FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Thursday, February 10, 2022

10:00 a.m. to 2:46 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

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

My name is Dr. Pamela Kunz, and I will be chairing this meeting. I will now call the February 10, 2022 meeting of the Oncology Drug Advisory Committee to order. Commander LaToya Bonner is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

CDR BONNER: Good morning. My name is LaToya Bonner, and I am the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Advani?

(No response.)

CDR BONNER: Dr. Advani, can you please unmute your phone?

DR. ADVANI: This is Dr. Advani from Stanford.

CDR BONNER: Thank you.

Dr. Conaway?

DR. CONAWAY: Mark Conaway, biostatistics, University of Virginia.

CDR BONNER: Thank you, sir.

DR. CRISTOFANILLI: Yes. Good morning. Dr. Massimo Cristofanilli, oncologist from Weill Cornell, New York.

CDR BONNER: Dr. Garcia?

DR. GARCIA: Good morning. Jorge Garcia, GU medical oncologist, chief of medical oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

CDR BONNER: Thank you, sir.

Dr. Kunz?

DR. KUNZ: Good morning. Dr. Pamela Kunz. I'm a GI medical oncologist at Yale Cancer Center in New Haven, Connecticut.

CDR BONNER: Thank you.

Dr. Lieu?

DR. LIEU: Good morning. I'm Chris Lieu, GI medical oncologist from the University of Colorado Cancer Center.

CDR BONNER: Thank you.

Dr. Madan?

DR. MADAN: Good morning. I'm Ravi Madan. I'm a senior clinician and GU medical oncologist at the National Cancer Institute.

CDR BONNER: Thank you, sir.

Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative. I'm a multiple myeloma patient, and I'm founder of Patients for Affordable Drugs.

CDR BONNER: Thank you, sir.

Dr. Nieva?

DR. NIEVA: Hi. I'm Jorge Nieva. I'm a section head of solid tumors and a thoracic medical oncologist at the University of Southern California Norris Cancer Center in Los Angeles, California.

CDR BONNER: Dr. Rosko?

DR. ROSKO: Good morning. I'm Ashley Rosko from the Division of Hematology, and also the medical director of the Oncogeriatric Program at The Ohio State University.

CDR BONNER: Thank you.

Dr. Sung?

DR. SUNG: Anthony Sung, hematology-oncology, Duke University.

CDR BONNER: Thank you, sir.

Dr. Cheng?

DR. CHENG: Good morning. Jonathan Cheng. I'm a medical oncologist, and I'm the industry rep, and I'm affiliated with Bristol-Myers Squibb.

CDR BONNER: Thank you, sir.

Dr. Arscott?

DR. ARSCOTT: I'm Karen Arscott. I'm a primary care physician and addiction medicine specialist, and a two-time lung cancer survivor.

CDR BONNER: Thank you, ma'am.

Dr. Dagogo-Jack?

DR. DAGOGO-JACK: Good morning. I'm Ibiayi

Dagogo-Jack. I'm a thoracic medical oncologist at Massachusetts General Hospital.

CDR BONNER: Thank you, ma'am.

Dr. Deeken?

DR. DEEKEN: Hi. John Deeken. I'm a head and neck medical oncologist and president of the Inova Schar Cancer Institute in Fairfax, Virginia.

CDR BONNER: Thank you.

Dr. Wozniak?

DR. WOZNIAK: Yes. I'm Antoinette Wozniak. I'm a thoracic medical oncologist at the UPMC Hillman Cancer Center in Pittsburgh.

CDR BONNER: Dr. Pazdur?

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

CDR BONNER: Dr. Beaver?

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

CDR BONNER: [Inaudible].

DR. SINGH: Good morning. I'm Dr. Harpreet

Singh, division director of the Division of Oncology 2 at the FDA.

CDR BONNER: Dr. Vellanki?

DR. VELLANKI: Hi. I'm Paz Vellanki. I'm a clinical reviewer on the thoracic head and neck team at FDA.

CDR BONNER: And last is Dr. Drezner.

DR. DREZNER: Hi. Dr. Nicole Drezner. I am an oncologist on the thoracic head and neck team, in the Division of Oncology 2 at the FDA.

CDR BONNER: Thank you. I will now turn this meeting back over to our chair, Dr. Kunz.

DR. KUNZ: Wonderful. Thank you.

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 today is that this meeting will be fair and an open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if

recognized by the chairperson. We look forward to a productive meeting.

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

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

Now I'll pass it to Commander Bonner, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

CDR BONNER: Thank you, ma'am.

The Food and Drug Administration is convening today's meeting of the Oncologic Drugs

Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a

special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the 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 purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of the biologics license application 761222, for sintilimab injection, submitted by Innovent Biologics Company Ltd. The proposed indication for this product is in combination with pemetrexed and

platinum-based chemotherapy for first-line treatment of patients with stage IIIB, IIIC, or stage IV non-squamous non-small cell lung cancer with no epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumor aberrations.

This is a particular matters meeting during which specific matters related to Innovent Biologics' BLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by 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. Ashley Rosko and Jorge Nieva.

Dr. Rosko's waiver involves her employer's contract for two studies. One study is funded by GlaxoSmithKline and competing firm. Dr. Rosko's employer receives between $0 to $50,000 per year with GlaxoSmithKline. The second study is funded by a competing firm, and Dr. Rosko is not aware of the funding about the amounts being provided to

employer.

Dr. Nieva's waiver involves his employer's research contract funded by competing firms for which his employer receives between $300,000 to $350,000 per year, and Dr. Nieva receives between $0 to $5,000 per year in salary support.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reason for issuing the waivers are described in the waiver documents, which are posted on FDA's website at https://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 at 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. Jonathan Cheng is participating in this meeting as a non-voting industry representative acting on behalf of a regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Bristol-Myers Squibb.

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

I will now turn the meeting back over to our chair.

Dr. Kunz?

DR. KUNZ: Thank you, Commander Bonner.

We will proceed with FDA introductory remarks at this point from Dr. Harpreet Singh.

FDA Opening Remarks – Harpreet Singh

DR. SINGH: Thank you, everyone, and good morning. I'm Harpreet Singh, a medical oncologist and director of FDA's Division of Oncology 2. We convened today's Oncologic Drugs Advisory Committee to discuss an application for use of sintilimab for locally-advanced or metastatic non-small cell lung cancer.

Today's ODAC will not follow the traditional paradigm of assessing the benefit-risk profile of a single drug. Rather, the concept of generalizability and applicability of single-country foreign data to a U.S. population is the central issue for which we referred this application to the committee.

I will provide a high-level overview of ORIENT-11, a study conducted exclusively in China, followed by regulations and guidances with which to consider foreign data in support of a U.S.

marketing application. We will then move to key issues with ORIENT-11, ending with our voting question for the committee.

I will note that while FDA recognizes the societal implications of cost of drugs, pricing and competition may not be considered as part of FDA regulatory decision-making and should not be included in our discussions today.

ORIENT-11 randomized patients in a 2-to-1 ratio to either chemotherapy plus sintilimab, an anti-PD-1 monoclonal antibody, or chemotherapy alone as initial treatment for metastatic non-small cell lung cancer. The primary endpoint was progression-free survival by an independent review committee with crossover permitted at time of progression.

ORIENT-11 met its primary endpoint demonstrating PFS by blinded independent central review with a hazard ratio of 0.48. Overall survival and overall response rate were descriptive endpoints not formally tested. Conducted exclusively in China, the trial design enrollment

criteria and statistical assumptions of ORIENT-11 closely resembled landmark trials, which established immune checkpoint inhibitors as part of initial treatment for non-small cell lung cancer.

Rather than an isolated case, this application reflects an increasing number of oncology development programs based solely on, or predominantly on, clinical data from China. This strategy is in contrast to multiregional clinical trials, which have been promoted by the global regulatory community as the preferred development strategy.

FDA regulations are established by Title 21 of the Code of Federal Regulations, which contains specific criteria on accessibility of foreign data. Guidances from the International Council of Harmonisation also stand as FDA guidance and represent our current thinking on a particular topic.

A marketing application based solely on foreign clinical data may be approved if foreign data are applicable to the U.S. population and U.S.

medical practice; studies are performed by investigators of recognized competence; and there is FDA validation of trial data through on-site inspection or other appropriate means. Failure to meet any of these criteria will result in an application not being approvable based on the foreign data alone. Notably, the FDA does have flexibility in applying this policy according to the nature of the drug and the data being considered.

International consensus guidelines on global drug development have evolved from the late 1990s with ICH E5 to more current thinking in ICH 17. E5 describes strategies to extrapolate foreign data through bridging studies from one often heterogeneous region to a typically homogeneous population.

The goal was to fulfill an unmet need and brought in global access to novel therapy. However, bridging studies are inherently limited in their ability to demonstrate applicability to a new population. They were conducted sequentially after

completion of international multiregional trials which actually delayed access to important drugs.

With this in mind, the ICH reconvened with additional global partners, including China, and in 2017 issued guidance calling for concurrent global registration strategies. This guidance reflected an emerging consensus that trials requiring international collaboration were preferred over single-country trials.

In keeping with the shift from a local to global mindset, the historical underrepresentation of Asian countries in international multiregional trials and subsequent reliance on bridging studies has led many Asian countries to increase their participation in multiregional trials over the past decade.

An FDA analysis of the relative patient contribution for registrational studies submitted to oncology by geographic region shows that China, depicted in blue, has had limited participation in multiregional trials relative to other Asian countries as depicted in orange.

The true value of international multiregional clinical trials are emphasized in the ICH E17 framework. These trials have typically formed the basis for new drug registration. By drawing from diverse geographic areas and ethnic populations, multiregional trials allow for evaluation of regional consistency of treatment effect, avoid duplicative efforts and the need for bridging studies, and ultimately promote international harmonization of best medical practices.

ORIENT-11 was initiated in China in 2018 after this international guidance was issued despite China's regulatory authority joining the ICH in 2017. Per the U.S. Code of Federal Regulations and applicability standards outlined in ICH E5, ORIENT-11 is not applicable to a U.S. population.

The KEYNOTE-189 trial forms the basis for a U.S. standard of care at the time ORIENT-11 was initiated. The 2017 accelerated approval followed by the 2018 regular approval of pembrolizumab with

chemotherapy, based on a formally tested, statistically significant improvement in overall survival, shifted the treatment paradigm, moving immune checkpoint inhibitors to a frontline setting and rendering chemotherapy alone an inappropriate initial regimen.

Four-year follow-up from this landmark trial shows a median overall survival of 22 versus 10.6 months and approximately one year of overall survival improvement for patients treated with pembrolizumab.

ORIENT-11 could not have been conducted in the United States, as it was no longer applicable to U.S. Medical Practice. Investigators would not have enrolled patients to a chemotherapy control arm given available FDA-approved options conferring substantial survival benefit.

Had FDA been consulted regarding ORIENT-11, a formal head-to-head comparison of sintilimab to an FDA-approved checkpoint inhibitor would have been recommended as an initial registration strategy. This type of trial could help address

the need for clarity in a crowded field by comparing regimens directly. Instead, ORIENT-11 only contributes to the lack of coordination and redundancy in the checkpoint inhibitor space.

ORIENT-11 was powered for progression-free survival without statistical testing for overall survival. Overall survival is generally the preferred endpoint in oncology clinical trials when it can be reasonably assessed. To date, all FDA approvals of first-line immunotherapy-based regimens for metastatic non-small cell lung cancer have been based on a statistically significant improvement in overall survival.

Given this precedent, single-country foreign data powered for a less meaningful endpoint -- progression-free survival -- provides no therapeutic advantage to patients; rather only offers uncertainty given the lack of formal testing for overall survival.

ORIENT-11 shows a lack of diversity by design and does not reflect the ethnic and racial makeup of a U.S. population notably with regard to

groups traditionally underrepresented in clinical trials. There are both known and unknown factors which may impact study interpretation and generalizability. Acceptance of single-country data would be incongruent with calls to address the underrepresentation of racial and ethnic minorities in drug development.

The Code of Federal Regulations requires that data be validated through on-site inspection or other appropriate means, however, only a handful of sites are clinically inspected, which does not account for heterogeneity in trial conduct and data quality.

The FDA's Office of Scientific Investigation inspected two of the 48 clinical sites for ORIENT-11. They found that the investigators underreported both adverse events and concomitant medications. Corrective actions were taken, including training on good documentation practices. For both investigators, this was their first FDA inspection. These findings underscore the need for international, multiregional clinical trials with

investigators who have gained experience in regulatory submissions to the FDA, which may mitigate concerns regarding data integrity.

The applicant claims to fulfill the Code of Federal Regulations on foreign data based on similar clinical practice standards to the U.S. However, standard of care was not similar at the time of trial initiation, resulting in an inapplicable comparator arm. While the applicant claims similar pharmacokinetics and pharmacodynamics of sintilimab between Chinese and U.S. patients, there's insufficient data provided to make this conclusion given the vast diversity of a U.S. population.

Finally, the applicant cites an exploratory FDA analysis to show similar efficacy of checkpoint inhibitors between Chinese and U.S. patients, however, multiple or retrospective analyses, including FDA analyses, have shown mixed results, and this would be best evaluated in a prospective international, multiregional clinical trial.

ORIENT-11 fails to meet criteria outlined in

the Code of Federal Regulations. As discussed, the trial endpoint and comparator arm are not applicable to U.S. regulatory standards. The population is not reflective of the diversity within the United States, and there are concerns regarding compliance with good clinical practice, or GCP, as well as data integrity. Lung cancer is not a rare disease or endemic to China. Thus, international, multiregional clinical trials can easily be performed.

To address FDA concerns regarding applicability to a U.S. population, the applicant proposed a randomized non-comparative study, including 150 patients from the U.S., EU, and China, comparing 2 doses of sintilimab. The FDA does not consider this dose-finding study adequate to address issues of generalizability. A possible strategy would be a formal comparison of sintilimab to an approved immune checkpoint inhibitor in an international, multiregional trial with an overall survival endpoint which could be conducted prior to FDA registration.

The current landscape of me-too drugs was not envisioned in ICH E5 when considering bridging studies as a means of extrapolating foreign data. In an already crowded space of approved checkpoint inhibitors, sintilimab offers uncertain benefit. What is best for drug development is to bring China into the fold as a key player in international, multiregional trials.

Neither company involved in the development of sintilimab engaged the FDA through mechanisms. It is critical to maintain the survival advantage for U.S. patients demonstrated with multiple approved therapies. The applicant utilizes post hoc, cross-trial comparison to address the uncertain benefit sintilimab provides.

If ORIENT-11 had been designed as a well-conducted, multiregional trial, there would have been early communication with international regulatory authorities, and FDA would have provided appropriate advice on selection of a comparator arm and study endpoint. An international, multiregional trial would have permitted direct

evaluation of safety and efficacy across geographic regions and would have addressed concerns regarding applicability to a U.S. population.

Multiregional trials can be strengthened by adding participants such as China, Africa, and Latin American countries. This greater diversity may help the U.S. in answering calls to address underrepresentation of racial and ethnic minorities in drug development. Increased participation in these trials provides a framework to establish experience in submitting data to multiple regulatory agencies around the world. This patient-centered approach will expedite global access to therapeutic advances in oncology and should be widely adopted.

The committee will be asked to discuss the generalizability of ORIENT-11 to a U.S. population and U.S. medical practice, as well as what potential trials, if any, may address issues of applicability.

After the discussion, we will ask the committee to vote on the following question.

Should additional clinical trials demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?

Thank you. This concludes my opening remarks.

DR. KUNZ: Thank you, Dr. Singh.

We will move on to the next section.

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, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant'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 this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Innovent and Eli Lilly's presentations.

(No response.)

DR. KUNZ: We cannot hear anyone speaking.

Applicant Presentation – Lana Shiu

DR. SHIU: Good morning, FDA and members of the Oncologic Drug Advisory Committee. I'm Dr. Lana Shiu, global head of Regulatory Affairs at Innovent Biologics. We are joined today by Eli Lilly and Company, our global development partner for sintilimab. We want to thank the FDA for giving us the opportunity to present the data in support of sintilimab's BLA.

Innovent is a global pharmaceutical company headquartered in Suzhou, China -- [inaudible –

audio gap] -- 25 products in development and 6 approved in China. Our mission is to develop high-quality pharmaceuticals that are more affordable. In 2015, we entered into a global collaboration with Eli Lilly to co-develop multiple products. Now, based on the sintilimab's compelling safety and efficacy in non-small cell lung cancer, we are seeking to bring it to the patients in the United States.

Sintilimab is a well-characterized, novel recombinant, human IgG monoclonal antibody that binds PD-1 with high affinity. It is well tolerated in multiple GLP toxicity studies. Sintilimab has been evaluated in more than 4,000 clinical trial patients across multiple tumor types, including first-line, non-small cell lung cancer studies that enrolled more than 700 patients.

As you might expect, a PD-1 monoclonal antibody, sintilimab has demonstrated significant clinical benefit in multiple tumor types, including lung, GI, and hematologic. We have approval in

four indications in China and postmarketing safety data in over 170,000 patients.

Based on ORIENT-11, the pivotal registration study, this is the proposed indication and dosing for patients with stage IIIB, IIIC, or stage IV non-squamous non-small cell lung cancer with no eGFR or ALK mutations.

This slide shows the timing of approvals in China. ORIENT-11 was originally designed and conducted to support regulatory approval in China, so regulatory interactions leading to its initiation were held with the China health authority. Now, I would like to focus your attention on the regulatory interactions with FDA.

Given the compelling interim results from ORIENT-11, existing regulatory pathways that already defined a use of foreign data, and the agency's comment at AACR in 2019 indicating an openness to accept data from China, we decided to pursue FDA submission. We met with FDA on three occasions in 2020, and then submitted our BLA in March of 2021.

At these clinical meetings, FDA indicated that they might request postmarketing data in a population representative of U.S. patients. Accordingly, we proposed such a study during our Type C meeting with FDA in October of 2021. We remain committed to generating postmarketing data in a diverse non-small cell lung cancer population representative of U.S. patients.

Outlined in FDA's briefing book, we are here to discuss today the applicability of ORIENT-11 data to support U.S. approval. The agency has raised a number of key review issues. Consequently, we will briefly summarize the efficacy and safety of sintilimab, and then focus on the data supporting the applicability and address FDA's review issues.

Today you're being asked to vote on whether additional clinical trials to demonstrate applicability should be required prior to final regulatory decision. The data we will share with you today will demonstrate the efficacy and safety of sintilimab do support approval.

