FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Topic 2

Virtual Meeting

Wednesday, April 28, 2021

12:45 p.m. to 3:12 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

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**Philip C. Hoffman, MD**

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

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The University of Chicago

Section of Hematology/Oncology

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**Christopher H. Lieu, MD**

Associate Professor of Medicine and Associate
Director, Clinical Research
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**David E. Mitchell**

*(Consumer Representative, April 28 and 29 Only)*
Founder, Patients for Affordable Drugs
Bethesda, Maryland

**Anthony D. Sung, MD**

*(April 28 Topic 2 and April 29 Topic 3 Only)*
Assistant Professor of Medicine
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**(Non-Voting)**

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Acting Director, Office of Oncologic Diseases (OOD)

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*(April 27 and 28 Only)*

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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

(12:45 p.m.)

**Call to Order**

DR. HOFFMAN: Good afternoon 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 second topic of the April 28, 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: Thank you, Dr. Hoffman. I'm just waiting for my slides to load for the introductions.

(Pause.)

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

DR. HOFFMAN: Now I can.

DR. YU: Okay. Thank you. I'm waiting for

my introduction slide, if we can have that pulled up. Thank you.

(Pause.)

**Introduction of Committee**

DR. YU: Good afternoon. My name is Joyce Yu, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Halabi?

DR. HALABI: Yes. Good afternoon. Susan Halabi, biostatistician, Duke University.

DR. YU: Dr. Hoffman?

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

DR. YU: Dr. Lieu?

DR. LIEU: This is Chris Lieu, medical oncologist, University of Colorado.

DR. YU: Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative, and I'm also a cancer patient with multiple myeloma.

DR. YU: Dr. Sung?

DR. SUNG: Anthony Sung, hematopoietic stem cell transplant physician at Duke University.

DR. YU: Dr. Apolo, we can't hear you. Could you unmute your phone?

DR. APOLO: Can you hear me?

DR. YU: Yes.

DR. APOLO: Hi. This is Andrea Apolo, medical oncologist at the National Cancer Institute in Bethesda, Maryland.

DR. YU: Thank you.

Dr. Graff?

DR. GRAFF: Hi. This is Julie Graff. I'm a medical oncologist at the Portland VA Healthcare System.

DR. YU: Ms. Johnston?

MS. JOHNSTON: Yes. My name is Colette Johnston. I'm the patient representative. I have served on IRBs and various other organizations for over 20 years.

DR. YU: Dr. Madan?

DR. MADAN: Good afternoon. My name is Ravi

Madan. I'm a medical oncologist at the National Cancer Institute.

DR. YU: Thank you.

Dr. Rettig?

DR. RETTIG: My name is Matt Rettig. I'm a G [ph] medical oncologist at VA in West Los Angeles and the affiliated academic institution at UCLA.

DR. YU: Dr. Siddiqui?

DR. SIDDIQUI: Hi. This is Mohummad Siddiqui. I'm a urologic oncologist at the University of Maryland and the Baltimore VA Medical Center.

DR. YU: Dr. Kraus?

DR. KRAUS: Good afternoon. My name is Albert Kraus. I work in oncology, research, and development, bringing new cancer medicines from the lab through to the patient. I work for Pfizer.

DR. YU: Now, I'll introduce the FDA participants.

Dr. Pazdur?

DR. PAZDUR: Hi. This is Rick Pazdur. I'm the director of the Oncology Center of Excellence

at the FDA.

DR. YU: Dr. Beaver?

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

DR. YU: Dr. Amiri?

DR. AMIRI-KORDESTANI: Hi. Laleh Amiri-Kordestani. I'm a hematologist/oncologist and division director for the Division of Oncology 1.

DR. YU: Dr. Hoffman?

DR. HOFFMAN: Okay.

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 the meeting.

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

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

**Conflict of Interest Statement**

DR. YU: Thank you.

