FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Tuesday, April 27, 2021

1:00 p.m. to 5:21 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICERS (Non-Voting)

Joyce Yu, PharmD

(April 27 and 28 Only)

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Susan Halabi, PhD

Professor of Biostatistics and Bioinformatics

Duke University Medical Center

Durham, North Carolina

Philip C. Hoffman, MD

(Chairperson, April 27, 28, April 29 Topics 2 and 3 Only)

Professor of Medicine

The University of Chicago

Section of Hematology/Oncology

Department of Medicine

Chicago, Illinois

Christopher H. Lieu, MD

Associate Professor of Medicine and Associate

Director, Clinical Research

Director, Gastrointestinal Medical Oncology Program

University of Colorado

Aurora, Colorado

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Albert L. Kraus, PhD

Global Regulatory Portfolio Lead, Oncology

Pfizer, Inc.

Guilford, Connecticut

TEMPORARY MEMBERS (Voting)

Harold J. Burstein, MD, PhD

(April 27 Only)

Professor of Medicine

Dana-Farber Cancer Institute

Harvard Medical School

Boston, Massachusetts

Matthew J. Ellis, MD, PhD

(April 27 Only)

Professor and Breast Center Director

Baylor College of Medicine

Houston, Texas

Sandra Finestone, PsyD

(Acting Consumer Representative, April 27 Only)

Executive Director

Association of Cancer Patient Educators

Irvine, California

Stan Lipkowitz, MD, PhD

(April 27 Only)

Chief, Women's Malignancies Branch

CCR, NCI, NIH

Bethesda, Maryland

Alberto J. Montero, MD, MBA, CPHQ

(April 27 Only)

Clinical Director, Breast Cancer Medical Oncology Program

Diana Hyland Endowed Chair for Breast Cancer

University Hospitals Seidman Cancer Center

Professor of Medicine

Case Western Reserve University

Cleveland, Ohio

Jennifer M. Spotila, JD

(Patient Representative, April 27 Only)

King of Prussia, Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director, Oncology Center of Excellence (OCE)

Acting Director, Office of Oncologic Diseases (OOD)

Office of New Drugs (OND), CDER, FDA

Julia Beaver, MD

Chief of Medical Oncology, OCE

Deputy Director (Acting)

OOD, OND, CDER, FDA

Laleh Amiri-Kordestani, MD

(April 27 and 28 Only)

Director

Division of Oncology 1 (DO1)

OOD, OND, CDER, FDA

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. HOFFMAN: 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 Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Philip Hoffman, and I will be chairing today's meeting. I will now call the April 27, 2021 meeting of the Oncologic Drugs Advisory Committee to order. Dr. Joyce Yu is the designated federal officer for this meeting and will begin with introductions.

DR. YU: Hi. Can you hear me?

DR. HOFFMAN: Yes, we can hear you.

DR. YU: Thank you.

Introduction of Committee

DR. YU: Good afternoon. My name is Joyce Yu, and I'm the designated federal officer for today's meeting. When I call your name, please

introduce yourself by stating your name and affiliation.

Dr. Halabi?

DR. HALABI: Yes. Hi. Good afternoon. This is Susan Halabi, and I'm at Duke University.

DR. YU: Dr. Hoffman?

DR. HOFFMAN: This is Philip Hoffman. I'm a medical oncologist at the University of Chicago.

DR. YU: Dr. Lieu?

DR. LIEU: Hi, everybody. I'm Chris Lieu, a medical oncologist from the University of Colorado.

DR. YU: Dr. Burstein?

DR. BURSTEIN: Harold Burstein, a medical oncologist at Dana-Farber Cancer Institute and Harvard Medical School.

DR. YU: Dr. Ellis?

DR. ELLIS: Matthew Ellis, director of the Lester and Sue Smith Breast Center at Baylor College of Medicine.

DR. YU: Dr. Finestone?

DR. FINESTONE: Yes. Sandra Finestone. I'm the acting consumer representative. I'm the

executive director of the Association of Cancer Patient Educators in Irvine, California.

DR. YU: Dr. Lipkowitz?

DR. LIPKOWITZ: Stan Lipkowitz. I'm a medical oncologist at the National Cancer Institute.

DR. YU: Dr. Montero?

DR. MONTERO: Hi. I'm Alberto Montero. I'm a medical oncologist at University Hospitals Seidman Cancer Center and also a member of Case Western Reserve University Medical School.

DR. YU: Ms. Spotila?

MS. SPOTILA: My name is Jennifer Spotila. I'm a patient representative. I was a caregiver for my mother who died of triple-negative breast cancer.

DR. YU: Dr. Kraus?

DR. KRAUS: Yes. Hello, everyone. I'm Albert Kraus. I work in oncology research and development for the Pfizer company.

DR. YU: Thank you.

We'll now introduce our FDA participants.

Dr. Pazdur?

DR. PAZDUR: Richard Pazdur. I am the director of the Oncology Center of Excellence at the FDA.

DR. YU: Dr. Beaver?

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

DR. YU: Dr. Amiri?

DR. AMIRI-KORDESTANI: Hello. My name is Laleh Amiri-Kordestani. I'm the division director for the Division of Oncology 1.

DR. YU: Thank you.

I'll turn it over to you, Dr. Hoffman.

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

Thus, 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 this meeting.

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

Dr. Joyce Yu will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. YU: The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the

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

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

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

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

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

Today's agenda involves receiving updates on biologic license application, BLA, 761034, supplement 018, for Tecentriq, atezolizumab, submitted by Genentech, Incorporated, indicated in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative

breast cancer, whose tumors express PD-L1, PD-L1 stained tumor-infiltrating immune cells of any intensity greater than or equal to 1 percent of the tumor area, as determined by an FDA-approved test.

The committee will hear updates on this supplemental biologics license application approved under 21 CFR 601.40, subpart E, accelerated approval regulations, with confirmatory trial or trials that have not verified clinical benefit. These updates will provide information on: 1) the status and results of confirmatory clinical studies for the given indication; and 2) any ongoing and planned trials.

Confirmatory studies are postmarketing studies to verify and describe the clinical benefit of a drug after it receives accelerated approval. Based on the updates provided, the committee will have a general discussion focused on next steps for this product, including whether the indication should remain on the market while additional trial or trials are conducted. This is a particular matters meeting during which specific matters

related to Genentech's sBLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Philip Hoffman, Christopher Lieu, Harold Burstein, Matthew Ellis, and Ms. Jennifer Spotila.

Dr. Hoffman's waiver involves his employer's research contract funded by Merck. His employer receives $0 to $50,000 per year from Merck.

Dr. Lieu's waiver involves his employer's research contract funded by the National Cancer Institute. The NCI has an agreement with Roche/Genentech, sponsor of Tecentriq, atezolizumab. His employer receives $25,000 to $75,000 per year from NCI.

Dr. Burstein's waiver involves two clinical trials by the Alliance for Clinical Trials in Oncology. One trial is funded by NCI and Genentech, sponsor of Tecentriq, atezolizumab. The Alliance receives $2.5 to $3.5 million per year for

this trial. The second trial is funded by NCI and Abraxis, sponsor of Abraxane, nab-paclitaxel. The Alliance receives $950,000 to $1.5 million per year for this trial.

Dr. Ellis' waiver involves his investment holdings in a healthcare sector mutual fund.

Ms. Spotila's waiver involves stock holdings in four competing or affected firms.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted at 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, 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 would like to disclose that Dr. Albert Kraus is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. HOFFMAN: We will now proceed with FDA

introductory comments from Dr. Julia Beaver.

FDA Introductory Comments – Julia Beaver

DR. BEAVER: Thank you.

Good afternoon, Chairman and members of the committee. My name is Julia Beaver. I'm a medical oncologist and chief of medical oncology in the Oncology Center of Excellence, and acting deputy director in the Office of Oncologic Diseases at FDA.

I will be giving opening remarks to provide background on accelerated approval and set the stage for your discussions in this session. I will provide similar remarks to introduce the other sessions in this three-day accelerated approval advisory committee meeting.

I will first explain the regulatory background and history of the accelerated approval program in oncology and the intent of the program. I'll then discuss our oncology experience with accelerated approval so you can use this historical knowledge to inform your decisions regarding the indication to be discussed. I will begin with the

regulatory background and requirement for granting an accelerated approval.

In 1992, the accelerated approval regulations were added as an alternative pathway to regular approval in order to expedite the delivery of promising drug products for serious or life-threatening illnesses that lacked satisfactory treatment.

Cancer meets this serious and life-threatening requirement, and like regular approval, accelerated approval still requires substantial evidence of efficacy and safety. However, for accelerated approval, the efficacy evidence can be based on an earlier endpoint reasonably likely to predict clinical benefit and needs to be an endpoint other than survival or irreversible morbidity.

In oncology, this endpoint is most commonly response rate or progression-free survival, earlier endpoints that can be used for either regular or accelerated approval depending on the magnitude of the results, safety data, and disease context. To

receive accelerated approval, the drug product should also provide meaningful therapeutic benefit over that of existing therapies, meaning over therapies that are approved under regular approval or set standards of care.

Because of the uncertainty associated with accelerated approval, confirmatory postmarketing trial or trials may be required to verify the clinical benefit, and these trials would usually be underway at the time of the accelerated approval; can be carried out in a different treatment setting, for instance, an accelerated approval as monotherapy in a refractory setting and a confirmatory trial in the same disease but in an earlier setting in combination with chemotherapy, and need to be carried out with due diligence. The majority of accelerated approvals have been for oncology products, and I will now go over the oncology experience with accelerated approval.

Over the last three decades, there have been over 150 oncology accelerated approvals and 35 anti-PD-1 or PD-L1 antibody accelerated

approvals, with close to half of the accelerated approvals converting to regular approval with a median of three years and only 10 withdrawals.

As discussed, accelerated approval indications may be withdrawn if postmarketing trials do not confirm clinical benefit or are not conducted with due diligence. FDA appreciates that a clinical trial that does not meet its endpoint or does not demonstrate a meaningful outcome does not necessarily mean the drug is not effective. This failure to demonstrate meaningful efficacy rather than a true lack of efficacy can potentially be explained by differences in trial design, including endpoints, statistical testing, or biomarker selection.

If clear reasons exist for a trial not to achieve its primary endpoint or to demonstrate a small benefit that is not meaningful and an unmet medical need still exists, FDA will work with companies to identify subsequent clinical trials to verify benefit while retaining the original accelerated approval on the market.

In cases where withdrawal is appropriate, drugs have typically been removed voluntarily by the company through communication and consultation with FDA. The one exception to this voluntary withdrawal was bevacizumab for the treatment of HER2-negative metastatic breast cancer, where FDA initiated withdrawal proceedings.

I will now discuss the content and background of the advisory committee meeting over these three days.

FDA and the FDA Oncology Center of Excellence continuously evaluate the accelerated approval program to make sure the benefit to patients is maintained, and to increase transparency in the future, we may continue public discussions of these evaluations on a more periodic basis.

Over the last six years, there has been an unprecedented level of drug development for the anti-PD-1 or PD-L1 antibody class, with more than 75 indications approved in oncology, with 35 accelerated approvals, with development for

these indications reflecting a high unmet medical need.

The FDA Oncology Center of Excellence evaluated these accelerated approvals and identified 10 indications for anti-PD-1 or PD-L1 antibodies where accelerated approval had been granted, and results from confirmatory trial or trials did not meet their primary efficacy endpoint.

While these antibodies have definitive disease activity for specific patients, given the results of the confirmatory studies, the risk-benefit calculation for these indications may have changed in the contemporary treatment landscape and thus warrant further examination.

FDA therefore initiated discussions for these respective indications with the companies, recommending withdrawal or alternatively bringing the indication to a public discussion at this advisory committee meeting.

Four antibody indications in small-cell lung cancer and in urothelial carcinoma, shown here,

appropriately chose to voluntarily withdraw their indications in consultation with FDA. It is notable that both the small-cell lung cancer and urothelial indications here have seen a changing landscape of disease treatment, meaning after these accelerated approvals were granted, alternative anti-PD-1 or PD-L1 therapies have demonstrated survival benefit either in the same line of therapy or an earlier line, thus calling into question the benefit of these four indications above that of current available therapies. These withdrawals therefore maintain the integrity of the accelerated approval program.

While the four withdrawals were warranted, the remaining six indications that will be discussed during this three-day advisory committee meeting warrant further discussion and we hope to hear further advice. This session will discuss atezolizumab in combination with nab-paclitaxel for the treatment of patients with metastatic PD-L1 positive triple-negative breast cancer.

There are some key issues for this session

we would like the committee to consider. First, it is important to note that the available therapies have not changed for this indication. Thus, the unmet medical need still exists.