In addition to the package data we used for regulatory approval in China, our U.S. application is supported by PK data from the United States. FDA regulations, as well as ICH guidelines, have established the framework to allow for the use of foreign data to support a U.S. filing. We will present data to show how ORIENT-11 meets this framework and provides substantial evidence of safety and efficacy of sintilimab, and we will demonstrate that the data are applicable to the U.S. population and clinical practice.

We understand that the agency's view on drugs developed in China has recently changed. It is also important to remember that Innovent and Lilly have operated in good faith throughout this process, adhering to the FDA's continued advice. We believe sintilimab can be a valuable treatment option, and we want to work with you to find a path forward to make it available. The totality of the data we will present today will demonstrate that sintilimab has a positive benefit profile in the proposed indication. We will show that the

diagnosis and treatment of non-small cell lung cancer are similar in China and the U.S.

ORIENT-11 has met the primary endpoint of PFS at the interim analysis, and secondary analysis of overall survival showed a robust and meaningful treatment effect that is comparable to other agents in this class. We will also show that sintilimab plus chemo has an acceptable safety profile consistent with other approved PD-1 inhibitors.

Finally, we will provide evidence that the data from ORIENT-11 is applicable to the U.S. population based on these three principles here; a comprehensive review of clinical practice standards, intrinsic and extrinsic factors, as well as efficacy of safety across the PD-1 class clearly demonstrate that the results of ORIENT-11 are applicable to the U.S. population. There is no evidence to suggest that efficacy and safety of sintilimab in the U.S. patients would differ from the results observed in ORIENT-11.

Here's the agenda for the remainder of our presentation. The Treatment Landscape of Non-Small

Cell Lung Cancer will be presented by Dr. Mark Socinski from Advent Health Cancer Institute. Dr. Eduard Gasal for Innovent will summarize the efficacy data and conduct of ORIENT-11. Our safety data will be summarized by Dr. Maria Fernandes from Eli Lilly. And finally, Dr. David Ferry from Eli Lilly will present the evidence that the data from ORIENT-11 are applicable to the U.S. population and discuss in detail the key review issues. These additional experts will be available to answer your questions, and Dr. Ben Anderson will moderate the question and answer on behalf of the sponsor team.

Thank you for your attention. Now, I will like to hand the presentation over to Dr. Socinski.

Applicant Presentation – Mark Socinski

DR. SOCINSKI: Thank you, Dr. Shiu.

My name is Dr. Mark Socinski, and I'm the executive medical director of the Advent Health Cancer Institute in Orlando, Florida. I'm a paid consultant for Innovent and Eli Lilly, but have no financial interest in the outcome of this meeting. I have been the chair of the steering committee for

the four IMpower clinical trials, two of which have led to FDA approvals. I also chair the steering committee for the ADVANTAGE 302 [ph] clinical trial, and formerly a member of the steering committee for CheckMate 026. I've also served as a member of several data monitoring committees [inaudible – audio gap].

I will now present an overview of the current treatment landscape in non-small cell lung cancer by the comparison between the United States [inaudible].

In the United States, lung cancer is the leading cause of cancer deaths, and non-small-cell histology dominates the landscape. Current clinical practice includes comprehensive genomic testing for a growing number of oncogenic driver mutations or alterations for which there are FDA-approved, first-line targeted therapies. Patients without oncogenic alterations are typically treated with chemoimmunotherapy or single-agent immunotherapy depending on PD-L1 status.

You can see here the characteristics of patients with stage IV non-small cell lung cancer based on patients enrolled in multiregional clinical trials. Roughly 60 percent have a PD-L1 tumor proportion score of 1 percent or higher; 60 percent have an ECOG performance status of 1. As shown in the bar graph, approximately 30 percent of U.S. patients have an oncogenic alteration.

Now, turning to the population of stage IV non-small cell lung cancer patients in China based on the population enrolled in ORIENT-11, PD-L1 status and performance status are similar to what is seen in multiregional clinical trials that supported approval in the U.S. One big difference is the higher proportion of patients with oncogenic alterations, principally eGFR mutations in the Chinese population. Approximately 65 percent of Chinese patients have driver mutations or alterations.

This is the typical treatment algorithm for non-squamous non-small cell lung cancer in the United States. It is critical to do comprehensive

genomic testing at the time of diagnosis, as patients who are positive for oncogene driver alterations are eligible for targeted therapies. Today, we will focus on the approximately 70 percent of patients without oncogenic driver alterations who are treated with immunotherapy.

We have a number of PD-1 or PD-L1 agents currently approved in the United States as shown on the right. It is typical that patients would get one of these agents either as monotherapy or more typically in combination with platinum-based chemotherapy.

The options for second-line therapy in this population depends on prior therapy. For patients not previously treated with immunotherapy, a PD-1 or PD-L1 inhibitor can be used, where with those previously treated with immunotherapy would get cytotoxic either as single agents or the combination of ramucirumab and docetaxel.

The treatment algorithm for non-small cell lung cancer patients in China is similar to what occurs in the U.S. As I mentioned, the one

striking difference, as shown on the left, is the higher proportion of patients with oncogenic alterations. On the right is the treatment algorithm for patients without oncogenic alterations.

Similar to the U.S., there are a number of approved PD-1 or PD-L1 agents in China that currently use first-line setting either as monotherapy in high PD-1 expressors or more commonly in combination with platinum-based chemotherapy.

When we put the diagnostic and treatment standards of the two countries side by side, we see they're quite similar. Treatment guidelines in the U.S. are dominated by the NCCN guidelines. Chinese guidelines are largely derived from the NCCN [inaudible] -- same staging and pathologic classification system. Molecular testing and PD-L1 biomarker testing are routinely done, and first-line immunotherapy options are mostly overlapping.

Finally, the chemotherapy backbone used in

the United States and China tends to be very similar. Cisplatin or, more commonly, carboplatin plus pemetrexed is the most common doublet used in both countries.

PD-1 and PD-L1 inhibitors have transformed the treatment landscape in non-small cell lung cancer, and they are now the first-line standard of care for patients with stage IV disease without oncogenic alterations. They were first approved in 2015 as single agents in the second-line setting. Beginning in 2016, they moved to first-line therapy with the approval of single-agent pembrolizumab for PD-L1 high tumors based on the results of KEYNOTE-024.

Then starting in 2018, with the full approval of pembrolizumab based on KEYNOTE-189, PD-1 or PD-L1 inhibitors were combined with standard chemotherapy regardless of PD-L1 status. Since that time, multiple other PD-1 or PD-L1 inhibitors, in combination with various chemo regimens, have been approved as first-line therapy for both squamous and non-squamous non-small cell

lung cancer [inaudible]. However, the only PD-1 inhibitor approved in combination with pemetrexed plus platinum chemotherapy is pembrolizumab.

Throughout this time frame, standard of care for non-small cell lung cancer has continuously evolved in both the U.S. [inaudible]. As a consequence, what may be considered an appropriate control arm also evolved.

For example, pembrolizumab monotherapy became first-line standard of care in the U.S. for patients with PD-L1 greater than or equal to 50 percent [inaudible]. This occurred during the accrual of IMpower 110, which continued to use chemotherapy alone as the control arm, and it led to the approval of atezolizumab in 2020.

Meanwhile, the EMPOWER-Lung 1 trial was initiated solely outside the U.S. after the approval of pembrolizumab and led to the approval of cemiplimab. All three trials, the control arm was chemotherapy doublet even though KEYNOTE-024 established a new standard of care in the U.S. in 2016. Together, these three FDA-approved options

provide choices for patients, prescribers, and payers.

This forest plot compares the reported progression-free and overall survival improvements [inaudible] with various PD-1 and PD-L1 inhibitors when combined with chemotherapy in the first-line setting. It shows that this class of agents all have broadly similar efficacy in non-small cell lung cancer regardless of the chemotherapy backbone used. And as you will see later in the presentation, they also have broadly similar [inaudible].

Results from KEYNOTE-189 established it as a standard of care for non-small cell lung cancer. [Inaudible] states progression-free survival in the pembrolizumab plus chemo arm was 9 months compared to 4.9 months [inaudible] plus chemo arm. The final overall survival analysis shown here demonstrated a 22-month median overall survival in the pembrolizumab arm versus 10.6 months in the control arm with a hazard ratio of 0.56.

In conclusion, the disease characteristics

of both Chinese and U.S. patients are similar with the exception of patient percentage with oncogenic alterations. Diagnostic and treatment patterns are similar between [inaudible]. In both the U.S. and China, immunotherapy has dramatically improved outcomes for lung cancer patients, and pemetrexed plus platinum is the most widely used chemotherapy backbone. But despite the large number of PD-1 and PD-L1 agents approved in non-small cell lung cancer, only pembrolizumab is approved in the U.S. in combination with pemetrexed plus platinum chemotherapy.

Thank you for your attention. I will now turn it over to Dr. Ed Gasal.

Applicant Presentation – Eduard Gasal

DR. GASAL: Thank you, Dr. Socinski.

My name is Eduard Gasal, and I'm the president of the U.S. branch of Innovent Biologics. Today I will discuss the conduct of ORIENT-11 and its efficacy outcomes.

ORIENT-11 was a randomized, double-blind, placebo-controlled phase 3 study. It enrolled

patients with previously untreated non-squamous non-small cell lung cancer without genetic alteration. The study started in August 2018, and over a period of 11 months, 397 patients were randomized 2 to 1 who received pemetrexed and platinum-based chemotherapy in combination with either sintilimab or placebo.

Treatment was continued until disease progression, unacceptable toxicity, or a maximum duration of two years. The primary endpoint was PFS as assessed by a blinded, independent radiology review. Secondary endpoints included overall survival, objective response rate, and safety. The randomization was stratified by sex, type of platinum-based therapy, and PD-L1 expression level using the tumor proportion score.

Patients in the placebo arm were allowed to cross over to sintilimab monotherapy by design and confirmed disease progression was observed. This provided patients with access to second-line PD-1 therapy, as it was not yet widely available in China.

Pemetrexed in combination with platinum-based chemotherapy was selected as the control arm because it was considered standard-of-care first-line therapy for non-squamous non-small cell lung cancer in China where PD-1 checkpoint inhibitors were not available for this indication. In fact, in China, PD-1 checkpoint inhibitors were not approved or available in first line until March 2019, four months before the last patient was randomized in ORIENT-11. At this point, nearly 80 percent of the patients were enrolled. While pembrolizumab was approved, it was not listed on the National Reimbursement Drug List.

Considering the clinical relevance of PFS and the expected high level of crossover by design, PFS was selected as the primary endpoint, as PFS is not confounded by post-progression therapy. The study design and the endpoint were also discussed with the China health authority in early 2018.

Assuming a PFS hazard ratio of 0.65, 263 events yielded 90 percent power to detect the

superiority of sintilimab at a two-sided alpha level of 0.05. As defined in the protocol, an interim analysis was planned after 184 events. Overall survival was a secondary endpoint. Although no alpha was assigned to overall survival, the method of analyzing was prespecified in the statistical analysis plan.

ORIENT-11 was conducted in China at 48 academic centers with oncology expertise and high patient volume. The study sites were located across a wide range of large, medium, and small cities, and all sites have previous experience with multiregional clinical trials.

The FDA conducted 17 inspections at 10 of the 48 study sites with two of these inspections being part of this BLA review. Four inspections resulted in observations that were adequately addressed through appropriate corrective actions by the sites, 12 inspections resulted in no findings, while one inspection result is still pending.

Additionally, 23 of the 48 sites participated in at least one clinical trial that

ultimately led to the drug being approved by FDA. All investigators were board-certified oncologists trained on ICH GCP, and nearly all have previously participated in a multiregional clinical trial. In fact, nine investigators participated in at least one clinical trial that ultimately led to the drug being approved by FDA.

To minimize bias, PFS was assessed by blinded independent radiology review using a globally validated vendor which was Parexel. The committee was comprised of experienced radiologists from major cancer centers. Further PD-L1 status and all PK and drug antibody samples were assessed centrally by Covance.

An independent data monitoring committee was established at the start of the study, and they reviewed the interim analysis results. At the time of the interim analysis, the predefined efficacy boundary was met, and the IDMC recommended to the sponsor to continue the study as planned.

The data cutoff for the interim analysis was November 2019, which corresponds to a median study

follow-up of nine months. The most common reason for treatment discontinuation in both arms was progressive disease. Adverse events led to treatment discontinuation in only 3 percent in the sintilimab arm and 6 percent in the placebo arm.

Demographics and baseline disease characteristics were generally well balanced between the treatment arms. The median age was 61 and the majority of patients had an ECOG performance status of 1. Ninety percent of the patients had stage IV disease. The majority were PD-L1 positive defined by a tumor proportion score of greater than or equal to 1 percent.

ORIENT-11 met the primary endpoint of PFS by a blinded independent radiology review at the time of the interim analysis. At this timepoint, 198 PFS events had occurred and ORIENT-11 demonstrated clinically meaningful improvement of PFS. The hazard ratio of 0.48 is a highly significant p-value. The hazard ratio translated into an improvement of median PFS from 5 to 8.9 months.

The treatment effect for PFS in stage IIIB/C was consistent with the effect observed in the ITT population. On the left, we see the Kaplan-Meier curve for stage IIIB and C. A total of 36 patients with stage IIIB/C at baseline were enrolled. Consistent with the ITT population, an early and clear separation of the curve was observed. The hazard ratio for PFS was 0.17.

Finally, I would like to present the overall survival data. Overall survival favored sintilimab at the interim and subsequent analysis. At the time of the interim analysis, 90 death events had occurred and 27 percent of patients in the placebo arm had crossed over to sintilimab monotherapy. The Kaplan-Meier curve shows an early separation with a hazard ratio of 0.61.

The data cutoff for the final overall survival analysis was September 2021. This provided an additional follow-up of 22 months to a total median study follow-up of 31 months. The final OS analysis confirmed the OS benefit with a hazard ratio of 0.65 despite the increase in

crossover rate. At this point, the per protocol crossover rate with sintilimab was 47 percent. These data demonstrate the robust and clinically meaningful treatment effect.

A total of four survival analyses were conducted as shown here. The OS hazard ratio was consistent, ranging from 0.6 to 0.65 despite the increase in crossover rate over time. To better interpret the overall survival results, we retrospectively calculated O'Brien-Fleming and Bonferroni boundaries to adopt for multiplicity.

At the time of the final analysis, the observed p-value based on the log-rank test was 0.00135, which is smaller than both the O'Brien-Fleming and Bonferroni boundary. This indicates that had the overall survival been tested sequentially after meeting the primary endpoint, it would have met conventional statistical significance.

To summarize, ORIENT-11 was a high-quality study conducted by competent investigators and experienced sites. Sintilimab in combination with

chemotherapy demonstrated a clinically meaningful treatment effect across all endpoints tested. The study met the primary endpoint of PFS with a hazard ratio of 0.48. A strong overall survival result favoring sintilimab was seen consistently despite the high crossover.

I will now turn it over to Dr. Fernandes, who will summarize the safety profile for sintilimab.

Applicant Presentation – Maria Fernandes

DR. FERNANDES: Thank you, Dr. Gasal.

My name is Maria Fernandes, and I am sintilimab's safety lead at Eli Lilly. Given the brevity of FDA's comments in their briefing document on safety, I will only present a high-level summary of the safety profile of sintilimab. I will focus primarily on the safety assessment in ORIENT-11, but I will also provide data on immune-related adverse events in the all-sintilimab treated cohort for comparison.

ORIENT-11 provided safety data on 266 patients treated with sintilimab combined with

chemotherapy. This is an overview of the safety profile during the double-blind period. It does not include data from crossover. As you can see, the overall incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation of sintilimab or placebo were well balanced across treatment groups.

The incidence of treatment-emergent adverse events leading to discontinuation of sintilimab or placebo was low, 5 percent in the sintilimab arm compared with 7 percent in the placebo arm. The majority of deaths in both arms was due to disease progression, and the incidence of death due to adverse events was low in both arms.

The most frequently reported TEAEs in ORIENT-11 by preferred or consolidated terms were within expectations for a PD-L1 inhibitor plus chemotherapy. Overall, the incidence of these adverse events was similar in the sintilimab and placebo arm, indicating that the addition of sintilimab to chemotherapy did not seem to increase the incidence of the most common TEAEs associated

with chemotherapy.

Now I would like to turn your attention to immune-related adverse events observed in ORIENT-11 and in the overall sintilimab-treated population. The overall pattern of immune-related AEs associated with sintilimab was consistent with that associated with other anti-PD-1/L1 antibodies. The most frequent IR AEs in ORIENT-11 were endocrinopathies, mainly thyroid hormone disturbances, as well as amylase increased and pneumonitis. This is consistent with the all-sintilimab treated population, suggesting that the incidence and pattern of IR AEs is not driven by tumor type.

In summary, the safety profile of sintilimab, in combination with pemetrexed and platinum chemotherapy in patients with non-squamous non-small cell lung cancer, is acceptable and consistent with the known safety profile of other PD-1/L1 inhibitors in combination with chemotherapy for the same indication.

Based on more than 1,000 patients treated

with sintilimab in clinical trials and more than 170,000 patients treated in the postmarketing setting in China, the safety profile of sintilimab is consistent with other PD-1/L1 inhibitors with no new safety signal identified. We will continue to manage the risks associated with sintilimab with standard pharmacovigilance and proper labeling.

Thank you for your attention. I will now turn it over to Dr. David Ferry.

Applicant Presentation – David Ferry

DR. FERRY: Thank you, Dr. Fernandes.

My name is David Ferry, and I'm the vice president of Oncology Medical Strategy at Eli Lilly. In the preceding presentations, we showed you the data from our pivotal trial conducted in China, demonstrating that sintilimab has a favorable risk-benefit ratio when added to the first-line pemetrexed plus cis [ph] or carboplatin in non-squamous non-small cell lung cancer.

I will now address the evidence that the data from ORIENT-11 are generalizable, and it would be reasonably expected to be replicated in the U.S.

population in this indication. I will then address the key FDA review issues.

Earlier in our presentation, we shared our conclusion sintilimab [inaudible] met the U.S. Code of Federal Regulations for the use of foreign data as the sole basis for marketing approval. These regulations state that studies must be performed by clinical investigators of recognized competence, and FDA must be able to validate the data through on-site inspection or other appropriate means. We've covered those elements in the clinical presentation by Dr. Gasal. In addition, foreign data must be applicable to the U.S. population and to U.S. medical practice.

These regulations in conjunction with ICH E5 provide a framework for evaluating the applicability of sintilimab data based on three principles. First, there must be similar clinical practice standards in China and the U.S., second, we must show that the drug is insensitive to ethnicity and there are no clinically meaningful differences in the PK or PD of the drug between

Chinese and U.S. patients; the methodology for evaluating the impact of ethnic factors on a medicine's effect described in ICH E5; third, must be reasonable to anticipate, based on evidence, that the drug is insensitive to ethnicity and that the efficacy and safety of sintilimab in the U.S. population will be similar to that demonstrated in the Chinese population studied in ORIENT-11.