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; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves receiving updates on biologics license application 761034/supplement 1, trade name Tecentriq, atezolizumab, submitted by Genentech, Incorporated, indicated for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

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 trials 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, a conflict of

interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Christopher Lieu. 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 $75,00 per year from NCI.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which is posted on FDA's website at https://www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information division, 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: 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 will 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 requirements for granting

an accelerated approval.

In 1992, the accelerated approval regulations were added as an alternative pathway to regular approval 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, those 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 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 these 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 accelerated approvals in oncology and 35 anti-PD-1 or PD-L1 antibody accelerated approvals, with close to half converting to regular

approval in 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.

As 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 meetings over these three days.

FDA and the 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 anti-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-L1 and anti-PD-1 antibodies where accelerated approval had been granted, and results from confirmatory trial or trials did not meet their primary efficacy endpoint or only demonstrated a small benefit not deemed clinically meaningful.

While these antibodies have definitive disease activity for this specific patient, 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 have seen a changing landscape of disease treatment, meaning after these accelerated approvals were granted, alternative anti-PD-1 or anti-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 for the treatment of patients with advanced or metastatic urothelial carcinoma who are cisplatin ineligible.

There are some key issues for this session we would like the committee to consider. For

urothelial carcinoma, an alternative anti-PD-L1 therapy, avelumab, has demonstrated clear clinical benefit as maintenance therapy, and this change in available therapy may result in a changed risk-benefit profile compared to that at the time of the initial accelerated approval.

In addition, for atezolizumab, the current results of the confirmatory trial do not yet confirm benefit and there are other trials of atezolizumab in patients with early-stage urothelial carcinoma and with later-line metastatic urothelial carcinoma that have not met their endpoint, further questioning the use of atezolizumab for use in this disease type.

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 meet their primary objective, 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 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 the first-line therapy for patients with advanced urothelial cancer.

My background 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 2017, based on the results of the IMvigor210 trial, pembrolizumab was granted accelerated approval for the treatment of patients

with previously untreated advanced urothelial carcinoma who were ineligible for cisplatin. 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 will discuss today, there remains an unmet medical need for well-tolerated chemotherapy free treatment options in the first-line therapy of patients with advanced urothelial cancer. Moreover, data emerging since the original accelerated approval from both the and IMvigor210 and Imvigor130 trials continue to support the favorable benefit-risk profile for atezolizumab in this setting.

Ultimately, in light of this continued unmet need and the durable responses associated with the atezolizumab monotherapy, we believe that the accelerated approval should be maintained while we await the final readout for the IMvigor130 trial.

Today, I'm joined by Dr. Corey Carter, Genentech global development lead for genitourinary

and renal cancers; Dr. Maoxia Zheng, Genentech senior director of biostatistics; Dr. Alexander Vilimovskij, Roche Genentech safety strategy lead; and Dr.. Jonathan Rosenberg, professor of medicine at Weill Cornell Medical Center and chief of genitourinary medical oncology at Memorial Sloan Kettering Cancer Center. Dr. Rosenberg also served as the principal investigator of the IMvigor210 trial.

My colleague, Dr. Carter, will now review the data underlying the accelerated approval in urothelial 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. Carter?

**Applicant Presentation – Corey Carter**

DR. CARTER: Thank you, Dr. Fuchs.

Good morning and good afternoon, esteemed panel members, and thank you for being here today. My name is Corey Carter, and I am the global development lead for both bladder and renal cell

cancer for Genentech Roche. I've spent over ten years as a practicing oncologist at both the National Cancer Institute, as well as Walter Reed Medical Military Center, before joining biopharma. I've been the principal investigator in over 25 immunotherapy trials, spanning most approved checkpoint inhibitors, to include the investigation of atezolizumab.

Over the course of this presentation, we will explain the rationale for maintaining accelerated approval for atezolizumab in frontline metastatic urothelial carcinoma. Patients who are diagnosed with metastatic bladder cancer and who are not eligible to receive cisplatin remain an area of high unmet need, and there have been very few changes to the treatment landscape.

