and places patients at undue risk. We know that accelerated approval without a confirmatory trial initiated at the time of approval requires several more years to verify or refute clinical benefit than those which already have a confirmatory trial underway. The recent approval of trastuzumab deruxtecan in the same

space may make it infeasible to conduct a proposed confirmatory trial, further delaying confirmation or refutation of benefit.

I will now present the discussion topic and voting question for the advisory committee. We ask that the committee discuss the overall risk-benefit of poziotinib 16 milligrams daily given the following: slow response rate with poor durability; high rate of toxicity; lack of dosage optimization; and significant delay in confirmation or refutation of benefit with a randomized trial.

We ask that the committee vote on the following. Do the current benefits of poziotinib outweigh its risks for the treatment of patients with non-small cell lung cancer with HER2 exon 20 insertion mutations? Thank you for your attention.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Malinou.

We will now take clarifying questions for the presenters, Spectrum Pharmaceuticals, Inc. and the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to

clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all of my questions," so we can move on to the next panel member.

Let's just go to the committee. We have heard the FDA presentation, and we have heard the applicant presentation as well, and I would like to open the group to ask the questions to specific people.

Let's start with Dr. Lieu.

DR. LIEU: Hi, everybody. This is Chris Lieu. This question is for the FDA. I just want to clarify the status of trastuzumab deruxtecan for this. It's been brought up in the presentations, and we've seen the overall response rate. But we

need to know if this is considered to be an available therapy or not, just in terms of how we view the current data.

DR. SINGH: Hi. This is Harpreet Singh, director. I will take that question.

Yes, I agree that there is a lot of discussion around trastuzumab deruxtecan, and before I answer your question directly, there is a point of clarification that a lot of the data that the sponsor cites in terms of rates of ILD and pneumonitis, they're actually citing, particularly in Dr. Heymach's presentation, toxicity data from the higher dose, the 6.4 mg/kg dose.

We did not approve that dose. We asked the company, much like we asked Spectrum, to conduct a dose-finding study comparing the 6.4 dose to a lower dose because of the toxicity we were seeing. They did do that study. We did receive the results of that study during the course of our review, and thus we approved a lower dose by 0.4 mg/kg dose, which has substantially less ILD and pneumonitis pulmonary toxicity in general and maintains a

50 percent or so -- 50 to 60 percent -- response rate.

So I'd like to make that point of clarification because I did feel that that particular toxicity information, conferring the [inaudible – audio gap] -- discussion about availability of therapies. Available is a regulatory issue, and we don't necessarily want the committee to make this too complicated.

The point is that HER2 or trastuzumab deruxtecan is clinically available to providers. Yes, it is under accelerated approval. This means that, from a regulatory standpoint, when we are comparing available therapies, we are not looking at that 60 percent response rate as the bar to beat, so to speak. However, I think this has implications in terms of the confirmatory trial, which both Dr. Drezner and Dr. Malinou point out, and how feasible is it -- will it be -- for Spectrum to conduct this confirmatory trial, given that trastuzumab is available to providers with a 60 percent response rate.

So I think that is really how this comes into play. But then back to even if you are considering it from an FDA regulatory perspective -- which we're not asking you, the committee, to do; that's our role -- we still assert that poziotinib does not represent a meaningful advantage, even if you take trastuzumab off the table.

So I hope that that answers your question, but I would like to bring in Dr. Julia Beaver if she'd like to contribute anything to that.

DR. BEAVER: Yes. Thanks. Hi. This is Julia Beaver. Exactly as Dr. Singh stated, for the regulatory purpose of available therapy as defined in our guidance, that is a therapy approved under regular or traditional approvals or set standard of care. Those are regulatory distinctions we will consider. We'd like the committee to view this from a clinical standpoint from risk-benefit, and as Dr. Singh mentioned, we want the committee to consider if the availability of HER2 will impact the feasibility to enroll patients on the

confirmatory trial.

We also note that the sponsor mentioned a number of times potential sequencing of their drug, potentially even after a trastuzumab-based ADC, which is not something that we are aware of, has been studied, so we do not feel that particular indication would be appropriate. Thank you. That is all.

DR. LIEU: That answers my question, and thank you so much.

DR. GARCIA: Thank you.

Dr. Madan, you have a question?

DR. MADAN: Yes. Hi. Ravi Madan, NCI. I have a question for the sponsor regarding the unmet need. There are assertions that trastuzumab is perhaps not available for patients with certain pulmonary conditions, and that poziotinib would be an option for those patients.

Does the sponsor have any data in those specific populations demonstrating safety and efficacy?

DR. LEBEL: Thank you for your question.

I'd like Dr. Heymach to address this question.

DR. HEYMACH: Yes. With that, I'll also bring up something that Dr. Singh had mentioned earlier. In my presentation, I mentioned the doses, both at the 6.4, originally in the DESTINY 01 study, where 26 percent was seen, and then with the dose reduction to 5.4, and this data has not been presented publicly for us to review, so we're basing it on the package insert.

For DESTINY 02, they did two things. They lowered the dose from 6.4 mg/kg to 5.4, but the eligibility also changed. So here from clinicaltrials.gov is the eligibility criteria for poziotinib versus the trastuzumab deruxtecan in this space. You can see poziotinib has a standard grade 2 pneumonitis, or high pneumonitis, exclusion, which is seen in all studies in this space. For trastuzumab deruxtecan, they said not only a history of non-infectious interstitial lung disease requiring steroids or the other things that were suspected -- ILD or pneumonitis that can't be raised out -- but they also said other conditions

that put you at pulmonary risk, including pulmonary emboli within 3 months of the study, severe asthma, severe COPD, restrictive lung disease, pleural effusion, et cetera.

Now, in our study we know 17 percent of patients had pleural effusion. As an example, we know that COPD and restrictive lung disease are common in this population, and we know that if you take the lung cancer population as a whole, 19 percent have some history of pneumonitis in the past, often restricted pneumonitis.

So the point here -- and I know this meeting isn't about trastuzumab deruxtecan, but it's to say that what they've done in DESTINY 02 is exclude a substantial number of patients that have pulmonary risk factors that are extremely common for the lung cancer population, including the 17 percent in our study that did have pleural effusion treated with poziotinib.

DR. MADAN: So just to clarify, do you have any safety or efficacy data in those 17 percent of patients?

DR. HEYMACH: We haven't broken out the 17 percent with pleural effusions. We do have data for patients treated with prior HER2-directed therapies. As was mentioned, the response rate was 24 percent, median PFS was similar to the overall population, 5 plus months, and specifically in patients that were treated with TDM-1 -- which was the HER2 ADC that was available at the time. Again, trastuzumab deruxtecan wasn't available during the poziotinib study, so there isn't the history of many patients. There were I know at least some that are on the study, but we had 6 patients treated with TDM-1. The response rate in that group was 33 percent, and you saw the response rate with prior HER2 TKI. Obviously, the study was powered for these rare subgroups, but the message was that activity was consistently seen regardless of prior immunotherapy, HER2-directed therapy, and so forth.

DR. MADAN: Okay. But just to clarify, in the unmet need discussion, the patients with these pulmonary conditions, you don't have data showing

safety or efficacy.

DR. HEYMACH: Right. One could search for that data, but I'll say that the trastuzumab deruxtecan data hasn't been reported publicly, so we don't know all the different conditions. But if --

DR. MADAN: No, I was asking about the poziotinib data.

DR. HEYMACH: Right. Yes, but we could pull out the pleural effusion subgroup, for example, to look for efficacy.

DR. MADAN: Okay.

One other question along the same lines is there's this kind of implication that an oral medication would be more accessible even though it's a novel agent that's under special approval, and it would be more accessible than an IV agent that's administered every 3 weeks, although it still requires access to probably pretty cutting-edge oncology service.

Is there any data that actually demonstrates that oral agents are more accessible to patients

than an IV agent?

DR. LEBEL: Thank you for your question. I'm going to ask Dr. Socinski to address that.

DR. SOCINSKI: Thank you. Dr. Socinski. I'm not aware of any specific data with regard to that. I can tell you in my clinical experience in the field of lung cancer, a number of the targeted agents are obviously oral agents, and it's not unusual when you have a situation where you have an oral and an IV after patients have received first-line IV therapy, that they kind of want to break from the IV experience.

So my clinical experience is that patients often very commonly do favor the oral route of administration because of the convenience. I view many of these situations as a plan for sequential therapy. So whether you do one first, the other one, that sort of thing, from a clinical point of view, we have those sorts of discussions, and patients often prefer the oral route; that's more convenient. Thank you.

DR. MADAN: I thank the sponsor for taking

time to answer my questions. That is all.

DR. GARCIA: Thank you.

Dr. Waldman, do you have a question?

DR. WALDMAN: I do. This is Scott Waldman, Thomas Jefferson University. I have two questions. The first question is for the FDA, and this plays a little bit off of Dr. Lieu's question that was asked before.

I understand that trastuzumab deruxtecan doesn't set the bar for response rates and duration of response. I understand that, but can we consider that it's part of the armamentarium that's available to the patients that we're considering here? In other words, I understand it doesn't set the bar, but is it available when we consider what's available and what gaps poziotinib might be filling? Can we consider this agent available to the patients?

DR. SINGH: Hi. This is Harpreet Singh, director. I will take that question. I understand that this particular point is causing a bit of consternation, so I will take this, and then I will

ask Dr. Richard Pazdur to please come on and maybe clarify any fine points.

I just want to make one comment on the last question about oral therapies being available and being the preferred regimen, and I want to make two points about that. Yes, certainly patients may prefer oral options, however, I would say that, first, they would not prefer an oral regimen that is inferior to what is available IV, whether we're talking about a ram [ph], docetaxel, or an IO -- or to get to this point about trastuzumab -- or trastuzumab. Secondly, the sponsor did not adequately collect patient-reported outcomes data as we highlighted, so we know that chronic daily, low-grade -- and with this drug high-grade -- toxicities like diarrhea and rash really contribute negatively to quality of life.

Back to this question about what is available, yes, you may consider trastuzumab as available to providers. It is available to you, the oncologist, in clinic, every day. And what we are asking ourselves, and you must ask yourself, is

if you were presented with a patient with this rare mutation, and you had the option of pulling this ADC off the shelf, which has two other indications that is known to providers, versus enrolling them on this confirmatory trial, which we are telling you the dose may not be optimized; and you know the toxicity; and you know the response rate; and you know that the comparator is single-agent docetaxel, what would you choose? And I think that's something we're asking the committee to consider when we think about the context of what's available to you in the clinic. Let FDA worry about the regs and the bar.

So in answer to your question, yes, I do believe you should consider this as available to you as providers because it is.

Dr. Pazdur, would you like to add any further comment to this?

DR. PAZDUR: Well, let me go through what the guidance actually says, and I was partly responsible for putting this in guidance, is that we would consider, in making a regulatory decision,

that available therapy is the approved therapies that we have, and not those under accelerated approval; so that's in FDA guidance.

I think the reason why we have brought this up, the issue of this particular drug, here again, is the issue of having a trial that has not been yet initiated, is it conceivable, really, to do this trial? I think that was one of our major points of view.