Furthermore, there is sufficient clinical experience with the drug class to provide reassurance that the class behaves similarly in patients in the two regions [inaudible] with respect to efficacy and safety.

First, let's talk about clinical practice standards. As you heard from Dr. Socinski, both U.S. and Chinese use the AJCC-8 staging system, which included 44 percent East Asian patients; disease classification is by WHO 2015; genetic testing is comparable; and the PD-L1 biomarker testing uses the same companion diagnostics.

Although clinical practice standards are constantly evolving, at the time ORIENT-11 was

initiated in 2018, the chemotherapy backbone of platinum plus pemetrexed, followed by maintenance pemetrexed, had been standard of care in China for many years. Second-line PD-L1 monoclonals were available in China, but first-line immunotherapy had not yet been adopted. Today, PD-L1 monoclonals combined with chemotherapy is an approved first-line option and clinical practice guidelines in this area have converged in U.S. and China.

Next, we looked at the pharmacology of sintilimab. The pharmacokinetics is linear across the dose range 1-to-10 milligrams per kilogram with a half-life of 14 days. Following a single infusion of sintilimab in patients with advanced solid tumors, PD-1 was saturated on circulating T cells across the dose range.

We observed greater than 95 percent PD-L1 occupants over 28 days and at the lowest dose, meaning that there is a wide therapeutic dose range for efficacy. This implies the 200-mg 3 weekly dose, which is equivalent to about 3 mgs per kilogram, has at least a 3-fold margin to deliver a

full pharmacologic affect in both Chinese and U.S. populations.

The pharmacokinetics of sintilimab are being characterized based on data from 514 patients. We examined a wide range of intrinsic factors, including body weight and race shown here, which are the most relevant to demonstrating applicability to U.S. population, and none had a clinically important effect on the PK of sintilimab.

ICH E5 highlights ethnic factors that are important when considering the applicability of foreign clinical data. This guidance states that it may be easier to conclude that the pharmacodynamic and clinical behavior of a medicine will be similar in the foreign and new regions if other members of the pharmacologic class have been studied and approved in the new region with dosing regimens similar to those used in the original region.

As seen in this table, for those PD-1/L1 medicines approved for the same indications in both

the U.S. and China, the dose and schedule is the same regardless of weight, race, or ethnicity. In fact, for all PD-1/L1 monoclonals approved for non-small cell lung cancer in the U.S. [inaudible], there are no requirements for dose adjustment according to weight, race, or ethnicity.

Now turning to efficacy and safety, where guidelines indicate that class effect is often a component of the assessment [inaudible] of efficacy, we looked for evidence that there are differences in clinical outcomes associated with PD-1/L1 inhibitors based on race or ethnicity.

This FDA meta-analysis, based on data from randomized clinical trials, compares clinical outcomes in non-Asian and Asian patients with metastatic non-small cell lung cancer who were treated with immune checkpoint inhibitors in the first-line setting. As you can see, the Asian group, although smaller, demonstrated relatively consistent OS and PFS outcomes compared to non-Asian. The authors concluded that although Asians appear to have better prognosis than

non-Asian, a unique better or worse benefit was observed from checkpoint inhibitors compared with chemotherapy.

When we offered our ORIENT-11 data onto these published data, the hazard ratios of both OS and PFS are consistent with the FDA meta-analysis. I might also point out that ORIENT-11 has greatly extended the available data on the efficacy and safety of PD-1/L1 inhibitors in each [inaudible] patient.

Lastly, we have done a comparison of the safety profile of sintilimab across Chinese and West populations. Recently, a large meta-analysis was published by academics comparing the safety profile of first-line immunotherapy combinations with non-small cell lung cancer. This analysis includes data from 8,278 patients enrolled in 16 randomized-controlled trials.

The data shown here is the odds ratio for grade 3 or higher adverse events. The safety profile of sintilimab in combination with pemetrexed and platinum chemotherapy, shown in the

red box, is comparable to that of other agents in the class.

In conclusion, based on the totality of the data, sintilimab in combination with pemetrexed and platinum chemotherapy demonstrated a positive benefit-risk profile in Chinese patients. Data are applicable to U.S. patients. We've shown that clinical practice standards are similar between China and the United States.

Second, the PK/PD characteristics are insensitive to ethnicity. Third, there is ample evidence, based on extensive clinical [inaudible] with PD-1/L1 antibodies across different populations, to provide reassurance that efficacy and safety of sintilimab in the U.S. population will be similar to what was observed in ORIENT-11. Taken together, these data demonstrate that the data from ORIENT-11 are applicable to the U.S. population and [inaudible] indication.

Before we close, it's important to acknowledge and address FDA's key review issues as outlined in Section 8 of their briefing document

[inaudible].

First, with regard to the alignment of ORIENT-11 with ICH E17 guidelines [inaudible] multiregion studies [inaudible]. Because ORIENT-11 was designed as a single-country study registration in China, ICH E17 was not applied. In this situation, the requirements for accepting foreign data as the sole basis for marketing approach are outlined in U.S. regulation, and we've met these requirements.

We [inaudible] understand the agency's [inaudible] drugs developed in China has changed, but it's also important to remember that Innovent and Lilly have operated in good faith throughout this process with FDA [inaudible], prior to submission of our BLA and adhering [inaudible].

Regarding the applicability [inaudible of U.S. standard of care, as Dr. Gasal [inaudible – audio gaps]. This control arm was also [inaudible] with China regulatory agency and approved by IRBs. Further, this control arm is identical with the comparator used to establish the current U.S.

standard of care [inaudible].

In terms of the choice of endpoints, our FDA guidance, OS is the preferred clinical endpoint to establish efficacy. Nevertheless, the guidance also states that PFS may be appropriate as a primary endpoint [inaudible] if the trial [inaudible].

In ORIENT-11, PFS was the prespecified primary endpoint [inaudible], large magnitude of treatment effect [inaudible] for [inaudible]. Although alpha was not assigned to OS, it was a prespecified secondary endpoint. Given the magnitude of OS observed, we conclude that it's highly unlikely that this result is due to the absence of a true treatment effect. In addition, PFS and OS results in ORIENT-11 are [inaudible].

With respect to applicability about data to U.S. patients, while we can never exclude the unknown, we've done a comprehensive analysis of intrinsic and extrinsic factors and provided evidence that none of these factors would affect generalizability of ORIENT-11 results to U.S.

patients.

We've demonstrated that the efficacy and safety data from ORIENT-11 are compelling and consistent with similar studies of PD-1/L1 inhibitors. We've also shown that there are no clinically meaningful PK differences with sintilimab between whites and Asians or based on body weight.

When considering ICH E5, it makes note of the importance of contributions that a class of drugs can have on the evaluation of acceptability of foreign data. ICH E5 also outlines properties of a compound that make it less likely sensitive to ethnic differences between regions such as linear PK, wide therapeutic dose range, and minimum metabolism.

We have considered these. Based on the available data, we concluded that sintilimab is not sensitive to ethnic differences. This lack of ethnic sensitivity is consistent with other anti-PD-1/L1 antibodies. Based on FDA's late cycle communications in January 2022, we are committed to

collecting additional PK data in diverse patients in the postmarketing setting.

Regarding generating data in a population representative of the U.S., we have demonstrated throughout this presentation that sintilimab and the class are insensitive to ethnic factors, therefore the data from ORIENT-11 are applicable to the diverse U.S. population. We also are supporting increasing diversity in clinical trials, and we are committed to continuing to work with the FDA to study sintilimab in a population representative of U.S. cancer patients.

In our pre-BLA meeting, the FDA noted they may request postmarketing data in a population representative of the diverse U.S. population. In their briefing material and recent public comments, FDA's implied that sintilimab should be compared directly to an approved immune checkpoint inhibitor and a multiregional clinical trial to ensure that the survival advantages [inaudible].

Such a trial would face significant feasibility challenges. Using standard statistical

assumptions for FDA guidance for noninferiority studies, it would require enrollment of over 2,000 patients and take more than seven years to complete. In addition, such a study would be wasteful of the contribution of patients involved in clinical research.

Instead, we propose a more focused, efficient postmarketing study that generate additional data in a diverse Western population. We met with FDA in October to discuss such a proposal. The study shown here takes into account FDA's feedback to include a direct comparison of sintilimab plus chemotherapy between Western and Chinese patients.

The intent of this postmarketing study is to provide additional efficacy, safety, and PK data in a diverse population representative of U.S. patients. An additional cohort to evaluate a patient-centric, 6-week dosing schedule will also be investigated. We look forward to continuing discussions with FDA to further optimize this study concept.

With respect to FDA consultation, ORIENT-11 was conducted for registration in China, so we did not meet with the FDA prior to concluding the study. However, the study conformed to globally accepted GCPs and U.S. regulations for foreign clinical studies not conducted under an IND.

Based on the encouraging interim results, established regulations, and guidance, as well as the agency's comments to AACR in 2019 regarding openness to China data, we decided to pursue a U.S. application. Subsequent to the interim results and in accordance with federal regulations, we had three productive meetings with the FDA, where we received guidance on the application prior to submitting the BLA.

In terms of our informed consent form, at the time of study initiation, informed consent form was reasonable and appropriate. It stated that the investigators should discuss with their patients other treatment options or any new information that could affect their participation in the study. We acknowledge that the description of alternative

treatment options in the ICF was not as explicit as it should have been, and the onus to discuss treatment options with each patient was left with the investigator.

In retrospect, once pembrolizumab was approved in China as first-line therapy for non-squamous non-small cell lung cancer, approximately four months before accrual was completed, the trial-level consent form should have been updated to be more explicit on the potential new treatment option and to further facilitate the informed consent process [inaudible] according to their policies and procedures.

With respect to site inspections and investigator experience, as Dr. Gasal pointed out, 10 of the 48 sites associated with ORIENT-11 have been previously inspected by FDA, including a total of 17 inspections. FDA has conducted two GCP site inspections as part of this BLA review. Moreover, all sites have multiregional clinical trial experience, and 48 percent of the sites have participated in at least one clinical trial that

led to FDA approval. With respect to the investigators, all were board-certified oncologists trained on ICH GCP, and 95 percent of the primary investigators have participated in multiregional clinical trials.

Finally, with regard to FDA's comment about regulatory flexibility, regulatory judgment is applied when evaluating all applications. In this case, we have provided substantial evidence of the efficacy and safety of sintilimab. Further, there is a need for additional treatment options in this setting, including the stage IIIB/IIIC non-small cell lung cancer population. While price is not a topic of today's discussion, there is a need for more affordable options and [inaudible] provide one.

In summary, sintilimab has demonstrated a positive benefit-risk profile in patients with non-squamous non-small cell lung cancer, and the BLA should be approved based on the merits of the data submitted. The data are applicable and generalizable to the U.S. population and medical

practice.

We are committed to continuing to work collaboratively with the agency to provide additional data in the postmarket setting. These data can best be obtained through a focused, efficient study to provide additional efficacy, safety, and PK data in a diverse Western population. We think sintilimab can be a valuable treatment option, and we want to work with you to find a path forward to make it available.

Thank you for your time and attention. We look forward to your questions.

DR. KUNZ: Thank you very much to the Innovent and Eli Lilly presenters. We will now begin with the FDA presentations.

Dr. Vellanki?

FDA Presentation – Paz Vellanki

DR. VELLANKI: Good morning. I am Paz Vellanki, a medical oncologist at the FDA. The application for sintilimab in non-sqaumous non-small cell lung cancer was submitted by Innovent, who I will here on refer to as the

applicant.

This slide lists the members of the FDA multidisciplinary review team. My presentation reflects their collective input. Today's discussion will not revolve around the traditional ODAC question of risk-benefit for an oncology drug; rather, today's ODAC will focus on whether the applicant has adequately demonstrated applicability to the U.S. population and U.S. medical practice.

The application for sintilimab in non-squamous non-small cell lung cancer is based on the ORIENT-11 trial. Conducted exclusively in China, the trial design, enrollment criteria, and statistical assumptions of ORIENT-11 closely resemble landmark trials which established immune checkpoint inhibitors as part of initial treatment for non-small cell lung cancer. Rather than an isolated case, the application reflects an increasing number of oncology development programs based solely or predominantly on clinical trial data from China with at least 25 applications planned to be submitted or currently under review

at the FDA.

This increasing number of single-country trials is inconsistent with the International Consensus Guidelines, ICH E17, which promote multiregional clinical trials as the preferred approach to global drug development.

For years, multiregional clinical trials have been performed as the basis for drug marketing applications with the U.S. having substantial enrollment. Multiregional clinical trials allow for evaluation of regional consistency to directly compare safety and efficacy results across geographic regions and subpopulations of patients.

Single-country trials generally require duplication or sequential bridging of studies to demonstrate applicability in a new region, thus leading to delays and asynchronous international drug approvals. In contrast, enrollment of a global study population enables earlier access and more concurrent approvals worldwide.

Multiregional clinical trials promote international harmonization of standard-of-care

practices, allowing for more cohesive drug development around the world, as patients have access to similar therapies. ORIENT-11 was not conducted as a multiregional clinical trial; rather, it was conducted in a single region outside of the U.S.

The key review issues for this application revolve around applicability of the single-country trial to U.S. patients and medical practice. An outline of the presentation is shown here which will begin with a brief overview of the ORIENT-11 study design and results.

The applicant has stated that part of their development strategy includes making cancer drugs more affordable through competitive pricing. While FDA acknowledges drug cost as an important societal issue with great impact on patients, FDA cannot consider drug pricing in regulatory decision making, and this should not be part of the committee's consideration or discussion today.

You are now familiar with ORIENT-11, which randomized patients in a 2-to-1 ratio to

sintilimab, an anti-PD-1 antibody, or placebo in combination with pemetrexed and platinum chemotherapy. I will highlight here the primary endpoint was progression-free survival by an independent radiologic review committee with crossover from the control arm to sintilimab therapy permitted at time of progression. At the final analysis, with a data cutoff date of September 15, 2021, the applicant reports 47 percent of patients have crossed over from placebo to receive sintilimab.

Most patients enrolled in ORIENT-11 were male, had good performance status, and were either current or former smokers. The median age of patients was 61. Per the applicant, all patients were Chinese and from mainland China, which is considered a single region. These demographics are not reflective of the U.S. population of patients with non-squamous non-small cell lung cancer in which patients are older and include more women and smokers.

ORIENT-11 met its primary endpoint,

demonstrating a 3.9-month improvement in PFS with a hazard ratio of 0.48, favoring the addition of sintilimab. Overall survival, overall response rate, and duration of response were descriptive secondary endpoints and were not formally tested. High-level safety results are summarized here and are further detailed by the applicant.

While FDA acknowledges the reported safety and efficacy of sintilimab in ORIENT-11, acceptance of foreign data is predicated on applicability to a U.S. population and U.S. medical practice. The applicant did not consult with FDA until study completion and selected an endpoint and control arm not applicable to current U.S. regulatory standards. As we will further discuss, given the timing of this trial and standard-of-care therapies, ORIENT-11 would not have been feasible to conduct in the U.S.

A critical issue is the study population comprised entirely of Asian patients from a single country. While China is a multiethnic country, the ORIENT-11 study population is not reflective of the

racial and ethnic diversity of patients with lung cancer in the U.S. Acceptance of a study and similar studies conflicts with an industry-wide renewed commitment to equitable representation in clinical trials.

Patients enrolled in ORIENT-11 may not have been fully informed of the substandard chemotherapy control arm despite multiple contemporary immunotherapy-based approval. While inspections of limited clinical sites are conducted, the applicant has had limited prior experience in multiregional clinical trials, leading to FDA registration. In other words, they do not have a long-standing history with FDA or other international regulatory agencies which would garner confidence and data integrity.

Given multiple approved anti-PD-L1 antibodies have demonstrated a statistically significant advantage in OS for lung cancer, an additional anti-PD-L1 antibody with a PFS endpoint and several major issues regarding applicability does not warrant a flexible regulatory approach.

The Code of Federal Regulations provides clear criteria with which to consider U.S. marketing applications based solely on foreign data. ICH guidances also provide considerations for the evaluation of ethnic factors when assessing foreign data and more recently described multiregional clinical trials as the preferred approach in the setting of globalization of oncology drug development.

FDA is governed by Title 21 of the Code of Federal Regulations, which is a codification of the general and permanent rules published in the Federal Register by the executive department and agencies of the U.S. federal government. Guidance documents are issued by the FDA, including guidances endorsed by the International Council of Harmonisation, which represent the FDA's current thinking of specific subjects.

Per Section 314 of the CFR, a marketing application based solely on foreign clinical data may be approved if foreign data are applicable to the U.S. population and U.S. medical practice;

studies are performed by investigators of recognized competence; and there's FDA validation of trial data through on-site inspection or other appropriate means. Failure to meet any of these criteria will result in an application not being approvable based on the foreign data alone. The CFR also states that FDA will apply this policy in a flexible manner according to the nature of the drug and data being considered.

A flexible approach to the requirements for evaluation of foreign data may be warranted in select circumstances, none of which applied to ORIENT-11. If the data fulfills an unmet medical need for patients in the U.S., a flexible approach for the acceptance of foreign data may be warranted.

Acceptance of foreign data may also be important for rare diseases of the U.S. such as nasopharyngeal carcinoma, in which would be very difficult to carry out a trial in the U.S., but more feasible in countries of which the disease is more common. An application for a novel drug

without existing therapies approved in the same class may also merit flexibility.

The International Council for Harmonisation, or ICH, has established international guidance for evaluation of foreign data and conduct of global clinical trials. The ICH was established in 1990 to harmonize requirements of clinical trials and medicinal products. The ICH brings together global regulatory authorities and the pharmaceutical industry with a mission of ensuring safe, effective, and high-quality medicines worldwide. Currently, ICH is comprised of 19 members, including China's regulatory authority, the National Medical Product Administration, and 35 observers.

ICH guidances are used and applied by the FDA and are often incorporated into the U.S. Code of Federal Regulations. ICH E5 was envisioned in the late 1990s as a mechanism to fulfill unmet needs for patients historically not representative in clinical trials, such as patients from certain Asian countries.

Given potential regional differences and ethnic factors that may affect the safety and efficacy of drugs, ICH E5 provided a framework for extrapolation of foreign data from one region to another with guidance on appropriate bridging studies. In order to be considered for extrapolation, the trials must first be adequate, well controlled, and applicable to the regulatory standards of the new region, including the selection of the primary endpoint and control arm. Based on the likelihood that the drug is sensitive to ethnic factors, the need for additional bridging studies is determined.