Today we will review the clinical development history of atezolizumab for first-line metastatic bladder cancer, and I will walk you through the most recent efficacy and safety data from both the IMvigor210, which has led to the accelerated approval, and the second interim

analysis from the ongoing phase 3 study, the IMvigor130, which is the designated postmarketing requirement. We will end by summarizing the benefit-risk profile for atezolizumab in first-line metastatic urothelial cancer and Genentech's ongoing commitment to patients.

Tecentriq, or atezolizumab, is an engineered monoclonal antibody against PD-1 receptor. Atezolizumab activates T cells by interfering with both inhibitory interactions of PD-L1:B71 and PD-L1:PD-1. Atezolizumab is currently approved in six different cancer indications and in over a hundred countries.

Let's first take a look back and examine the clinical development timeline. The initial accelerated approval was granted in April of 2017. This prescribed indication was modified in June of 2018 as a result of the ongoing IMvigor130 trial's independent data monitoring committee.

Single-agent atezolizumab is currently indicated in patients with metastatic urothelial cancer who are not eligible for cisplatin

containing chemotherapy and whose tumors express greater than 5 percent PD-L1 by an FDA-approved test. It is also indicated regardless of PD-L1 expression in patients that are ineligible for platinum-based chemotherapy.

The confirmatory study was initiated in May of 2016, which initially enrolled all patients regardless of PD-L1 staining in the monotherapy arm. Importantly, IMvigor130 study was modified in March of 2018 after an independent data monitoring committee recommended restricting enrollment to only patients who had high PD-L1 expression. This is also what led to the label modification in June of 2018. Final overall survival results for IMvigor130 are anticipated this time next year.

Now, let's turn our attention to the current treatment landscape for frontline metastatic urothelial cancer. Urothelial cancer is the 10th most common cancer worldwide. This is a deadly cancer with a very poor five-year survival rate of only approximately 5 percent. Cisplatin-based chemotherapy is the preferred platinum in

metastatic bladder cancer.

Patients with bladder cancer are generally diagnosed at an advanced stage with most patients having multiple comorbidities. Unfortunately, only about 50 percent of patients are eligible to receive the recommended cisplatin-based chemotherapy. There are limited options for patients who cannot receive cisplatin, and even fewer options to patients who are determined unfit for chemotherapy. NCCN guidelines recommend atezolizumab as the preferred treatment option in PD-L1 high cisplatin-ineligible patients.

Seen here, this slide breaks down patients into two separate groups: cisplatin eligible and cisplatin ineligible. Since 1978, cisplatin has become the treatment choice for patients diagnosed with advanced bladder cancer. Patients are evaluated to determine their ability to tolerate cisplatin chemotherapy, which is a clinical decision.

Guidelines have been published to assist providers, and this evaluation includes the

evaluation of performance status, renal function, and evidence of neuropathy. Carboplatin, although inferior, can be given as an alternative to cisplatin, and it is given in some patients that even may be eligible for cisplatin.

For nearly 40 years, platinum-based chemotherapy was the only option. Today, patients who respond to chemotherapy and patients who cancers have not progressed after 4 cycles of platinum-based therapy are eligible to receive a avelumab as maintenance therapy. Avelumab is indicated in patients that have received benefit from chemotherapy.

We all know not all patients are good candidates for chemotherapy and not all patients tolerate chemotherapy. Looking at the yellow boxes, in 2017, both atezolizumab and pembrolizumab were given accelerated approval in the cisplatin-ineligible patient populations. Both of these indications were later modified and now restrict this option to only PD-L1 high patients.

These remain the only chemo-free options and

the preferred treatment options based on current guidelines. Atezolizumab remains important to both patients and providers. The National Comprehensive Cancer Network assists providers with published guidelines. These have been updated as recently as February of this year.