Here again, at the end of the day, if you could see our question that we're asking you to vote on, we're not asking you whether or not the drug should be approved; we're asking you at this point in the context of what is out there, does this represent basically a positive risk-benefit for patients. But in making that regulatory decision, the FDA will not consider, basically, the drug under accelerated approval as available therapy. Okay?

DR. WALDMAN: Okay. Again, Scott Waldman, and thank you for the answers. I appreciate that. I have one more question for the sponsor, Spectrum.

There's a disconnect between the dose of poziotinib that you're going after in the confirmatory study, 8 milligrams BID, and the dose that you are seeking approval on, 16 milligrams QD. It's clearly a disconnect. Can you address the disconnect? Because I didn't get it from your original presentation, how those two facts are congruent with each other. They seem incongruent to me.

DR. LEBEL: Sure. Thank you.

We believe that dose is clear. It's 16 milligrams per day given in the QD [indiscernible] or 8-millgram BID. [Inaudible - audio gaps].

DR. SINGH: Hi. I'm sorry to interrupt. This is Dr. Singh. I cannot hear you very well, and I'm getting word from my team that this is universal. I really do want to hear this response.

Could we try to work on the audio?

DR. LEBEL: We've repeated the audio has been a problem. As far as the comments from Dr. Pazdur, [inaudible] --

DR. GARCIA: Dr. Lebel, we still cannot hear you really well. You're breaking up.

(Pause.)

DR. GARCIA: Dr. Chen, do we know if he's reconnecting?

DR. SINGH: Hi, Dr. Garcia. This is She-Chia Chen. Just a moment. Let me check real quick. Thank you for all your patience.

(Pause.)

DR. GARCIA: This is Dr. Garcia. I'm looking forward to getting back to in-person meetings some time soon. This virtual technology is fairly pretty lumpy for all of us.

DR. CHEN: Okay. The sponsor should be reconnected. Thank you.

DR. LEBEL: Yes. This is Dr. Lebel. Can you hear me now? Dr. Lebel here.

DR. GARCIA: Yes. Please proceed.

DR. LEBEL: Okay. Thank you.

As I was saying -- I don't know when it broke off, so I'll start from the start.

We believe the dose is quite clear, and the

16-milligram per day is the dose that was shown to be safe and effective in Cohort 2 and was supported by two independent studies. We did the body of evidence clearly over time as it evolved, and it seems like the 8 BID would have the same activity, and potentially a slightly better adverse event profile.

So there were extensive discussions with the agency. I think there were at least five, including as late as March of this year, in terms of arriving at the final dosing for the PMR. There's an urgent need to be addressed, and also we wanted to be in compliance and initiate this study. So after many discussions, the agency and we agreed that the 8-milligram BID would be the way to go forward. I would additionally mention that in part of my formal presentation that we're certainly open to additional discussion if another dose or schedule would be identified, but we believe that patients needed that option as soon as possible.

DR. WALDMAN: This is Scott Waldman again. Can I ask a follow-on clarifying question of the

FDA, please.

DR. GARCIA: Please, go ahead, Dr. Waldman.

DR. WALDMAN: Thank you very much.

So hearing that -- this is a regulatory question -- is it the case that for an accelerated approval of a drug, if the accelerated approval is at 16 milligrams Q-day, and the confirmatory study is at 8 milligrams BID, does that confirmatory study support the accelerated approval of the original dose?

Again, I'm dealing with this incongruity, and I neither understand it from a drug development perspective, nor from a regulatory perspective. Sorry. Apologies.

DR. SINGH: This is Harpreet Singh, director. Thank you for the question. Let me just respond briefly to the sponsor because I do feel -- although Dr. Fourie Zirkelbach did state in her presentation, let me reiterate, we did not come to any formal agreement about the 8-milligram BID dose. It's very limited data, and we told the sponsor that it would be at their own risk to move

forward with this incongruent dose.

The safety ER analysis, exposure-response analysis, conducted by our clinical pharmacologist shows fairly comparable safety profiles between the 8 milligrams twice daily and the 16 milligrams once daily. I think a lot of this speaks to the sponsor kind of rushing this development program and trying to take catch-up steps, whereas the steps should have been taken slowly, and methodically, and appropriately early in development.

Basically, you're asking the question, how will FDA deal with a different dose in the confirmatory trial versus the dose which was studied? Frankly, it's a bit of uncharted territory. I don't think it's a question we need to deal with today, but certainly if the accelerated approval is granted -- if -- if then the confirmatory trial is conducted, if it is a positive study with this different dose, then we will be faced with a labeling challenge; obviously, a point of confusion for patients and providers, but I don't necessarily find this to be the most

problematic issue that we're faced with.

I don't know if that answers your question directly. I'm going to call for backup from my team, if anyone would like to add anything to that. But I don't think that's kind of the major issue about whether there's a different dose in the confirmatory trial versus the accelerated approval. It is an issue, but I think that if everything lined up, we would manage that later, where we would probably look at adding all of this information to the label and making a decision at that point with the data in hand. Right now, we cannot answer that question. We frankly do not have enough data from the 8-milligram BID dose to sanction it, so to speak, as an approvable dose moving forward.

So give me one moment, and let me --

DR. PAZDUR: Hi. This is Rick Pazdur. I just want to emphasize to you that your confusion is well warranted because what this really represents is poor drug development. Obviously, before somebody launches a large phase 3 trial,

they should have confidence in what their dose is, and the dose optimization should occur beforehand.

What would we do if the large phase 3 trial -- if it can accrue, and that's a big if -- is negative? Is it because they chose the wrong dose? We have a whole program here at the FDA on dose optimization, and this just points to one of the problems that we have here when one attempts to launch a phase 3 study without adequately looking at what the dose is and having confidence in it.

I said this before, and I'll say it again. Proceeding with a drug development program when you don't have a well-founded dose is literally building a house on quicksand here, and this is one of the problems. Your confusion regarding this point is well taken.

DR. WALDMAN: This is Scott Waldman. I appreciate the enthusiastic discussion, and I'm finished with my questions.

DR. GARCIA: Thank you, and thank you to the FDA for their answers as well.

Next will be Dr. Thomas. Do you have a question?

DR. THOMAS: Anish Thomas, NCI. Maybe just to follow up on the previous question, the other idea that I found quite a disconnect and the lack of congruence is the phase 3 study. Is the confirmatory trial really underway?

I mean, the FDA documents seem to indicate that it's much delayed, but the sponsor's discussion seems to suggest it's well under way, although patients are not enrolled. Where is that at this point? Some of the concerns were said about enrollment. Is that going to be a problem? That's one question.

DR. LEBEL: Thank you for the question. Let's bring up the slide. Yes, the study is underway. I'm sure you can appreciate, and many members of the committee would understand, that when you do a large global, randomized-controlled trial, it takes time to get things going. If you go to an average academic center, for example in the U.S., it can take as much as 6 months to get

through the various committees, and it can be in other places as long as a year.

We have a body of experience. We have done the largest collection of patients with exon 20 mutation in HER2 and others globally, and we are connected, again, with the site -- I believe there are 50 of them -- and they're very enthusiastic about getting going. We have 3 sites open right now. We're going to get close to 30 in the next few months, and we're targeting many more sites.

Different from what I have on the slide here, we actually have 107 sites qualified. We are filed in various countries. We recently got approval in Korea, where we plan to have 8 sites, and we're in various stages of activation of the trial. Our best enrolling site, if you look at the top five enrolling sites in the past, they're all coming in, and there's various process of approval at their site.

So this study is very much underway, and we acknowledge there are no patients right now, but if you look at the curve on the right, we never

expected patients at this stage, and we're on track. Clearly, we understand there's a bit of safety involved, but we've done these studies before, so we remain very optimistic, and we have good progress, and we're committed to carry out this study.

(Crosstalk.)

DR. SINGH: May I please --

DR. GARCIA: I think Dr. Pazdur has a question or a comment.

Dr. Pazdur?

DR. SINGH: Dr. Garcia, this is Harpreet Singh. May I be permitted to respond to that, or is that acceptable?

DR. GARCIA: Yes, please, Dr. Singh. Go ahead.

DR. SINGH: Very quickly, I just want to say that I think it's a great question from Dr. Thomas. While there are no patients enrolled, it takes us back to this feasibility issue of whether or not patients in the United States would be feasibly enrolled in this trial given what providers do have

in their armamentarium, which we've discussed at length. So if this study is completely off shore, so to speak, or completely done ex-U.S., this would be antithetical to the entire oncology community's statement and commitment to diversity and having a patient population that's reflective of the U.S. patient population.

I do think that this is an important point, and it's kind of an extension of this question. You hear the company talking about opening sites basically in other countries. You must ask yourself why they must do this, and if we would get any U.S. patients in this study. So I just wanted to add that small point. Thank you for allowing me.

DR. GARCIA: Thank you.

DR. LEBEL: Mr. Chairman, can I --

DR. GARCIA: Dr. Pazdur, do you have a comment?

DR. PAZDUR: Yes. The company might be happy; we're not, and let me make this real clear.

I'll refer you to an article that we just

published in the New England Journal that came out yesterday, last night, on this whole topic. It's called The On Ramps and Off Ramps of Accelerated Approval, and it has important numbers in there for you to consider, and I'll give you some of these.

The issue here is we want companies to come in and have a comprehensive discussion with us very early on regarding what their plans are for accelerated approval and what their plans are to confirm their study. FDA guidance, that has been there for more than a decade, clearly states that it is anticipated that these trials should be ongoing, and by ongoing, we mean accrual of patients to the study at the time of the accelerated approvals.

To give you an idea -- and let me quote some of the numbers out of that paper, which shows the importance of having the studies actively accruing patients -- if the confirmatory trial was ongoing at the time of the accelerated approval, which was 66 actions, the median time to conversion was 3 years. If the confirmatory trials had not been

initiated, it was 5 years. However, if you take a look at the trials that did not demonstrate or were not converted, it is very impressive that if the trials were ongoing, it's 3.8 years, however -- rather, if they were going, it was 3.8 years, and if they weren't, it was 7.3 years, so a significant delay.

The other important point is not only the delay, but can the trial be done? And this is where we have gotten into problems with accelerated approval, is that sponsors agreed to these studies, and then they come back in a year and say, "Oh, we don't have sufficient accrual," and then we're looking at alternative trial designs.

So really, the point that we want to get across is that we want early discussions on these trials and them to be ongoing, and it's really only fair to the patients because you're really putting patients significantly at risk, and you're also putting your development program at risk because many times response rates will not really project what the true benefit of the drug is, and that will

only be seen with a randomized study that looks at overall survival. In other words, these response rates may not be good correlates or surrogates for overall survival, so you could actually be abandoning drugs just looking at response rates.

But the point I want to get across is really we'd want to have these trials ongoing, and it really is to the detriment of patients not to have these trials ongoing, and this has been in the FDA guidance for many months. I will give you some additional numbers.