The primary objective of ICH E5 was to minimize the need for duplicative clinical trials by outlining these steps to determine whether clinical trial data obtained from one region of the world such as the U.S. were sufficient to support a marketing application in another region of the world.

Both ICH E5 and E17 address the concept of differing intrinsic and extrinsic factors across

geographic regions which may impact the safety and efficacy of drugs. Intrinsic factors include genetic and physiological characteristics such as racial distribution, inherited risk factors for diseases, and genetic polymorphisms that affect drug metabolism. Extrinsic factors are related to the environment, including exposure to pollution or carcinogens, cultural practices, and the practice of medicine, including the diagnosis and management of diseases. While some of these factors may be evaluated by controlled pharmacokinetic studies, others are truly unknown differences and cannot be reliably studied outside of a multiregional clinical trial.

ICH E5 describes use of bridging studies to extrapolate foreign data from one region to another. In prior decades, this scenario often applied to Asian countries like Japan, requiring bridging studies to their population from a multiregional clinical trial. While the spirit of ICH E5 was to share innovation, this strategy has two major issues.

First, bridging studies may not fully address concerns regarding generalizability since they are smaller, tend to be non-randomized, and rely on response rate or pharmacodynamic comparisons rather than the endpoint used in the original trial, such as overall survival. Second, reliance on bridging trials usually conducted after completion of the original trial result in delays of important drugs reaching patients. As a result, many Asian countries have increased their participation in multiregional clinical trials to avoid reliance on duplicative trials and sequential bridging studies.

You heard from Dr. Singh regarding the evolution of ICH thinking from the late 1990s to 2017. The international regulatory community no longer views a sequential bridging strategy an ideal approach. Rather, they have emphasized multiregional clinical trials for more efficient drug development and concurrent global approvals.

You also heard from Dr. Singh that over the last decade, China has had limited involvement in

multiregional clinical trials as compared to other Asian countries, as depicted in blue and orange, respectively. The goal is to bring patients from China into the fold as participants in multiregional clinical trials.

The top of this diagram depicts an independent strategy of conducting duplicative local clinical trials in different regions of the world, which often leads to delays and asynchronous drug approvals. Alternatively, for ICH E17, the current ideal is multiregional clinical trials. As shown on the bottom, global trials can be employed at all phases of drug development to enable earlier access to new drugs worldwide and negate the need for bridging studies. ICH E17 promotes international harmonization of drug development and facilitates similar standards of care around the world.

The guiding principles of ICH E17 illustrate why strategic use of multiregional clinical trials is so important. Highlighting the fifth principle, which we find most important to this application,

multiregional clinical trials readily permit structured evaluations of regional consistency of results across subpopulations of patients. This is an important distinction from clinical trials from a single country such as ORIENT-11, which does not allow direct comparison of results across geographic regions and other subgroups. As a single-country trial, ORIENT-11 does not follow any principles for global drug development outlined in ICH E17.

Another important consideration regarding single-country clinical trials is the lack of ethnic diversity by design. Trials done exclusively in single countries will never have the appropriate range of diversity that is possible in a multiregional clinical trial. While the pharmaceutical industry has championed a renewed commitment to inclusion and diversity in clinical trials, acceptance of foreign data from a single country is antithetical to the concept of racial and ethnic diversity. Alternatively, enrollment of a diverse study population in an international

trial may help improve representation of underrepresented groups in drug development.

Improved diversity and representation in clinical trials will require continuing commitment and effort from FDA, the pharmaceutical industry, professional societies, patient advocacy groups, and healthcare providers. Project Equity is one such FDA oncology initiative focused on increasing diversity in clinical trials, generating data and more representative patient groups throughout the drug development process and developing policies to advance equity.

ORIENT-11 is not applicable to a U.S. population. The applicant was aware of many of the issues that were discussed and chose not to seek FDA guidance in advance of initiating the trial. KEYNOTE-189 was a landmark study that completely transformed the first-line treatment of metastatic lung cancer.

This FDA approval of pembrolizumab in combination with platinum-based chemotherapy was based on a statistically significant improvement in

overall survival with a hazard ratio of 0.49 over chemotherapy and a p-value of less than 0.0001. Importantly, this regimen was approved in the U.S. at the time ORIENT-11 was initiated. In a four-year follow-up of KEYNOTE-189, median overall survival was almost one year longer for patients treated with pembrolizumab at 22 months compared to 10.6 months on the placebo arm.

The FDA initially granted accelerated approval for pembrolizumab plus chemotherapy for non-squamous non-small cell lung cancer based on a PFS endpoint in KEYNOTE-189 in May of 2017. Overall survival data for KEYNOTE-189 were available by the spring of 2018, and these results were highly publicized before receiving FDA regular approval on August 20, 2018. Unbeknownst to FDA, ORIENT-11 was initiated after this landmark change to the U.S. standard of care.

ORIENT-11 duplicated the trial design for KEYNOTE-189, which the applicant highlighted in their first interaction with the FDA on April 21, 2020. This first interaction between the applicant

and FDA was after ORIENT-11 was well underway and after the primary endpoint for ORIENT-11 had already read out. FDA stated that as ORIENT-11 was conducted solely in China, a BLA submission must demonstrate how the study population adequately represents the U.S. patients in terms of disease characteristics, sex, race, ethnicity, age, and standards of care per 21 CFR 314.50. In another meeting, FDA indicated the impact of intrinsic and extrinsic ethnic factors on the exposure, efficacy, and safety of sintilimab must also be addressed.

While an anti-PD-L1 plus chemotherapy combination was not approved in China at the time of study initiation, pembrolizumab with chemotherapy was granted approval in China during the ORIENT-11 study period, approximately seven months after the first patient was enrolled.

Per the Code of Federal Regulations, foreign data must be applicable to U.S. medical practice. At the time ORIENT-11 was initiated, the standard of care for frontline metastatic lung cancer had substantially changed, rendering chemotherapy an

inappropriate comparator arm.

ORIENT-11 could not have been conducted in the U.S., as it was no longer applicable to U.S. medical practice. Investigators would not have been able to enroll patients to a chemotherapy control arm given that the pembrolizumab chemotherapy regimen demonstrated clinically and statistically significant benefits in overall survival. Enrollments of U.S. patients in ORIENT-11 would have denied patients the current standard of care and risk loss of gains in overall survival.

The applicant did not consult FDA at any point regarding study design or trial conduct. Had FDA been consulted, a formal head-to-head comparison of sintilimab to an FDA-approved anti-PD-L1 antibody with an overall survival endpoint would have likely been recommended.

To date, all first-line immunotherapy approvals for metastatic lung cancer have been based on statistically significant and formally tested improvements in overall survival. Overall

survival is considered the most reliable cancer endpoint and is preferred when it can be reasonably assessed.

The American public has benefited from multiple approved regimens with significant gains in survival. Trials were designed with OS endpoints in consultation with the FDA as early as 2015. Despite the precedent for an OS endpoint, it was not statistically tested in ORIENT-11. This application relies on a less clinically meaningful endpoint, namely PFS.

The applicant expressed concerns of confounding the observed treatment effect on OS due to crossover, however, crossover was permitted in other studies of immunotherapy-based regimens for lung cancer, which ultimately demonstrated OS benefit, and thus weakens the applicant's position. The applicant also emphasized cross-trial comparisons and compared themselves to several other FDA-approved anti-PD-L1 antibodies with statistically significant OS benefit. However, we cannot rely on cross-trial comparisons for

regulatory decision making and each application must rely on its own merits.

The applicant states there are three principles which demonstrate ORIENT-11 study results are applicable to U.S. patients. First, the applicant states there are similar clinical practice standards between China and the U.S. However, the standard of care in China at the time of trial initiation in 2018 was not applicable to U.S. patients in which first-line treatment of lung cancer had already shifted to include immunotherapy.

Second, the applicant states sintilimab has similar pharmacokinetics and pharmacodynamics between Chinese and U.S. patients. However, insufficient PK data are provided, particularly an underrepresented minority patients, to conclude similarity.

Third, the applicant states there is similar efficacy and safety of sintilimab between Chinese and U.S. patients. However, sintilimab has not been studied in any U.S. patients with lung cancer

to arrive at this conclusion. Furthermore, retrospective exploratory analyses of other anti-PD-L1 antibodies for the treatment of lung cancer suggest potential differences between Asian and non-Asian patients. The pharmacokinetics, safety, and efficacy of sintilimab for U.S. patients would be best evaluated in a multiregional clinical trial with a trial population applicable to U.S. patients.

There are key differences in the study population for ORIENT-11 compared to U.S. patients, which impact interpretability of the study results. The median age of patients was 61 in ORIENT-11, which is younger than the median age at diagnosis for U.S. patients.

Seventy-six percent of patients in ORIENT-11 were male, which does not reflect that closer to 50 percent of patients in the U.S. are female. Sixty-five percent of patients were current or former smokers, which is less than the percentage for U.S. patients. And while all patients in the study were Chinese, patients in the U.S. are approximately

79 percent white, 15 percent black, and 6 percent Asian.

To further consider the ORIENT-11 study population and applicability to U.S. patients, for comparison, here are the demographics for the KEYNOTE-189 trial which led to the approval of pembrolizumab plus chemotherapy. KEYNOTE-189 was a multiregional clinical trial which enrolled patients from 16 countries, including from Europe, the U.S., Canada, Japan, Israel, and Australia.

The percentages of male patients and current or former smokers in KEYNOTE-189 compared to ORIENT-11 are more like the characteristics of U.S. patients. Patients in KEYNOTE-189 were also older than patients in ORIENT-11, more closely approaching the median age at diagnosis for U.S. patients. Notably, a substantial majority of patients in KEYNOTE-189 were white with only 2.3 percent black patients and 2.9 percent Asian patients. This also is not optimal and does not fully represent U.S. patients with lung cancer.

Despite FDA's history and public health

interest, and surmounting disparate rates of trial participation, our efforts have been insufficient and more work is necessary. An important part of this work is to directly call attention to and address inequities in recent ongoing and planned clinical trials. Compared to single-country trials which lack ethnic diversity by design, enrollment of a global trial population can improve representation of underrepresented groups.

In addition to known factors, which are prognostic or predictive of treatment response, there may also be regional differences that have an unknown impact on the efficacy and safety of sintilimab. The applicant states the diagnosis of management of lung cancer are similar in the U.S. and China, however, it is not our intention to compare regional medical practices; rather, the question is whether medical care of the trial population is applicable to U.S. patients.

Given the chemotherapy control arm in ORIENT-11, this was not consistent with clinical practice standards in the U.S. in which first-line

treatment already included immunotherapy at the time of study initiation. Regional differences in concomitant medications, including herbal medications, may also impact applicability of study results, and the applicant reported that most patients in ORIENT-11 received at least one herbal medication during the study period.

Differences in body weight and composition of the trial population compared to U.S. patients may also impact efficacy and safety, and there may be additional unexpected regional differences with an unknown impact. Due to both known and unknown ethnic factors, regional consistency of clinical outcomes for sintilimab would be best evaluated in an international trial.

For this application, the applicant provided population PK analyses to compare the PK characteristics of 475 Chinese patients and 39 American patients with various cancers in the sintilimab development program. Of the U.S. patients, none of whom had non-small cell lung cancer, 30 were white, 5 were black, 3 were Asian,

and one was Native American.

For modeling and simulation analyses, the data provided by the applicant suggest no clinically significant difference from PK between whites and Chinese patients or a significant effect of body weight on PK. However, the number of patients are too small for PK comparisons with underrepresented minorities in the U.S., including black patients. It is standard for the FDA to request sparse PK collection in a U.S. patient cohort for the proposed indication, and additional PK data are needed to support efficacy and safety for U.S. patients.

In general, large epidemiological studies suggest Asian ethnicity is an independent favorable prognostic factor for overall survival for patients with non-small cell lung cancer. Regarding anti-PD-L1 antibodies for lung cancer, the applicant states sintilimab has similar efficacy and safety between Chinese and U.S. patients based on cross-trial comparisons of sintilimab in Chinese patients, with other anti-PD-L1 antibodies in more

Western populations, including U.S. patients.

They also cite an FDA abstract in which the benefit from anti-PD-L1 antibodies relative to chemotherapy for lung cancer did not appear to differ between Asian and non-Asian patients. However, the applicant does not mention that the analysis also showed that Asian patients had longer overall survival compared to non-Asian patients, suggesting ethnic differences may affect prognosis. This is consistent with findings in other exploratory analyses.

The applicant also does not mention that some exploratory analyses suggest potential differences in safety for anti-PD-L1 antibodies, including increased rates of immune-mediated pneumonitis in Asian patients compared to non-Asian patients. A composite of genetic and clinical demographic factors, along with regional variability in clinical practice, may underlie differential outcomes. A multiregional clinical trial would generate the strongest evidence and allow direct comparison of sintilimab in Asian and

non-Asian patients around the world.

A requirement for U.S. acceptance of foreign clinical trial data per 21 CFR Section 312 and 314, per good clinical practice and per ICH guidances, is that the clinical trial design and conduct are of high quality. This includes that patients should be well and adequately consented for study participation.

The applicant states that ORIENT-11 was a well-designed trial conducted in accordance with good clinical practice, however, there are concerns patients were not adequately consented. All three versions of the ORIENT-11 consent form relied on the study doctor to discuss alternatives to enrolling to the trial. The consent forms did not acknowledge the approval of pembrolizumab with chemotherapy as the new standard of care, albeit not yet approved in China at the time of study initiation.

When pembrolizumab plus chemotherapy was approved in China in March 2019, the informed consent document was still not revised to

explicitly describe this treatment option with demonstrated survival benefits.

Site inspections are required for applications of new molecular entities such as sintilimab. They are performed to ensure the safety and welfare of patients and verify the accuracy and reliability of clinical trial data. However, only a sampling of clinical trial sites are investigated, which does not fully capture the heterogeneity of data quality and study conduct across sites.

In 2016, China's State Food and Drug Administration issued a report that in an investigation of over 1600 drug applications in China, 80 percent of the applications should be withdrawn due to concerns of fraudulent or substandard data. While steps have been taken to address concerns raised in 2016, ORIENT-11 was initiated shortly after in 2018, and it is unclear if any sites included in the 2016 report were involved in ORIENT-11.

Prior participation in multiregional

clinical trials and interactions with FDA and other international regulatory agencies provide confidence in trial conduct and data integrity. Investigators in ORIENT-11 have had an uncertain level of prior participation in global trials and limited interactions with the FDA. Per the applicant, 10 of 48 sites have had prior FDA inspections for multiregional clinical trials in oncology or hematology. The applicant was unable to indicate how many patients were enrolled at these sites or whether the trials led to U.S. approvals.

FDA's Office of Scientific Investigations have inspected two clinical sites for ORIENT-11. Underreporting of both adverse events and concomitant medications was found. Corrective and preventive actions were taken, including training the staff regarding good documentation practices and emphasizing the importance of accuracy and completeness of the required data reporting.

For both investigators, this was their first FDA inspection. These findings underscore the need

for multiregional clinical trials with investigators who have gained experience in regulatory submissions to the FDA to ensure high data quality and accurate reporting.

The applicant compared sintilimab to other first-line therapies, stating that their demonstrated PFS advantage would translate to an OS advantage given similar hazard ratios across trials. However, each individual drug must be evaluated on its own merit and cross-trial comparisons are not appropriate.

While numerous FDA-approved anti-PD-L1 antibodies have demonstrated statistically significant OS benefit, this application only offers uncertainty given lack of formal testing for OS and questions regarding applicability to U.S. patients.

To address FDA concerns regarding applicability and generalizability to a U.S. population, the applicant proposed a randomized non-comparative study, including 150 patients from the U.S., Europe, and China, evaluating 2 doses of

sintilimab. The primary endpoint is overall response rate for the sintilimab arm dosed at 200 milligrams every 3 weeks.

The FDA does not consider this proposed study adequate to address issues of generalizability or applicability; rather, this appears to be a dose-finding study. Additional limitations are the small study size and the use of a less clinically meaningful endpoint. Importantly, ORR has not been established as a surrogate endpoint for OS in this disease setting. A better strategy to address applicability would be a formal comparison of sintilimab to an approved anti-PD-L1 antibody with an OS endpoint, with a study population that is representative of U.S. patients.

The 1998 ICH E5 guidance was not intended to demonstrate applicability of foreign data for me-too drugs like sintilimab that do not fulfill an unmet regional need. ORIENT-11 is a single-country trial with an endpoint and comparator arm not aligned with FDA regulatory standards, and

consideration of a bridging strategy envisioned in ICH E5 would not be appropriate here.

If ORIENT-11 was conducted as a multiregional clinical trial per ICH E17, there would have been early communication with international regulatory authorities, and FDA would have likely recommended direct comparison with an FDA-approved anti-PD-L1 antibody with a trial design utilizing an OS endpoint.

Importantly, a multiregional clinical trial would have permitted evaluation of safety and efficacy results across geographic regions and would have thereby addressed concerns about applicability of data to U.S. patients.

In summary, the applicant did not consult with FDA until study completion and selected an endpoint and control arm which are not applicable to U.S. medical practices or regulatory standards. The ex-U.S. study population from a single country is not representative of the diversity of U.S. patients with non-squamous non-small cell lung cancer.

While site inspections are an essential component of FDA review, they are limited in scope to verify study conduct and data integrity across all trial sites, and regulatory flexibility for this application in which there are concerns about applicability to U.S. patients is not warranted given the current therapeutic landscape.

The FDA must maintain the survival advantage seen in several approved therapies for U.S. patients with metastatic lung cancer. We would risk losing this by relying on cross-trial comparisons and approving sintilimab based on an PFS endpoint. Approval of this application would not signify progress in drug development, but rather takes a step backwards on issues of applicability and diversity, offering uncertain clinical benefit relative to available therapies.

Multiregional clinical trials are the preferred approach with increasing globalization of oncology drug development. They can be further strengthened by providing support and welcoming countries such as China, as well as countries in

Africa and Latin America which are currently underrepresented in oncology trials.

Greater diversity may provide additional information to assist the U.S. in generating data and addressing the underrepresentation of racial and ethnic minorities in drug development. Increased global participation in multiregional clinical trials provides a framework to establish regulatory experience for countries around the world. This patient-centered approach expedites global access to novel therapeutics and oncology.

Given the key review issues centered around applicability to U.S. patients and medical practices, we would like the advisory committee to discuss the following. First, discuss the generalizability of ORIENT-11 to a U.S. population and U.S. medical practice, and second, discuss potential clinical trials, if any, which may address issues of applicability of ORIENT-11 to a U.S. population.