Seen here, a patient's treatment recommendations are broken down by cisplatin eligible and cisplatin ineligible, seen on the left-hand side. Again, comorbidities often limit patients from receiving the preferred platinum chemotherapy agent. As such, only about half of patients are able to receive cisplatin. Testing for PD-L1 expression is important in patients who are deemed ineligible for cisplatin, allowing both patients and providers to consider chemo-free options. Atezolizumab is recommended as the preferred option in these patients.

Now, let's turn our attention to the data produced using atezolizumab in the frontline setting, and we will focus our attention on the PD-L1 high patients.

We have sponsored two pivotal trials that were performed in treatment-naïve metastatic urothelial cancer. IMvigor210 was performed with a registrational intent. The results from IMvigor210 in both overall response rate and duration of response led to the FDA granting accelerated approval. IMvigor130 was performed as a confirmatory study.

IMvigor210 was a phase 2, single-arm study, enrolling patients into two separate cohorts. We will focus our attention on Cohort 1, and these are the blue boxes. Cohort 1 enrolled 119 cisplatin-ineligible patients, regardless of PD-L1 status, in untreated metastatic bladder cancer. All patients received single-agent atezolizumab, and the primary endpoint of this study was overall response rate assessed by an independent review facility.

IMvigor210 showed a clinical meaningful overall response and duration response. IMvigor210 showed a response rate of 23.5 percent in the intention-to-treat population [inaudible – audio

gap].

(Pause.)

DR. HOFFMAN: I think we're having some technical difficulties.

Dr. Carter, we've lost you.

DR. FUCHS: Dr. Carter, can you hear us?

(No response.)

DR. CARTER: Hello? Can you hear me?

DR. FUCHS: We can now. You cut out, Dr. Carter.

DR. CARTER: Okay. Sorry about that.

DR. FUCHS: Perhaps just back up your slides.

DR. CARTER: Alright.

We'll start on slide 15. I apologize for that.

We see IMvigor210 showed a clinical meaningful overall response rate and duration of response. IMvigor210 showed a response rate of 23.5 percent in the intention-to-treat population, but more importantly, the response rate was 28.1 percent in the PD-L1 positive patients;

67.9 percent of the responders had an ongoing response at two years.

These early and positive results in response rate in both the PD-L1 positive patient population and the intention-to-treat population, coupled with the unmet need, led to the first-line setting of our confirmatory trial of IMvigor130.

I do feel very fortunate to report the impressive median duration of response of almost 5 years. This type of response is clearly life changing for patients.

Shown here, we see the Kaplan-Meier curve for the independent review facility duration of response, demonstrating the median duration of response of the 5 years. Previous reports have shown the median duration of response was non-evaluable.

Now we will focus on IMvigor130, which is our designated conversion study. IMvigor130 is a randomized, 3-arm, phase 3 trial. It enrolled newly diagnosed metastatic bladder cancer patients. This is a robust study that enrolled over 1200

patients.

Arm A studied the addition of atezolizumab to standard chemotherapy, Arm B enrolled patients into single-agent atezolizumab, and Arm C was a placebo-controlled arm added to chemotherapy. This trial was written with dual primary endpoints shown in the far right-hand side of the slide.

Investigator assessed progression-free survival between Arms A and C are the addition of atezolizumab to chemotherapy as compared to chemotherapy, and overall survival in both the addition of atezolizumab compared to chemotherapy, and then the monotherapy atezolizumab compared to chemotherapy.

We will look at both the completed and pending analysis. I would like to draw your attention to the column on the left. The first primary endpoint was progression-free survival, which has been met. Again, this compares the addition of atezolizumab to chemotherapy, to standard chemotherapy assessed by the investigator, and the progression-free survival showed a hazard

ratio of 0.82 and a one-sided p-value of 0.007.