We took a look at this. If one takes a look at the accelerated approvals over the past three or four years, probably 85 percent of these accelerated approvals have ongoing trials. So industry has heard us loud and clear, and this trial is obviously -- or this application is not consistent with many of the current trends that we're seeing with other sponsors, including the other drug that they kept on bringing up in HER2, that had a trial that was actively improving patients. I hope that helps.

DR. GARCIA: It does. Thank you.

DR. LEBEL: Mr. Chairman, can I try to clarify two points that were made by the two last speakers?

DR. GARCIA: Yes, you can. Please identify yourself so we know who's talking.

DR. LEBEL: Yes, sure. Dr. Lebel from Spectrum. I just want to clarify -- and we're at the location of the site. The plan is to have about 20 percent of the sites in the U.S. We already have three opened in the U.S., and we anticipate those are going to open pretty fast now, within the next couple of weeks. Then separately, we're very aware to maintain ongoing countries where the practice of medicine is not identical to the U.S. of course, but very much in line so that the data can be representative when we get it.

As to the feasibility, we have two points to make. The first one is we clearly have been able to recruit the largest collection of HER2 exon 20 patients than anybody else, even though we're a small company. Then the last point is given that

there potentially is an available or approved drug in the market, [inaudible – audio gaps] -- we think actually that it may enhance recruitment in the U.S., and obviously ex-U.S., the drug is not necessarily approved, and therefore there would be no real competing group there.

Dr. Heymach, do you want to make an additional comment?

DR. HEYMACH: To give a clinical perspective on this and expand on it, just to clarify because I'm not sure this came through earlier, in the randomized phase 3, patients with prior trastuzumab deruxtecan, or trastuzumab emtansine, or any HER2-positive therapy are eligible for the confirmatory phase 3 study, and that's a really important point because I've heard this raised, this important issue about the feasibility, but actually those patients are included. So in the same way those patients are eligible for the poziotinib study, they're eligible for the confirmatory study.

The reason this is important is when we have

a brand new disease space, up until this last month, there was no clinical reason that mandated checking for HER2 mutation for patients with lung cancer. But as of this past month, now with the drug approved, this means the standard of care will be to check for HER 2 mutations, so the number of HER2 mutant patients we expect is going to dramatically rise, and many of those will be treated with prior trastuzumab deruxtecan or trastuzumab emtansine, so that we believe will increase the total number of patients eligible for the clinical study.

So given that those patients are eligible, I think this confirmatory study meets a really important unmet need for what happens after HER2 ADC, whether patients receive it or don't receive it.

If I could just make one more clinical comment -- I've heard some points raised about the size of the different studies in terms of the dose modification -- and give a clinical perspective here, this is by far the largest study ever in this

rare population. In fact, it's more than twice as large as any other study for HER2 exon 20 mutations that I'm aware of. So for studies like this, the amount of dose optimization done, I'm not aware of anything comparable. But from a clinical perspective, I think that our management would be similar with 8 BID or 16 Q-day.

I think the difference from a clinical perspective and how we manage those will be similar. Like with drugs we use like dacomitinib or afatinib, both of which the majority of patients get dose reductions in the randomized studies and in clinical use, we explain to patients that during the first 2 to 8 weeks, they'll have side effects, we expect that they commonly will need dose modifications, and then we prepare them for that, so this is not something that's unexpected.

And just to remind people, with afatinib, FDA approved -- or dacomitinib for lung cancer. The majority of patients required dose reduction, but this doesn't prevent us from using it effectively. We prepare patients for this, we dose

reduce where needed, and we're able to manage that clinically.

So from a clinical perspective, we think it's more important that patients have the ability to use the drug and let clinicians modify it, as they're used to do it, then delaying it for a while, while additional dose optimization is happening.

DR. LEBEL: Thank you.

DR. GARCIA: Thank you, Dr. Heymach, for your clinical insights.

In the interest of time, we're just going to move on. We have a few additional questions from the committee members. Next will be Mr. Pantelas.

MR. PANTELAS: Yes. Thank you. This is Jim Pantelas. I'm a patient representative, and I've got two questions for FDA.

I understand the FDA's assertion that poziotinib may not present an option over existing and available therapies, but many lung cancer patients tend to look at survivability in more of an iterative fashion. As such, I found the

proposal of using a second- and third-line treatment reflected in the applicant's slide CO-73 -- if we can put that up, that would be really helpful -- and I found that side compelling.

My first question is, can the FDA comment on this slide, including its validity and proposed used for the drug? And second, where will trastuzumab fit into this slide from the FDA's perspective?

DR. SINGH: Okay. This is Harpreet Singh. Thank you for the question. Let me just address two points that you raised.

First, you say that FDA is asserting, which we are -- correct you are in that we are asserting that poziotinib does not represent a meaningful advantage to patients over what is currently available. That is the legal requirement in the Code of Federal Regulations for accelerated approval. This is different than a regular or traditional approval in which the drug just has to be better than what it was compared to. Here, in this single-arm setting, it must be clinically

either efficacy or safety-wise, and represent an advantage to patients over what they have available. So we do not believe this to be true based on what we've shown you.

Now, your question about trastuzumab, I seriously understand how one could find this compelling, however, it is inaccurate and misleading, and I'll tell you why. Sponsors often present slides that look like this, but the applicant is proposing basically to insert poziotinib post-trastuzumab as a sequencing, as part of your regimen for patients who have this rare mutation, that poziotinib could come after trastuzumab. The fact that they're even placing it after I think is indicative that they believe that most providers would reach for that ADC first, but I digress.

So let's go back to the sequencing issue. This is not a population which they studied. This is not the indication which they are seeking. They are seeking an indication for poziotinib post one prior therapy. They are not seeking indication for

poziotinib post-trastuzumab. If they were to conduct a trial in which all patients received trastuzumab and then poziotinib, and then presented us with that data and were seeking that indication, the conversation may be different. But here you see the sponsor try to make the case for an indication they simply have not studied, and therefore we cannot consider this argument in our risk-benefit assessment.

Dr. Beaver, is there anything you'd like to add to this?

DR. BEAVER: Hi. Julia Beaver, FDA. Just to summarize the main points, for accelerated approval, the drug needs to represent improvement over available therapy for that line of therapy it was studied in. And in this case, the available therapies are clearly taking HER2 off the table -- the available therapies, docetaxel, ramucirumab, and also includes IO because not all patients in the poziotinib study presented for accelerated approval received that therapy, therefore IO is considered available therapy.

We cannot invent new indications without data demonstrating benefit in those populations, and as such, it's purely hypothetical that poziotinib would have benefits in different lines of therapy or in different sequencing. Thank you.

MR. PANTELAS: Thank you so much.

DR. GARCIA: Thank you.

We have a few minutes for a couple of questions before the break. Let's go with Dr. Harrington. And I will please remind the committee members, once you have completed your question, if you can lower your hand. That would be great.

Dr. Harrington?

DR. HARRINGTON: Thank you. I have a question and a comment. I understand the values and the weaknesses of accelerated approvals, and clearly there's some uncertainty here regarding a risk to proceed with accelerated approval. Perhaps the FDA could verify for me, if accelerated approval is not granted, can the sponsor proceed -- I believe they can -- with their phase 3

randomized trial?

DR. SINGH: This is Harpreet Singh. Yes, they may. Some think [indiscernible] this randomized trial is independent, we would hope, of whether or not accelerated approval is granted, and I will quote Dr. Pazdur here. "Accelerated approval was designed and created for the benefit of patients. They are not meant to be a financial incentive or any incentive for drug companies to rush drugs to market."

So we encourage and promote, and we sincerely hope that the sponsor aggressively pursues this randomized trial to really demonstrate if there is true benefit of this drug in a time-to-event endpoint in a randomized setting. Absolutely, yes they may. The two are independent of each other. Thank you.

DR. HARRINGTON: Thank you.

DR. GARCIA: Thank you.

I think we're going to probably have one final question if we have to get to break.

Dr. Halmos?

DR. HALMOS: Hi. It's Balazs Halmos here from Montefiore Einstein. As a thoracic oncologist, myself actually sitting in clinic, I definitely recognize the unmet needs for this patient population. Indeed, these are typically younger patients with limited, if any, benefit from immunotherapy, so that probably is not a fair comparison here, as I said before, and a very limited benefit from second-line chemotherapy. Even if we consider trastuzumab deruxtecan, I think poziotinib, a TKI, oral TKI, could thoroughly be a potentially attractive additional choice, a very different mechanism of action, and likely no cross-resistance and reported CNS activity.

I also really appreciate the tremendous effort it has taken to collect this large and unique experience in this orphan disease. I recognize that the study met its efficacy endpoint with some long-term benefits, and actually carefully read the patient testimonials submitted to the FDA, demonstrating the desire to have access to this option.

However, certainly one has to be concerned about practically each patient facing significant toxicities. As much as these are anticipated, I'm familiar as a clinician [indiscernible] of EGFR, TKI experience, and this is just a very narrow therapeutic window. There actually may be a perfect dose across the board but just not be definable.

So my questions to the sponsor are, are there actually identifiable molecular clinical features that could highlight populations with a higher chance of response benefit, and similarly any clinical or PK features that would help identify patients at higher risk for excessive toxicity, where the potentially approved dosing clearly would not be advisable or safe in order to help enhance the risk-benefit profile? And if approved, what efforts will the sponsor take to further study those critical issues in real-world patient populations, understanding that the confirmatory study will take a long time to provide results, if at all feasible, which is indeed in

question? Thank you.

DR. LEBEL: Thank you for your question.

Dr. [inaudible – audio gap].

DR. GRAY: Absolutely. This is Dr. Jhanelle Gray from Moffitt Cancer Center. I certainly understand the concerns that have been raised, and as a reminder of what was just presented by Dr. Heymach, we know in clinic that we are very familiar with taking care of patients with dose reductions, dose adjustment, and managing these toxicities.

You can see here for the second/third-generation TKIs -- and again, I'm showing data here that is in addition to what was included in the FDA data; those are the slides that were just presented -- you can see that over 50 percent of patients with afatinib were [indiscernible] treated over years and years in clinic, and have a lot of experience and familiarity with -- that these patients require a dose reduction. There are actually lower dose reductions with dacomitinib than there are with poziotinib. These

discontinuation rates across these medications are similar, and in the MD Anderson study, interestingly, only one patient required discontinuation from medications in the poziotinib study.

Another thing I want to just share with you is that as clinicians, we are also very familiar with treating toxicities. This is across rash. This is across diarrhea. We do these every day in our clinic. This is my life every day in clinic. We look at poziotinib compared to some medications like mobocertinib, with neratinib. The grade 3 or higher diarrhea rates are the same. We've been doing this already, so it's 21 to 22 percent.

When in clinic, what do I do? I set expectations with my patients. I let them know that there is a big clinical team working together in partnership with them, for them, to get this done. These patients, they have nurses. They have nurse navigators. They have my physician assistants. They have me to help them through this. And those expectations, I talk to them

what's going to happen in those first 2 to 8 weeks. I let them know that we may need to adjust doses. We may change your medication, the dosing. We may talk about your dietary changes. We may prescribe more medications to take care of these toxicities. Eventually, we'll get to a point where we're stable and we feel comfortable.