However, the original accelerated approval for atezolizumab was based on a small improvement in PFS and survival results were not statistically significant, and the confirmatory trial in the same indication, although with a different combination regimen, showed a concern for worsened overall survival.

In conclusion, accelerated approval provides a trade-off of expediting approvals of drugs with increased uncertainty. Oncology has successfully applied the principles of accelerated approval over the last 28 years, making transformative oncology indications available to patients years earlier.

The percentage of drugs that do not ultimately confirm clinical benefit should not be viewed as a failure of the program, but rather an expected trade-off to expedite drug development of promising agents for severe and life-threatening

diseases like cancer. However, since the goal of accelerated approval is patient benefit, when postmarketing studies do not need their primary objectives, the drug product should be re-evaluated in the context of currently available therapy, and if deemed to no longer benefit patients, the accelerated approval indication should be withdrawn.

Therefore, we would like the advisory committee to discuss if the indication should be retained on the market while additional trials are conducted or completed. Thank you for your attention.

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

For this reason, FDA encourages all participants, including the Genentech'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 presentations from Genentech, Incorporated, immediately followed by the FDA presentation.

Applicant Presentation – Charles Fuchs

DR. FUCHS: Good afternoon. I'm Dr. Charles Fuchs, senior vice president and global head of oncology and hematology product development at Genentech and Roche. I want to thank Dr. Hoffman, the committee members, Dr. Pazdur, and the FDA

staff for this opportunity to discuss with you maintaining the accelerated approval for atezolizumab in combination with nab-paclitaxel in advanced triple-negative breast cancer.

My background is as a medical oncologist. I previously worked at the Dana-Farber Cancer Institute in Boston and subsequently served as director of the Yale Cancer Center in New Haven, Connecticut. In March of this year, I had the privilege of joining Genentech and Roche to lead oncology and hematology drug development.

Since the 1990s, the accelerated approval process has fundamentally enhanced our ability to bring novel therapies to the benefit of patients with unmet medical needs, most notably cancers with limited treatment options.

In 2019, on the basis of the results of the IMPassion130 trial, the combination of atezolizumab and nab-paclitaxel was granted accelerated approval for patients with advanced triple-negative breast cancer, whose tumors were PD-L1 positive. Since that time, we've continued our efforts to further

define the role of atezolizumab for patients with this malignancy, and we look forward to reviewing those data with you today.

As we'll discuss today, the first-line treatment of advanced triple-negative breast cancer continues to represent an unmet medical need, and data emerging since the accelerated approval continue to support the favorable benefit-risk profile for the combination of atezolizumab and nab-paclitaxel in these patients.

While our confirmatory trial IMPassion131 did not meet its primary endpoint of progression-free survival, Genentech has been in active discussions with the FDA to define a new agreed-upon confirmatory trial, which is detailed in our briefing document supplement. Moreover, while the FDA comments in our supplement raises reservations to some of the ongoing studies as potential confirmatory trials, we submit in our presentation today that these trials meaningfully add to our understanding of atezolizumab in triple-negative breast cancer, and as such represents a clear path

to confirm the favorable benefit-risk for atezolizumab in this patient population.

Today I'm joined by Dr. Steve Chui, Genentech global development lead for Tecentriq in breast and gyn cancers; Dr. Claude Berge, Genentech project lead statistician; Dr. Vidya Maiya, Genentech safety strategy lead; Dr. Adam Brufsky, professor of medicine at the University of Pittsburgh School of Medicine and medical director of the Magee-Women's Cancer Program; and Dr. Melinda Telli, associate professor of medicine at Stanford University and director of the Breast Cancer Program at the Stanford Cancer Institute.

My colleague, Dr. Chui will now review the data underlying the accelerated approval in triple-negative breast cancer, as well as the data that have been generated since, to support our position that the accelerated approval should be maintained as additional data are generated.

Dr. Chui?

Applicant Presentation – Steve Chui

DR. CHUI: Thank you, Dr. Fuchs.

Good afternoon. My name is Steve Chui, and on behalf of Genentech, we appreciate the opportunity to explain to this committee our rationale to maintain the accelerated approval of atezolizumab, in combination with nab-paclitaxel, in PD-L1 positive metastatic triple-negative breast cancer.

As many of the clinicians on this panel know, metastatic triple-negative breast cancer is an aggressive disease that results in poor patient outcomes. In the U.S., breast cancer is the most common cancer in women, with over 279,000 new cases diagnosed in 2020, and triple-negative breast cancer represents 10 to 20 percent of these breast cancers. It is defined by the lack of expression of estrogen and progesterone receptor in the absence of HER2 overexpression.

Metastatic TNBC, TNBC which is spread throughout the body outside of the breasts, has the worst outcome as compared to all other breast cancer subtypes. Median survival after diagnosis is short, and it's reported in the literature as

only 12 to 18 months despite palliative chemotherapy. The 5-year survival rate is estimated at 15 percent. Unfortunately, nearly all patients with metastatic TNBC will ultimately die from the disease.

Patients with metastatic TNBC, even today, have significant ongoing need for effective therapeutic options. Chemotherapy has been the mainstay of therapy for triple-negative breast cancer to date, but chemotherapy has limited efficacy benefits, a short progression-free survival, and ultimately poor overall patient survival.

Most of the other treatment options that have become available only provide benefits to small subsets of TNBC, are used in later-line therapy, or have not reported survival benefits to date. Therefore, the availability of anti-PD-L1 and anti-PD-1 treatment has offered another important therapeutic option for the approximately 40 percent of patients whose TNBC tumors express PD-L1, and there are two options.

We're here today to talk about atezolizumab plus nab-paclitaxel, which received accelerated approval based upon progression-free survival benefit. Genentech has also reported upon the overall survival data for this combination, which we will talk about further in this presentation. The combination of pembrolizumab plus chemotherapy recently received accelerated approval in November 2020 based upon progression-free survival data.

Tecentriq, or atezolizumab, is an engineered IgG1 antibody that activates T cells by blocking the interactions of PD-L1 with its receptors. As an anti-cancer therapy alone or in combination, Tecentriq has been approved in six different cancer indications in over 100 countries.

Here's an outline of what I will cover over the remainder of this presentation. I will start by reviewing the data supporting the initial accelerated approval and then the studies and data that were intended to confer clinical benefit, the IMPassion131 postmarketing requirement and the

IMPassion130 final overall survival analysis postmarketing commitment.

Finally, we will go over the multiple options that Genentech has worked up and discussed with the FDA as potential next steps to generate data that confirms the benefit of atezo in TNBC. I'll start with the IMPassion130 study and the data which led to the initial accelerated approval.

IMPassion130 is a phase 3 study that investigated whether adding immunotherapy to a standard-of-care chemotherapy provides benefits for metastatic triple-negative breast cancer patients. 902 patients with newly diagnosed metastatic or inoperable locally-advanced TNBC were randomized in 1-to-1 fashion to receive nab-paclitaxel plus atezolizumab or nab-paclitaxel plus placebo. They were then treated until progressive disease or unacceptable toxicity.

There were four co-primary endpoints for this study: progression-free survival in the intent-to-treat and PD-L1 positive population tested in parallel and overall survival and the

intent-to-treat and PD-L1 positive populations tested hierarchically based upon a hypothesis that adding chemotherapy to atezo could extend the benefits of cancer immunotherapy to tumors that do not initially express PD-L1. The study was powered for these endpoints in all the primary populations.

Here's the data from the IMPassion130 primary analysis that led to the FDA accelerated approval. IMPassion130 did meet its co-primary endpoints, demonstrating statistically significant progression-free survival in both the intent-to-treat and PD-L1 positive populations, with hazard ratios of 0.79 and 0.60, respectively.

At the time of the primary analysis for progression-free survival, the first interim, overall survival analysis was also performed. It was observed to be a hazard ratio of 0.84 for overall survival in the intent-to-treat population, but this did not cross the boundary for statistical significance.

A hazard ratio of 0.62 was seen for overall survival in the PD-L1 positive population, although

this difference did not undergo formal p-value testing because the overall survival in the intent-to-treat population did not reach statistical significance first.

Importantly, the treatment benefits that are observed in IMPassion130 are being driven entirely by the benefit seen in the 41 percent of patients whose tumors were PD-L1 positive, and this is the indication that Genentech sought after seeing these data. And while the IMPassion130 sBLA was originally intended to support regular approval, the FDA considered accelerated approval more appropriate since the overall survival improvement in PD-L1 positive tumors was viewed as exploratory, as statistical significance was not formally tested and the PFS increase of 2.6 months in PD-L1 positive tumors was considered a small absolute benefit.

At the time of the IMPassion130 primary readout, the IMPassion131 study was ongoing. This is the study that was designated as the PMR with the atezo plus nab-paclitaxel accelerated approval.

Let's review this study and its outputs.

Genentech initiated the IMPassion131 study since we felt that it was important to generate robust, stand-alone data to assess the impact of different chemotherapy regimens in combination with the atezo in TNBC, in part, given limitations in the availability of nab-paclitaxel in many countries around the globe.

IMPassion131 is a phase 3 study that investigated whether adding atezolizumab to paclitaxel chemotherapy can provide benefits to metastatic TNBC patients. The study had some similarities to IMPassion130. It also enrolled newly diagnosed metastatic or inoperable locally-advanced TNBC, randomized patients to receive atezolizumab or placebo, and treated them until progressive disease or unacceptable toxicity. The primary endpoint of this study is PFS in the PD-L1 positive population falls hierarchically by PFS in the intent-to-treat population.

As previously mentioned, at the time of the IMPassion130, atezo plus nab-paclitaxel primary

accelerated approval, the IMPassion131 atezo plus paclitaxel study was still recruiting. Even though IMPassion131 was asking a different question than IMPassion130, it was not intended upfront as a confirmatory trial. It was felt that IMPassion131 could potentially provide confirmatory data. IMPassion131 ultimately was designated as a PMR.

The primary analysis of IMPassion131 showed that treatment with atezo plus paclitaxel did not show a statistically significant improvement in progression-free survival when compared to placebo plus paclitaxel in the PD-L1 positive population. The safety profile of atezo plus paclitaxel observed in IMPassion131 was comparable to the safety profile of atezo plus nab-paclitaxel from IMPassion130 and did not reveal a safety concern. As stated in the briefing book, FDA did conduct an independent analysis and have arrived at a similar conclusion.

Given the lack of efficacy improvement and the associated risks and toxicities for the addition of atezo to paclitaxel, the Tecentriq USPI

was updated with a limitation of use and a new warning and precaution not to substitute nab-paclitaxel with paclitaxel in combination with atezolizumab when treating patients with metastatic TNBC.

While this PMR study was insufficient to convert the accelerated approval to regular approval, Genentech's position is that the results of IMPassion131 with the atezo plus paclitaxel do not undermine the clinically meaningful and durable benefit for atezolizumab plus nab-paclitaxel observed in the IMPassion130 study.

So the question that arises is what factors resulted in the difference in efficacy outcomes between IMPassion130 and IMPassion131? After performing extensive analyses, we identified the following differences between the studies. While IMPassion131 is a very similar study to IMPassion130 and enrolled a similar population, the primary endpoints and the statistical design and assumptions were different. For instance, IMPassion131 had a 2-to-1 randomization and the

median follow-up is different. They are both, of course, a blinded randomized study, the gold standard for clinical research.

Turning to control arm for performance, there is notably a difference in overall survival control-arm performance between the two studies with a median overall survival from IMPassion131 appearing not to be in line; survival outcomes described in prior literature for patients treated with chemotherapy only. Chemotherapy partners are different, but it is difficult to assess clearly in cross-trial comparisons if the different formulations of nab-paclitaxel and paclitaxel, which share the same active molecule, impact the activity of atezo differently.

The study differed in the use of steroid premedications. Now, steroids are potentially immunosuppressive, but steroids were also used similarly in both studies to treat immune-related adverse events. Also, potential chemo combinations in different cancers such as lung cancer commonly used steroid premedication, and atezo showed

efficacy benefit there.

The study is different according to the enrollment of patients by region, more North American patients in IMPassion130 and more patients from Asia in IMPassion131. However, the treatment effect of atezo plus chemo across patients from different regions appears generally consisted in each study.

In the end, it has been challenging for us to point to any single factor that clearly accounts for the difference in efficacy outcomes between the two studies. It is possible that one of these factors, or perhaps a combination of several factors, did result in the difference in the readouts. Nonetheless, we see that both IMPassion130 and IMPassion131 provide important information that has been included in the USPI to describe how to best use atezo to treat metastatic TNBC.

I'll shift now to talk about the additional data from the final overall survival analysis in IMPassion130, which has now become available since

the accelerated approval was granted. And over the next few slides, I will review this updated and mature data with you. Let's begin with progression-free survival.