After the discussion, we would like the advisory committee to vote on the following

question. Should additional clinical trials demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?

Thank you. This concludes my presentation.

Clarifying Questions to Presenters

DR. KUNZ: Thank you very much.

We will now take clarifying questions for all presenters. Please use your raised-hand icon to indicate that you have a question and remember to put your hands down after you have asked your question. Please remember to state your name for the record before you speak and to direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know that slide number, if possible. And finally, it would be helpful to acknowledge the end of your question with either a thank you or "That is all for my questions."

Of note, we are about 10 minutes over time. We will be stopping promptly at 12:25 for lunch. We can resume some of these clarifying questions

after the open public hearing.

I am looking in our raised-hand, and I'm going to start with Dr. Garcia.

DR. GARCIA: Thank you, Dr. Kunz.

I have a couple comments and a clarifying question directed to the FDA team. My comments are I'm somewhat perplexed to hear the clinical investigator in the United States, that the consent for that trial was not updated to reflect the standard changes in the management of that disease for those patients; so quite perplexing because in the United States we wouldn't be able to do that and continue clinical trial enrollment without that updated consent.

Second, it would be very hard today in North America to discuss with a patient the results of ORIENT and how that would apply to that patient's treatment with lack of survival data, when we have survival data in the United States based upon the KEYNOTE-189.

But since the FDA is not asking the committee to assess safety and efficacy of the

trial, and therefore the applicant, clearly to me, my interpretation throughout the morning is that there is really no need for regulatory flexibility based upon the existing data and certainly the standard of care in the United States.

My two questions for the FDA -- probably one -- specifically is, when you look at the CFR 314, I want to try to get a sense as to I understand that there was an inspection of two sides, but when you talk about data validation and recognize investigator competence, number one, did the FDA recognize the competence of the investigators on that trial, number one? And number two, with the inspection that you guys did, is the data considered validated by the FDA?

Those are my two questions.

DR. SINGH: This is Harpreet Singh. Thank you, Dr. Garcia, for your question. Your first question is about CFR 314 and data validation and whether the inspectors are considered to be, I think you said, of good standing, or whether they have recognized competence.

I think that is somewhat subjective in terms of what recognized competence is. You heard both the FDA and the applicant provide general background on the level of experience the investigators have had. They all seem to be GCP trained. Despite that, 2 of 48 sites, which were inspected -- I will add that they were inspected remotely given travel restrictions in China -- did find underreporting of, as you heard, adverse events in concomitant medications.

So while the volume of the underreporting was not deemed to be significant enough to necessarily alter the study findings per se -- that was per our Office of Scientific Investigations -- whether or not we would consider this data validated I think is questionable.

I'm sorry. I'm receiving a clarification from my team that, in fact, the investigator sites were inspected in person; the sponsor was inspected remotely.

I hope that answers your question, but I think from an FDA perspective, what we're seeing is

that both investigators who were inspected have never undergone an FDA inspection, and we did find underreporting. So I think it calls into question the overall data integrity given that this was only 2 of 48 sites, so it's unknown what we would find. There's certainly heterogeneity across sites in terms of data integrity and validity.

I hope that answers your question, and that ends my comment. Thank you.

DR. GARCIA: Thank you. Yes.

DR. KUNZ: Thank you, Dr. Singh.

DR. GARCIA: That's the end of my questions, Dr. Kunz. Thank you.

DR. KUNZ: Thank you, Dr. Garcia. I'll remind you to just lower your hand if possible.

I would like to go next to Dr. Nieva.

DR. NIEVA: This question is also for Dr. Singh, and maybe also for Dr. Vellanki.

Was there evidence of inappropriate randomization, inappropriate unblinding, synthetic data, or any other misconduct, and does the FDA feel that their inspections were in any way

inadequate or hampered for any reason? Thank you.

DR. SINGH: Dr. Vellanki, would you like to take that question?

DR. VELLANKI: Sorry. Thank you.

Yes. Thank you, Dr. Nieva, for your question. So far, based on the two clinical trial sites that have been investigated and the remote assessment of the sponsor, we haven't found any evidence of any issues with the data or issues with data integrity.

As Dr. Singh already pointed out, there was some underreporting of concomitant medications and adverse events, however, we don't see any evidence of fraud if that's the question you're trying to get at.

DR. NIEVA: Yes --

DR. SINGH: May I just add to that? Because, Dr. Nieva, you're asking about randomization and synthetic data, and it appears that you are kind of getting at the 2016 Woodhead report of really massive fraud in clinical trials in China, which is public information.

I think that one point that the FDA really needs to stress is that inspections and data validation is limited in its scope. We cannot go to every single site and backtrack every piece of data that's presented to the FDA. That is where prior history and reliance on investigators having experience with confirmed data has met its muster over the course of time, and I don't think we have that here with ORIENT-11.

That ends my comment.

DR. PAZDUR: This is Dr. Pazdur. Could I add in something?

This is one of the things why we're emphasizing the multiregional trials. When you do have a multiregional trial, you can take a look at sites in different countries and take a look at differences, so to speak, and adverse event reporting and efficacy, and compare them, and to see if there's any outlier here.

That is one of the major advantages of why we're really emphasizing future development and worldwide development on these multiregional

trials. They do give you an internal look at what is going on at various sites and look for consistency between sites, both in efficacy parameters as well as safety parameters.

So we feel that that's important. I just want to jump in with that.

DR. NIEVA: Thank you.

DR. KUNZ: Thank you very much.

I'd like to go next to Dr. Wozniak, please.

(No response.)

DR. KUNZ: Dr. Wozniak, please unmute yourself.

DR. WOZNIAK: Okay. Can you hear me now?

DR. KUNZ: Yes, we can. Thank you.

DR. WOZNIAK: Okay. Thank you, Dr. Kunz.

I have a couple questions for the sponsor and one for the FDA.

For the sponsor, I can understand considering PFS as a primary endpoint, but why not overall survival as a co-primary endpoint that was done in some of the other trials, specifically KEYNOTE-189?

DR. ANDERSON: My name is Ben Anderson. I'm the global product team lead at Eli Lilly, [inaudible], and Dr. Ferry will [inaudible].

Your question regarding a viable endpoint, that was an endpoint that was described [inaudible] as an appropriate one. We do not discount the importance of survival, overall survival, as an important secondary endpoint.

Slide up, please. Although not alpha controlled, overall survival was prespecified as a secondary endpoint. The endpoint is unambiguous. There was a high degree of patient follow-up, so the magnitude of the outcome makes it highly unlikely [inaudible].

DR. WOZNIAK: Okay, another question. Looking at your control arm, the patients seemed to do better than you would anticipate. It's hard not to do some cross-trial comparison, and that is with chemotherapy alone.

So I guess my question is, could that potentially represent differences in the patient population? For instance, if you broke it down by

sites of metastases, did these patients have less liver metastases?

DR. ANDERSON: Dr. Ferry?

DR. FERRY: It's been recognized for some time, patients from Asia Do have marginally better outcomes than patients in the West. And I would like to ask Dr. Socinski to weigh in on this point.

DR. SOCINSKI: Thank you, Dr. Ferry, and thank you, Dr. Wozniak, for the question.

We've known for quite some time -- and I think it was pointed out in the meta-analysis discussion -- that the observation has [inaudible] for several decades that Asian population, in general, with stage IV disease do have slightly better outcomes if you look at the point estimate [inaudible] survival. We've known that for quite some time.

Your comment about the control arm doing better on ORIENT-11 is interesting. I actually think the control arm on KEYNOTE-189 grossly underperformed. A median survival of 10.5 [inaudible] months is unusually low. And just

to put that in perspective at a trial that that was done around the same time IMpower, either 130 or 132 -- I can't recall -- used the same control arm, platinum pemetrexed, had a median survival of 13 [inaudible] months, a concurrent trial done it the same [inaudible] -- kind of underscoring the issues of what was going on.

So I don't know if that addresses your question, Dr. Wozniak, or not, but thank you.

DR. WOZNIAK: Just a follow-up. Did you look at the patient characteristics in terms of sites of metastases, like I said, liver metastases, and more of a breakdown by PD-L1 status, like how many had greater than 50 percent PD-L1 positivity?

DR. ANDERSON: Excuse me. I'm sorry. We had difficulty hearing the question. I apologize for the request to repeat.

DR. WOZNIAK: Okay. As a follow-up, I was just wondering if you did break down the patient characteristics by sites of metastases, such as liver metastases, and also a further breakdown of PD-L1, for instance, how many patients were greater

than 50 percent?

DR. ANDERSON: We do have data on PD-L1 status, and I'll ask Dr. Ferry to comment on that. Regarding sites of metastases, we would need to follow up with that, but we'll ask Dr. Ferry to address the PD-L1 expression status, please.

DR. FERRY: Thank you. The PD-L1 expression status was assessed by the companion diagnostic as used in the USA.

DR. ANDERSON: Slide up.

DR. FERRY: Slide up, please.

When we look at the data on our slide, you can see the PD-L1 data. As it was stratified for the randomization by less than greater than 1 percent, you can see it was balanced across both arms of the trial.

DR. WOZNIAK: As a follow-up, did you break it down any further, like 1 to 49, greater than 50 percent?

DR. FERRY: We did. Which data would you like to see?

DR. WOZNIAK: Greater than 50 percent, if

possible?

DR. FERRY: Yes, okay.

May I have the slide? Slide up.

This is the data for the primary endpoint, progression-free survival, and you can see that all subgroups less than 1 percent, greater than 1 to 49 and greater than 50 percent, benefited. And the distribution of patients, indicated in the brown brackets underneath the bold type, it was a 2-to-1 randomization in the trial, of course.

DR. WOZNIAK: Okay. Thank you.

I have just one question for the FDA. The sponsor did meet with you once the trial was ongoing and the primary endpoint I think read out. I'm just curious what advice was given at that first meeting, just to clarify.

DR. SINGH: Thanks for the question. This is Dr. Harpreet Singh. I'm glad that you brought this up because I found the sponsor's depiction of this to be a bit misleading to the committee. So let me take this moment to clarify.

The FDA had no knowledge that this trial was

ongoing until the primary result, efficacy results, became available. The trial had completed accrual. They came to us with their progression-free survival results. We told them at that time that there were concerns regarding applicability and generalizability to a U.S. population, and we did discuss the possibility of asking for additional data.

We did not elicit exactly what type of data that would look like. This is a topic that has evolved over time within the agency and has involved multiple high-level discussions. But we certainly did express our concerns with the data, with the fact that the study population did not adequately represent the U.S. population, and we invoked the Code of Federal Regulations as you've heard today.

So I do want to take this moment to clarify because I do believe that the applicant presented this in a way that was somewhat misleading.

I'd like to ask Dr. Julia Beaver to follow up on this topic as well.

Dr. Beaver?

DR. BEAVER: Hi. This is Julia Beaver, FDA. Yes, along these points, it's really well known across industry that in order to receive formal regulatory advice or potential agreement on a drug development plan, discussion with FDA is critical in a formal setting. And this is the way most programs are developed, as it allows for that mutual understanding of appropriateness of a trial design and formal discussion regarding FDA's opinions, compared to, for example, interpreting informal discussions at a public meeting.

Actually, I'd like to ask the applicant a follow-up question because we're still, I think, confused, and we'd like the applicant to comment on why you did not come to FDA for discussion of this trial, either prior to initiation or perhaps earlier on in development, and instead came only after the trial results were obtained.

DR. ANDERSON: Thank you for the question. Related to the timing of our interaction and sponsor's interaction with FDA, as we've stated in

our presentation, this was an application initially intended for approval in China. After seeing the data and recognizing guidance provided a pathway for use of that data in filings in the U.S., the sponsor sought meeting with the FDA per Code of Federal Regulations, guiding sponsors to have meetings to discuss potential applications prior to submission. So that was the sequence of events. If we mischaracterized that in our presentation, we apologize, as well as with respect to the feedback that was received at that meeting as well.

If we might take the opportunity to share feedback that was received at the meeting, at least from our perspective, just to ensure that we're not mischaracterizing that -- slide up -- the feedback that we've been acting on is highlighted here in the slide from the meeting minutes that address the comments that we have been actively discussing with the FDA on the potential for postmarketing data in a population representative of the U.S. population. Thank you.

DR. SINGH: This is Harpreet Singh. I find

this incredibly misleading. I show you data, word for word, comments from our meetings package from April 2020 in which we use much stronger language invoking the Code of Federal Regulations. So we're happy to break -- the public record and show all of our correspondence, and we can do that.

DR. KUNZ: Thank you all. This is Dr. Kunz. We have reached 12:25. I would like to propose that we pause the clarifying questions. We can get back to these. We have taken note of who currently have their hands raised, and we'll get back to that after the open public hearing.

We will now break for lunch. We will reconvene in 35 minutes at 1 p.m. Eastern time. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at around 12:55 p.m. Eastern to ensure that you are connected before we reconvene at 1 p.m. Thank you very much.

(Whereupon, at 12:26 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. KUNZ: Welcome back, everyone. I'd like to remind everybody to please mute their lines. This is Dr. Pamela Kunz again. 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.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself by stating your name and any organization you are representing for the record. Thank you.

DR. ZUCKERMAN: Thank you. Can you hear me?

DR. KUNZ: Yes, we can. Thank you.

DR. ZUCKERMAN: Okay.

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our center is a non-profit think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

My expertise is based on postdoctoral training in epidemiology and public health and as a faculty member and researcher at Vassar, Yale, and Harvard. I've also worked at HHS and the White House, and I'm on the board of the non-profit, Alliance for a Stronger FDA, which educates Congress about the need to support the work of the FDA. On a personal note, I am a cancer survivor, so I understand the pressure to find new

treatments. My goal today is to be as objective as I can in evaluating the evidence regarding sintilimab.

There are many problems with the data supporting this application, but let's start with the first mistake. Number one, the sponsor did not consult with the FDA regarding the trial design or conduct. That's almost always a big mistake, and it definitely is in this case. The result is a very inadequate trial design, including a non-representative group of patients.

Number two, most important to me, the study relied on progression-free survival rather than overall survival. We agree with FDA scientists that other drugs in the same class have shown highly significant improvement in overall survival. What matters most to cancer patients is how long they'll live and the quality of their remaining lives, not whether or not they die of the cancer they're being treated for.

So what could possibly justify approving a cancer drug that's not as good as those already

available for the same indication?

Number three, FDA is sometimes flexible about its usual requirements, especially when there's an unmet need. We agree with the FDA scientists that this drug does not address an unmet need, and several treatments proven to improve overall survival are already available. This drug review therefore, quote, "does not warrant regulatory flexibility," unquote.

Number four, as you know, the data are all based on patients in China. For the FDA to consider foreign data as the sole basis for marketing approval, the data are supposed to be applicable to the U.S. population and to U.S. medical practice.

We agree with the FDA that the data presented today are neither. The population studied is not at all representative of the US' diverse population, and equally problematic, the studies' comparative control arm was based on chemotherapy alone, and that's not consistent with the U.S. standard of care. Therefore, a different

control group would be needed to determine the benefits and risks of sintilimab.

FDA notes that the studies have not been performed by clinical investigators of recognized competence and that FDA has not had enough contact with the investigators to be confident of their competence, and that's obviously terribly important.

Number five, the sponsor has proposed an additional study, but their proposed study does not address the serious design issues that have been criticized at today's meeting. We agree with the FDA reviewers that this additional study does not, quote, "address the concerns regarding endpoint selection," unquote.

In conclusion, you've been asked to vote on whether additional clinical trials with data applicable to U.S. patients and U.S. standard of care are necessary before a final regulatory decision is made. I'm very concerned about the inadequate informed consent for patients in this study, as well as other issues that have been

raised today. So I hope you'll agree that, yes, additional trials are needed, and they need to address all the major shortcomings of the data submitted so far before the FDA decides whether to approve it.

Overall survival is the essential endpoint at a level that's meaningful to patients. The patients studied must be representative of U.S. patients in terms of race, age, and other key variables, and the comparison group needs to have the kind of medical care that's the standard care in the United States.

My final note, FDA notes that they have had more than 25 applications whose studies are at least predominantly based on clinical trial data from China. Each study should be evaluated on its own merits, but the FDA's decision regarding sintilimab should not set a precedent for FDA approval decisions of medical products that are not appropriately studied to determine the risks and benefits of patients in the United States. Thank you so much for the opportunity to speak today.

Clarifying Questions to Presenters (continued)

DR. KUNZ: Thank you, Dr. Zuckerman.

We have no further speakers for the open public hearing portion. We will now take remaining clarifying questions.

Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you have asked your question. Please remember to state your name for the record -- even after I state your name -- 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.

As a gentle reminder, it would 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 for my questions," so that we can move on.

We previously had -- and I will list in order -- Dr. Conaway, Dr. Madan, Dr. Arscott, and Dr. Dagogo-Jack. We will go in that order.

Dr. Conaway, please?

DR. CONAWAY: Yes. Mark Conaway, and a question for the applicant.

You enrolled in ORIENT-11 397 participants across 48 centers. Can you describe how the enrollment was distributed across them? Was there a majority, say, in a few sites or distributed broadly across the 48 centers? Thank you.

DR. ANDERSON: Yes. We can provide that data. Before we get to that, I do want to quickly return to the discussion prior to the break and to be clear.

It's certainly not our intent to mischaracterize our interaction with the agency, and I apologize if comments or presentations did not align with the FDA perspective. Our goal is to work in good faith and find a path forward. I just want to make that comment before we provide the details in response to your question.

Dr. Ferry?

DR. FERRY: David Ferry, Eli Lilly and Company. You asked a question about the

distribution of recruitment across patients in the trial. Slide up. This slide shows a bar graph of accrual by site number.

Is this the information you request?

DR. CONAWAY: Yes.

DR. KUNZ: Dr. Conaway, do you have any further questions on these data?

DR. CONAWAY: I do not.

DR. KUNZ: Okay. Thank you.

Dr. Madan, your question is next.

DR. MADAN: Yes. Ravi Madan, and just a quick question.

This has come up a lot with the PFS endpoint, and we understand the survival data that you've shown. But can you provide any, maybe, understanding of the rationale to choose progression-free survival in a trial that was presumably designed with the intent to show definitive efficacy in a disease state where overall survival was the benchmark, well-established benchmark, for clinical benefit and success? Thank you.

DR. ANDERSON: I believe your question was the rationale for the selection of the PFS endpoint to the study. As we mentioned in our presentation, that endpoint was established based on an agreement with local regulatory standards or expectations in China, which is the country where the study was intended to provide the initial approval.