To your point about the education, I definitely want to allow the sponsor -- when these drugs post-approval, we certainly know that there's going to be management of these toxicities that are going to be outlined in the package insert. There's going to be a vast amount of education, not just to patients, but also to providers. What resonates with me when a new drug gets approved is what have I done before? Where have I seen this medication previously? And then I can say, "Okay. I know how to manage diarrhea from TKIs. This is no different."

We also know that in the setting of recent approvals, these medications, when I look at them and look at their outcome, it's very hard to think

that these medications that have similar overall responses, that I'm going to have to deny a patient access to poziotinib. We know the lung cancer burden. We recognize, as I heard on this, that access is something that's also very important, and the thought of the delaying patients access to a drug that could be potentially efficacious to them is something that is very, very challenging. And from my clinical perspective, we need this medication approved now for our patients and allow us, the clinicians, who do this every day in clinic, to manage these toxicities that we've been doing for years, over and over, and we feel comfortable doing this.

With that, I'll ask Dr. Socinski.

DR. GARCIA: I think we --

DR. SINGH: Okay. This is Dr. Singh from FDA. That was a very long response. FDA has to respond to this, to the safety. We cannot move on to efficacy until FDA responds to safety because there was some highly misleading information there. We have some backup slides that refute this

information, and also single-arm, time-to-event endpoints were shown, PFS, which we cannot consider, and were misleading, particularly for mobocertinib.

FDA, can you please pull up our backup slide? Dr. Malinou, do you have the slide number?

DR. GARCIA: Dr. Singh?

Dr. Singh, I'm going to give you a few more minutes to address those comments. In the interest of time, we're going to have to take a break because we have a pretty busy agenda after the break, but please go ahead and finish your comments.

DR. SINGH: Okay. If we can, pull the backup slides, which I'll ask Dr. Malinou to address, the slide that compares all the recent lung cancer FDA-approved targeted therapies and their efficacy. Mobocertinib keeps getting invoked. Yes, this had a similar response rate, but the duration of response was in excess of, I believe, over a year. It was quite long. Here we are. Thank you; 17 months for mobocertinib. There

was no dosing issue with mobocertinib, so we were not struggling. The safety profile was established. It was [indiscernible].

You know, the sponsor keeps talking about how they have amassed the largest database in this rare need [indiscernible]. Thus, I find it unfortunate that they have missed several opportunities and several steps along the way to optimize this dose. If they had so many patients with this mutation, they should have moved forward either, or both, to adequately optimize the dose in larger patient cohorts, rather than 3 patients per cohort, as they did, or they should have initiated randomized trials.

This is a fatal [indiscernible] flaw in this development program, and we really needed to show this data in a different way. Look at this duration of response of mobocertinib. You cannot see single-arm PFS data; it is not interpretable. So I will close with that here.

DR. GARCIA: Thank you, Dr. Singh.

In the interest of time, Dr. Rosko, I

apologize. We probably will have the ability to have an active discussion in the group after the OPH. We're going to just take a quick break. We have to come back at 11:40 for the open public hearing, so take 6 minutes, and we'll reconvene at 11:40.

(Whereupon, at 11:34 a.m., a recess was taken.)

Open Public Hearing

DR. GARCIA: We will now begin the open public hearing session.

Both the FDA 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 participation in the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in 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 for today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully

and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

We have eight speakers, so will speaker number 1 please begin by stating your name and any organization you are representing for the record.

MS. JOHNSON: Yes. Hi. Thank you for giving me time to speak. My name is Susan Johnson, and I have no financial connection to any drug company, and no one is paying me for my testimony today.

(Pause.)

DR. CHEN: This is She-Chia, the DFO. Ms. Johnson, we cannot hear you. Can you try it again, please? Thank you.

MS. JOHNSON: Oh, yes. I'm sorry.

Thank you for giving me this time to speak. My name is Susan Johnson, and I have no financial connections to any drug company, and no one is paying me for my testimony today.

(Pause.)

DR. GARCIA: Ms. Johnson, do you have any

statements? We can see your PowerPoint slides, but we don't hear you.

MS. JOHNSON: Yes. Can you hear me now?

DR. GARCIA: Yes, we can hear you now.

MS. JOHNSON: Oh, okay. Are you ready for me to speak?

DR. GARCIA: Please proceed.

MS. JOHNSON: Oh, sure. Thank you. And you heard the part I have no financial connections to any drug company?

DR. GARCIA: We did, indeed.

MS. JOHNSON: You did. Thank you.

DR. GARCIA: Thank you.

MS. JOHNSON: Okay.

My husband was a poziotinib patient for a little over 13 months, and he did so well on this drug, with an initial reduction of over 90 percent, so much so that he was able to return to work full-time at a job that he loved. He was working in a classroom with fifth grade students

This drug allowed him to do the things and to visit the places that he loved the most. He was

able to travel to places like Hawaii, Alaska, and to hike in these beautiful places. Even close to home, there was a great hike, that upon reaching the peak, you could actually view the ocean. He was determined to make it to the top soon after starting poziotinib, and he did just that. He was able to go out and have his lunch with friends and family daily. That was one of his goals once he was able to retire, and he was able to live life as normal as you can get with a stage 4 terminal cancer diagnosis.

Were there side effects? Sure. They were very minimal for him, thankfully, and as long as you work with your clinicians, they will work with you, and they'll help you to get through them. So definitely, these side effects can be managed.

Poziotinib offers a chance at a normal life style, probably similar to pre-diagnosis, and that's how we felt. For two years, we traveled out of state getting on an airplane each month, and it was nearly 23 months. To receive this drug, it was that important to us, and thankfully it later

became more easily available.

As we talked to many cancer patients and many folks that had the opportunity to try poziotinib, we would let them know that poziotinib is a targeted drug that will focus on a particular mutation. As an angel buddy and a volunteer patient navigator for exon 20 in HER2 patients, for the last five years I've had the opportunity to share our amazing poziotinib experience and let them know that poziotinib will focus on their particular mutations.

Another thing with my husband, who started out teaching students for 38 years, is he ended up a huge teacher of adults and advocating and praising poziotinib for letting him live an amazing life. Another thing that I thought was amazing was that my husband weighed 180 pounds, and he was on the full dose the entire time. At the same time, a very slight woman weighing much less, she too was on the full dose, and they were both receiving great results. So this drug was truly our miracle drug. It was a blessing to our family, and I will

forever fight for poziotinib and for those patients that can benefit from it.

So for us, poziotinib has been a lifesaver. It gave us a quality of life for my husband and allowed him to do many things, and it allowed him to see three grandchildren be born. So as I mentioned, we will forever be grateful to poziotinib. Thank you.

DR. GARCIA: Thank you, Ms. Johnson.

MS. JOHNSON: Absolutely.

DR. GARCIA: We'll now start with speaker number 2. Speaker number 2, please begin by stating your name and any organization you are representing for the record.

MR. FILIPIAK: Good morning. My name is James Filipiak, and I appreciate the opportunity to speak with you today about my experience with poziotinib. I would like to state for the record that I have no financial interest whatsoever with Spectrum Pharmaceuticals or any other, and I'm not being compensated for my time today.

I feel that I have a unique perspective as a

caregiver for many years of my wife Bobbi, who had exon 20 mutated lung cancer and was enrolled in the poziotinib trial for 18 months. Additionally, I've been the co-sponsor of the leading social media site for poziotinib patients at the HER2 exon 20 group in the Bobbi Fight Club, which has helped to navigate HER2 exon 20 patients from around the world for the last five years, with side effects, et cetera.

Having been at my wife's side 24/7 throughout her poziotinib treatment, I can conclude that not only are the side effects manageable, but a high quality of life can and was maintained throughout her 18 months on the drug. In concert with our local oncologist, local pharmacist, and dermatologist, we found that reasonably simple solutions worked to counteract the side effects.

For example, diarrhea was mostly remedied by over-the-counter medicines. Paronychia and skin rash was helped with tea tree oil, Aquaphor, and Saran wrap for a short period, and other moisturizers. Magic mouthwash with lidocaine for

mouth irritations worked well, and the occasional few days break from the drug let things calm down when necessary, and it seemed to work quite well. We've since share these remedies with other patients with similar success. Additionally, some patients found a short course of steroids help as well, although we did not require that. Lastly, a dose reduction from the initial 16 milligrams helped greatly and did not alter the effectiveness of the drug for us.

My wife and others, after some adaptations, were able to work and have excellent quality of life. What I'd like to leave you with mostly today is over the past five years, I personally know of no HER2 exon 20 patient who left the poziotinib trial because of the side effects, and I feel that with these guidelines, it's manageable, and so many have extended their lives, some up to 2 years and possibly beyond.

Sadly, after a 7-year fight, my wife did pass away, but I cannot express enough how grateful are young daughter, my wife, and I were to have

that time that poziotinib gave us. We were proud to be a part of the trial and the solutions that have helped so many. Thank you.

DR. GARCIA: Thank you.

Will speaker number 3 begin by stating your name and any organization you are representing for the record?

MS. URBANO: Thank you. My name is Maria Urbano. I live in Tampa, Florida. First of all, I wanted to thank you for allowing me to speak today and share my personal perspective as a sister who has lost her brother to HER2 exon 20 non-small cell lung cancer. I apologize for my accent since I was born in Colombia, so I ask for a little bit of patience.

Before I begin, I would like to let you know that I have no financial relationship to any drug company or its competitors. I'm here only to share my family experience, hoping that it can save at least one cancer patient.

Today is really hard to speak for me, today. Two months ago exactly, my brother passed away. He

was diagnosed with stage 4 cancer back in March. At the beginning, he had very few symptoms; actually, only one pain in his back, so it was a really complete surprise to everybody. We were shocked to know that he had metastases everywhere: brain, bone, lungs, of course.

One case, my brother was a very difficult one. His disease moved through his body extremely fast. It was made worse by the fact that he lives in Colombia. He only had access to one treatment, and that was chemotherapy, and chemotherapy failed him. He had a long [indiscernible] with a lot of complications, and passed away really quick, just months after diagnosis.

It's impossible to know if this medication, poziotinib, would have helped him, but here is what I do know. All he had access to in Colombia was a therapy, a chemotherapy, a therapy that was not targeted to his specific generic HER2 exon 20 mutation. Chemotherapy was the best and only thing he had access to, and that one therapy didn't help him.

Had Juan [ph] lived, I had hopes to take him to the Moffitt Cancer Center here in Tampa to get access to poziotinib, the trial. We like the idea of an oral therapy, a targeted therapy, a therapy for only HER2 exon 20, a target therapy that can be used as the first line of treatment, especially for patients in stage 4, I'm pretty sure that would make a difference.

I appreciate the chance to speak here today about the needs of HER2 20 patients like my brother, hoping that it can save one's life and can help somebody else in the future. Thank you.

DR. GARCIA: Thank you.

We'll move on now. Speaker number 4, please begin by stating your name and any organization you're representing for the record.