While PFS was already mature at the time of the primary analysis, here we show a descriptive updated PFS analysis with a few more PFS events. This updated analysis shows clear consistency with the primary analysis with a PFS hazard ratio of 0.61 in PD-L1 positive tumors.

The median improvement in PFS goes from 4.8 months for placebo plus nab-paclitaxel to 7.5 months for atezo plus nab-paclitaxel. You can see that the Kaplan-Meier progression-free survival curves separate early and remain separated for the duration of follow-up.

At the time of the accelerated approval, there was an overall survival benefit seen that was clinically meaningful, but no p-value testing was performed due to the hierarchy of analysis. We have now reached the prespecified final analysis for IMPassion130, performed now after 70 percent of

the enrolled patients have died. These represent the most mature survival data available from the phase 3 study of atezolizumab and nab-paclitaxel.

We see a hazard ratio of 0.67 that corresponds to a clinically meaningful 33 percent risk reduction for death. There's an improvement in median overall survival, from 17.9 months for placebo plus nab-pac to 25.4 months for atezo plus nab-pac. This is a 7-and-a-half-month median improvement in overall survival. You can see that the Kaplan-Meier survival curves separate early and remain separated for the duration of follow-up.

The secondary efficacy endpoint of overall response rates showed consistency with the PFS and overall survival endpoints. With the addition of atezo to nab-pac, there was a numerical improvement in the overall response rate for PD-L1 positive tumors, from 33 percent to 53 percent, and a higher complete response rate, 1 percent of the control arm and 11 percent in the experimental arm.

The predefined patient-reported outcomes data further support the clinical meaningfulness of

the IMPassion130 PFS in overall survival endpoint. Now, the patient-reported outcomes data from IMPassion130 is unique for an add-on therapy, but we might expect that an add-on therapy would add additional treatment burden.

Patient-reported outcomes data from IMPassion130 showed that patients' health-related quality of life and day-to-day functioning was maintained -- it did not worsen -- over the duration of study treatment when atezo was added to nab-paclitaxel.

Updated safety data from IMPassion130 also support continuation of the accelerated approval. The safety profile of atezolizumab is well characterized and established across several approved indications and an extensive experience in nearly 125,000 patients. The updated safety results from IMPassion130 now have an additional 5.9 months of median safety follow-up since the primary analysis.

There were no clinically meaningful differences observed in the safety profile of

atezolizumab plus nab-paclitaxel with longer follow-up. There were no new safety signals or evidence of late onset toxicity at the time of the primary or the final overall survival analysis. The addition of atezolizumab did not compromise the patient's ability to receive nab-paclitaxel.

Here's the IMPassion130 safety data side by side with atezo monotherapy for reference. With the additional follow-up, there were no clinically significant differences observed in the safety profile of the combination specifically. There were no additional fatal toxicities.

There were minimal changes in the nature and frequency of the serious and severe adverse events. There was also minimal change in the adverse events of special interest, or AESIs, which are events based on the presumed mechanism of action of atezolizumab.

The most common adverse events are shown in this tornado plot. The adverse events are relatively similar between the two arms; that you can see from the descriptive terms on the left side

of the slide, the adverse events really describe the toxicities of the chemotherapy. There are no changes from the previous analyses. Treating physicians could manage most of the adverse events with early recognition and intervention.

The adverse events of special interest were similar to that observed during the primary analysis and are mostly low grade. Most patients could continue atezo if AESIs were recognized and managed appropriately by their treating physician.

In summary, this mature safety data for atezolizumab with nab-paclitaxel continues to support a favorable benefit-risk assessment for the combination in metastatic TNBC. I will finish by describing the options that Genentech is considering to confirm the clinical benefit of atezo in TNBC.

Given the ongoing unmet need in triple-negative breast cancer, and therefore the importance of keeping the atezo/nab-paclitaxel combination available for patients, Genentech met with the FDA on December 1, 2020 to discuss what

additional data could confirm the benefit observed in IMPassion130.

We had comprehensively assessed multiple options, starting with potentially running a new randomized trial of nab-paclitaxel with or without atezo. We also evaluated whether one or more of the ongoing phase 3 TNBC trials might be able to provide confirmatory data. We even considered some innovative approaches to generating supportive data such as a non-randomized interventional study with a historical control-arm comparison or even looking into real-world data sources.

Let me walk you through the most likely options for confirmatory data generation. The most rigorous approach for generating confirmatory data would be to repeat the original pivotal clinical trial; enroll patients with PD-L1 positive metastatic TNBC, otherwise identical to those from IMPassion130, and randomize them to receive either. nab-paclitaxel plus atezo or nab-paclitaxel plus placebo.

However after the positive data readout from

IMPassion130, we see that it could be challenging to randomize patients to receive nab-paclitaxel without cancer immunotherapy in metastatic TNBC that is PD-L1 positive

The hurdles to repeating the IMPassion130 randomized design are due to the inclusion of the atezo/nab-paclitaxel combination in global clinical practice guidelines, the worldwide approvals of the combination in now 89 countries around the globe, and reluctance from physicians and patients to now participate in a trial that has a possibility of receiving chemotherapy only for a PD-L1 positive metastatic TNBC.

Seeing there are some challenges to repeating the IMPassion130 trial, we also looked at whether one or more of the ongoing randomized trials of atezolizumab TNBC could provide confirmatory data.

At our December meeting with the FDA, the agency stated that they were open to further discussion on utilizing data from IMPassion132, another one of our metastatic TNBC trials, as well

as one of the early setting randomized trials for confirming the clinical benefit of atezolizumab.

Let's talk more in detail about the ongoing trials. They all randomized to concurrent atezo or placebo. These studies are highlighted at the top of this slide in blue.

Here is the schema of the IMPassion132 study. This study is enrolling patients who have suffered metastatic relapse of TNBC less than 12 months after prior therapy for early disease. This is a particularly poor prognosis in a treatment-resistant group of tumors and a different population than those enrolled into either IMPassion130 or IMPassion131; and the backbone chemotherapy investigator's choice of either carboplatin, gemcitabine, or capecitabine. The study does have the gold standard endpoint of overall survival.

Here's the schema of the IMPassion030 study. This study is enrolling patients with early triple-negative breast cancer who are receiving adjuvant paclitaxel followed by AC or EC

chemotherapy. The long-term primary endpoint is invasive disease-free survival.

Here's the schema of the NSABP B-59 study. This study is enrolling patients with early triple-negative breast cancer who are receiving neoadjuvant chemotherapy with paclitaxel/ carboplatin, followed by AC or EC, followed by surgery. The co-primary endpoints are pathologic complete response rate at surgery and also the long-term endpoint of event-free survival.

As you may have seen in the briefing package, the FDA expressed uncertainty regarding the appropriateness of generating confirmatory data in the ongoing early TNBC studies. However, Genentech sees that these trials do have the potential to confirm clinical benefit for the following reasons.

We see the potential for atezo to have more broad activity in the early TNBC study compared to what has been observed in the metastatic setting. For instance, when atezo was added to neoadjuvant chemotherapy for early breast cancer in the

IMPassion131 study, the pathologic complete response rates were improved in the all-comer population, and these results are consistent with biomarker data, showing that the tumor-immune microenvironment is more rich in early TNBC.

As you can see from the schema on the slide, there are several chemotherapy agents, including paclitaxel, being combined with the atezo in the early study. With the additional chemotherapy agents, atezo may demonstrate a different efficacy profile than in the metastatic setting. As they continue to enroll and treat patients with the combination regimen, each study does have an independent data monitoring committee ensuring the ongoing safety of the clinical trial participants.

So in summary, we do think that it is reasonably likely that the benefit of atezo in TNBC could be confirmed in a study in early disease. While the ideal PMR would be a randomized-controlled trial essentially replicating IMPassion130, there are some obstacles to this approach that would need to be overcome.

You've also heard how there is data being generated that will describe how to best utilize atezo across all of TNBC. Building upon agency guidance, suggesting that confirmatory data generated in similar but related populations might be capable of verifying benefits and a recent PMR precedent in TNBC setting, characterizing clinical benefit using efficacy endpoints from multiple studies, we do see that one or more of the ongoing studies could contribute data that confirms the benefit of atezolizumab treatment in triple-negative breast cancer.

To conclude with a summary of Genentech's position on maintaining the accelerated approval for atezolizumab plus nab-paclitaxel in PD-L1 positive metastatic TNBC, there continues to be high unmet need for patients with metastatic triple-negative breast cancer. Treatment with atezolizumab and nab-paclitaxel has helped to address some of this unmet need for patients with biomarker-defined PD-L1 positive metastatic TNBC.

The IMPassion130 study demonstrated

statistically significant progression-free survival, clinically meaningful overall survival benefits, and a manageable safety profile for treatment with the combination of atezo plus nab-paclitaxel in PD-L1 positive metastatic TNBC.

The data for the clinical efficacy and the safety for atezo plus nab-paclitaxel that resulted in the accelerated approval has held up with increasing data maturity. While atezo plus paclitaxel did not improve PFS in the IMPassion131 study, this does not change the benefit-risk profile of atezo plus nab-paclitaxel on the pivotal phase 3 study, which is now read out as pre-planned final overall-survival analysis.

Genentech is committed to generating the data which is necessary to confirm the clinical benefit of atezo in TNBC. As we have outlined, we have several options to generate these data. Atezolizumab plus nab-paclitaxel is the only therapy that has reported improvement in overall survival in first-line metastatic TNBC. In light of the ongoing unmet need, it should remain

available to patients with PD-L1 positive metastatic triple-negative breast cancer.

Thank you for your attention. Here, I'll conclude the formal presentation. We do look forward to hearing from the panel.

DR. FUCHS: Dr. Chui, thank you.

Dr. Hoffman, this concludes our presentation, and we look forward to answering the committee's questions during that portion of the meeting.

DR. HOFFMAN: Okay. Thank you very much.

We'll now proceed with the FDA presentation from -- [inaudible – audio lost].

DR. YU: Dr. Hoffman, are you still there?

DR. HOFFMAN: Sorry. I cut off there. Sorry.

DR. YU: Okay. Can you hear us now?

DR. HOFFMAN: Yes. Thank you.

DR. AMIRI-KORDESTANI: Thank you, Dr. Hoffman.

FDA Presentation – Laleh Amiri-Kordestani

DR. AMIRI-KORDESTANI: Good afternoon,

Chairman and members of the committee. My name is Laleh Amiri-Kordestani. I am a hematologist/ oncologist at the FDA. Today I will present FDA's perspective on the accelerated approval of atezolizumab in combination with paclitaxel protein-bound, or nab-paclitaxel, for the first-line treatment of patients with PD-L1 positive metastatic triple- negative breast cancer that was submitted by Genentech, who I will refer to as the applicant for the rest of the presentation.

Here is the outline of my talk. I will first summarize the key FDA concerns for this accelerated approval; then I will explain the regulatory history of the initial accelerated approval of atezolizumab in combination with nab-paclitaxel, including the trial results that led to this approval and the trial that was designated to confirm the benefit.

Then I will review the treatment landscape of patients with metastatic triple-negative breast cancer and will conclude my presentation with the

voting question.

Should the indication for atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced, or metastatic triple-negative breast cancer, whose tumors are PD-L1 positive, be maintained on the market while additional trials are conducted or completed? If your answer is yes, please discuss after the vote what ongoing or alternative trials may serve to confirm clinical benefit.

The following are the key FDA concerns for this accelerated approval. First, there is uncertainty regarding the efficacy of atezolizumab in combination with nab-paclitaxel for the treatment of patients with PD-L1 positive triple-negative breast cancer.

The improvement of median PFS in the PD-L1 positive population was modest, and the overall survival results in the PD-L1 positive subgroup did not reach statistical significance. The observed 7-and-a-half month difference may be due to chance

alone.

Additionally, the benefit was not confirmed in the confirmatory IMpassion131 trial that enrolled a very similar population, and the apparent possible detriment in overall survival in this trial is concerning. Therefore, the benefit of atezolizumab has not being verified.

In March 2019, atezolizumab in combination with nab-paclitaxel was granted an accelerated approval based on the IMpassion130 trial results. Last year, the results of the confirmatory trial IMpassion131 were reported, which did not confirm the clinical benefit in this population. Due to the concerning overall survival results of this study, a safety alert was issued and the label was updated.

The IMpassion130 trial results were the basis of the initial accelerated approval. The trial was a multicenter, international, double-blind, placebo-controlled, randomized study that enrolled 102 patients that had not received prior chemotherapy for metastatic disease.

Patients were randomized 1 to 1 to receive either atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. The primary endpoints of the trial were investigator-assessed, progression-free survival and overall survival, first to be tested in the intention-to-treat population and then in the PD-L1 positive patient population.