Despite the primary endpoint, overall survival was prespecified as a secondary endpoint, and I mentioned earlier, that endpoint, unambiguous in a high degree of patient follow-up, gives us confidence, along with the magnitude of the outcome, that it's unlikely to be a result of chance.

DR. SINGH: This is Dr. Harpreet Singh. I would like FDA statisticians to comment on that because we have the lay public listening to this, and I think not everybody understands what it means to have an alpha-controlled endpoint. That's a scientific term, and I want to make sure that we are all very clear that overall survival was purely descriptive, and we cannot do these backwards

calculations regarding whether or not overall survival would have been statistically significant if certain analyses were done.

I think we have a slide up. Can we put up slide 59 from the FDA? I think we do need to address this for the committee.

Dr. Vellanki, do you want to take this?

DR. MISHRA-KALYANI: Dr. Singh, this is Pallavi Mishra-Kalyani from FDA statistics. Would you like for me to reply?

DR. SINGH: Yes, please. Thank you.

DR. MISHRA-KALYANI: Sure. I think Dr. Vellanki was going to indicate a slide. Slide 59 is the slide that I need from the FDA presentation.

Thank you very much for holding up this slide. Yes, as Dr. Singh mentioned, the endpoint of overall survival was prespecified as a secondary endpoint of the study, but there was not a formal statistical analysis plan prespecified for this endpoint.

The issue with that is that we don't have

any concept for how many events or deaths are needed for a robust analysis of this endpoint, so any evidence that we are collecting post hoc, or any observed results post hoc, can't be interpreted with the same amount of rigor as we would in a setting where we were allowed -- or where we have prespecified an analysis plan.

For example, in the briefing document, the sponsor indicated that they could have considered conducting different interim analyses with control of type 1 error for these analyses. However, they did not have a prespecified number of deaths for the final analysis, nor did they have a number of analyses to be conducted for OS.

So all of these exploratory endpoints don't allow for a typical control of type 1 error, and any post hoc calculations or boundaries are invalid because we didn't have the information that we needed a priori to determine whether or not those boundaries would be accurate.

So as highlighted here on this slide, without a detailed and prespecified analysis plan

for statistical testing, the post hoc results that we've observed are really only considered hypothesis generating because we don't have the scientific rigor that we need to rely upon considering whether the results are true findings or whether they are observed due to chance. And I can clarify any points here, if needed. Thank you.

DR. KUNZ: Thank you very much.

Dr. Madan, do you have any further follow-up on that question?

DR. MADAN: No, I do not. Thank you.

DR. ANDERSON: If the chair would permit, we would like to make some comment regarding our statistical assessment of the endpoint, if appropriate.

DR. KUNZ: Can you please identify yourself, and I will allow a brief response.

DR. ANDERSON: Dr. Yong Lin?

DR. LIN: This is Yong Lin, Eli Lilly and Company, biostatistics. I want to address two questions related to the overall survival analysis.

First, we acknowledge that the final overall

survival analysis timing has not been defined prior to the interim analysis. However, after the interim analysis, it goes through the protocol amendment to define the final overall analysis timing to be approximately two years after last patients are being randomized; so that will give us a pretty similar majority, comparing to other checkpoint inhibitors in a similar class.

Regarding the robustness of the overall survival data, we acknowledge that there is no alpha prespecified, and also we cannot argue the p-value significance as well. However, I want to show you in the sensitivity analysis, the overall survival, as we demonstrated for ORIENT-11, is strong and robust.

Slides up. Here on these slides, we presented a retrospective constructive graph of the overall survival p-value over the duration of follow-up since the interim analysis of PFS. This can be a useful indicator for how strong the overall survival results are and how they [inaudible] as the follow-up data [inaudible].

The black and the purple lines represent a standard conservative boundary commonly used for significance testing. You can see after the 160 overall survival events, the p-value stabilized at a low level, and it's consistently below the boundary representing the typical benchmark for a statistical and a clinical meaningful result.

This isn't a case of a lucky trial outcome where the p-value just happens to be looking very good at a specific timepoint of the analysis. The analysis of the p-value over time suggests that there couldn't be any other reasonable interpretation than to say there is a clinical impactful overall survival effect of sintilimab. Thank you.

DR. KUNZ: Thank very much.

I'd like to remind all of our panel members, applicant, participants, and the FDA to please raise hand in order to best determine order of speakers or questions.

I'd like to move next to Dr. Arscott, please.

DR. ARSCOTT: Yes. Thank you. This is Dr. Karen Arscott. I'm directing my question towards the FDA, please.

As a physician who also is a patient with stage III lung cancer, I was offered the opportunity of curative treatment 15 years ago, and I'm sitting here talking to you as a result of my curative treatment.

That stated, I'm concerned with ORIENT-11 stating that 3 percent of the patients screened were excluded from the study to the possibility of curative treatment, and I'm wondering what the percentage of curative potential is in the United States for stage IIIB and IIIC lung cancer. If they included people who could have had curative treatment, I believe it may have skewed the results.

So that is my question. Thank you so much.

DR. SINGH: This is Harpreet Singh. Give me one moment while we identify an FDA oncologist to answer your question.

DR. VELLANKI: Hi. This is Paz Vellanki

from the FDA. I'm the clinical reviewer for this application. Thank you for your question.

Just taking a look at the patient demographics for this trial, I believe there are about 9 percent of patients who had stage IIIB or III3C non-small cell lung cancer. So per standard of care in the United States, if patients aren't resectable for their lung cancer, we still are aiming for curative intent therapy. The standard of care in the U.S. at this point is to undergo concurrent chemo radiation, followed by durvalumab. So that was a potential concern for us as well, that there were some patients that might have been denied potentially curative treatment.

I would have to talk with the sponsor about what was the standard of care in China at that time. I'm not sure about the availability of that therapy there, so I don't know about the proportion of patients that might not have been eligible for chemo radiation. That information I do not have, so that's something that we could potentially ask the sponsor to address that question as well.

Does that answer your question?

DR. ARSCOTT: Yes. Thank you very much.

DR. KUNZ: Thank you.

I'd like to move to Dr. Dagogo-Jack, please.

DR. DAGOGO-JACK: Thank you. Ibiayi Dagogo-Jack here. This is a question for the sponsor.

It has been stated a few times that this study was initially designed with the rationale to be conducted and to pursue regulatory approval solely in China. I just wanted to get a sense about the rationale behind that and the rationale for now seeking expansion of that indication or the approval. Thank you.

DR. ANDERSON: You are correct. The intent, original intent, for ORIENT-11 was to seek approval in China. It was part of a broad program for ORIENT-11. Given the outcome of that study, the magnitude of benefit that was observed in the trial, the regulatory paths that we understood exist to use foreign data for applications in the United States, we made the decision to consult with

FDA in a pre-IND and pre-BLA meeting, and subsequent to those interactions made the decision to file. Thank you.

DR. KUNZ: Dr. Dagogo-Jack, does that answer your question, or do you have any further?

DR. DAGOGO-JACK: It does answer my question. Thank you.

DR. KUNZ: Thank you.

I'd like to move to Dr. Deeken, please.

DR. DEEKEN: Thank you. I have a related question, actually, to this point because there's been a lot of discussions about the timelines here, and I just want to make sure I understand the timelines. This is a question to the sponsor.

The early slides identified that the collaboration between the sponsor and Eli Lilly started in 2015. ICH E17 was approved in 2017. The KEYNOTE-189 study was released in April of 2018, and the first patient enrolled on ORIENT-11 was August of '18, and the first FDA meeting was April 2020.

I guess just to follow up on that previous

question, from the collaboration, it seems like the intent was still to only seek approval by the China NMDA [ph], and only when the results came out, or was known internally for PFS, was that attention and discussions with FDA initiated.

Is that an accurate timeline and summary of the decision with Lilly to engage the FDA after all those different [inaudible]? That's the end of my question. Thank you.

DR. ANDERSON: Yes. The decision to investigate opportunities in the United States did follow the outcome of the interim analysis for ORIENT-11, which included the primary endpoint and available survival data at that time. That's correct.

DR. KUNZ: Thank you.

Dr. Deeken, any further questions?

DR. DEEKEN: No. Thank you.

DR. KUNZ: Great. Thank you.

DR. DEEKEN: Okay.

DR. KUNZ: Dr. Cristofanilli, you are next.

DR. CRISTOFANILLI: Yes. I have a question

for the sponsor, a consideration or question.

First of all, we recognize that the drug is efficacious. Clearly, the studies show there is an improvement in progression-free survival, but you also need to recognize that this was not a study that was conducted according to regulation that will allow the approval in the U.S.; but for that matter, for any other country.

In fact, even China would not accept a study conducted only in the U.S. without having testing Chinese patients. In fact, I think Dr. Cheng, who is a member of the committee, has done similar things with Merck when he was actually extending KEYNOTE-42 to the Chinese population in order to achieve that approval.

So the question is two questions. First of all, are you looking for requesting approval in Europe also based on the fact that you have this strong data that may be supporting approval in other countries outside the U.S.? And second, are you thinking, or have you already planned a different study design compared to the dose finding that you

proposed to the FDA?

DR. ANDERSON: I'll answer your question regarding our regulatory intent outside of the United States.

At this stage, our only application for this study is with the FDA. Regarding your second question, related to alternative study designs, I think one of the key elements of feedback that we received from FDA in our October 2020 meeting was input related to the study design that we propose today.

In addition to that, FDA highlighted that the outcome of this meeting may also provide additional direction as to what an appropriate study design might involve. So we look forward to continuing our conversation with FDA, and we believe that the conversation from today's meeting will shape the final proposal here. Thank you.

DR. KUNZ: Dr. Cristofanilli, does that answer your question, and do you have any further ones?

DR. CRISTOFANILLI: Yes; no other questions.

DR. KUNZ: Excellent.

There appear to be no further questions or no further raised hands. I'll pause and ask if there are any other questions.

Dr. Singh has a question. Please go ahead.

DR. SINGH: Yes. This is Harpreet Singh. I have a question to the applicant.

As physicians, which we all are, our first obligation really is to patient care, and patients on clinical trials, we all understand, should be getting the best available therapy. But as brought forth today, patients enrolled to the control arm in ORIENT-11 were being denied a known therapy, which conferred survival benefit, and you yourself, the applicant, admitted that the consent form never explicitly addressed this issue, omitted the approval of pembrolizumab not only in China but worldwide corporate stance on this.

I feel that this could potentially erode trust in clinical trials. Were you comfortable with the chemotherapy arm that deprived patients of a therapy that prolonged overall survival, and how

many times has Eli Lilly conducted trials that have deprived patients of therapies with known survival advantage? Thank you. That ends my question.

DR. ANDERSON: I'd like Dr. Matt Rotelli to please respond.

DR. ROTELLI: Matt Rotelli, Eli Lilly and Company, bioethics. There are a couple questions in there, and the first was around the company policy.

Certainly, it's important for patients to understand there are other treatment options as part of the informed consent process for clinical trials. The ORIENT-11 informed consent document set the expectation for patients that their study doctors would discuss other approaches to treat their disease, as well as any new information that became available.

So while the informed consent process was ethical throughout the trial, it would have been ethically preferable for the sponsor to update the trial-level informed consent upon the approval of pembrolizumab as recommended in the ICH guidance.

This would have ensured that the IRB, the local IRBs, explicitly made the determination whether it made sense to update the site-specific informed consent accordingly.

Now related to the local reviews and the availability, which is a factor in their decisions, you still have to remember that informed consent goes beyond the document and it is a process through which patients need to understand the benefits and risks of the research, as well as the alternatives. Part of this is the documentation, and part of it is also the ongoing interactions between study doctors and patients.

The study included all the components for the ethical process. The ICH GCP guidelines include specific informed consent documentation steps under investigator responsibilities with IRB oversight. This content must be appropriate for local needs and requires judgment on both the part of the investigator and the IRB. Investigators or IRBs may not update informed consent documents, even when a new product is approved, if they feel

there is limited availability or low likelihood that most patients will have access. Rather, this information can be better disseminated in a conversation with the patients. Thank you.

DR. ANDERSON: I'd just like to continue. Of course, Lilly has policies to address this, and Dr. Rotelli can provide that detail in granular form, but I'd like Dr. Lana Shiu from Innovent to characterize the issue in the ORIENT-11 case, please.

DR. KUNZ: And please be sure -- this is Dr. Kunz -- that you introduce yourself by name. Thank you.

DR. SHIU: Sure. Dr. Lana Shiu, Global Regulatory Affairs for Innovent Biologics. We do want to acknowledge that the trial-level ICF could have been amended when pembro was approved in China so that the local IRBs can make their own assessment whether or not to update the site ICF.

Our previous approach, as stated in our ICF, was that the investigators should have the conversation with their patients to communicate

available alternative treatments, and later we discovered that this process could be much improved. And now that our process has already been updated, our mandatory documentation of the conversation between the investigator and the patients, and IRB form, can update available treatments as they become available in those countries.

We do trust our investigators to be very well experienced in clinical trials in that we do know that patients who withdrew from the ORIENT-11 trial have actually undergone other IO treatments, and it's been documented in their hospital records. Thank you.

DR. SINGH: This is Harpreet Singh. Thank you for that. I think your response really underscores the FDA positioning that this trial, ORIENT-11, was not conducted in compliance with GCP and with good clinical practice in which a central tenet is adequate informed consent. So thank you so much for your responses. That concludes my question and my response to your remarks. Thank

you.

DR. PAZDUR: This is Rick Pazdur. I'd like to follow up on that question. I would like this discussed during the discussion period because I feel very uncomfortable about this issue of having a known therapy that has an improvement in median survival of over a year, and patients are not getting it. I'd like some discussion on that part among the committee members.

I know that a drug may not have been available commercially there, but I think a discussion of when one has a major sea change in the standard of care, that it isn't just left at hand to have at-random discussions with people. So if we could have some discussion on this whole issue because it will come up with other trials that are emanating from potentially China or other regions.

I'd also like to follow up with Lilly with another question, and this is somewhat related.

Over the past two years since the pandemic ended, every major cancer society -- ASH, AACR, and

ASCO -- has had conferences on ethnic and racial diversity with the intent of increasing racial and ethnic enrollment in clinical trials, and I believe Eli Lilly participated in this. This trial that you presented here is an example of what we call lack of diversity by design. You cannot have any diversity here because it is emanating from one geographic area.

Could Lilly comment and reconcile to me why you're making comments on a podium of endorsing racial and ethnic diversity, and then on the other hand submitting this trial to the FDA?

DR. ANDERSON: The topic of representative U.S. population that supported this application has been a conversation that has been consistent with FDA over the course of the pre-BLA and our proposal that was shared in our discussions in October. It is a topic in which FDA and Lilly share the clear objective of making improvements to address diversity in clinical trials.

DR. PAZDUR: Well, sir, let me --

DR. ANDERSON: I'd like to --

(Crosstalk.)

DR. PAZDUR: -- go ahead.

DR. KUNZ: This is Dr. Kunz. Please be sure you're identifying yourself.

DR. ANDERSON: Oh, I'm sorry. This is Ben Anderson from Eli Lilly.

DR. KUNZ: Thank you.

DR. ANDERSON: I'm sorry.

I just want to maybe take a step back as I address in more detail Lilly's commitment to diversity in clinical trials to sort of remind us of the point that ORIENT-11 was originally designed to support an approval in China.

It was appropriate to enroll a Chinese population for that purpose, and we discussed our assessment based on the outcome of that study, the regulatory paths that we thought available through the Code of Federal Regulations and ICH E5 guidance, as well as our assessment for the lack of ethnic sensitivity, and that we brought this application to the FDA, as we've done with our partner Innovent.

That said, Lilly has developed a comprehensive set of behaviors to support diversity and equity across not only development programs in oncology but across the entire development portfolio of Lilly. These include best practices for clinical trial design; conduct; investigator site selection; stakeholder engagement, all intended to help drive diversity in our trials. And we're committed to ensuring that we exercise each of those levers in the studies that we've been discussing with FDA related to this application.

We're happy to discuss these further and welcome your ideas, as well as the ideas from stakeholders. But while we hold these as core values, we do not believe they should preclude consideration of a previously generated data set that meets the criteria for approval that we believe ORIENT-11 does.

DR. PAZDUR: Well, the reason why I'm bringing this up, obviously, is that this is not the only application that is going to be coming from China, and I just want people to have an

understanding that if we move in this direction of accepting these applications, of accepting data from one geographic area, this is a step backward in all of our conversations about ethnic and racial diversity. And I'm very unhappy to have this conversation on this month, which is, obviously, Black History Month.

I think we really have to do a better job of this. We have several programs at the FDA on this, including Project Equity, trying to address this issue. But this whole issue of a single country that is unrepresentative of the United States and submitting data from this is a step backwards in all of our approaches of addressing this issue, and I think the American public has to know it.

We just had a meeting yesterday with external groups to celebrate Black History Month, and the primary thing that many people said -- and I'm sure all of you on this call have heard it that our clinicians -- is we want people that look like us on this trial. And I'd like to emphasize that the representation of ethnic and racial minority

groups is not just a biological reason that we want people on these trials, it is to build confidence in the clinical trial system and also a confidence after these drugs are approved, that they should be used in these groups. Actions speak louder than words.

I'd like to next ask my second question to Lilly, and this has to do with the issue of 80 percent of the clinical trial data being fraudulent found in 2016 by the Chinese regulatory authorities.

Did any of your investigators or any sites withdraw voluntarily or were asked by the Chinese FDA to withdraw data; any site investigators, either involuntarily or requested by the Chinese FDA to withdraw data?

DR. ANDERSON: We are going to have to follow up and try to confirm that.

DR. PAZDUR: Eighty percent of clinical trial data was [inaudible]. We would appreciate --

(Crosstalk.)

DR. ANDERSON: I'm sorry. Please continue.

DR. PAZDUR: We would appreciate that data. Here again, one of the issues that we have is an issue of data integrity, and that needs to be examined. And here again, we look at the past history of clinical trials.

As was stated by Dr. Singh, we cannot inspect every site. Inspections are limited. We have to build quality into clinical trials by, number one, having investigators that have experience in clinical trials, that have submitted to the FDA, and also part of that is any sites that have had past regulatory indiscretions. We need to know about that, and it's somewhat unnerving that you don't have that data for us.

DR. ANDERSON: Thank you, Dr. Pazdur. We will endeavor to collect the specific numbers. I do want to ensure, though, that it's clear to the panel the quality attributes of ORIENT-11, and some of that data is going to be shared by Dr. Ferry and followed up with Dr. Shiu.