MR. BRAND: Hi. My name is Bill Brand, and I live in Redondo Beach, California. I have no financial interest in your decision today of any kind. I was diagnosed with HER2 exon 20 stage 4 lung cancer 3-and-a-half-years ago. It was discovered when out of the blue I suffered a

seizure during a flight on my way to go surfing in Mexico. I had felt fine up to that point, so it was quite shocking to wake up from what I thought was a short nap, only to have a nurse sitting next to me with an oxygen tank and a mask, telling me I had suffered a seizure.

Since then, I have survived because of numerous radiation treatments and infusion of various chemicals. My success is in HER2, which gave me 18 months of a normal life. HER2 is not FDA approved for my condition, but it is for breast cancer. There are very few treatments for HER2. All the various drugs I've been on are crap shoots. One never knows if they're going to work on you, how long if they do, or will they produce side effects that make it impossible to continue.

HER2, for me, it proved to be a huge success, but for some HER2 patients, it only works for a short time or not at all. One never knows if something's going to work until they try it, so options like poziotinib are all we have. There is no cure for us, so we jump from treatment to

treatment, knowing if it does work, it will likely stop working and another one will be required. Once we are out of options, well, that is the end for us, which it is for about 200,000 people per year in the U.S.

My next drug will likely be poziotinib. Please do whatever you can to make this readily available. While it has side effects, it is one of the most successful drugs treating HER2 exon 20, of which we have very few options; please, please, please, on behalf of patients like myself looking for the next treatment for our rare condition and those who have passed who benefited from poziotinib, which you heard about just now, but who are not here today to testify about the extra months or even years of life this drug gave them.

Please advocate for FDA approval. Thank you to James, Susan, and Mary Lee [ph] for calling in, and anyone who wants to contact me can email me at the number 1billbrand@gmail.com. That's a number 1-B-I-L-L-B-R-A-N-D@gmail.com. Thank you.

DR. GARCIA: Thank you.

Will speaker number 5 please begin by stating your name and any organization you are representing for the record?

DR. BOCKER: Hello. My name is Michael Bocker. By way of disclosure, I work in cancer drug discovery, but would like to make clear I have no financial relationship with Spectrum Pharmaceuticals.

I'm here today speaking on behalf of my mom, who was diagnosed in November 2018 with non-small cell lung cancer, HER2 exon 20 insertion. The first line of therapy was carboplatin and pemetrexed for this [indiscernible] tumor. Overall, this treatment allowed a good quality of life, however, the chemo had to be dropped 9 months later to increasing anemia [indiscernible].

Then a couple of months later, she started second-line therapy consisting of docetaxel combined with ramucirumab [indiscernible]. This treatment was not well tolerated and resulted in hospitalization after the first cycle. During this time she could not live a normal life. Further,

the treatment did not control her brain metastases. Luckily, we were already in the process of applying for early access of poziotinib as her third-line therapy, which she started 2 months later. She remained on poziotinib for the next 18 months.

The treatment with poziotinib did require dose reduction from 16 milligrams to 12 milligrams daily. In the last 6 months, my mom had to reduce the dose further to 8 milligrams daily, with occasionally 10 milligrams daily. However, during this period of time, my mom had a good quality of life. Yes, there were some side effects like broken skin and diarrhea, but in contrast to the previous lines of therapy, she was not bound to clinic-based infusions and could have a relatively normal life.

Further, the duration of stable disease for her was much longer than on any other of her previous lines of therapy. I strongly believe that the access to poziotinib allowed her to live long enough to gain access to a third/fourth-line of therapy, which is trastuzumab combined with

[indiscernible], which she's currently 13 months total so far.

I hope this accelerated approval of poziotinib, that other HER2 exon 20 non-small cell lung cancer patients get the same opportunity for a longer life. Thank you for considering my statement.

DR. GARCIA: Thank you.

Will speaker number 6 please begin by stating your name and any organization you're representing for the record?

MS. LENIZ: I have a slideshow with my presentation, if you could please start that now.

Good morning. My name is Kristen Leniz, and I'd first like to make it clear I have no conflict or financial interest in today's proceedings. All of those featured in the slideshow you see before you today have given their expressed consent to allow the use of their images as well.

My mom, Stella Martinson, has been fighting non-small cell lung cancer since 2011, and we were devastated when she received a stage 4 diagnosis in

2018. At that time, we learned of her rare exon 20 mutation and also that there were no approved drugs available. Consequently, when we learned she had qualified for the poziotinib trial, we were incredibly grateful. We did learn how to effectively manage the side effects she experienced working with her clinical team. After nearly a year on this regimen, poziotinib reduced her cancer significantly and was a critical bridge to future treatment.

As a volunteer patient advocate with the exon 20 group, I also have firsthand experience with hundreds of exon 20 patients being treated with poziotinib and other drugs, both at major research hospitals and local community cancer centers across the country. I've witnessed the challenges and the triumphs from many participating in this trial and walk with them through the day-to-day experience of what it's like to be on this regimen.

I've learned through that shared experience how the diverse range of healthcare teams are

handling side effect management and patient care. This has given me a unique opportunity to not only see the progression with dosing strategies but also how patients have been able to effectively manage the side effects of this drug with the help of their clinicians. As with many cancer drugs, the toxicities can be challenging but they are manageable. Overall, with the patients I've worked with, the side effects were similar to other TKIs in this class, and many patients have benefited greatly from this drug.

Taken since she participated in the poziotinib trial, the photos you see before you today are all gifts of time that poziotinib has given our family. Poziotinib has given my mother the ability to see her grandchildren graduate, spend countless birthdays with loved ones, celebrate holidays together, and create priceless memories we will treasure always. In short, poziotinib gave my mother an opportunity to make memories instead of just becoming one. Because of poziotinib, Mom also has a fighting chance to meet

her very first great-grandchild, Charlotte, who's due in early December.

In conclusion, based on my unique experience with my mom and many other exon 20 patients, I've seen that poziotinib is a safe, effective, and manageable drug. The meaningful benefits absolutely outweigh the manageable risks. I respectfully ask for your consideration to approve this critical drug so that other families like mine will have a chance at a better future. Thank you for your time.

DR. GARCIA: Thank you.

Will speaker number 7 please begin by stating your name and any organization you're representing for the record?

MS. MODICA: Thank you for the opportunity to speak today. My name is Mary Modica. My only relationship to this meeting is that you are talking about a drug that I take, as I have no affiliation with any company or organization.

After a long x-ray, my primary care doctor sent me for a consultation with a thoracic surgeon.

This was July 2019. I was told I had small cell, non-smoker's HER2 exon 20 lung cancer that was inoperable and incurable. Needless to say, I was devastated and dumbfounded.

From this appointment, I met with an oncologist to discuss treatment. I began with radiation and infusion, which is short of a nightmare for me. From there, I had chemotherapy and chemo maintenance. I also had a drain in my lung. Needing something more, I began to search for a trial program for something more than chemo. My biggest concern at that time was that I would not qualify for the poziotinib program, however, more than 2-and-a-half-years later, I am still on the drug and doing well. Without it, I don't think I would be here today.

In the beginning, I was always afraid I would be told I needed to come off the drug. The side effects are varied with different amounts of time and sometimes difficult. They can be a running nose, a bloody nose, eyelashes that stick together, burning and cuts in my hands, loss of

hair, and others. The two that have persisted are diarrhea and dry skin. I have learned how to manage to live with these side effects and am determined to continue with the treatment as long as possible.

My days are busy and productive. I get up and out, and amaze my family and friends with my positive attitude. I am president of an organization with over 380 members. This weekend I spent the day working at a street fair and attended a fundraiser. Yesterday, I volunteered at a charity golf outing. This is in addition to a number of doctor appointments and meetings.

I am speaking from my heart that I need this drug to continue living. I truly hope the FDA will approve it so that I and others can lead a full and productive life. Again, thank you for this opportunity.

DR. GARCIA: Thank you.

Will speaker number 8 please begin by stating your name and any organization you're representing for the record?

DR. SABARI: Hi. Good afternoon. I'm Joshua Sabari, thoracic medical oncologist at NYU Langone Health in New York. My clinical and research focuses on developing targeted therapies for patients with solid tumors, and I've been involved in the ZENITH20 study since 2018 as a co-investigator and have treated around 20 patients with poziotinib, including patients with HER2 exon 20 insertion mutant non-small cell lung cancer. It's important to note that I have no personal financial relationship to Spectrum, however, my institution, NYU Langone Health, receives funding for participation in the clinical trial. I'm speaking on behalf of myself and not my institution.

In my clinical experience, the first-line treatment options for patients with HER2 exon 20 insertion mutations remain platinum-doublet chemotherapy with response rates of about 30 percent and median progression-free survival of about 6 months.

With regards to the addition of

immunotherapy, response rates and durability of response to immunotherapy has largely been ineffective in this patient population, and of concern to me and to patients is the potential immune-related adverse events, including transaminitis, colitis, and pneumonitis, particularly in patients who go on to receive HER2-directed therapies post-immunotherapy.

As you all heard, trastuzumab deruxtecan recently received an accelerated approval, and we saw an updated data set at ESMO at the 5.4 milligrams per kilogram dose, which excluded patients with any pulmonary risk factor, and the rate of ILD or interstitial lung disease pneumonitis was about 12 percent. This is now a standard of care in my practice in the second-line setting, however, ongoing confirmatory phase 3 studies are underway.

There are patients who are not eligible for trastuzumab deruxtecan given cardiac or pulmonary comorbidities, particularly prior immune-mediated pneumonitis, as well as patients who may have poor

marrow function to trastuzumab deruxtecan and the payload is a topoisomerase 1 inhibitor, a potent and conventional chemotherapy. For those who are eligible, there's still a significant unmet need for patients who progress on trastuzumab deruxtecan, and the current standard of care includes docetaxel, which we've talked about has a response rate of sub-10 percent, and docetaxel and ramucirumab about 23 percent. I do not use single-agent checkpoint inhibitors in this population until all HER2 targeted therapies have been exhausted.

Poziotinib has toxicities, including rash and diarrhea due to EGFR and HER2 wild-type inhibition, but these toxicities are predictable and have been manageable in my clinical practice with routine follow-up. Diarrhea can be well controlled with the use of loperamide 4 milligrams twice a day, and rash has been manageable with topical emollients, topical steroids, oral antibiotics, and close dermatologic follow-up. Dose reduction and dose holds have been common, and

I've treated multiple patients with ongoing radiographic response and clinical benefit past one year, including patients with durable CNS, or central nervous system control, with patients with known brain metastases. In those patients who do not tolerate treatment, the drug is typically discontinued early.

Hence, the lower duration of response seen on the study and the side effects, including rash/diarrhea, in my experience are immediately reversible without long-term harm to our patients. There are other FDA-approved agents in the non-small cell lung cancer space, such as second-generation EGFR tyrosine kinase inhibitors like afatinib, which are commonly dose reduced in clinical practice and continue to maintain efficacy.

I agree further confirmatory dosing studies are needed, however, our patients need treatment options today and are not able to wait for 2 to 3 years for this data to be generated. Thank you for your time.

Questions to the Committee and Discussion

DR. GARCIA: Thank you.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will proceed with the questions to the committee and panel discussions. I would 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.