The efficacy results of IMpassion130 are shown here. This trial demonstrated a statistically significant difference in PFS in the ITT and PD-L1 positive populations. The improvement of INV-PFS in the ITT was only 1-and-a-half months, and in the PD-L1 positive population, it was 2.6 months. At both interim analysis 1 and 2, the overall survival results did not cross the prespecified efficacy boundaries and were immature and considered unreliable.

Safety results are not shown, but the safety review of IMpassion130 did not identify new safety signals and was acceptable for this patient population. While a statistically significant difference was seen for investigator-assessed

progression-free survival for the patients with PD-L1 positive tumors, the magnitude of improvement in median PFS, with the addition of atezolizumab to nab-paclitaxel, was small.

In addition, overall survival results for the ITT patient population at both the first and second interim analyses did not meet statistical significance. Based on hierarchical and statistical testing, the overall survival results of the PD-L1 positive patient population would be considered exploratory.

Therefore, more confidence was needed to show that the PFS results are reproducible and likely to predict clinical benefit for the use of atezolizumab in the intended patient population. Thus, atezolizumab in combination with nab-paclitaxel was granted accelerated approval as opposed to a regular approval.

As you heard earlier from Dr. Beaver's talk, a confirmatory trial may be required to confirm the drug's clinical benefit. At the time of approval, there were two potential avenues to confirm the

clinical benefit. The first was a statistically significant and clinically meaningful final overall survival from the same trial. The other was a positive result from another ongoing trial, the IMpassion131 trial. This study was designated as a confirmatory trial to confirm the benefit.

Last year, the final overall survival results of IMpassion130 were recorded. The prespecified final OS analysis did not reach statistical significance in the ITT population. Therefore, the difference in overall survival between the atezolizumab arm and the placebo arm in the PD-L1 positive population could not be formally tested.

Although a 7-and-a-half-month improvement in median OS in the atezolizumab plus nab-paclitaxel arm concurred with the placebo, plus the nab-paclitaxel arm was noted in the PD-L1 positive population, this was not statistically significant. Therefore, the final overall survival results from this PD-L1 positive population are considered exploratory and hypothesis-generating only, and

these results are not able to confirm the clinical benefit.

As mentioned earlier, the IMpassion131 trial was an ongoing study that was designated as one of the ways of confirmation of benefit. This trial was a multicenter, international, double-blind, placebo-controlled, randomized trial that enrolled 651 patients that have now received prior chemotherapy for metastatic disease. Patients were randomized 2 to 1 to receive atezolizumab plus paclitaxel or placebo plus paclitaxel.

A primary endpoint for PFS as assessed by the investigator evaluated first in the PD-L1 positive population, then in the ITT population. Note that the patient population enrolled in this study was very similar to IMpassion130. However, the backbone chemotherapy was paclitaxel and not the same as the chemotherapy backbone in the IMpassion130 trial.

In July last year, the applicant informed the FDA that IMpassion131 did not meet its primary analysis for PFS, and the first interim analysis of

OS from IMpassion131 showed a hazard ratio of 1.55, favoring the placebo in combination with the paclitaxel arm, with a data cutoff of November 15, 2019.

FDA issued a safety alert, informing the healthcare professionals, investigators, and patients that a clinical trial studying the use of atezolizumab and paclitaxel in first-line metastatic triple-negative breast cancer showed this drug combination did not work, and potentially patients had a worse overall survival.

Later, the FDA approved a new label and added a warning and precaution for an increase in the risk of death and a limitation of use, stating that atezolizumab is not indicated for use in combination with paclitaxel. Subsequently, the final results of IMpassion131 were recorded. The primary analyses did not demonstrate a statistically significant improvement in investigator-assessed PFS for atezolizumab plus paclitaxel compared with placebo plus paclitaxel in the PD-L1 positive population.

Although no [indiscernible] remains to test the additional endpoints of PFS in the ITT population and overall survival, an exploratory analyses of overall survival in the PD-L1 positive population showed a median OS for atezolizumab in combination with the paclitaxel arm of 22.1 months and 28.3 months in the control arm, corresponding to a hazard ratio of 1.11, favoring the placebo plus paclitaxel arm.

The efficacy results of the IMpassion130 and IMpassion131 trials are summarized here. The Kaplan-Meier curves of the PFS and OS results of IMpassion130 are on the top and IMpassion131 are on the bottom. Of note, only PFS results, shown in the upper left, for IMpassion130 is statistically significant.

The applicant and the FDA review teams have evaluated the differences between IMpassion130 and IMpassion131 trials. One hypothesis is that the difference in the outcome can potentially be explained by the differences in the chemotherapy backbone and/or differential use of corticosteroids

in these trials. However, other checkpoint inhibitors have been combined with paclitaxel, and they have even demonstrated overall survival advantage. Therefore, the use of paclitaxel or corticosteroids cannot be accounted for the overall differences in the outcome of these trials.

Earlier you heard from Dr. Beaver's talk that an important factor for consideration for accelerated approval is having an unmet medical need and the efficacy of the drug compared to available therapy. If a trial has not confirmed benefit, before additional confirmatory trials are considered, the current unmet medical need and drugs that constitute available therapy should be reassessed to determine if the condition for accelerated approval still exists.

The current treatment landscape for first-line treatment of metastatic triple-negative breast cancer is summarized on this slide. Although pembrolizumab has received accelerated approval for a similar indication, it is not considered available therapy by FDA given the

approval is under accelerated approval and the benefit remains to be confirmed. Therefore, since the initial approval of atezolizumab in combination with nab-paclitaxel, the available therapies have not changed, and the treatment landscape has not evolved.

Dr. Beaver discussed earlier that FDA appreciates when a clinical trial does not meet its endpoint and it does not necessarily mean that the drug is not effective. When an unmet medical need still exists, FDA can work with the applicant to identify subsequent clinical trials to satisfy the accelerated approval requirements.

The applicant has proposed other alternative trials to confirm the atezolizumab benefit in this patient population. The IMpassion132 trial is conducted in the same metastatic setting, however, the patient population and those in the trial is at slightly higher risk than those enrolled in IMpassion130.

The patients enrolled in IMpassion130 relapsed anytime after first-line treatment for

advanced or metastatic disease compared to patients enrolling in IMpassion132, who must have relapsed within 12 months of treatment for advanced or metastatic disease. Additionally, the chemotherapy given in combination with atezolizumab in IMpassion132 is different from IMpassion130. In IMpassion132, atezolizumab is combined either with gemcitabine plus carboplatin or capecitabine. This trial's results are expected in 2023.

Another proposed confirmatory trial is IMpassion030. This trial is an adjuvant trial. You've heard from Dr. Beaver's talk that the confirmatory trial can be performed in an earlier disease setting rather than in the identical indication approved under accelerated approval. This promotes further drug development and also reduces patient accrual challenges to trials evaluating an indication that has already been approved under accelerated approval.

The use of paclitaxel backbone in IMpassion031 may be problematic given the negative results of IMpassion131 with paclitaxel

chemotherapy backbone, and this trial may not be able to support the benefit of atezolizumab in combination with nab-paclitaxel. This trial's interim analysis results are expected in 2022, and the final results are expected in 2024.

Another proposed confirmatory trial is the NSABP B-59 trial. This trial is conducted in early setting. The co-primary endpoints are pathological complete response rates, or pCR, and event-free survival in the all-comer population. Note that pCR has not been established as an endpoint indicator of clinical benefit due to uncertainty regarding its relationship to event-free survival and overall survival, which are considered established endpoints of clinical benefit in early setting.

Events of paclitaxel backbone in this trial also may be problematic given the negative results of IMpassion131 with paclitaxel chemotherapy backbone. Therefore, the results of this trial may not be able to support the benefit of atezolizumab in combination with nab-paclitaxel in the PD-L1

positive population. This trial's primary completion is expected in 2023.

Another ongoing trial is IMpassion031. This trial is conducted in an neoadjuvant setting. The co-primary endpoints are pCR in the ITT population and pCR in the PD-L1 positive population. This trial is not powered to show a difference in event-free survival or overall survival in either population.

The results from this trial were reported and showed a statistically significant pCR improvement in the ITT population, however, the pCR improvement in the PD-L1 positive population was not statistically significant. Atezolizumab accelerated approval is only in the PD-L1 positive population. This trial's long-term endpoint results are expected in 2022.

In conclusion, there is uncertainty regarding the efficacy of atezolizumab in combination with nab-paclitaxel for the treatment of patients with PD-L1 positive triple-negative breast cancer. The PFS improvement in the PD-L1

positive population was modest, as the improvement of median PFS in the all-comer population was only 1-and-a-half months, and in the PD-L1 population, it was 2.6 months.

Additionally, the overall survival results in the ITT and PD-L1 positive subgroups did not reach statistical significance, and the observed 7-and-a-half month difference in the PD-L1 positive subgroup may be due to chance alone. Subsequently, the benefit was not confirmed in the confirmatory IMpassion131 trial that enrolled a very similar population, and a very possible detriment in overall survival in this trial is very concerning.

Of note, the pCR results from IMpassion131 in the PD-L1 positive population was not statistically significant, and these results are in contrast to the metastatic IMpassion130 trial results, where the benefit was mainly seen in the PD-L1 positive subgroup. However, since the initial accelerated approval of atezolizumab for triple-negative breast cancer, there remains an unmet medical need, as the available therapies are

unchanged.

Given the accelerated approval was based on a small PFS improvement with non-significant overall survival and the benefit was not verified in the confirmatory trial in the same disease setting, and a possible detriment in the overall survival seen in the confirmatory trial, should the indication for atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer, whose tumors are PD-L1 positive, be maintained on the market while additional trials are conducted or completed?

If your answer is yes, please discuss after the vote what ongoing or alternative trials may serve to confirm clinical benefit. Thank you for your attention.

Clarifying Questions to Presenters

DR. HOFFMAN: Okay. Thank you.

We will now take clarifying questions for the presenters, both Genentech, Incorporated, and the FDA. Please use the raised-hand icon to

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

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

Dr. Ellis, do you want to start?

DR. ELLIS: Yes. Hi. Thank you. That was a very interesting set of data sets, but somewhat confusing, obviously. My first question is for Dr. Chui.

Obviously, these trials are done in many countries around the world with highly, probably variable, quality of the ER/PR HER2 testing. What confidence do you have that you're really treating triple-negative breast cancer in these many

countries?

For the specific question, I know you did central PD-L1 testing, but did you do central ER/PR in HER2 testing to be sure that you're actually targeting the correct population around the world?

DR. FUCHS: Dr. Ellis, this is Charlie Fuchs. I'll turn to Dr. Chui to answer that question.

DR. CHUI: This is Steve Chui from Genentech. For the IMpassion130 study, eligibility for the study was triple-negative breast cancer ER/PR HER2 negative, according to local laboratory testing. We did actually perform central testing on these samples as a sensitivity analysis. We do not see any difference in the efficacy outcomes for patients, whether they're confirmed as being triple negative, according to ASCO/CAP, centrally versus locally.

DR. ELLIS: I have a follow-up question with respect to that. But the confusing result is the 131 result, with some older results with respect to the behaviors of the placebo arm, which you pointed

out. If the placebo arm is doing better than expected, that might suggest contamination with less aggressive forms of breast cancer.

So the next question is, did you do the same central testing for IMPassion131?

DR. FUCHS: Dr. Ellis, thank you, because we also recognize that disparity in the performance of the control arm in 131. Let me turn to Dr. Chui to answer your question.

DR. CHUI: Steve Chui from Genentech. Yes, we also performed central testing of the majority of the patients on IMPassion131, in addition to local testing. Over 95 percent of the patients did have central local testing performed.

We have similar results that we saw from IMpassion130, and no difference in the efficacy outcomes that we see, or the safety for that matter, regardless of whether the patients were centrally confirmed as being triple-negative breast cancer by ASCO/CAP or not.

DR. ELLIS: So no imbalance in ER/PR HER2 status on the two arms of IMpassion131?

DR. FUCHS: Dr. Chui?

DR. CHUI: Steve Chui, Genentech.

No, we did not see anything like that.

DR. ELLIS: Thank you. I have one final question, and it's a question of the practicality. I think, obviously, the right confirmatory trial would be in patients who had triple-negative breast cancer aligned with central testing showing positive PD-L1 status and repeating the randomization.

You made some comments about the impracticality of that, which of course I'm sympathetic to, but on the other hand, you also made the comment that nab-paclitaxel is not available in many countries around the world, which means the combination of atezolizumab and nab-paclitaxel is not available in many countries around the world. And those countries would be places where you could actually conduct such a trial. Of course, there wouldn't be regular availability of atezolizumab.

Have I misunderstood something or is that

actually the case?