Now looking at the column on the right, we will look at overall survival. Overall survival was tested in a hierarchical fashion as shown on the slide. The second primary endpoint is overall survival, comparing the addition of atezolizumab to chemotherapy. This is still ongoing. The second interim analysis showed a hazard ratio of 0.84 with a 95 confidence interval from 0.71 to 1. These results are event-driven and are expected to read out next year.

Moving down the column on the left, the next analysis is to compare atezolizumab monotherapy to chemotherapy. There has been a consistent positive trend in overall survival in the PD-L1 high patients.

Let's first look at the primary analysis data, comparing the addition of atezolizumab to chemotherapy as compared to chemotherapy. The comparisons are highlighted in the gold boxes. Here we see the Kaplan-Meier curve for progression-free survival. The blue line

represents patients receiving atezolizumab added to chemotherapy and the gray line represents patients receiving only chemotherapy.

The median for progression-free survival was increased by 2 months when atezolizumab was added to chemotherapy with a hazard ratio of 0.82 and a p-value of 0.007. The separation in the curve starts at around 6 months, and as you can see, the separation is both consistent and maintained.

Here we see the Kaplan-Meier curves for overall survival, comparing the addition of atezolizumab to chemotherapy versus chemotherapy in the intention-to-treat population. The first part of the curves lay on top of each other, and then at around 9 months you start to see separation. The separation is maintained into the tails of the curve.

The addition of atezolizumab to chemotherapy showed a hazard ratio of 0.84 and a p-value of 0.026. The clinical cutoff date was June 2020 with the median follow-up of 13.3 months. This study is ongoing, and the final results will be performed

once prespecified events have been reached.

Now I'd like to present the most recent monotherapy data from the second interim analysis. This data was just presented a few weeks ago in an oral presentation by Dr. Ian Davis at the American Association for Cancer Research annual meeting. Looking back at the design of the study, we will focus our discussion on the monotherapy data from this point on. We will look at Arm B for the monotherapy atezolizumab, and we'll compare that to the chemotherapy arm highlighted, again, in the gold box.

Here are the planned overall survival analyses for the monotherapy comparison, and again we've highlighted them in the yellow box for these. Here we see the Kaplan-Meier curve for overall survival in the intention-to-treat population, comparing atezolizumab monotherapy to chemotherapy. Again, the blue line represents atezolizumab monotherapy and the gray line represents patients receiving chemotherapy.

The Kaplan-Meier curve is similar to other

published overall survival curves in patients with treatment-naïve aggressive cancers in which a single-agent checkpoint inhibitor is given in an unselected patient population, and it is compared to chemotherapy.

In the early part of the curves, chemotherapy appeared to show benefit over atezolizumab. The largest separation occurs around 4 months. The curves then come back together and the curves cross at approximately 9 months. From this point on, we now see the atezolizumab group of patients appearing to do better than the patients receiving chemotherapy. This patient appears to continue throughout the tail of the curves.

The median improvement in survival was 2 months with a hazard ratio of 1. This curve and, in general, the phenomenon, has led to further studies and a better understanding of treatment in unselected patients. Our goal is always to determine which patients benefit the most from our chosen therapy.

We will now look at a side-by-side

comparison of the same patients, but this time we will separate the patients by PD-L1 status. PD-L1 low are patients with tumors that express less than 5 percent of a PD-L1 protein, on the left side, and PD-L1 high are patients who express greater than 5 percent, on the right-hand side curves.

The panel on the left, the PD-L1 low subgroup, shows curves that have a very similar shape to the ITT curves we just looked at, with chemotherapy demonstrating early benefit over atezolizumab. Again, the largest separation of curves occurs around 4 months, and then the curves come back together with a clear crossing at around 10 months. The median improvement in survival is only about one month, and this population has a hazard ratio of 1.05.

Now I'd like to focus your attention on the PD-L1 high patients, and I would like to make this curve easier for everyone to see; so in the next slide we will see just the left-handed Kaplan-Meier curve.