Question number 1 for the committee to discuss relates to NDA 215643, poziotinib, and the applicant is Spectrum Pharmaceuticals, Inc. The question is, discuss the overall risk-benefit ratio of poziotinib 16 milligrams once daily given its limited response rate with poor durability, high rate of toxicity, inadequate dosing optimization, and delayed confirmatory trial.

If there are no questions or comments concerning the wording of the question, we will now

open the question to discussion.

Let me just start with our voting committee members. It is clear that we had a pretty active and robust discussion during the clarifying questions to the FDA and also the applicant, and I'd like to actually prioritize our thoughts as a group in four sections.

One, really, is for us as a group to review and really discuss the efficacy and whether or not we as a committee feel that the efficacy we saw today, and was presented today by both groups, is better or no better in contrast with existing agents. It is clear that for us clinicians, we have to consider the HER2 antibody in that context as an existing clinical agent for us.

The second topic that I want to review is obviously talking about safety and the concerns that exist with regard to dose reduction, drug interruptions, and lastly, obviously, one of the biggest challenges that we clearly expressed as a group, which is the lack of drug optimization and the challenges that some of us see moving from

phase 1 to phase 2, and changing drastically the dose to the confirmatory phase 3 trial.

Also, to finalize our discussion, I want to actually ask this group to address how do we feel and think about the timing of the enrollment of that confirmatory trial that may actually take several years, based upon what Dr. Pazdur has discussed and based upon what the sponsor has presented today.

Please raise your hand.

Mr. Mitchell, we'll start with you.

MR. MITCHELL: Yes, Doctor. Thank you very much. First, I would like to say that I'm a little bit confused, and I would like to direct this question, kind of comment, to the FDA to help me.

The FDA appears to want us to look at poziotinib in light of real-world alternatives that are available, even if they are not yet granted full approval, which is apparently the standard for comparator treatments, in order for the FDA to grant accelerated approval. Yet, in sponsor's slide 73, which the patient representative raised,

the FDA wants us not to consider the real-world potential clinical use of poziotinib in sequence because it reflects a different indication for use than that sought by the sponsor for the accelerated approval.

It seems like the FDA wants it both ways, and I'm wondering if someone from the FDA can address that contradiction first, and then I have one other question.

DR. SINGH: Okay. This is Dr. Harpreet Singh. I'm the FDA. I will try to address it -- I [inaudible – audio gaps].

We believe that it is our regulatory purview at the FDA as regulators to deal with the regulatory confines of what is defined, technically, from a regulatory standpoint, as available therapy. In the same vein, taking that separately, we are asking the committee -- who is comprised of clinicians in clinic, as many of us are, but today we're wearing our regulator hats -- we are asking you to put on your clinical hats, which is why we seek your advice, and think

about what is available in the clinic to patients. There are layers of "uncertainty," to use the term that Dr. Drezner used, and whether or not HER2 is considered an available therapy from a regulatory standpoint is just a finer point.

Really, if you want to invoke this, you can invoke it in two ways. First, yes, we are asserting that poziotinib does not represent an advantage over even the regular approved drugs, so the drugs under traditional approval, however, we are also saying that we acknowledge and recognize, as everybody has -- and you the committee have told us on several occasions that you are not considering what we consider as available therapy from a regulatory standpoint; you consider what you are confronted with in clinic. And therefore, yes, HER2 is available to you and, yes, it likely will have a great impact on whether or not this confirmatory trial can be enrolled.

So I hope that it's not confusing. I see how it can be. We're not asking you to play both sides of the coin here. We're asking that you let

us make the regulatory decisions. We're asking you, in the face of this available therapy with a 16 percent response rate that is clinically available, how does that play into all these layers of uncertainty; and for this point, the uncertainty of whether or not the confirmatory trial can be reliably conducted?

Dr. Pazdur or Dr. Beaver, did you want to accentuate any of those points?

(Crosstalk.)

DR. PAZDUR: There is still much confusion about it. Let's -- go ahead.

DR. BEAVER: Go ahead, Rick.

DR. PAZDUR: I think just to make this simpler, let's take the monoclonal antibody off the table here, but give us your opinion both ways, basically, with it and without it, so to speak. But for making the regulatory decision, we would not consider this available therapy. So if that simplifies your discussion of this, considerate it that way because that's the way we are going to make it.

The other point I want to make very clearly is in the voting question, we are not asking you whether this drug should be approved or not. We are asking you for your consideration of the risk-benefit, and there are many things that come into play here, so to speak. So if it makes everybody's life simpler here, we will, when we make this regulatory decision, be looking at what is available, and the availability in HER2 drug is not going to be considered here in making that issue of comparing the two in HER2. But here again, there are many other issues here.

Is that helpful to you, Mr. Mitchell.

MR. MITCHELL: Yes, Dr. Pazdur. Let me just take it one step further.

We want to look at the overall risk-benefit based on what we know today. I understand the difficulty in enrolling the confirmatory trial given this other treatment, and it may take longer. On the other hand, if I'm looking at slide 73, maybe people would get the other drug first, and then enroll in the confirmatory trial. And by the

way, I'm a big believer in timely, quick, not delayed confirmatory trials, and the fact that not one patient is enrolled is a problem. But if we're looking at the overall risk-benefit based on what we know today, that's all we have. We don't have a confirmatory trial.

So what it feels like to me is, when I do whatever I will do in this discussion, I have to look at it based on what we know today. The delayed confirmatory trial is a problem, but it isn't going to help with overall risk-benefit, for me.

DR. GARCIA: Okay. Thank you both.

DR. BEAVER: Hi. This is Julia Beaver. Can I just add very quickly another related point? We are asking the committee for a risk-benefit discussion for the studied indication with the data that we have; not as a potential sequencing agent, not as an agent to have available. We're asking you really to discuss the studied indication and the data that we have today --

MR. MITCHELL: Only the study that --

(Crosstalk.)

DR. BEAVER: -- as we have said. Thank you.

MR. MITCHELL: Only the study that's [indiscernible], period.

DR. GARCIA: Correct, Mr. Mitchell.

Dr. Kraus?

DR. KRAUS: Yes. Hi. Albert Kraus, industry representative. I think those clarifications/discussions that Dr. Mitchell drove are very helpful. I'd like to add an additional point, and this often is a point of industry concern, broadly. It's around assumptions within a question.

There are a number of adjectives here that members should judge a bit for themselves because there is alternate interpretation from FDA versus the industry presentation we saw. Words like "poor durability" as opposed to what the durability is, it's a relative concept; "high rate of toxicity," again, a relative concept; "inadequate dose optimization," it's a relative concept; and "delayed confirmatory trial." I'll leave

confirmatory trial off the table because I think Dr. Mitchell emphasized it's a problem, but it's a little separate than today's benefit-risk, but it is an issue.

But I would say for ODAC discussion, I think it's important that ODAC members themselves assess their sense of that data when they're coming to risk-benefit rather than of a bit directional leading of the question for discussion, but I think the discussion topics are excellent. Thank you.

DR. GARCIA: Thank you, Dr. Kraus.

Dr. Madan?

DR. MADAN: Yes. Ravi Madan, NCI. I think one point that's worth highlighting here is a little bit, in my opinion, the disconnect between the response rate and the durability of response. Generally, it looks like poziotinib maybe has a similar response to other agents, but a much shorter clinical benefit or duration of response period; and often we see that in the clinic because of toxicity because the patients can't tolerate the drug after initial clinical benefit, and it either

has to be reduced to a dose where it loses its efficacy or isn't as effective.

I think that's an interesting point to make when you're looking at this question, and I think that factors into my opinion quite a bit.

DR. GARCIA: Thank you, Dr. Madan.

I just have a comment also related to that. I think the notion that an applicant or a company develops an agent, and leaves the -- if indeed the agent gets to the market -- management of that agent to the discretion of a clinician, although I do understand the ability that I have as a clinical person to adjust up or down the dosing, I really think that today, at least for me, the drug development of these agents clearly stresses the importance and the need for us, when we're thinking of drug development, for a major redo of how we develop agents from the traditional phase 1, phase 2, and phase 3.

Because it is clear that when you look at the data, you look at actually optimization of therapy, drug discontinuation, time to dose

reduction within 29 days, the time that it takes patients to get back on therapy at a lower dose of around 9 days or so, or 8-and-a-half days, the half-life of the agent, it is pretty predictable, then, that data we applied, that a significant proportion of our patients getting this agent -- which I'm not disputing the decision -- appears to have some efficacy; there's no doubt in my opinion based upon the data that I have reviewed.

But my concerns are how the agent got developed; how the dose got picked; and more important than that, it is predictable, based upon the data that we saw, that a significant proportion of those patients do not get adequate dose, meaning that they get therapy, but maybe they're not getting the appropriate dose for their disease. So it's something that I think we all have to also think as we get to voting today.

Dr. Halmos, do you have a question or a comment?

DR. HALMOS: Hi. Balazs Halmos. I have

more of a comment than a question just to render discussion. Clearly, if you think about to a physician, poziotinib here, there are a number of concerns in terms of limited efficacy, limited durability, and high toxicity. It's certainly a very, very complex development task and somewhat poorly defined dosing, but it's hard not to see that it's clearly beneficial for some patients, and in fact for some people long term.

It really seems to be desired by patients, and I want to highlight the comments from a major patient advocacy group, the exon 20 group that represents truly hundreds of patients with this disease. Also, it has a very well anticipated and well known AE profile, so indeed they've had 20 years of experience with the class of agents as to how to optimize dosing for the individual, not for the cohort. In terms of efficacy, the profile is not too dissimilar from recently approved drugs, as highlighted, the reasonable dose-adjustment options.

So if I put my clinical hat on and I don't

have another one in the way, yes indeed, I think I would feel comfortable offering this to a patient, if approved, and I think some or many of our patients could potentially benefit from it. So I do feel that the overall benefit profile, based on that, is acceptable.

DR. GARCIA: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu from University of Colorado. I'm going to tag along to Dr. Halmos' point, and a question to the FDA.

The way this question is framed in terms of the vote, I need to know if the FDA wants us to consider this in a complete vacuum. When we think about the current benefits and the risks for a patient population that really has limited treatment options, I agree with Dr. Halmos in terms of there aren't a ton of options here, and there is a response rate, even if the durability of response is quite short. And in regards to the toxicity and risks, I think as oncologists, we have pretty good experience modifying doses of TKIs and certainly

have a lot of experience with this as well.

But my issue with the question is, really, how much can we look at this question in a complete vacuum in the setting of other agents that are available? I think that actually influences the vote. If we just take it at face value, to me, the answer is fairly clear, but if we look at the bigger picture, which is what I would like to do, then I think that influences the vote significantly.

So I guess that is a real question to the FDA of how much of a straight, in a vacuum, do you want this answered by the committee, because I think it's hard to ignore the landscape, the current treatment landscape.

DR. SINGH: Okay. This is Dr. Singh, Harpreet Singh from FDA. We do not live in a vacuum; we live in the real world. And when we bring things to ODAC, to you our esteemed committee, we do ask you to consider these questions we're asking you in the context of the world you live in; and in that world you live in,

you have the available FDA-approved therapy in your tool bag, and you also have the therapies under accelerated approval.