DR. CHUI: Well, Dr. Ellis, we agree that the ideal confirmatory trial would be to repeat the 130 trial. And the issue is, as you rightly point out, that the regimen, the combination, is approved in 89 countries around the globe; 86 are full approval.

There are some countries where it is not approved and perhaps where nab-paclitaxel is not available. But I think what we've learned in our discussions with physicians and patient groups is there is a reluctance to participate in those countries basically because of the inclusion of the atezo/nab-paclitaxel combination in global clinical practice guidelines, as well as the fact that they're uncomfortable having patients participate where there's a chemo-only arm in PD-L1 positive, triple-negative breast cancer.

That said, we certainly want to work with the agency in coming up with the ideal confirmatory trial and want to ultimately confirm the benefit that we're seeing in 130, either through that or

through the other studies that you've heard about, namely 132, B-59, and 030.

DR. ELLIS: Thank you very much. They were my three questions.

DR. HOFFMAN: Dr. Montero?

DR. MONTERO: Hello. Thank you for a very informative presentation. I had a question for Dr. Chui from Genentech regarding, if the FDA allowed the accelerated approval indication to stand, contingent on IMpassion132 results, is it in 2023 that you would expect the results from that study to mature?

DR. FUCHS: This is Charlie Fuchs. Let me just confirm with Dr. Chui on the date for maturity for IMpassion132.

Dr. Chui?

DR. CHUI: Hi. Steve Chui from Genentech. IMpassion132 is an ongoing enrolling study. The date of 2023 is a projection based on anticipated enrollment, and of course the endpoint survival and event-driven survival. But 2023 is our best guess at this point.

DR. MONTERO: Thank you very much.

A follow-up question to that is if those results are also negative, assuming that the accelerated approval indication would stand, how would Genentech's position change regarding IMpassion130's results?

DR. FUCHS: Dr. Montero, I think for starters, I think we all agree, including the FDA, that there continues to be an important unmet need for patients with advanced triple-negative breast cancer given the outcome we see with chemotherapy alone. We're committed to working with the FDA to arrive at an appropriate confirmatory trial.

What you've heard are the updated data from 130, which show a benefit in PFS and what we think is an improvement in OS, which is clinically meaningful in PD-L1 positive patients. It's difficult to predict what the outcome will be from the confirmatory trials until we decide what the confirmatory trials are. But regardless of what the trials are, once the outcome is available, we're committed to informing that immediately with

the FDA, the scientific community, the patient community, and arriving at what is ultimately best for patients, and we're committed to doing that.

DR. MONTERO: Thank you, Dr. Fuchs.

I had one other question for Dr. Fuchs regarding using the early-stage trials as a possible confirmatory. My question really relates to, using early-stage trials to support late-stage trials ignores many examples where a benefit in one didn't really translate into a benefit in another; for example, bevacizumab as adjuvant therapy in colorectal cancer not being beneficial even though beneficial in the metastatic setting, or bevacizumab in triple-negative breast cancer.

Why does Genentech think that that would be a good analogous trial for confirmation of 130's results?

DR. FUCHS: Well, I'm glad you asked the question because we think that the early trials do provide a means for confirmation, and just a few points that I just wanted to address in your question. One is the idea of using an early-stage

trial. The other that came up with the FDA is including all-comers as opposed to PD-L1 positive. Then lastly is related to paclitaxel, and then obviously more specifically your question.

Let me just start on the front of using early-disease trials. We've heard from Dr. Beaver, as well as from Dr. Beaver and Dr. Pazdur and their perspective in the New England Journal, that confirmatory trials have been performed in early-stage disease settings to confirm an accelerated approval. That allows the potential important advances to be extended to early stages and, as well, overcomes the issues of accrual when there's already an accelerated approval in the late stage.

We think that there would be benefit in that setting and frankly, IMpassion031 shows that there is an improvement in pathologic complete response with the combination of atezolizumab and chemotherapy.

The second consideration that I think we have to recognize in early disease settings is

these trials are looking at all-comers as opposed to PD-L1 positive patients. But in that front, I think emerging data is that in breast cancer, early and late cancers differ in terms of the tumor-immune microenvironment. Specifically, studies like 031 show that the benefit of atezolizumab appears to be independent of PD-L1 positive expression. It's not a marker.

And frankly, with regard to pembrolizumab, another checkpoint inhibitor, there are studies as well that show where the benefit is best in metastatic disease that are PD-L1 positive. Their neoadjuvant study 522 showed that it was irrespective of PD-L1 positive. So we think on that front, the use of all-comers is appropriate and reasonable confirmation.

The third point that I think we want to talk about in early-stage settings is the fact that paclitaxel is included in the trials, namely 030 and B-59. But there, I think as we're hearing, we're trying to make sense of 130 and 131 with regard to the use of somewhat similar chemotherapy

backgrounds but discrepant results.

What we can learn I think from those trials is, what is the utility of the combination of atezo and paclitaxel? And it should be mentioned that in both of those early-disease trials, 030 and B-59, there are ongoing independent data safety monitoring committees that are aware of 131 and are still recommending continuation of those studies.

So really to answer your question, given the data for atezolizumab from 031 and these other points, I think that the early studies would be a reasonable opportunity to confirm the accelerated approval and the benefits seen in 130.

DR. MONTERO: Thank you. I have no further questions.

DR. HOFFMAN: Okay. I have a question. This is Philip Hoffman. Maybe this is very elementary, but if the title of the original protocol, 130, was to atezolizumab and nab-paclitaxel in patients with PD-L1 positive, at least 1 percent, I'm confused then between what is the intent-to-treat population versus the PD-L1

positive population.

Wasn't PD-L1 positivity the entry point to get into the trial?

DR. FUCHS: Dr. Hoffman, are you asking about IMPassion130?

DR. HOFFMAN: Yes.

DR. FUCHS: Sure.

Dr. Chui, would you be able to answer that question for Dr. Hoffman?

DR. CHUI: This is Steve Chui from Genentech. So to clarify, IMPassion130 enrolled an all-comer population based upon a hypothesis that adding chemotherapy to atezolizumab would extend the benefits of cancer immunotherapy to a true all-comer population, including the PD-L1 negative patients.

The study was set up and designed to address the benefits of atezolizumab in both the intent to treat, the all-comer population, and the PD-L1 positive population. The benefit we saw was in the PD-L1 positive population, and that's where our label stands right now.

DR. HOFFMAN: Alright. I'm sorry. I was under the impression that the original protocol required at least 1 percent, but you've clarified that.

DR. HOFFMAN: Dr. Lieu?

DR. LIEU: Hi. This is Chris Lieu. This question is for Dr. Fuchs and Chui from Genentech, just to follow along with Dr. Ellis' question along the difference in the chemotherapy-only arms for both 130 and 131 in terms of their overall survival difference, which is, obviously, significant as to what's discussed.

Is there any data in regards to future lines of therapy or lines of therapy received following the study treatment?

DR. FUCHS: Dr. Lieu, let me turn to Dr. Chui to answer your question about post-study treatment.

Dr. Chui?

DR. CHUI: Hi. This is Steve Chui from Genentech. We did collect the later-line therapies that were received by patients who participated in

both IMPassion130 and IMPassion131, and what we see in both of these studies is that later-line therapies are actually very nicely balanced, regardless of which arm the patients were enrolled to.

DR. LIEU: Thank you. My last question is in regards to the reason for the difference seen between 130 and 131 in regards to -- I understand that you're suggesting that this is multifactorial, but is there a leading hypothesis from Genentech's side in regards to whether biologically there's a mechanism of difference in terms of immunotherapies interaction with Abraxane versus paclitaxel? Or you had mentioned the use of steroids in 131 versus 130, and then obviously differences in patient population and regional differences.

Is there an overarching hypothesis from Genentech or is there an assumption that it's just a combination of multiple factors?

DR. FUCHS: Dr. Lieu, as Dr. Chui shared with you, we've looked across all potential differences between IMPassion130 and 131, and what

we see is there are multiple differences, although it's difficult to account which of them could explain the disparity. That is why 130 demonstrates a benefit and 131 does not confirm that benefit.

Ultimately, our conclusion is that it's difficult to arrive at which one could do it. Perhaps it's a combination; and also recognizing that the median overall survival noted in 131 at 28 months is different than what is typically seen in the context of chemotherapy only for triple-negative breast cancer, which has historically been in the 12-to-18-month range.

Let me also, if I may, turn to Dr. Brufsky, one of our colleagues here who's obviously an expert in this field, just to see if he has any additional thoughts.

Dr. Brufsky?

DR. BRUFSKY: Dr. Fuchs, thanks for inviting me, and again, thanks to the committee for having me and Dr. Telli. I think that the 28-month overall survival seen I suspect may or may not be

unstable. It's the longest overall survival we've ever seen in any control arm in triple-negative breast cancer, as far as I know. I think that really is a mystery. I think everybody's trying to figure that out, and I think everybody is appropriately focused in on it.

DR. LIEU: Thank you. I have no further questions.

DR. HOFFMAN: Okay. Dr. Lipkowitz?

DR. LIPKOWITZ: Thank you. Thank you, both the FDA and Genentech, for very informative presentations. I do have a question that follows on from Matt Ellis' question about the subtyping.

Triple-negative disease is not a disease; it's a combination of several different subtypes of breast cancer, some of which behave better than others. Has any effort been made -- this is obviously for Genentech -- to look at the subtyping in the two studies to see if the difference was due to an imbalance in the type of triple-negative breast cancer?

DR. FUCHS: Well, Dr. Lipkowitz, let me turn

to Dr. Chui to answer your question.

Dr. Chui?

DR. CHUI: Hi. Steve Chui from Genentech. I assume you're talking about genomic subtyping of the triple-negative breast cancer, and that's how I'll answer this question.

We have been performing genomic subtyping of samples from IMPassion130. We still have underway this analysis from IMPassion131, so we are unable at this time to provide information regarding genomic subtype of the cancers enrolled on these studies and whether this might have contributed to the difference in efficacy outcomes.

DR. LIPKOWITZ: Generally, it would be transcriptome and genome that would classify the different types of triple-negative breast cancer, but thank you.

A question for the FDA and for Dr. Amiri-Kordestani is we've heard on a number of occasions that the confirmatory study doesn't have to include the same drugs, but then we have a glaring example here of a confirmatory study using

a different drug, which has left us scratching our heads.

How strongly does the FDA feel about that? Because if the drug matters, if paclitaxel versus nab-paclitaxel makes a difference, how comfortable would we be saying, well, using gemcitabine and carboplatin confirms the data then?

DR. AMIRI-KORDESTANI: Thank you for the question. We actually have seen other trials with other checkpoint inhibitors that have used paclitaxel as a backbone, and in fact they have shown overall survival advantage. At least our understanding is that the use of paclitaxel or [indiscernible] is not the reason that the IMPassion131 trial did not meet its endpoint.

The other thing that I want to comment is that, as you know, this trial was a very large randomized trial, so the possible heterogeneity in the triple-negative breast cancer, the randomization, should basically take care of that. So we also don't think that it's going to address -- you know, be the reason.

We have accepted postmarketing in other trials with different backbones in different settings as a PMR for other drugs, and this is really because we like to actually, with other trials, enroll patients and also ask new questions. But I understand the challenge here, that we're really puzzled that one trial has met the primary endpoint, but the PFS benefit was modest. But the other trial basically not only doesn't show any benefit in PFS, but also there is a possibility of detriment in overall survival.

That's why we're putting these trials together, and we are looking at the totality of the evidence, and we actually look at the benefit-risk assessment. So you can think if this trial has first -- actually, if we had this trial's results first and then we had the IMPassion130 trial results, that would have been a different scenario, right?

But I think now, basically, we're in the scenario that we had that initial trial with the modest PFS improvement and less benefit, which was

not confirmed in the final overall survival, and this other trial was with a very similar population and similar chemotherapy. We have looked at multiple factors, our team and Genentech's team, and we have not identified any particular reason why the second trial failed. One of the trials, the results may be due to chance alone, really, so it's just a question of which one of these.

DR. LIPKOWITZ: Thank you. That's my only question. Thank you.

DR. HOFFMAN: Dr. Burstein?

DR. BURSTEIN: Thank you, and thanks to the presenters. My first question is to Dr. Amiri-Kordestani.

A couple of years ago, the FDA gave full approval to alpelisib, a tyrosine kinase inhibitor targeting PIK3CA based on the SOLAR-1 trial, a randomized study in a PIK3Ca mutant population, showing a progression-free survival endpoint benefit. That study was around a 340-person randomized trial. There were no overall survival data available at the time of the approval.

Subsequently, reports indicate there is no overall survival benefit.