The Kaplan-Meier curve for the PD-L1 high

patients shows no difference between the two groups in the first 3 months. The curves lay directly on top of each other, then at approximately 5 months, you see separation of the curves with the atezolizumab patients showing improvement over chemotherapy.

The median improvement in overall survival is approximately 10 months with a hazard ratio of 0.67. Importantly, these curves also flatten out and show continued benefit with time. Patients with PD-L1 high expression are predictive of a response to atezolizumab in this setting.

In an attempt to give the panel a complete picture, we will further look at an exploratory subgroup of patients. These are patients enrolled that our most consistent with our current label, patients that are both ineligible for cisplatin, based on a patient's laboratory data and comorbidities, and tumors that express high PD-L1.

Here we see a similar beginning at the curves, and then further separation of the curves with time. These curves show a hazard ratio of 0.6

and a limited number of patients.

The key takeaways from the efficacy data, data from both the IMvigor210 and the IMvigor130, continue to show benefit of atezolizumab as monotherapy in the frontline setting. Both trials have shown clinical meaningful data in both overall response and duration of response.

IMvigor210 shows a median duration of response of almost 5 years. IMvigor130 has met its first primary endpoint, showing improvement in progression-free survival when atezolizumab is added to chemotherapy, with the final overall survival still not having crossed a prespecified boundary.

Both interim analyses have shown a positive trend in both overall survival in the PD-L1 high patients receiving atezolizumab, including cisplatin-ineligible patients. The PD-L1 biomarker, SP142, selects patients most likely to benefit from this therapy. The totality of the data supports the continued benefit of atezolizumab to this patient population.

Now let's take a look at the safety of atezolizumab, which is well-characterized, and we will particularly focus on the safety results of the IMvigor130 trial.

The safety profile of atezolizumab is well characterized and based on an extensive clinical development program, which has included over 18,000 patients of different clinical trials. Our postmarketing experience is in over 100,000 patients of which 24,000 of those patients are patients who had bladder cancer. Common adverse side effects include fatigue, cough, dyspnea and decreased appetite.

Looking at monotherapy atezolizumab adverse events, we see they are similar across the two trials and are consistent with the monotherapy pooled data from the USPI. Atezolizumab shows fewer grade 3 and 4 events as compared to chemotherapy.

Importantly, you have almost half as many of the number grade 3 or 4 events as compared to chemotherapy, and adverse events leading to

discontinuation of therapy were markedly lower in the atezolizumab group. Deaths or grade 5 events were relatively consistent across both IMvigor trials, as well as the chemotherapy arm. You may note there is a slight increase in deaths in the IMvigor130 monotherapy arm, however, these were determined not to be treatment-related deaths and appeared to be driven by the patients' comorbidities.

Here we see a tornado plot showing the most frequent adverse events by preferred term for the IMvigor130 trial. The atezolizumab monotherapy arm is shown in blue and the chemotherapy arm is shown in gray. The lighter shades of gray are grades 1 and 2 and the darker shades are grades 3 through 5.

This plot allows us to see atezolizumab has a lower incidence of all toxicities, occurring greater than 10 percent compared to chemotherapy. Importantly, atezolizumab has fewer hematological toxicities. As an oncologist, the reduction in toxicities is very important for patients to allow them to continue on therapy that they are

benefiting from.

We can also look at the adverse events of special interest or events known to be associated with either an anti-PD-1 or anti-PD-L1 inhibitor. Looking at adverse events of special interest, the majority were low grade and appeared to be consistent across both trials. The events leading to withdrawal of treatment were also consistent across all subjects with the expected slight increase in the events leading to use of steroids in the atezolizumab cohorts. Importantly, no new safety concerns associated with adverse events of special interest have been identified.

Now let's look at a tornado plot showing adverse events of interest. Particularly, you want to look at the immune-mediated events, and these are grouped by medical diagnosis or concept. Notably, these events will be captured in patients receiving both chemotherapy and monotherapy atezolizumab; the etiology may be very different.