I know this is a point of confusion for the committee but, yes, you must consider what is out there in the real world, particularly when you're talking about the uncertainties, and being able to confirm or refute benefit is a total package here. We're not asking you if poziotinib is efficacious and if you can manage the toxicities. We know it's a TKI, but I think we've shown you it is not comparable to other therapies. In fact, Dr. Malinou accurately stated -- and this is based on data -- if approved, this would be the lowest, least efficacious, most toxic TKI on the market; that all the numbers stand up to that. That is a numerical, factual piece of information for you.

Yes, you must consider the entire landscape given all the several questions that we're asking you. I hope that answers your question, but I'll open it up to my team for a few moments if they wanted to add.

(No response.)

DR. SINGH: Okay. I'm hearing nothing from my team, so thank you for the question.

DR. LIEU: Yes. I appreciate it, and I have no further questions or comments.

DR. GARCIA: Thanks, Dr. Lieu and Dr. Singh.

Dr. Rosko?

DR. ROSKO: Hi there. Ashley Rosko. One of the concerns I have about the dosing schedule is that it didn't seem like it served the majority of patients. One of the misses [indiscernible] from the applicant, they provided health-related, quality-of-life data for patients that was largely incomplete, really, to get a better sense of what the patient experience was.

One thing, I think oncologists are very familiar with managing rash and diarrhea, and an oral option is appealing for patients. Whether that increases access or not, I do think patients at times would prefer that. But what wasn't clear to me is that is there something where if there's an oral agent, that patients have to come in weekly

for fluid food resuscitation, and patients are coming in with this grade 3 toxicities?

That wasn't abundantly clear; because if you're going to offer something and have typical TKI management, or alternatively you're bringing patients in much more regularly, impairing their health-related, quality-of-life, that wasn't clear to me, and I'm not sure if the applicant has that data regarding increase of frequency to the clinic or what the management was beyond typical management for diarrhea related to TKIs. So that's just something that was looming in my mind as we're discussing this.

I also do want to lean on that point that they did enroll patients with CNS mets [ph], which I think is also an important part of the discussion, and can you assure that an agent is available to be able to address that as well; so more comments than anything else, and those are things that were weighing on my decision.

DR. GARCIA: Thank you, Dr. Rosko.

I think when you think of that as well, and

for us as committee members, there's no doubt that patient convenience is critical when we're thinking of patient care, and oral agents may actually have the perception of easy administration, as you're describing, Dr. Rosko, compared to IV agents. But at the end of the day, I think most of us, from the patient perspective and/or from the physician perspective, will likely pick an agent that has the most activity and the least side-effect profile over the route of administration, and I think that's something that I think is important to stress as well.

Dr. Madan, do you have an additional comment?

DR. MADAN: I just want to follow up what you said and what Dr. Rosko said. It's a good point. The benefits of an oral agent are you're not in the doctor's office, but if the toxicities required dose reduction within a month, you're back in the doctor's office pretty quick, so that I think is a great point.

The only other thing I'll say is, from a

committee standpoint, this whole should we consider the other option as an accelerated approval, as an acceptable alternative or not, from my perspective, it's hard for me to say. While the other agent has accelerated approval, so I can't guarantee my patient will get that, but if this gets accelerated approval, it will be good to have that option, I think they're both kind of in the same category, best case scenario.

That keeps coming up amongst the committee. I think they'll be equally, equivalently available. I don't think we would say one would be more available than the other in this circumstance if this agent got accelerated approval as well, at least that's my perspective. I don't know if that helps the committee or not.

DR. GARCIA: Thank you, Ravi.

Dr. Thomas?

DR. THOMAS: Hi. Anish Thomas, NCI. This comment is in line with an earlier comment that Dr. Halmos brought up. There's a lot of discussion in terms of dose optimization, but I would like to

see maybe -- I know it's a difficult-to-enroll population, very rare and so forth, but are there any patient variables that predict benefit? I mean, this is a unique population and not too many of those patients, but from this drug's experience with the EGFR setting, it seems that the sensitivity to poziotinib is highly dependent on where the mutation is located.

There are some mutations where the drug is highly active, so up to 45 percent versus no activity. Even within the same EGFR exon 20 insertion, a different mutation results in very low activity. Again, you're sort of dissecting an already small population, but that might really influence the risk-benefit.

I know that earlier there was a question, but I didn't hear any direct responses to that question. But again, not relevant to this discussion, I think it would be really helpful if early in the drug development process, we focus on -- in addition or probably more so than dose optimization -- what are the patient variables that

might influence the efficacy.

DR. GARCIA: Thank you, Dr. Thomas.

I'm perhaps curious to hear other committee members comment on how do we all feel about the potential delay of that phase 3 trial, meaning having an agent out there for several years without having a real clear understanding as to what is the optimal dose for our patients, and maybe actually, as we reviewed earlier, the potential of having also an antibody drug conjugate that may actually also pan out to be effective for the same patient population, obviously recognizing that the confirmatory trial that the applicant has put forward may allow patients to get the TKI after HER2 therapy. Any thoughts or any comments on that?

Dr. Thomas?

(No response.)

DR. GARCIA: Dr. Scilla, do you have any comments?

DR. SCILLA: Yes. I was going to say I do think that that's a concern. Ideally, we would

have already had patients well enrolled in the confirmatory study, and I know we've been having a lot of discussion about the side-effect profile of the medication, and the overall response rate, and duration of response. We're potentially exposing patients to potential risk and toxicity for a long period of time before we have any of these confirmatory trials. And being that the confirmatory trial is going to be at a different dose than what has been studied in the majority of patients previously, I think there are a lot of questions about what this means for our patients, and we probably won't have those answers for quite some time.

DR. GARCIA: Thank you.

Dr. Harrington, do you have a comment or a question?

DR. HARRINGTON: I do. Thank you, and it is about the confirmatory trial.

ODAC has been asked to make a decision at this point in time about the accelerated approval, and so we can only make a prediction about the rate

at which the confirmatory trial will enroll. But if we lift that barrier for a second that we have at this point in time, it should be known relatively soon how well that confirmatory trial will enroll. In fact, if it goes reasonably well, it would be one route of access for the agent to patients who have this particular mutation.

So I would urge the sponsor and the FDA, as I said before, to focus on that confirmatory trial to get that done as quickly as possible, and the FDA and the sponsor will soon learn whether that is a feasible trial or not. But I don't think it will take six years to find that out. Thanks. That's all I have on that.

DR. GARCIA: Thank you.

Dr. Kunz?

DR. KUNZ: Hi, everyone. I just wanted to also comment on the question that was just posed around the timing of the confirmatory trial. I also agree and am concerned about not knowing the appropriate dosage and about delays and enrolling patients. I agree that it may perhaps end quickly

than the six-year time frame, but I think given that we don't have that information or have a trial that's currently enrolling, that certainly weighs into my decision, and I have some concerns about that.

DR. GARCIA: Thank you.

Dr. Waldman?

DR. WALDMAN: Yes. I'm going to sort of pile on here a little bit. I think the importance of the confirmatory trial is amplified by the FDA statements that this agent, if it gets approved, is going to be one of the most toxic of the TKIs for the indication that gets approved. I think that really showcases how important the confirmatory trial is, and that confirmatory trial is going to be at least two years out from, if I understand correctly, the first evaluation. It will take two years to get to a first evaluation from the start of enrollment. That's a ways off to put patients at risk.

The other thing that I'll come back to that we heard just a minute ago was it's not clear what

the right dose is, and therefore using a dose in this confirmatory trial that is not the dose that's being asked to be approved, and that's problematic. It communicates a lack of confidence in the dose that's up for approval. That's a problem. I'll finish here.

DR. GARCIA: Thank you, Dr. Waldman.

Are they any other comments from committee members?

Dr. Kraus?

DR. KRAUS: Yes. Thank you. Albert Kraus, industry representative.

I just have commentary. As someone who has some 30-plus years experience in drug discovery and development, dose selection/ dose optimization is a very tricky business and very difficult. And it's true that we can do better, and we should do better, particularly in oncology where a lot of the doses in many drugs I've worked through discovery, development, and approval, had subsequent dose adjustments for a variety reasons, being misled by pharmacodynamic markers because you did a bunch of

work but then you found more things out later, et cetera, et cetera. So certainly, we need to do robust dose-schedule finding, and I think obviously FDA is emphasizing that, and I think it's the right thing.

That said, I just want to give a commentary that in my estimation you can always declare dose schedule as being inadequate in a sense because it's a totality argument with all sorts of data pieces. You never have the perfect clinical data. Often a dose is focused on maybe more than schedule, so it is a tricky, tricky business and difficult business, and determination of adequacy is tough. It's certainly true that if there's a lot of toxicity, it becomes even more imperative, and it's also true that many, many drugs are well used, delivering great patient benefits with very significant dose treatment holiday and dose reduction schema.

So I just wanted to, from a drug development perspective, lay that out, which many may know, but some may not, given the point of inadequate dose

optimization on the table, and emphasize, remember, this is a rare orphan disease. It's not just orphan, but there aren't a lot of patients to do a lot of work on. You can always look back and say we could have done different things; the old hindsight's 20/20. But that said, this company has done a fair bit of work, let's just say. So anyways, I'll stop there. Thank you.

DR. GARCIA: Thank you, Dr. Kraus.

Mr. Mitchell, do you have a comment?

MR. MITCHELL: Yes, Doctor. First, I want to clarify -- and I have to do this periodically during these meetings -- I'm not a doctor. I'm the consumer rep, and I'm a multiple myeloma patient.

I want to go back to this issue of whether oral is superior to infused for a minute, and just state that I think that's really a subjective kind of issue for the patient. It turns out that of the four drugs I'm on, the two oral drugs take a much greater toll on me right now than the infused drugs, which I tolerate just fine. I think that someone said earlier that what a patient is looking

for is the drug that works best with these toxicities, and right now that would be my infused drugs; the oral drugs are tough.

Second, if you believe in financial toxicity in cancer treatments, oral drugs can frequently be burdensome, as you all know, because I can buy a supplement policy that covers Part B completely, but I'm on Medicare; I can't buy a supplement to absorb the cost of my oral Part D drugs. So I'm just saying that when someone puts forward, kind of blithely, isn't oral better than infused, I don't think that that's always the case. It's subjective and it's specific to given patients. I would offer that as a consumer and a patient.

DR. GARCIA: Thank you, Mr. Mitchell, for that helpful comment.

Perhaps if I can summarize some of our points that we have discussed and comment on, I think when you look at the activity, I think most of us do feel that this agent does have efficacy, at least for some patients. And certainly based upon the treatment sequences that we have right

now, from front-, to second-, to third-line therapy, then an agent like poziotinib would have, in fact, a role through the natural history of non-small cell lung cancer, specifically HER2 mutations.

It doesn't appear that the committee is too worried about side effects. It seems that we all feel quite comfortable for many years now treating toxicities from AES, and it does appear that the group feels comfortable with dose titration, if you allow me to express it like that, perhaps because it's similar to many of the agents that we have used over the last two decades or so.