DR. FERRY: David Ferry, Eli Lilly and

Company. The quality attributes of ORIENT-11 were consistent with the expectations of a phase 3 study. Slide up. Here we document the sites and the investigators in ORIENT-11, and Dr. Lana Shiu will now follow up and describe the detail.

Dr. Shiu?

DR. SHIU: Yes. Dr. Lana Shiu, Global Regulatory Affairs, Innovent Biologics. From this slide that you have shown here, we demonstrate that at least half the sites and quite a bit of our investigators in ORIENT-11 have participated in trials that have led to FDA approval. As you know, in order to obtain FDA approval, many of these sites have actually undergone FDA inspections in the previous years.

I also want to make a correction in that the data that you're citing from the British Journal, it was in actually 2016, which was actually more than 6-7 years old. And since then, China has enacted significant reform of those GCP inspection regulations and law.

Can we please pull up the slide O-6?

Please bear with me.

(Pause.)

DR. SHIU: Slide up. China, prior to its joining ICH in 2017, underwent significant reform of its GCP inspection regulations and law, and later on enacted it, as you see on the slide in 2017, making it a crime, and it's punishable in 2017. In 2018, in June, the British Medical Journal actually said in their article, "Due to the strict regulation supervision and high cost of breaking the law, deliberate fraud in China is almost impossible."

So we would like to acknowledge that although there has been previous media attention to this in the last seven years, we do want to say that since joining ICH E7, China has adhered to the regulations and laws and has played on an equal footing with all the other international regulatory agencies. Thank you.

DR. KUNZ: Thank you.

DR. PAZDUR: Nevertheless, I would like to have that data that was alluded to, to be submitted

to the FDA.

DR. KUNZ: Thank you, Dr. Pazdur.

DR. ANDERSON: Thank you. We've acknowledged that, and we'll pursue follow up.

DR. KUNZ: Thank you.

Before moving to Dr. Cristofanilli, I would like to remind prior question askers to please lower their hand if they have completed their questions.

Dr. Cristofanilli, please?

DR. CRISTOFANILLI: Yes. I want to go back to what Dr. Pazdur brought up with regard to the appropriate information provided to the patient with availability of agents that may prolong survival. This is a responsibility of the clinicians/investigators, the IRB, but there wasn't any point of IDMC questioning the possibility that, in fact, the treatment that was being delivered to the control arm was actually not ethical. This is a question for the sponsor.

DR. ANDERSON: I apologize. It's a difficult connection here. Could you repeat your

question, please?

DR. CRISTOFANILLI: Yes.

With regard to the availability of an approved drug like pembrolizumab for patients with non-small cell lung cancer that would improve the survival of these patients, if there were any questions raised by the IDMC with regard to the ethical continuation of this treatment for the control arm in the study, in the ORIENT-11 study?

DR. ANDERSON: I think if I heard correctly, the question is, was there guidance from the IDMC regarding the appropriateness of the control arm at the approval of pembrolizumab? Did I understand that correctly?

DR. ANDERSON: Yes. I'd like Dr. Lana Shiu to comment on the guidance from IDMC on that point, if it was so provided.

DR. SHIU: Dr. Lana Shiu, Regulatory Affairs, Innovent Biologics. IDMC recommended continual of the study. Thank you.

(Pause.)

DR. KUNZ: To the sponsor, have you

identified who is speaking, please?

DR. ANDERSON: They've completed their response to the question.

DR. KUNZ: Okay. We will move on. I'd like to move next to Dr. Nieva, please.

DR. NIEVA: Yes. To follow up on this issue, I think it's important that we understand how egregious the GCP issue is.

Can you comment on, or have any data on, the market penetration of checkpoint inhibitors in lung cancer in China during the final year of the study?

DR. ANDERSON: I'll just preface with some detail prior to asking Dr. Lana Shiu to comment. At the point of pembrolizumab approval in China, the ORIENT-11 study was enrolled to about 80 percent. The last four months of enrollment, pembrolizumab was approved.

I'll ask. Dr. Lana Shiu to comment on accessibility and availability during that period of time.

DR. SHIU: Dr. Lana Shiu, Global Regulatory Affairs at Innovent Biologics. You are correct,

Dr. Anderson, that 20 percent, which is 84 patients, enrolled in the last three to four months of this trial when pembrolizumab was approved in China. And I also want to point out that pembrolizumab was approved in China with only Western data before there was actually any China data.

Pembrolizumab in China was not easily accessible because there was only about 30-plus hospitals around China that was actually able to write for pembrolizumab, so it was very, very limited.

Also, the local sites also needed to make an assessment of the cost to the patient and whether or not they can have availability, and that is also based on the fact that pembrolizumab cost over half a million RMB per year. So there was limited availability and accessibility to this drug at that time. Thank you.

DR. KUNZ: Thank you.

Dr. Nieva, does that answer your question?

DR. NIEVA: Yes. Thank you.

Questions to the Committee and Discussion

DR. KUNZ: Great. Thank you.

At this point, there appear to be no further questions or no other hands raised, so we will move to the next section.

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 now proceed with the questions to the committee and panel discussion.

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. After I read each question, we will pause for any discussions or comments concerning its wording, then we will open the question to discussion.

Question 1. Discuss the generalizability of ORIENT-11 to a U.S. population and U.S. medical practice. I'd like to first open to see if there are questions or comments concerning the wording of the question.

Dr. Pazdur, I see that your hand is raised. You have a question about the wording or --

DR. PAZDUR: I just wanted to give some general comments before we begin this discussion of our thinking in the agency over the past couple of years. There was an allusion to some comments that I made at AACR in 2019, and I wanted to address that issue since it has been published in the press, and to note how our thinking has evolved and how the world has really evolved since that time.

Since that time, there's been at least seven approvals for non-small cell lung cancer. All of them are based on overall survival. In addition to that, the data, survival data, on pembrolizumab has been updated, which now shows over a year improvement in overall survival.

We strongly believe in the FDA that we should not lose this year of overall survival, and that's why we have brought this forward to make sure that people understand that the world has changed here. Comments that were made at an AACR meeting should not be viewed as regulatory policy.

Conversations should be held, especially when it regards the regulatory submission of an application within the FDA. But nevertheless, we believe that the landscape has significantly changed since those comments, especially with the demonstration of the overall survival and the maturation of that over time. So the landscape has changed here, folks.

Number two, over the past two to three years, especially since the pandemic, this country has experienced significant social change, and there has been a tremendous outcry for diversity in clinical trials and representation. We as a public agency, the FDA, has to adhere to what patients want in the United States. And clearly, as I stated before, we've heard clearly from all patient groups that they want faces like theirs presented in their clinical trials. So we have a huge commitment to diversity.

Single-country submissions is a step backward in achieving the racial diversity that we need in the United States, and I just want people to understand that this is going to be a major goal

of not only oncology submissions but also the missions throughout the FDA.

The third point I want to address with regard to change in our perception of what we want from international trials is this issue of multiregional trials. We want to bring China into the multiregional arena here. We feel that we would all benefit by having China participate fully in multiregional trials with the U.S., with Europe, with South America, Central America, and hopefully Africa.

The world will be a better place with having all countries participate in these multiregional trials. Here again, the single-country trials are a step backward in that regard. We don't want to pit one country against the world. We want to have everyone participate together.

So as far as our thinking that has evolved, these are three major points that I want to bring out here that have evolved and have changed. The landscape has changed; the world has changed since those comments were made. So here again, the

landscape's changed in the treatment of lung cancer. We have mature survival data. We have 10 approvals in this disease setting. We have to bring some order to the treatment of lung cancer and have trials that really compare themselves to current standards of care in the United States.

Secondly, we have to address this issue of ethnic and racial diversity. This came out in the last two years at every single cancer meeting, and we cannot be deaf to this. Number three, we have to work on having a global regulatory environment. We are all going to be stronger with a global regulatory environment. This will help bring in China to the region. It will build confidence in their clinical trial structure and their results that emanate.

The benefits of a multiregional trial was brought out by the FDA, and I'm not going to go over them, but these are the three central issues that I want to bring up here to reflect our evolving thinking on acceptance of foreign data. So I'll return it back to you.

DR. KUNZ: Thank you, Dr. Pazdur.

At this point, I would like to open the panel specifically to question 1 to discuss the generalizability of ORIENT-11 for the U.S. population and U.S. medical practice.

I see that. Dr. Garcia has his hand raised. Please ask your question.

DR. GARCIA: Thank you, Dr. Kunz. Jorge Garcia.

I don't know if I can just expand or perhaps ask Dr. Pazdur, while we recognize the importance of global practices, I have a feeling, as you indicated and the FDA group has indicated, we will continue seeing single-country trials being presented in the FDA or at the FDA.

I wonder if there is any way that policy, or regulatory policy, can be changed until such global community gets formed, if you will, because I think it's very hard to go through these processes, recognizing the need, or lack thereof, of regulatory flexibility. And I think that may be a way to avoid future trial designs that are not

consistent with what we're trying to accomplish, certainly in the researcher's space for cancer patients.

I wonder if there's a step in the FDA's thinking to change policy, whether it's the CFR 314 or the IHC [sic] policies that you guys have.

DR. PAZDUR: Well, I think the IHC policy E17 really addresses this, and for people that have not read it, it's really an excellent document. It really addresses the importance of this.

I think when sponsors come with a single-country submission, we have to ask ourselves why are they doing this. And if it is to avert doing the appropriate trial that would be done in the United States, and if they're looking at a regulatory loophole because the drug has not been approved, the comparator drug -- the new standard of care had not been approved and they're just doing it in a foreign trial to avoid doing what they would need to do in the United States -- that is extremely problematic, and we really have to address this.

DR. SINGH: Dr. Pazdur, this is Dr. Singh.

Dr. Garcia, may I just add to that? I think if you read quite carefully the Code of Federal Regulations, actually, in my humble opinion, I don't think it needs to be changed. I think it absolutely covers and allows for applications. It says the nature of the drug and the nature of the data being considered may call for regulatory flexibility.

Dr. Vellanki laid out indications, rare indications like nasopharyngeal cancers or even some pediatric tumors, where really it may be very challenging to conduct a multiregional international trial, and we would ask sponsors to come to us a priori and talk to us about it. But I think the Code of Federal Regulations broadly covers both this application in a way that has allowed us to take quite a negative opinion, as you see, but also could take a more favorable opinion where there is flexibility that may be warranted. So we're not moving to change the law. I think it covers all scenarios quite nicely. Thank you.

DR. KUNZ: Thank you very much, Dr. Singh.

I'd like to ask the panel to please redirect to the question at hand around the generalizability to a U.S. population and U.S. medical practice.

Dr. Nieva, did you have a question?

DR. NIEVA: Yes. I have a question for Dr. Pazdur and Dr. Singh.

DR. KUNZ: Dr. Nieva, is it on this question? We need to really focus on the discussion question right now.

DR. NIEVA: Yes. Well, I'll hold it then. Thank you.

DR. KUNZ: Okay.

We have two questions -- I'll just remind everybody -- prior to the voting question. The goal is to try to have a discussion amongst the panel of these questions prior to the voting question, and we'd like to have a discussion amongst the panel. So let's try to focus on discussing the generalizability.

Dr. Madan, I see that you have your hand raised.

DR. MADAN: Yes. Ravi Madan. I think from my perspective, it's really hard to generalize this data given that this is a trial that, at least for regulatory purposes leading to approval, wouldn't have been done this way in the United States. I think there are a lot of other issues here to do with country origin, et cetera, but just from a clinical trial standpoint, for me that's a fundamental obstacle in generalizing this to an approval situation.

DR. KUNZ: Thank you for comment.

I see Dr. Wozniak, please.

(No response.)

DR. KUNZ: Dr. Wozniak, we cannot hear you yet. Please unmute.

(No response.)

DR. KUNZ: We can come back to you.

I will go to Dr. Lieu next, please.

DR. LIEU: Yes. I agree with the comments that have already been made. I think when you look at the mechanism of action and the data that's been shown today, it's going to be hard to believe that

the data would be extraordinarily different in the United States population.

So I think it potentially has the applicability, but the thing is that it hasn't been proven. So with a single study, single country, with this statement, the generalizability, we don't know the answer to that because it hasn't been proven, although we can make some assumptions. So I think it's problematic from that standpoint.

DR. KUNZ: Thank you, Dr. Lieu.

I'd like to go to Dr. Deeken, please.

DR. DEEKEN: I just want to echo and agree with what's been said. I think that's the key challenge here, is it's not generalizable to the U.S. population, from fewer smokers and a younger population; a big difference in terms of gender representation here was dominantly met, and we didn't see that in 189 and we don't see that in the general population; and obviously to the ethnic and racial disparity that we see here.

So I just want to echo and agree with what Dr. Pazdur and others have said. We can

hypothesize that it would be applicable, but we don't know that, and that's too big of a leap to make, I think, in an indication application like this. That's the end.

DR. KUNZ: Thank you, Dr. Deeken.

Dr. Dagogo-Jack, your comments, please?

DR. DAGOGO-JACK: Yes. All my comments reflect what was said before in that I think that while it is not inconceivable -- unconceivable or inconceivable, my apologies -- that data would, in the end if applied to the United States or Western population, generate the same outcomes as we've seen with other studies in this space, I think we don't have the data at hand, and I think that the data that were presented to us don't directly draw the conclusion that this is generalizable.

DR. KUNZ: Thank you.

Dr. Wozniak, we'll come back to you if you can unmute your microphone, please.

DR. WOZNIAK: I think I'm unmuted. Can you hear me?

DR. KUNZ: Yes, we can.

DR. WOZNIAK: Sorry. I have to apologize; I disconnected myself.

Anyway, I'd like to echo what everyone else says, and I'd like to emphasize the importance of a multiregional approach to clinical trials because it would generalize the efficacy, the side effects, and also allows patients access to new treatments and allows new investigators to be involved. So I believe that a multiregional approach is the way to go.

DR. KUNZ: Thank you very much.

Dr. Nieva?

DR. NIEVA: Yes. I'm going to dissent a little bit from the discussion. I think our clinical trials have many areas in general [inaudible].

DR. KUNZ: Dr. Nieva, we're having a hard time hearing you.

(No response.)

DR. KUNZ: You may be disconnected, so we'll come back to Dr. Nieva.

Dr. Rosko, you are next, please.

DR. ROSKO: Thank you. Ashley Rosko, Ohio State here. I just wanted to emphasize the second part about this regarding the generalizability with the U.S. for ORIENT-11 on the U.S. medical practice.

I think it's important that supporting a study which undermines the faith, and the rigor, and the clinical trial process in terms of the informed consent would be a major step backwards. Having an informed consent process was described in the China health authority IRB, and it's not in alignment with the U.S. medical practice.

I just wanted to emphasize that portion of that and how this would be a major setback for the faith and the rigor of the clinical trial process within the U.S., and again to reiterate that the factors, independent of ethnicity, as has been outlined, such as never smokers, far less women, and a far younger age, is also not generalizable to the U.S. population in a disease that's primarily diagnosed in older adults.

DR. KUNZ: Thank you, Dr. Rosko.

Dr. Conaway, your comments, please?

DR. CONAWAY: Yes. Mark Conaway. I wanted to echo what Dr. Rosko just said. I think the generalizability fails on both of the clauses in the end; that even if this were a study that were done in a study population that matched the U.S. population, which it didn't, the choice of the comparator group makes it not generalizable to U.S. medical practice. That's the end of my comment.

DR. KUNZ: Thank you, Dr. Conaway.

For Drs. Rosko, Dagogo-Jack, and Conaway, if you have completed your questions, please lower your hand. If you have a further question, you may remain with your hand raised.

Dr. Nieva, we'll try to go back to you.

DR. NIEVA: Can you hear me now?

DR. KUNZ: Yes. Thank you.

DR. NIEVA: Okay, great.

I'm going to dissent a little bit from the mood of the discussion. I think most of our clinical trials have a significant defect in their generalizability to a U.S. population. We enroll

patients in our clinical trials of a higher performance status, a younger age, and a more urban academic oriented setting of different ethnicities, on average, to our clinical trials from a U.S. medical practice.

So I think the question here is not whether or not there is perfect generalizability, but is the generalizability too far away from what happens in the U.S. population that it cannot be considered good science? This is not an unknown drug class. We know a lot about this drug class, and I think we know enough that the fact that it was done in an Asian population does not detract from its applicability since we know that the response rates, the pharmacokinetics, and other features of the drug are going to be very similar.

With regard to the use of the older comparator arm, I'm not concerned about that because all the approved drugs use the same comparator arm. And I'm concerned that if we don't allow these types of trials for me-too drugs, we're going to be limited in our ability to have more

drugs for our patients, and that's going to lead to higher costs, in general, for them. Thank you. That concludes my comment.

DR. KUNZ: Thank you, Dr. Nieva, very much.

I would like to summarize our discussion for this question before we move to discussion question 2.

I would say that the majority of our panel members felt that there was not generalizability of ORIENT-11 to a U.S. population and U.S. medical practice. Though there were some comments that there may be a class effect, it had not yet been proven in a U.S. or Western population.

There were also comments that a multiregional clinical trial approach is important and should be embraced, and that in not doing so, it undermines the rigor of the current clinical trial process. I will note Dr. Nieva's comment in dissenting with that.

Let's move to question 2, please. Thank you.

Question 2 for discussion, discuss potential

clinical trials, if any, which may address issues of applicability of ORIENT-11 to a U.S. population. So again, we are discussing potential clinical trials which may address the issues of applicability. I'd like to open this up for panel discussion, please, and this is our last discussion question prior to the voting question.

Dr. Nieva, I see your hand still raised. Do you have a comment on this question as well?

DR. NIEVA: I do. I think that, obviously, the same design --

DR. KUNZ: Actually, Dr. Nieva, if I can interrupt; I forgot to just mention one thing before we go into discussing, so I'll push pause just for a moment.

I'd like to ask the panel if there's any question on the wording of the question? Are there any clarifying questions around the wording before we move to Dr. Nieva's comments?

(No response.)

DR. KUNZ: Okay. It appears it's not.

So, Dr. Nieva, please continue.

DR. NIEVA: Obviously, the ORIENT-11 clinical trial design cannot be done in the United States, but I think there's a great deal of latitude that would be available to understand applicability to the U.S. clinical trial population.

There simply could be a randomization against a comparator, where the drug did not need to show necessarily superiority. Additionally, there could be studies done that focus on the specific missing ethnic groups and underrepresented minority populations, that didn't have the opportunity to see the drug before, in order to try to get the kind of fundamental pharmacologic and pharmacodynamic data that would justify ongoing use in the U.S.

DR. KUNZ: Thank you, Dr. Nieva.

Dr. Lieu, your comment, please?