So my question is, why in that instance would you advise a full approval, or give a full approval, when this study came forward, IMPassion130, and it was said to be an accelerated approval in a molecularly-defined or a cellularly-defined cohort, which had essentially the same size of the test population as was seen, for instance, in the targeted therapy with SOLAR-1, and in that subset was already showing a survival benefit?

DR. AMIRI-KORDESTANI: Are you asking why one drug got full approval versus atezolizumab in combination with Abraxane got accelerated approval --

DR. BURSTEIN: Yes. I guess sort of the thinking on --

DR. AMIRI-KORDESTANI: -- based on why, for example, progression-free survival for one trial can be used for regular approval, versus in another setting we can actually only give an accelerated

approval?

Actually, I think, as I stated earlier, in general, we just look at the amount of data that we have at the time of the review of the application and the uncertainties about the benefit-risk assessment. If the benefit is modest and there are associated toxicities and also, basically, for example, we are uncertain about the benefit for the patient, then that constitutes an accelerated approval.

So it's really not the question of the use of endpoints; it's just we look at the totality of the evidence and the benefit-risk assessment.

I don't know if anyone else -- maybe Dr. Beaver can actually add some comments.

DR. BEAVER: Sure. Hi. This is Julia Beaver. Yes, so we are able to use progression-free survival as an endpoint to recommend an accelerated approval in some cases or a regular approval, as Dr. Amiri said. And it very much depends on our clinical review of the trial, including the magnitude of the results.

In the case that Dr. Amiri described for atezolizumab, the progression-free survival difference was quite small in an add-on trial. We also look at the safety data and the general disease setting as well.

Whenever we evaluate progression-free survival as an endpoint for either accelerated approval or regular approval, we always look also at the overall survival benefit to make sure there's not a detriment in survival. So if we were to grant a progression-free survival approval, be it accelerated or regular, we would want to make sure there was no detriment in overall survival.

We are able to use progression-free survival as a regular approval endpoint in certain scenarios and do not require overall survival benefit in those as long as there's not a decrease in overall survival.

DR. BURSTEIN: Thank you.

DR. BEAVER: Thank you.

DR. BURSTEIN: I guess my second question could go to either the FDA analytics or to the

Genentech team.

Essentially, the argument that 130, the subset of PD-L1 positive does not show a statistically significant survival benefit, as I understand in lay statistical terms, we sort of ran out of power or ran out of analytic capacity, if you will, to do a formal test for survival in that subset, given all the previous analyses and the hierarchical testing.

Having said that, there is a reported p-value in the briefing materials, and it would look to the casual eye to be highly statistically significant. It is arguably clinically significant. And I'm wondering if a sensitivity analysis has been done to see how wrong would this have to be to infer that there is no true survival benefit for atezo in first line with nab-paclitaxel.

DR. HOFFMAN: Who is that directed to?

DR. BURSTEIN: Well, if either the FDA review team did a statistical sensitivity analysis or if the Genentech team has done something like

that.

(No response.)

DR. BURSTEIN: Charlie, do you have an answer?

DR. FUCHS: Sorry, Dr. Burstein.

Let me turn to Dr. Berge regarding your question about the probability of the finding for the improved overall survival in patients with PD-L1 positive.

DR. BERGE: Claude Berge, Genentech. As you have perfectly highlighted, and what we have discussed during the presentation, we were not able to do a formal testing in the PD-L1 positive population due to the hierarchical testing. So unfortunately we have spanned all the [indiscernible] of ITT population, and because it was not significant, we were not able to formally test overall survival in the PD-L1 positive population.

However, we have done not sensitivity analysis maybe as you expect, but we wanted first to assess if we have a difference between PD-L1

positive and PD-L1 negative, and to assess this, we have done an interaction test between the treatment and the PD-L1 status for overall survival, and we observed a small p-value significant at 5 percent for this interaction, which means that we have a different effect between PD-L1 positive and PD-L1 negative.

If you refer to the p-value that you have observed in the PD-L1 positive population, even if it's only descriptive, it shows you that with this small p-value, in fact there is a low probability that the difference that we have observed in the PD-L1 positive population is due to chance. This probability is about 0.16 percent.

So in fact these two exploratory analyses support the clinically meaningful benefit that we have observed in overall survival. I hope it will answer your question.

DR. BURSTEIN: I think that's helpful. Thank you.

Then my final question would be for the Genentech team. Several others have already asked

about trying to understand the difference between 130 and 131. The dichotomous cutpoint for PD-L1 expression of the 1 percent IC score, was there a difference in the distribution of those results that might account for this? If you set a different cutpoint, do the data shift in some way, or is that known?

DR. FUCHS: Dr. Burstein, let me turn to Dr. Chui to answer your question.

Dr. Chui?

(No response.)

DR. FUCHS: Dr. Chui?

DR. CHUI: Apologies. I was just cut off from the audio. Could you repeat the question, please?

DR. BURSTEIN: Several have asked about subsets that might account for -- or tumor testing that might account for differences between 130 and 131, and my question was with regards to definitions of PD-L1 positivity. Was there different distribution of the levels beyond 1 percent?

In other studies of immunotherapy and breast cancer, the threshold of PD-L1 expression, variously defined, has certainly correlated with potential benefit, and I'm wondering if that's part of the story here.

DR. CHUI: Steve Chui, Genentech. We did look at the expression of PD-L1 status and any correlation it might have to the efficacy outcomes. Actually, what we showed and what we demonstrated -- and Dr. Emens presented this, actually, previously in a conference -- is that the benefit of atezo plus nab-paclitaxel, both PFS and overall survival, is consistent regardless of whether the tumors are so-called PD-L1 low or PD-L1 high.

So we do see that if the patients do have tumors that are PD-L1 positive, that they have the potential to derive efficacy benefit from treatment with atezolizumab plus nab-paclitaxel.

DR. BURSTEIN: And there was nothing in your analysis of 131 that would suggest that the distribution of PD-L1 positivity was an explanation

for the lack of the benefit seen in the PD-L1 positive cohort?

DR. CHUI: No, we don't see anything along those lines. No.

DR. BURSTEIN: Thank you. Those are my questions.

DR. HOFFMAN: Okay. Why don't we --

DR. AMIRI-KORDESTANI: Thank you.

The FDA statistician would also like to comment. Thank you.

Erik?

DR. BLOOMQUIST: Sure. Hi. This is Dr. Bloomquist, FDA statistician, just to reply a little bit to the previous comment.

I think what there isn't mentioned here is the multiple testing plan is typically prespecified in this case. And what it does is when we do see statistically significant findings, we are able to infer them as, let's say, not being due to chance.

When the statistical target [indiscernible] was defined here, I think Genentech and I, we both agreed that there's no alpha left to test that

PD-L1 positive OS endpoint. And while we can sort of use the comments of how long it would be, I think in this case we both agree that we can't make an inferential decision on that PD-L1 positive. There simply was no alpha left to test. And if we attempt to do that for that subgroup in a PD-L1 positive for OS, we may be making false positive claims on 2.6 percent here.

So I think in this case, then, I believe we're both in agreement that while it, let's say, looks very positive, in this case we can't make an inferential statement regarding the OS in PD-L1 positive. I hope that addresses the concerns.

DR. HOFFMAN: We're going to take a break now. We will resume with the open public hearing. And then we do know who still has their hands up for clarifying questions, and we'll get to that after the open public hearing. But first, we'll take a break and reconvene at 3:08, almost 15 minutes. Thank you.

(Whereupon, at 2:54 p.m., a recess was taken.)

DR. HOFFMAN: We'll now begin with 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.

DR. YU: Hi, Dr. Hoffman. I'm so sorry. Could we take one brief pause? We want to make sure the broadcast is available.

DR. HOFFMAN: Okay.

DR. YU: I'll let you know, and we can start

with the OPH once more. Thank you.

(Pause.)

DR. YU: Dr. Hoffman --

DR. HOFFMAN: Ready to start?

DR. YU: -- I apologize for that.

Yes. Please, could you read again opening up the open public hearing session? I apologize for that.

DR. HOFFMAN: Okay, so Section 10.

DR. YU: Please. Thank you.

Open Public Hearing

DR. HOFFMAN: 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 the 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, 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? Please state your name and any organization you're representing for the record.

DR. ZUCKERMAN: I am Dr. Diana Zuckerman, president of the National Center for Health Research. Thanks so much. We're 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. I'm trained in statistics, clinical trial design, epidemiology, and public health, and was a faculty member and researcher at Yale and Harvard, and I've also worked at HHS.

There's an unmet need for effective treatments for triple-negative breast cancer, and we agree with FDA that a randomized clinical trial

that evaluates overall survival is the best way to determine if the benefits outweigh the risks. That's important because this drug has substantial risks.

We agree with Genentech that conducting a randomized-controlled trial is difficult when a drug is approved in other countries, but FDA grants accelerated approval with requirements for postmarket RCTs to evaluate overall survival to confirm clinically meaningful benefit.

How could FDA continue to offer accelerated approval if postmarket RCTs can't be done? And given the co-pay requirements, aren't there cancer patients who would welcome free treatments in a clinical trial so that these studies could be conducted here or in other countries?

So what are the study alternatives? It's valuable to study patients who relapse within 12 months instead of after 12 months, but those are different groups. Isn't that why they were studied separately? Can a different study be used? NSABT-B59 and IMPassion030 both include patients

that aren't PD-L1 status. Both use Taxol, a type of chemo that when used in combination with Tecentriq resulted in lower overall survival for patients in IMPassion131.

Our analysis agrees with FDA that neither an interventional, non-randomized, single-arm trial nor real-world study can confirm benefit. And most important, triple-negative breast cancer patients deserve proven treatments. These patients were rarely studied decades ago since triple negative was relatively rare among white women.

As we all know, triple-negative breast cancer is more common and apparently more lethal in black women compared to white women, and yet black women comprised only 6 percent of the patients in IMPassion130 and only 5 percent in IMPassion131. So the studies done so far are inadequate in addition to not confirming the indication. That's another reason why a new randomized-controlled trial that includes a larger percentage of black women is needed. All patients deserve to know if there are meaningful benefits for them that

outweigh the meaningful risks.

We all want to give patients hope, real hope, not false hope. FDA wants to help patients get timely access to treatments, but as a public health agency, FDA's first priority needs to be evidence. Evidence should be based on the patients that most need the treatment. Convoluted analyses and back flips should not be necessary.

In conclusion, it doesn't help patients to continue to approve a treatment that is not proven to benefit them and is proven to harm many patients, and that's why we support continued research but not continued approval. Thanks very much.

DR. HOFFMAN: Thank you.

DR. YU: Thank you. This is Joyce. I'm so sorry to interrupt. We are just confirming another audio issue. I apologize for the inconvenience.

Dr. Hoffman, we'll let you know when we're resuming with speaker number 2. Thank you.

(Pause.)

DR. YU: You can do it again. Thank you.

Please go ahead.

DR. HOFFMAN: Please introduce yourself and state your name and the organization you're representing for the record.

DR. ZUCKERMAN: Sure. Thank you.

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. We're 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. I'm trained in statistics, clinical trial design, epidemiology, and public health, and was a faculty member and researcher at Yale and Harvard, and I've also worked at HHS.

There's an unmet need for effective treatments for triple-negative breast cancer. We agree with FDA that a randomized clinical trial that evaluates overall survival is the best way to determine if the benefits outweigh the risks. That's important because this drug has substantial risks.

We agree with Genentech that conducting a

randomized-controlled trial is difficult when a drug is approved in other countries, but FDA grants accelerated approval with requirements for postmarket RCTs to evaluate overall survival to confirm clinically meaningful benefit.

How could FDA continue to offer accelerated approval if postmarket RCTs can't be done? And given the co-payment requirements, aren't there cancer patients in this country who would welcome free treatments in a clinical trial and also those in other countries where the drug is not available?

So what are the study alternatives? It is valuable to study patients who relapse within 12 months, as well as those who relapse after 12 months, but these are two different groups, and isn't that why they were studied separately?

Can a different study be used to continue the research? The NSABT-B59 and IMPassion030 both include patients that aren't PD-L1 status. Both use Taxol, a type of chemo that when used in combination with Tecentriq resulted in lower overall survival for patients in IMPassion131.

Our analysis agrees with FDA that neither an interventional, non-randomized, single-arm trial nor a real-world study can confirm benefit. Most important, triple-negative breast cancer patients deserve proven treatments. These patients were rarely studied decades ago when research focused on white women.

As we all know, triple-negative breast cancer is more common and apparently more lethal in black women compared to white women, and yet black women comprised only 6 percent of the patients in IMPassion130 and 5 percent in IMPassion131. So the studies done so far are inadequate in addition to not confirming the indication. That's another reason why a new randomized-controlled trial that includes a larger percentage of black women is needed. All patients deserve to know if there are meaningful benefits that outweigh meaningful risks for them.