We agree that efficacy and side effects probably would be far more important than the route of administration for the vast majority of our patients. We also talked about dose optimization, and it is clear and consistent that we all think that the dosing and the dose escalation schema, how this agent got developed, is spotty at best, and we still don't know the ideal dose or the optimal dose with regards to efficacy and also side effects.

Looking at the confirmatory trial, I think we all -- at least most of us -- agree that it is critical for the sustainability of an agent such as this. There are concerns about the timing of the trial and certainly significant concerns as to how one goes from 16-milligram QD dosing to a confirmatory trial with an absolute different dose of 8 milligrams BID without having clear and consistent data from the phase 1-2, suggesting perhaps, as someone described, a lack of confidence in the dose selection, and perhaps, obviously, implying the potential risk that patients may embark on if we have to wait three to five years for that trial to be [inaudible – coughing].

Are there any questions or any final thoughts before we move on to question number 2?

(No response.)

DR. GARCIA: If there is no further discussion on this question, we'll now begin the next question.

We will now move on to question number 2, which is a voting question. Dr. She-Chia Chen will

provide the instruction for the voting. I will read the question, or perhaps, Dr. Chen, if you can just proceed with the instructions before.

DR. CHEN: Yes. Thank you, Dr. Garcia.

Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

Are there any questions about the voting process before we begin?

(No response.)

DR. CHEN: Over to you, Dr. Garcia.

DR. GARCIA: I will now read the question for us to vote, and the question reads, do the current benefits of poziotinib outweigh its risks for the treatment of patients with non-small cell lung cancer with HER2 exon 20 insertion mutations?

Are there any questions about the wording of this question?

(No response.)

DR. GARCIA: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question number 2.

DR. CHEN: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. CHEN: The voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. CHEN: The voting has closed and is now complete. The vote results are displayed. I will read the vote totals into the record: 4 yeses; 9 noes; and zero abstentions.

The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state a reason why you voted as you did, if you want to. Thank you.

DR. GARCIA: Thank you, Dr. Chen.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish to.

We'll start with Dr. Thomas.

DR. THOMAS: Anish Thomas, NCI. It's definitely an unmet need for a subgroup that was probably first identified probably more than a decade ago now. The drug poziotinib seems to be active, and there are patients who definitely benefit from this agent. But for the overall population of HER2 exon 20 insertion patients, and in the specific setting where this accelerated approval is sought, there are several open questions, so it's hard to make a case, although as an oncologist I would love to see more options for these patients.

The big advantage seems to be that it is an oral administration or available therapies, but it is somewhat offset by toxicities, as well as uncertainties around the dose itself. While I recognize that this is a rare patient population

and that the dose and schedule is not always straightforward, I feel like it needs to be looked at, and it has not been so far in its extended development course, and I think that could benefit the patients in the long run. I also feel like given the low therapeutic index, that better predictors of response to this should be sought. Thank you.

DR. GARCIA: Thank you.

Dr. Sung?

DR. SUNG: Anthony Sung, Duke University. I voted no for many of the same reasons as Dr. Thomas just outlined. I think part of it comes down to me; if I have a patient before me and I could give them trastuzumab or I could give them poziotinib, I would probably give them trastuzumab. There may be a role for poziotinib in patients who failed trastuzumab, but the data's not there yet, and there are a number of concerns around the drug that have already been highlighted such as around the dosing and the confirmatory trial, and I think just currently it's not there yet.

DR. GARCIA: Thank you.

Dr. Rosko?

DR. ROSKO: This is Ashley Rosko, Ohio State. I found the patient and the caregiver statements incredibly persuasive. I believe the dosing schedule may not serve many of the patients, but it does serve a population of the patient population. I understand that there are dose reductions for the patient population and that oncologists are familiar with TK management of toxicities. That being said, I recognize that this patient population requires additional therapy, and there's much to be explored in this area.

DR. GARCIA: Thank you.

Dr. Halmos?

DR. HALMOS: I'm Balazs Halmos. I voted yes. I believe the [indiscernible] of poziotinib has a very narrow therapeutic index. It could fill a niche, and the treatment continues for patients with ErbB-2 mutated non-small cell lung cancer. The expertise we've gained over the last two decades could be supported appropriately despite

its adverse event profile.

DR. GARCIA: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu, University of Colorado. I voted no. To look at the fact that accelerated approval requires meaningful benefit over existing therapies, while I have no doubt that poziotinib has efficacy as well as toxicity that can be managed, I think the issue here is twofold.

One is, is the agent potentially more efficacious than trastuzumab deruxtecan? We don't have evidence to suggest that. Two, could poziotinib be sequenced in a way to salvage patients that have progressed on trastuzumab deruxtecan? We, unfortunately, don't know that answer. Of course, my hope is that the answer is yes; that the current phase 3 study will answer that question and increase options for this patient population that really needs more treatment options. That concludes my statement.

DR. GARCIA: Thank you.

Dr. Harrington?

DR. HARRINGTON: Thank you. David Harrington, Dana-Farber Cancer Institute. I voted no. I agree with the reasons that others have stated for a no vote. I also think that statistically there is just not sufficiently a strong signal to justify giving this accelerated approval and exposing patients to this while the definitive phase 3 trial at a different dose will be in the field. So I think it would be premature to give this one accelerated approval.

DR. GARCIA: Thank you.

Mr. Mitchell?

MR. MITCHELL: I voted yes, and I'll start by saying that it was very clear that we're not supposed to vote on whether to give accelerated approval but whether we deemed the benefits to outweigh the risks, which I do. The drug clearly has efficacy for some patients who are in real need of additional options. The toxicities, I think from all the clinicians we heard from, are manageable. Dose reductions are so common based on what I think I know. That doesn't worry me.

Overall, this drug belongs in the armamentarium of those clinicians who are trying to treat these patients that lack sufficient numbers of options. The challenges of the confirmatory trial are important and didn't overcome my overall sense that, yes, the benefits outweigh the risks.

DR. GARCIA: Thank you, Mr. Mitchell.

Mr. Pantelas?

MR. PANTELAS: I'm Jim Pantelas, patient representative. I voted yes. I think that the drug has meaningful benefits and that most of the risks are manageable, and it's a population much in need of options. Thank you.

DR. GARCIA: Thank you.

Jorge Garcia. I voted no. I think that I echo the sentiments from everybody else who voted no. I think that there is no doubt, based upon the data that we have, that this agent has, or may have, a role in the natural history of this disease. I just fundamentally believe that the way that this agent got developed -- the dose finding studies and the drug optimization, which is not

ideal -- I'm just afraid that we don't have the ideal dose for that ideal or from patient population, so I voted against it.

Certainly, I believe the confirmatory trial needs to be maybe not redesigned, but certainly it needs to be looked at better. We don't want to have an ex-U.S. patient population that may complicate the interpretation of that data if, in fact, the bulk of the patients in the United States are going to be getting HER2-based therapies.

Dr. Scilla?

DR. SCILLA: Hi. Katherine Scilla. I voted no. I think my reasons are similar to what others have already mentioned. I definitely feel that there is an unmet need for this patient population, and we have heard about the efficacy and the potential ways to improve tolerability. But for me, the main issues are I'm not sure that this represents a meaningful therapeutic benefit over other agents that we have, as we've heard about, and I have concerns about the dosage and whether that's the most appropriate dose, and the fact that

we're probably not going to have answers about a confirmatory trial for many years. Thank you.

DR. GARCIA: Thank you.

Dr. Kunz?

DR. KUNZ: Thank you. This is Dr. Pamela Kunz, and I voted no. I agree with comments made. The main reasons for my vote were that I had concerns about efficacy over existing treatments, and I also have concerns about dose finding and finding the appropriate dose. Thank you.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: Hi. Ravi Madan, NCI. I voted no, and this is in the context of an existent therapy with trastuzumab that is available for this population. I view the poziotinib data has very compelling preliminary evidence that I look to find confirmation in future trials. I think we discussed a lot of interesting hypotheses today; that this agent may be effective in patients who are not able to tolerate or not able to get the other HER2 directed agent or it may have better CNS

penetrants.

While we should always respect the ability of the oncologists in the clinic to manage toxicities, I think we have to set the providers, but more importantly the patients, up for success as best we can by getting them the best data on what doses are best tolerated. Thank you.

DR. GARCIA: Thank you.

Dr. Waldman?

DR. WALDMAN: Scott Waldman, Thomas Jefferson University. I voted no for many of the same reasons that everybody else has articulated. Clearly, there's a clinical unmet need for the drug. The drug has activity, but I don't know that it has a meaningful improvement over other drugs that in the real world are available to patients right now. It has a high level of toxicities associated with it. Yes, they can be managed, but there's still a high level of toxicities associated with that.

That's complicated by the fact, as many have pointed out, that the dose of the drug has not been

adequately optimized, and that that uncertainty is going to be carried through now into the potential confirmatory trial, which has an endpoint that is far away, given that these patients are at risk for toxicity and, again, isn't studying the same dose that's seeking approval right now for the agents. So for all of those reasons and others, I voted no.

DR. GARCIA: Thank you, Dr. Waldman.

Just to summarize to some extent the voting, it is clearly evident that it wasn't an easy decision for most of us, and for those who voted yes, it does appear that it relates to the efficacy of these agents in a patient population who is in need of active therapies instead of orphan disease. Those who voted yes were not too enthusiastic, or rather were not too worried or concerned about the tolerability of these agents based upon prior experience and years of practice, and clearly were not concerned as to confirmatory trials and the need for those drugs to be here, ongoing at least.

For all of us who voted no, I think that the theme is the, quote/unquote, "non-meaningful

difference compared with existing agents." Clearly, we all were concerned about not ideal dosing and the dose finding or the dose optimization issues that have been noted, and certainly the lack of an ongoing confirmatory trial that may take a long while before we know the true dose and the true efficacy of an agent.

I certainly believe that all of us were quite sympathetic to the statements by the public, by all the presenters from the FDA, and also from the applicant's perspective. Clearly, I believe we did have a robust discussion and a pretty active session of clarifying questions, and I think that probably is reflected in the vote as we see it.

Before we adjourn this topic, are there any last comments from the FDA?

DR. SINGH: This is Harpreet Singh. No. We at the FDA would simply like to thank you, Dr. Garcia, for your moderating of this panel, and certainly the members of the committee, we thank you, and we appreciate the robust discussion. We take into account more than just your yes or no,

but also alls the comments, very thoughtful [indiscernible – audio gaps]. We thank the patients for spending their time with us today, and we appreciate the committee's time, and thank you again.

Adjournment

DR. GARCIA: Thank you.

We will now adjourn the first topic and break for lunch. We will reconvene at 1:50 p.m. Eastern Standard time. Panel members, please remember that there should not be chatting or discussions of the meeting topics with other panel members. Additionally, those panels member participants in the second topic should plan to rejoin the call at 1:20 p.m. Eastern Standard time just to ensure that we are connected before we reconvene at 1:50.

Thank you again, and I appreciate all of you.

(Whereupon, at 1:10 p.m., the morning session was adjourned.)