DR. LIEU: When you think about potential clinical trials, this idea of a noninferiority overall survival benefit study, to me, seems rather not feasible, and I'm not necessarily sure that

that's a good use of limited resources and, honestly, limited patient participation.

Having said that, on the flip side, if you design a one- or two-arm study looking at overall response rate, that level of evidence likely is too low to justify. But to Dr. Nieva's point, I think the data that we have already provides a level of evidence that suggests that this is going to be similar to a lot of the trials that we've already seen in non-small cell lung cancer.

But then, how much latitude do you have of maybe not accepting overall response rate, not going all the way to overall survival, which may take close to a decade to do, and what would an endpoint like progression-free survival in a more diverse or United States representative population look like?

I think that that should be considered, to find some type of middle ground where you aren't doing some gigantic phase 3 study, but you have enough evidence to justify potential approval. That concludes my comment.

DR. KUNZ: Thank you, Dr. Lieu.

Dr. Cristofanilli, please?

DR. CRISTOFANILLI: Yes. I think the question is can we design a study in a reasonable amount of time to show equivalence in terms of efficacy and safety? And of course, if the primary endpoint is overall survival, you have to make sure that you have an adequate number -- as was just mentioned by Dr. Lieu -- that you [inaudible].

So should you be using some statistical design approach that allows looking at maybe two endpoints at the same time, eventually overall survival and progression-free survival, and maybe a 2-to-1 randomization, and other approaches that allow those [inaudible] the primary question. And the comparison arm should be the standard of care. That could be any of the checkpoint inhibitors approved in combination with chemotherapy, particularly with the regimen that was approved in ORIENT-11.

DR. KUNZ: Thank you, Dr. Cristofanilli. Are you completed?

DR. CRISTOFANILLI: Yes.

DR. KUNZ: Okay.

DR. SINGH: This is Dr. Harpreet Singh. May I interject for one moment?

I hear the committee kind of pondering around feasibility of a noninferiority design and the time which it may take, but I am not sure what the rationale is for any urgency to approve this drug. So I'm not certain that the time it may take to conduct what may be considered the right thing to do, or the appropriate thing to do, should be factored in here. That's just something I'd like to ask the committee to consider. Thank you.

DR. KUNZ: Thank you, Dr. Singh.

We will continue with panel member contributions.

Dr. Deeken, you are next, please.

DR. DEEKEN: I guess I would pick up on that point. I don't know how we do anything less than a noninferiority overall survival randomized trial to show efficacy and comparability, but I would agree with Dr. Singh that we don't need another trial

with another PD-1 inhibitor and with a standard chemo backbone.

I guess the encouragement I would have was to try to push the ball forward and see what additional trials and combinations this drug could be with other immunotherapies to try to advance the ball, rather than looking for a me-too trial short of a definitive trial proving efficacy, which at this time would have to be a standard-of-care arm that's chemoimmunotherapy. That's the end of my comment.

DR. KUNZ: Thank you, Dr. Deeken.

Dr. Wozniak, your comment, please?

DR. WOZNIAK: When I was reviewing the data, I actually thought about what kind of trial you could do, and what came to mind is a noninferiority trial. But I realized the number of patients, and it would take a long time, and a lot of patients would need to be involved.

I think that the trial proposed by the sponsor probably won't answer the question, so is there a middle ground? I'm not a statistician, and

I just wonder whether a trial could be designed with a diverse population and maybe compare certain aspects to standard of care that could be done just to find a middle ground, and I don't really have an answer to that.

DR. KUNZ: Thank you, Dr. Wozniak.

Dr. Dagogo-Jack, your comments, please?

DR. DAGOGO-JACK: Yes. I just wanted to echo what's been said, and particularly what was said by Dr. Singh. I don't think that we should compromise appropriateness for convenience for a study like this, and I think what we've heard across the board and what we've seen with other studies in this space that have gained FDA approval is that OS was the primary endpoint, and I think an ideal study has to have formal powering for an OS endpoint.

At the same time, I think that it would be remiss not to acknowledge that we are now kind of existing in a crowded space, so even that estimate of a seven-year enrollment or accrual period, I think that it probably is an underestimate with

other competitors in this space.

DR. PAZDUR: Could I just jump in here? This is Rick Pazdur.

The size of the noninferiority trial depends on percent retention of effect, and we could have discussions about that to limit the size, lowering potentially the percent retention of effect. I don't want to get into the design of any trial, but this idea, basically, of a noninferiority trial and the size can be looked at by determining what you are willing to accept as far as a loss of retention of effect.

The trial that was presented by the sponsor had the highest possible retention of effect that was generally what we would recommend, but given the circumstance, with an additional trial here, we could take a look at potentially other issues here.

DR. KUNZ: Thank you, Dr. Pazdur.

We'll move on to some of the other panel members.

Dr. Madan, please.

DR. MADAN: Ravi Madan. I want to echo what

Dr. Deeken said. I think as opposed to looking for a way to match what has already been done, how can future studies look to improve on the standard? I think that is one path forward here. Then to echo Dr. Singh's point, I agree that we shouldn't sacrifice quality for expediency, especially because it's not just about getting a ball over a goal line; it's having enough data where there's confidence in the practitioners to use it.

So your trial has to convey that confidence, and if an alternate endpoint or underpowered study doesn't do that, then it may not convey that confidence, and you don't want other mitigating situations such as cost or something driving people to use something without the sufficient data. Thank you.

DR. KUNZ: Thank you very much.

Dr. Garcia, please?

DR. GARCIA: Thank you, Dr. Kunz. Jorge Garcia. I think what is intriguing to me, as I hear the presentations and the comments from my committee colleagues, is the fact that, to me at

least, I don't think I have heard that we're questioning the efficacy and safety of this ORIENT trial, at least the combination of the PD-1 and chemotherapy, but rather I think the fundamental discourse that we're having right now is the makeup of the patient population that was enrolled in the clinical trial. It makes me wonder if we had been presented today with a multiregional ORIENT-11 trial, if our discussion would actually be different.

So to me, as I think of a trial design, it sounds to me that the trial design really is -- the hallmark of that is really a multiregional, multiracially -- if you allow me to use that expression -- multiethnic clinical trial where we all feel comfortable than what we see right now in this presentation, and could be applicable and could be consistent across many different ethnic groups.

I don't think that any of us on the committee -- and certainly I'm not a lung cancer expert -- dispute the safety and efficacy of this

combination, granted that ORIENT-11 does not have survival data as of yet. So to me, the question is not so much, or doesn't appear to be, of the efficacy, but rather the makeup of the composition of the clinical trial in question.

I don't know, from the statistics perspective or maybe from the FDA perspective, if outside our noninferiority trial, what kind of trial design in a multiregional setting would suffice for looking at safety and efficacy that is consistent with what was presented today.

DR. PAZDUR: We really have to discuss that. And here again, I think we can't get into, with limited time here, really designing a trial. What we're really looking for are large concepts that we could take back and discuss internally. Okay? But thank you for your comment.

DR. GARCIA: Thank you, Dr. Pazdur.

DR. KUNZ: Thank you.

We will go to Dr. Arscott next, please.

DR. ARSCOTT: Yes. Thank you. This is Karen Arscott. I'm a physician and the patient

representative, and I feel obligated to respond to the discussion about the clinical trials.

I think that if I was given the option, I would struggle with joining a noninferiority trial. I would probably prefer to go with the trial that was completed -- or medication that was completed in the demographic in which I fall, where I have some knowns; or I think it was mentioned by some of my other colleagues about taking this and moving it as a jumping-off point to try to improve upon the results of this therapy.

I just thought I should make a point that I don't know about a noninferiority trial at this point. It would take a long time, and I would struggle with signing on for something like that at this point. Thank you.

DR. KUNZ: Thank you, Dr. Arscott.

Dr. Madan, you still have your hand raised. Do you have another comment?

DR. MADAN: No. That's a mistake. I apologize.

DR. KUNZ: Okay. No worries.

Dr. Sung, you had your hand raised previously. Do you have a comment?

DR. SUNG: I was just going to respond to Dr. Garcia, but Dr. Pazdur seemed to suggest that that would be outside the scope, so I think I'm ok. I lowered my hand.

DR. KUNZ: Okay. Great. Thank you.

If there are no further questions from panel members, I'd like to just briefly summarize the conversation.

I think along the lines of Dr. Pazdur's comment, we are not out of scope to exactly design a new clinical trial, but I'll just summarize I think there was consensus on a desire to have a multiregional diverse population. There's recognition that this is already a crowded space. I think where there was lack of consensus is specifically around the type of study design, whether it be a noninferiority or a standard design, looking for efficacy of one arm over another and a desire to move the field forward with a novel combination.

Those were things that were all discussed, in addition to should there be a meeting in the middle, some middle ground, recognizing that there is likely a class effect with this agent, and is there an opportunity to look at progression-free survival in a U.S. population; so no consensus on the specific trial design, but a robust conversation.

Dr. Pazdur, did you have any further comments? And then we will move to question 3.

DR. PAZDUR: No, I don't. Thank you.

DR. KUNZ: Okay. Great. Thank you.

So we will now move on to the next question, which is a voting question. Commander Bonner will provide the instructions for the voting.

CDR BONNER: Thank you. Commander Bonner.

Question 3 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 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 circle 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 question will be displayed on the screen. I will read the vote results from the screen into the record. 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 choose to.

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

(No response.)

CDR BONNER: Okay. I will now turn the meeting back over to our chair.

DR. KUNZ: Thank you, Commander Bonner.

Question 3 is the voting question. Should additional clinical trials demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?

I'm going to ask if there are any questions or comments concerning the wording of the question?

(No response.)

DR. KUNZ: If there are no further questions or comments, we will now begin the voting.

CDR BONNER: Commander Bonner. We will now move voting members to the voting breakout room to vote. There will be no discussion in the voting breakout room.

(Voting.)

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

(Pause.)

CDR BONNER: The vote results are displayed. I will read the vote totals into the record: 14 yeses, 1 no. 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 the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any

I return this meeting back to the chair. Thank you.

DR. KUNZ: Thank you, Commander Bonner.

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. Garcia.

DR. GARCIA: Thank you, Dr. Kunz.

Jorge Garcia. I voted yes, additional

trials are required prior to U.S. regulatory approval. I don't think the applicant and their data can be applicable to our U.S. patient population. I have to admit that I'm disappointed to hear the lack of engagement between the applicant and the sponsor early on during the trial design. I would like to believe that if those meetings were held, we probably wouldn't be actually having this conversation today. Thank you.

DR. KUNZ: Thank you, Dr. Garcia.

Mr. Mitchell? And I'll remind everyone, please state your name first.

MR. MITCHELL: I'm David Mitchell. I voted yes. There's no need for regulatory flexibility because this application does not address an unmet need. We have treatments that are safe and effective and show an improvement in overall survival, rather than this drug which was tested against a primary endpoint of progression-free survival and not against current standard of care, but instead against chemo and a placebo.

At a time when the FDA and the industry are trying to increase diversity in clinical trials to ensure they are representative of the patient population to be treated, it makes no sense to move in the opposite direction with this application. Thank you.

DR. KUNZ: Thank you, Mr. Mitchell.

Dr. Cristofanilli?

DR. CRISTOFANILLI: I voted yes for reasons that were discussed, primarily because this was a single-country ran study and doesn't apply to the variety of diversity that we are in the U.S., and in other countries, for that matter.

We should actually support and recommend that this be followed since the beginning of the design of the initial studies. Then of course, for the primary endpoint, there was not overall survival and progression-free survival.

DR. KUNZ: Thank you.

Dr. Rosko?

DR. ROSKO: Hi. Ashley Rosko. I voted yes. My vote reflects my concern on the clinical trial

integrity, particularly as it applies to the informed consent process, and also is supported by the prior comments regarding diversity and clinical trial inclusion.

DR. KUNZ: Thank you.

Dr. Deeken?

DR. DEEKEN: I voted yes as well. I do not think it's applicable to a U.S. population. It needs a more diverse, as well as gender balance, in terms of the patients we have here in the U.S. It doesn't meet an unmet need. It didn't have overall survival. I'm concerned about the inclusion of III3 B and C patients. I'm concerned about the reporting of adverse events, and very concerned about the patients who were enrolled to the standard-of-care arm after pembrolizumab was approved in China.

So I voted yes, that additional studies with a diverse population are required before a final regulatory decision is made. Thank you.

DR. KUNZ: Thank you.

Dr. Arscott?

DR. ARSCOTT: Karen Arscott. I voted yes for the reasons stated previously, and in addition because of the inclusion of IIIB and IIIC patients who could have had curative treatment, and yet were included within this trial. Thank you.

DR. KUNZ: Thank you.

Dr. Dagogo-Jack?

DR. DAGOGO-JACK: Ibiayi Dagogo-Jack. I voted yes because, in my opinion, the value of a well-designed, multiregional clinical trial and the importance, as Dr. Pazdur stated, of the charge to have more diverse clinical trials I think was central to my vote. I believe the data that were presented don't support the applicability of ORIENT-11 findings to the diverse more heterogeneous U.S. population, and the primary endpoint of PFS, in my opinion, is a step backwards.

DR. KUNZ: Thank you.

Dr. Conaway?

DR. CONAWAY: Mark Conaway. I voted yes. There should be additional trials required that

provide a direct comparison of safety and efficacy of the proposed regimen to the current standard of care that's relevant in the U.S. population.

DR. KUNZ: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu, and I voted yes. I will echo what's already been said. There's no need for regulatory flexibility in this situation. The applicability I think is still questionable. I have no concerns regarding competence, but there was certainly a concern regarding FDA validation. I do think an additional study is warranted.

I would again stress I think that this is a known entity, and there's already a body of evidence that is available. And I have concerns about forcing a noninferiority seven-plus year study as a confirmatory study, but would hope that the FDA and the applicant would be able to work towards a potentially more feasible and efficient solution.

DR. KUNZ: Thank you.

Dr. Wozniak?

DR. WOZNIAK: Yes. Antoinette Wozniak. I voted yes. I think my issues were that this wasn't a multiregional trial and it lacked diversity. I echo everything everyone else said. I think that maybe discussions with the FDA regarding an additional trial that would promote the diversity will be useful, and I think that's it.

DR. KUNZ: Thank you.

Dr. Nieva?

DR. NIEVA: George Nieva. I voted no. This drug works, adding value over chemotherapy alone in the first-line therapy of advanced lung cancer patients. We have no evidence that the data presented is unreliable, synthetic, or otherwise fraudulent. We have adequate FDA inspections that were not hampered. If more inspections were needed, it is expected the FDA would have performed them. The PFS endpoint is appropriate with a crossover design. OS findings appear clear with no identified issues in randomization or blinding that would have raised questions about this.

I don't believe we have an excess number of drugs for lung cancer. If we did, we would have seen downward pricing pressure by now, and there has not been; nor is our job to decide how many drugs is too many. Rather, it's our job to determine if drugs are safe and effective.

Regarding the need for resolving health equity issues in the U.S., health equity I think will improve when there are fewer cost barriers to care, and having more drugs competing for those same patients will have, I think, greater impact on equity than the need for diversity in clinical trial enrollment, which I believe is important.

Multiregional clinical trials are ideal, but I do not believe they should be a fixed requirement for approval. Performing these trials requires a global infrastructure, and it creates unnecessary barriers to entry for new drugs, small firms, and eliminates middle-income countries from developing their own pharma drugs developed in nations that don't have access to new drugs, and this study is an example of that effect.

I think me-too drugs are good things. They bring down drug prices and increase access to care for all patients. It seems the chief sin that the applicant has committed is not doing things the way the FDA would like it to have been done. They failed to show a proper process, not that they failed scientifically. I think the FDA should be in the business of evaluating their science and not the process, unless the process used compromise the science.

So in not following the FDA process, the applicant has made the job of the FDA harder. And as the FDA has structured its approach to data integrity, as Dr. Pazdur pointed out, on the ability to make comparisons across national borders and look for irregularities, I think there needs to be some additional thinking on how well, other than MRCTs, we can overcome this risk. I don't think that's a sufficient concern that should impact approval in this case. That's the end of my statement.

DR. KUNZ: Thank you, Dr. Nieva.

Dr. Advani?

DR. ADVANI: This is Ranjana Advani. I voted yes. Basically, I would echo the talks of my colleagues who have voted yes, too, for the same reasons. Thank you.

DR. KUNZ: Thank you.

Dr. Madan?

DR. MADAN: This is Ravi Madan. I voted yes. This study was not intended to lead to approval in the United States. The primary endpoint therefore was not appropriate in progression-free survival, so for me, that's a fundamental issue. And while there is OS data, overall survival data, it lacks really the necessary robust statistical design.

I would also like to say that while data integrity is of utmost importance in clinical research, moral integrity is of greater importance. And we really need to do a better job to make sure -- especially in all clinical research, but especially in large studies like this -- that patients have the appropriate informed consent that

is updated as needed over time. Thank you.

DR. KUNZ: Thank you.

Dr. Sung?

DR. SUNG: Anthony Sung. I voted yes. While I agree with Dr. Nieva that this drug probably works, that is not the question we were asked to vote on, and I do believe there are problems with the process used, as others have mentioned, with the informed consent.

Although there's been discussion of FDA regulations and procedures, I think these are the regulations in place. We are not here to change those regulations, but advise on whether or not we think this process has been consistent with those established guidelines, and I do not think that the processes in this study were consistent with those guidelines.

DR. KUNZ: Thank you, Dr. Sung.

This, again, is Dr. Pamela Kunz. I also voted yes for many of the reasons previously stated. I will spend just a moment to briefly summarize the panel's discussion here.

Though this vote was not unanimous, at a vote of 14 yes to 1 no, I believe this does represent some consensus around the question, should additional clinical trials, demonstrating applicability to U.S. patients and U.S. medical care be required?

Key points around this included a need for multiregional trials to promote diversity of clinical trial participants and the fact that progression-free survival was not an optimal primary endpoint. Additionally, the sponsor did not get input early from the FDA and that the original intent of the trial was for regulatory approval in China. And lastly, there were some concerns raised around informed consent not being updated when standard of care changed.

I'd like to thank everybody for a robust discussion. Before we adjourn I'd like to ask if there are any last comments from the FDA?

DR. PAZDUR: No.

DR. SINGH: This is Harpreet Singh. I just appreciate the committee's time, and consideration,

and thoughtful comments. Thank you.

DR. KUNZ: Thank you, everybody.

I'd like to thank all participants today for a robust, respectful, thorough discussion, and I would like to now adjourn the meeting. Thank you very much.

Adjournment

(Whereupon, at 2:46 p.m., the meeting was adjourned.)