We all want to give patients hope, real hope, not false hope. FDA wants to help patients get timely access to treatments, but as a public

health agency, FDA's first priority needs to be evidence. Evidence should be based on the patients that most need the treatment. Convoluted analyses and back flips should not be necessary.

In conclusion, it doesn't help patients to continue to approve a treatment that is not proven to benefit them and is proven to harm many patients, and that's why we support continued research but not continued approval. Thanks very much for the opportunity to give this statement again.

DR. HOFFMAN: Thank you.

Speaker number 2, your audio is connected how. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. FAIRLEY: My name is Ricki Fairley, and I'm the founder and CEO of TOUCH, The Black Breast Cancer Alliance. Thank you so much for the opportunity to speak today about an option for triple-negative breast cancer. I'm very blessed to be approaching 10 years of survivorship of TNBC.

I'm not being compensated for giving my remarks today.

Imagine being diagnosed with TNBC, something that you never knew existed, being told it was associated with the worst prognosis and a very low survival rate, then being told there were no targeted treatment options for you.

That is exactly what happened to me in 2011. I was being thrust into a war, a fight for my life, with absolutely no weapons. I was given a death sentence with no hope. I was told I had two years to live. Obviously, God had another plan for me. He left me here to be an advocate, so I fight like a girl everyday to eradicate this disease that disproportionately affects women who look like me.

TNBC is a different disease. Because we don't have a drug to prevent recurrence, we fight a different fight. Black women are 2.3 times more likely to be diagnosed with TNBC. Black women are 42 percent more likely to die of breast cancer. Black women under 35 get breast cancer at twice the rate of white women and die at 3 times the rate.

Black breast cancer survivors have a 39 percent higher rate of risk of recurrence, but the risk of death for black women with breast cancer is 71 percent higher than for white women. Black women deserve better.

I founded TOUCH, The Black Breast Cancer Alliance, to bring attention to the science and breast cancer research conversations. My purpose, passion, and mission is to eradicate black breast cancer.

As you look at the faces of my TNBC breastees, know that a drug like Tecentriq could have stopped their cancer from advancing and possibly given the dead ones a better outcome. I'm ecstatic to have Tecentriq as a potential option, a new therapy for metastatic TNBC. An incremental 7 months of life could be a lifetime.

You hold the power to bring hope over fear, a chance to see a child grow, a chance to meet a new grandbaby. How many women will die while waiting for this life-saving therapy? How would you feel if one of your family members were at risk

and time is of the essence? I have about 10 years before Belle, my oldest granddaughter, has breasts. My goal is to put myself out of a job by then.

Though my presentation has focused on black breast cancer, I just lost a bestie who was of Ashkenazi Jewish descent. My precious Alison [ph] fought for two and a half years. Two weeks ago, when I gave her her last hug, tucked her into her hospice bed, and watched her close her eyes for the last time, all I could think about was how much longer we would have to deal with this madness.

Frankly, Tecentriq as an option cannot get to the market soon enough. Thank you in advance for helping me reach my goal for Belle, the other women in my family, and the black breast cancer community.

DR. HOFFMAN: Thank you.

Speaker number 3, your audio will be connected momentarily. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. ATLAN: Yes. Hello. My name is Michele Atlan, and I have no financial relationships to declare. I am an 8-year breast cancer survivor and a project-lead trained research advocate for the National Breast Cancer Coalition. NBCC opposes the continued approval of atezolizumab in the first-line setting of advanced or metastatic triple-negative breast cancer.

Having seen many friends and fellow advocates die from this horrible disease, NBCC does not hold this position lightly. We all want new treatments to work for breast cancer patients. For NBCC, that means treatments that have clinical benefit and significantly improve survival without diminishing quality of life. This must be demonstrated by well-designed and conducted randomized-controlled trials. Unfortunately, this has not been the case with atezolizumab in triple-negative breast cancer.

In 2018, many celebrated the reported results of the IMPassion130 trial of atezolizumab. These were based on an exploratory subgroup

analysis of patients with PD-L1 positive tumors that suggested, but did not prove, a 7-month overall survival benefit. The drug was granted accelerated approval based on a 2.6-month improvement in progression-free survival. A confirmatory trial, IMPassion131 was already underway.

We challenged several aspects of this confirmatory trial. It continued to use progression-free survival as a primary endpoint with overall survival as a secondary endpoint not likely to be eligible for analysis under the trial design. Worse, prior studies had fairly conclusively shown no benefit for patients who are not PD-L1 positive; yet IMPassion131 enrolled these patients, offering potential harm to many, with no likelihood of benefit.

In late 2020, we learned that the confirmatory trial failed to replicate any of the earlier trial results. Disturbingly, PD-L1 positive patients in the treatment arm demonstrated a reduction in median overall survival of more than

6 months compared to the control arm.

A key responsibility of the FDA is to protect the public by ensuring the safety and efficacy of drugs that enter the market. And frankly, that's what patients assume they're getting when a drug is offered to them.

In metastatic breast cancer, where there's currently no cure, drugs must ultimately confer some clinical benefit over standard of care to retain their approval status. In breast cancer, we still have no idea if this drug improves any clinically meaningful endpoint. We do know it can cause possible detriment. Under the rules guiding accelerated approval, approval must be withdrawn. Thank you for listening.

DR. HOFFMAN: Thank you.

Open public hearing speaker number 4, your audio is connected now. Will you please begin and introduce yourself? Please state your name and any organization you're representing for the record. Thank you.

MS. DINERMAN: Good afternoon. My name is

Hayley Dinerman, and I'm the executive director of the Triple Negative Breast Cancer Foundation. I thank you for the opportunity to speak here today. Please note that I have not been compensated for my remarks. I'm here as an advocate, and hope to give a voice to a community of breast cancer patients that's often overlooked.

I co-founded the TNBC Foundation in 2006 when my friend Nancy was battling this disease. At the time, very little research was being done in this area, and there were few places to turn for support. Fortunately, that is no longer the case.

The TNBC Foundation has grown to be the leading advocacy group for the triple-negative community. We work to make sure that the unique needs of the TNBC community are understood and considered, which is why I appreciate the opportunity to lend my perspective to this discussion, as I've seen firsthand how devastating this disease can be.

Despite giving it everything she had, Nancy died of TNBC at just 37 years old. She left behind

a close-knit family and friends who struggle with her loss to this day.

Unfortunately, I had many friends who lost their lives to TNBC. Fern Dixon and Annie Goodman are two such examples. Fern was 43 years old when she died and Annie was just 33. Another friend was Lori Redmer. She was the TNBC Foundation's executive director. Despite having every possible resource at her disposal, Lori died in her 40's.

I want you to know their faces. I want them to be in this virtual room with us today. These women were all in the prime of their lives and they deserved better. These are the faces of the women we serve. They're fighters. They're willing to do what it takes to battle this beast, but they need options, especially when they're faced with advanced disease.

The TNBC Foundation hears regularly from thousands of triple-negative patients, many with metastatic disease. As an organization, we have our ears to the ground. We know this patient population, we hear their fears, and understand

their desperate need for more treatment options, especially as their disease progresses.

For those diagnosed with metastatic TNBC, there are limited treatment options. When a therapeutic option presents itself, it should be available for consideration. Patients in consultation with their doctors should have the option to weigh the risks and make a choice.

The TNBC community is disadvantaged enough compared to other breast cancer patient groups. As we know, many of the greatest treatment breakthroughs do not apply to them. TNBC often strikes younger women, women with BRCA mutations, Ashkenazi Jewish women, and black women. As we heard from Ricki Fairley earlier, the data relating to black women is especially concerning. Black women are 2.3 times as likely to be diagnosed with TNBC and far more likely to die of this disease.

Given the severity of the disease, patients should have the option, together with their medical team, to consider therapies that might prevent their cancer from advancing further. I'm sure you

agree that they deserve to have as many weapons in their arsenal as we can safely offer them. I hope I was able to give you some insight into the very real unmet need faced by patients in our TNBC community. Thank you for listening.

DR. HOFFMAN: Thank you.

That was number 4, correct?

DR. YU: That's correct.

Clarifying Questions to Presenters (continued)

DR. HOFFMAN: Okay. Very good.

The open public hearing portion of this meeting has now concluded and we'll no longer take comments from the audience. We're now going to take remaining clarifying questions for all the presenters thus far who were not able to ask their questions earlier. I'm going to call on the people, Drs. Finestone, Halabi, and Kraus, who had their hands up before.

I'll just mention, if by some chance your question might have already been answered with some of the other discussion, that's great. And in the interest of time, if it's possible to be as concise

as possible, we'd appreciate it.

Dr. Finestone?

DR. FINESTONE: Were you able to hear me? I'm sorry. My question has been answered in the intervening conversation.

DR. HOFFMAN: Okay. Thank you.

Dr. Halabi?

DR. HALABI: Yes. Hi. My questions have been answered, too, and it was mostly related to the PFS, the choice of PFS as the primary endpoint, so I'm fine to move on. Thank you.

DR. HOFFMAN: Okay. Thank you.

Dr. Kraus?

DR. KRAUS: Yes. I had two, hopefully, brief questions. The first one digs into the area of the control arm in the 131 study and the discussion of the various durations of the effect, because it struck me that all studies aren't equal, and in this case, the number of patients isn't as relevant as the number of events in surety and variability of your answer.

I was going to ask Dr. Fuchs and Chui, if

you could give some perspective on that unexpected result. Having worked for a lot of years on Taxol, it's a higher number than I've seen, even in combinations with Taxol and with anthracyclines in better-prognosis patients.

Can you give us a sense of the numbers of events in survival in the control arm 131 -- because maturity is a factor, obviously -- versus 130, and versus some of the literature you referenced? Because the number of events, few events can have an impact the smaller that number is, right?

DR. FUCHS: Dr. Kraus, thank you. We can definitely turn to Dr. Chui. I know the statistician, Dr. Berge, was having trouble calling back in, so let me see if either Dr. Chui or Dr. Berge can answer that question.

DR. BERGE: I don't know if you can hear me.

DR. FUCHS: Yes.

DR. BERGE: Okay. Thank you. Claude Berge, Genentech.

I think we have observed that there is a

difference in the performance of the control arm with respect to OS between IMPassion130 and IMPassion131. What we need to consider is, really, as you mentioned, the low number of events that we are seeing in IMPassion131, because we have only 39 patients with an event over 101 patients in the control arm of IMPassion131, which translates into a high uncertainty with a wide 95 confidence interval.

In addition, yes, we have observed also a meaningful difference between the literature that we have highlighted, between 12 to 18 months, and with almost 28 months that we have observed in the control arm of IMPassion131.

Basically, what we can tell is that while for the IMPassion131 control arm, it should be viewed very cautiously due to the limited information, the IMPassion130 control arm showed, of course, robust data with almost 70 percent of the patients, who unfortunately died, which is consistent with the literature.

Maybe, Dr. Chui, if you would like to add

any clinical perspective?

DR. FUCHS: Dr. Berge, I couldn't understand. Who are you referencing to speak after this?

DR. BERGE: Yes. I don't know if Dr. Chui would like to add any additional clinical information on the control arm.

DR. FUCHS: Dr. Chui?

DR. CHUI: Hi. It's Steve Chui. Can you hear me?

DR. FUCHS: Yes.

DR. CHUI: As stated, there are a different number of events for the IMPassion131 versus the IMPassion130 data. We have more confidence in the IMPassion130 overall survival data, not only because of the consistency over time with the other endpoints, but also the fact that it is consistent with what we've seen in the literature upon the 18-month median duration overall survival for patients treated with chemotherapy only.

DR. KRAUS: Thank you. The second one, to save time, I looked it up while we were on pause.

I was going to ask the question of how long since the accelerated approval, but I knew it was in the FDA slides. It seems like it's about two years, so not a huge amount of time.

I was going to ask that because it's important to have due diligence for a confirmatory study, but not such a long time frame since the accelerated approval first occurred. That's the end of my questions.

Questions to the Committee and Discussion

DR. HOFFMAN: Okay. I think we've covered the key points and people's questions have been answered.

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

Today's question is a voting question, and that question is, should the indication for the atezolizumab in combination with nab-paclitaxel for

the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer, whose tumors are PD-L1 positive, be maintained on the market while additional trials are conducted or completed?

Then we can discuss later, if our answer is yes, discuss after the vote what ongoing or alternative trials might serve best to confirm clinical benefit.

Dr. Joyce Yu will provide the instructions for the voting.

DR. YU: Yes. Thank you. Can you hear me?

DR. HOFFMAN: Yes.

DR. YU: Okay.

Question 1 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson asks the voting question into the record, which you have, and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that the voting will begin.

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

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

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

Are there any questions about the voting process from any of the panel members before we begin?

(No response.)

DR. YU: Okay. Hearing none, I will turn it back to Dr. Hoffman to facilitate any questions or comments about the wording.

DR. HOFFMAN: Okay. Are there any questions or comments about the wording of the question as I read it a minute ago, and it's on the screen?

(No response.)

DR. HOFFMAN: Alright. Well, hearing none, I think then we should now begin the voting.

Dr. Yu?

DR. YU: Okay. Yes, we'll now move voting members into the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Pause.)

DR. YU: We have entered the voting breakout room. We will be muted. Please refrain from speaking. The vote is now open. Please vote.

(Voting.)

DR. YU: We're about to close the vote.

(Pause.)

DR. YU: The voting is closed. We're tallying the results, and we will momentarily return everyone to the main meeting room.

(Pause.)

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

The vote results are now displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also say the reason why you voted as you did if you want to.

The results are 7 yeses and 2 noes, and zero abstentions.

Dr. Hoffman?

DR. HOFFMAN: Yes. Let me start with Dr. Lieu because I understand you may need to leave quickly.

DR. LIEU: Hi, all. This is Christopher. Lieu. I voted yes, and believe that an alternative trial is needed to confirm clinical benefit. But given the results of 130, I believe that it should maintain its approval.

DR. HOFFMAN: Okay. Thank you.

I'm going to go down the list and ask, again, each member to state their name and their vote, and if they wish, why.

Dr. Halabi?

DR. HALABI: Yes. Hi. This is Susan Halabi. This was a difficult decision for me. I was almost on the fence. I voted no. And the main reason is while I do appreciate there is a huge unmet need, my concern is the choice of the endpoint. It seems to me that while PFS may be confirmed in another trial, I'm not totally convinced that this will translate into a meaningful benefit to the patient. Thank you.

DR. YU: Hi. Dr. Halabi, thank you so much. I may need to ask you to state that justification one more time for the record.

Could we please pause for just a moment? We're resolving one audio issue. Thank you.

DR. HALABI: Sure.

(Pause.)

DR. YU: Could Dr. Hoffman or someone give me a cue if you can hear me ok?

DR. HOFFMAN: I can hear you.

DR. YU: Okay. I appreciate everyone's patience. We are going to resume shortly.

Dr. Halabi, if you can hear me ok, would you mind restarting and stating what you had previously stated for your vote?

DR. HALABI: Yes. Sure. This is Susan Halabi. I voted no. And while I appreciate the unmet need for the patients, when I'm looking at the benefit-risk ratio, I wasn't convinced the PFS endpoint would translate to a clinically meaningful benefit to the patients, and taking into account the toxicity profile for those patients. Thank you.

DR. YU: Okay. Dr. Hoffman, do you want to proceed?

(No response.)

DR. YU: Dr. Hoffman, can you hear me?

(No response.)

DR. YU: Okay. While we try to reconnect with Dr. Hoffman, Ms. Spotila, if you can hear me, would you mind resuming with your vote and justification?

DR. MONTERO: Sorry. Who are you asking to speak now?

DR. YU: Ms. Spotila, if you can hear me, please unmute your phone on the Adobe Connect platform. It's at the top.

(No response.)

DR. YU: It looks like we will need to come back with Ms. Spotila.

Dr. Montero, can you hear us ok?

DR. MONTERO: Yes, I can hear you.

DR. YU: Okay. Would you mind resuming?

DR. MONTERO: Yes. I voted in favor of continuation, pending results from a confirmatory study in the metastatic setting, based on a principle of maximizing therapeutic options in

patients with aggressive terminal illnesses.

Most patients with stage 4 triple negative live less than two years. It's hard to discount the overall survival benefit observed in IMPassion130 based on the lack of statistical power. Based on the question and answer period, it seems that there's a low likelihood of this being due to chance.

Based on the atypical results of the control arm in 131, it seems proportionally more likely that that result may be due to chance, and that's why I voted in favor of continuation.

(Reverberation.)

DR. YU: Thank you.

I would just remind everyone to please mute your speakers. I'm hearing a little bit of an echo.

(Reverberation.)

DR. YU: I apologize. We're trying to track this echo.

Dr. Hoffman, can I ask if you've returned to the meeting?

DR. HOFFMAN: Yes. I'm sorry. I'm back. I got cut off again.

Whom have we covered; Dr. Lieu, and Dr. Halabi, and Ms. Spotila?

DR. YU: We will have to return to Ms. Spotila. You will be next, and you can proceed with the rest of the list.

DR. HOFFMAN: Okay.

This is Philip Hoffman. I voted yes. Basically, I felt that there were multiple possible reasons other than lack of efficacy that might play into the failure of the confirmatory trial to show benefit, and these multiple potential confounders were well stated by the applicant.

Although it's probably statistically not appropriate for me to do this, I do note a significant difference so far in survival for the PD-L1 positive patients. And I know, again, that I'm overstepping there statistically, but I don't feel there's enough evidence to say no to this and would agree that it should continue.

Dr. Montero?

DR. YU: Dr. Montero has spoken. Thanks, Dr. Hoffman.

DR. HOFFMAN: I'm sorry. Thank you.

DR. YU: I'm aware that -- actually, Dr. Ellis, if you can hear us ok, I would like to also allow you to provide your justification, if that's ok, and then, Dr. Hoffman, please proceed with the rest of the list.

Dr. Ellis, are you there?

DR. ELLIS: Yes. Very difficult. I struggled with this, as did you all. I'll just make the following obvious comments.

The 130 trial, the data is based on an underpowered subset analysis, and that's why they're struggling to show the overall survival benefit. And the replication study was similar enough for me in that essentially the drug was the same, and essentially the subset analysis, based on PD-L1, the same, to show an absolutely negative result. In fact, the survival trending in the wrong direction means that this is clearly not a replication study.

My concern is with the continued approval. As was stated by the company themselves, it'll be hard to do the correct validation study, which is to take the PD-L1 positive population and randomize them between nab-paclitaxel versus nab-paclitaxel plus atezolizumab. No other study makes any sense at all, and with the continued improvement there, it's going to be hard to do that study.

So that was my concern. The science will not progress with this continued approval. And it's not that I don't feel the tragedy of these women every day. I've done that for the last 30 years. I just think that the data are the data, and you can choose to interpret it in different ways. But in the end, the only correct interpretation is to use the statistics presented by the biostatisticians.

Incidentally, my opinion totally concurs with the professional groups who also looked at this question. Thank you.

DR. HOFFMAN: I'm sorry. Could you just, for the record, state your name and your vote?

DR. ELLIS: Oh, sorry. Yes. Matthew Ellis. The vote was no.

DR. HOFFMAN: Alright. Thank you.

Dr. Lipkowitz?

DR. LIPKOWITZ: This Is Stan Lipkowitz, and I voted yes. And like everybody else, this was a very hard decision. I think in some ways the purist in me said I should have voted no, but when I looked at the data, there are a couple things that struck me.

First of all, the landscape hasn't changed. There's really no therapy in the first line for triple-negative metastatic that's been shown to improve survival. I agree that it's not statistically valid at this point, but there's a hint of that in the study.

The confirmatory study, I agree with Matt that it was a negative study, but the degree to which the control arm is an outlier in that is really remarkable. I mean, in our various breaks just now, I looked through all of the studies I could pull up, and even with doublet, the best I've

seen is 18 months. So to see a 28-month overall survival in a control arm with single agent Taxol, it's just hard to explain.

So with all of that, I came to the conclusion that I think it would be better to leave this drug on the market, but there needs to be a confirmatory study. And the ideal study, as difficult as it would be, would be to repeat the study in the PD-L1 population. I guess the 132 study would be ok, but I think at the same time, there has to be some sort of time frame with which to complete this.

Also, I think, really, there has to be a concession, and I didn't really hear it from Genentech, that if they can't confirm it, this has to be withdrawn. And it shouldn't be another ODAC to make them withdraw it. It should be withdrawn if they can't confirm this data, and I'll stop there.

DR. HOFFMAN: Okay. Thank you.

Ms. Spotila, are you still on the call?

(No response.)

DR. HOFFMAN: Perhaps not.

Dr. Burstein?

DR. BURSTEIN: Hi. This is Dr. Harold Burstein, and I voted yes. First, I'd like to thank the public commentators in particular, who I thought spoke with really great passion. This is a difficult decision and a difficult disease to treat. And like many of those on the call, I have spent decades caring for these patients, and we all wish we had fundamentally better options.

Just a couple of comments by way of background; the first is that I think the accelerated approval on PFS here and the recent one given in a similar context for pembrolizumab were based on, really, very similar data in terms of the magnitude of benefit in progression-free survival.

Ultimately, in looking at the IMPassion130 data, I think that there is a biologically sound large sub group of approximately 350 patients with the PD-L1 positive tumors who clearly had, by any reasonable person's interpretation, a meaningful improvement in overall survival, a measurable

difference, and a 10-to-15 percent improvement at benchmarks of 2 years, 3 years, and 4 years, according to the Kaplan-Meier curve.

I realized that for a variety of complex statistical reasons, this is not exactly a kosher statistical analysis, but to ignore it strikes me as to do so at one's peril, even if fundamentally I wish we were seeing more overt benefit in all of these trials.

I also share what's already been said, that the impact of 131 data are problematic in trying to approve the drug, but there are also reasons to imagine that the populations are sufficiently different that I can't immediately reconcile the two.

I was also persuaded, for what it's worth, by the patient-reported outcomes data. I realize there are methodological challenges to that, but actually I think, to the company's credit, those data support the idea that patients are feeling at least as good with this treatment as they would be with the conventional therapy, and the other

toxicity data support that as well.

I want to just pick up on Dr. Ellis' point, which I think is well stated, that the only real confirmatory trial, which I think is necessary, would be essentially a repeat of IMPassion130 built around the nab-paclitaxel backbone. That poses logistical problems, but I think that is the right study to do.

I'm not persuaded at all that the early-stage trials speak to the same issues for approval in the late-stage setting, and I have concerns that should IMPassion132 be positive, it would be defining a very different cohort of patients in whom the product would be used.

So having said all that, I voted yes, and I'm certainly hopeful that a forthcoming study will resolve the matter; and until then, I think it's reasonable to leave this product on the market.

Despite what the FDA may think about what the market is, the reality is that practice has shifted in the United States. Women with triple-negative breast cancers are being tested for

PD-L1 positive tumors, and if positive, they're being offered checkpoint inhibitors and concurrent chemotherapy, and multiple guidelines and recommendations endorse that. And to, at the moment, withdraw this seems still somewhat premature. Thank you very much.

DR. HOFFMAN: Thank you.

Dr. Finestone?

DR. FINESTONE: Yes. Sandra Finestone. I voted yes. My vote was based on primarily one of need, but influenced by consideration of efficacy versus toxicity. Particularly, the data that showed adding atezo to the treatment did not add any toxicity, and in some instances looked like it actually reduced it.

DR. HOFFMAN: Okay. Thank you.

Have I called on everybody to vote; because I was disconnected briefly?

DR. YU: Thank you, Dr. Hoffman. We were missing Ms. Jennifer Spotila's vote, however, we have confirmed that her vote is as displayed. We appreciate her time.

Thank you, Ms. Spotila.

Please continue with the summary of the discussion.

DR. HOFFMAN: Okay.

As we can see, the vote was 7 approving to continue the accelerated approval and 2 against it. I think everyone felt that that was not an easy decision and there were multiple factors to consider. It seemed like some aspects of the confirmatory trial, which was a negative trial, were problematic in people's minds. I think that repeating the same study would be probably the best way to try to firm up the answer that we all need, and we know that that would be a difficult prospect, and we will have to see.

I heard Dr. Burstein's comments about IMPassion132. My sense would be that that probably comes closest to a replication of this trial. It's a different chemotherapy platform, but it's metastatic disease and it's placebo-controlled atezolizumab or placebo. So my two cents on that would be that that would be my preferred

alternative trial.

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

DR. AMIRI-KORDESTANI: No. This is Laleh Amiri from FDA. I want to thank the ODAC members to actually have this discussion, and we apologize for all of the audio issues that we had. Thanks, everyone, for your patience. I hope that we don't have any issues the next day.

Adjournment

DR. HOFFMAN: Yes. Well, I would imagine that putting together the details of a meeting where people are rather far-flung must be enormously complicated. So despite the glitches, I want to thank the folks at the FDA for their hard work in getting this together.

We will now adjourn the meeting. We'll reconvene tomorrow, April 28th, at 9 a.m. Eastern. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members, and we ask that the panel members participating in the first topic tomorrow

should plan to rejoin at 8:15 a.m. Eastern to ensure that you're connected before we reconvene at 9 a.m. Thank you very much for your participation today.

(Whereupon, at 5:21 p.m., the meeting was adjourned.)