We see the increases in immune-mediated events as compared to chemotherapy. Rash is noted

to be greater in the patients receiving chemotherapy, with the majority being low grades 1 and 2. You see atezolizumab having higher rates of immune hepatitis, although they are grades 1 and 2, and an increase in both hypothyroidism and hyperthyroidism. Overall, the majority of immune-mediated events were quite low.

The safety of atezolizumab is well defined in bladder cancer in the first-line setting and it favors a positive benefit-risk ratio. No new safety profiles have been identified and most adverse events are well managed. We do see substantial benefit in the safety profile of atezolizumab monotherapy over chemotherapy.

The data we have generated to date allows us to continue to support patients with metastatic urothelial cancer in the frontline setting. The landscape for first-line metastatic urothelial cancer in patients who cannot tolerate cisplatin chemotherapy has seen few changes, with the only new change being patients who actually received benefit from chemotherapy. The need for the

chemotherapy-free option remains.

Single-agent atezolizumab received accelerated approval based on overall response rate and duration of response with an improved and manageable safety profile over chemotherapy. Currently, the confirmatory trial of IMvigor130 studying patients in a frontline setting is ongoing. The trial has continued to show clinical benefit in the PD-L1 high patient population and the final overall survival results are expected next year.

The overall benefit-risk has remained favorable and is unchanged. Data generated to date we believe meets [indiscernible] accelerated approval for atezolizumab in the frontline setting for metastatic urothelial cancer, and this should be maintained, especially while the confirmatory trial of IMvigor130 reads out.

Genentech remains committed to providing this therapy [indiscernible] for both patients and their providers. I want to thank the panelists for their attention, and I'd like to turn it back over

to Dr. Fuchs.

DR. FUCHS: Dr. Carter, thank you.

Dr. Hoffman, this concludes our presentation, and we welcome answering your questions during that Q&A session.

DR. HOFFMAN: Okay. Thank you.

We'll now proceed with the FDA presentation from Dr. Amiri-Kordestani.

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. I will present FDA's perspective on the accelerated approval of atezolizumab for the first-line treatment of patients with urothelial carcinoma who are not eligible for cisplatin therapy 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 presentation. I

will first summarize the key FDA concerns with this accelerated approval. Then I will describe the regulatory history of the initial approval, and I will discuss the results of the trial that was designated to confirm the benefit of atezolizumab and other trials that have not demonstrated the benefit of atezolizumab in urothelial carcinoma.

I will then review the evolving landscape of treatment of patients with urothelial carcinoma, and I will conclude my presentation with a voting question.

Should the indication for the first-line treatment of cisplatin-ineligible patients with advanced or metastatic urothelial carcinoma be maintained pending final overall survival results from IMvigor130?

The key FDA concerns with this accelerated approval are the following. First, the FDA does not consider that atezolizumab's clinical benefit for the treatment of patients with cisplatin ineligible metastatic urothelial carcinoma has been adequately confirmed by the designated trial

IMvigor130.

Additionally, the clinical benefit of atezolizumab has not been shown for treatment of patients with urothelial carcinoma in an adjuvant setting and a second-line metastatic setting. Finally, the treatment landscape of patients with urothelial carcinoma is evolving with the approval of avelumab maintenance therapy. Therefore, the role of atezolizumab is unclear.

In April 2017, atezolizumab received accelerated approval for the treatment of patients with previously untreated locally-advanced or metastatic urothelial carcinoma who were not eligible for cisplatin. Based on the external data monitoring committee's findings of a decrease in overall survival, the first-line indication was restricted. Later, the results of the designated confirmatory randomized trial, IMvigor130, were reported.

The results from Cohort 1 of IMvigor210 were the basis of the initial accelerated approval. This trial was a phase 2, global, 2-cohort,

single-arm study. Cohort 1 enrolled 119 patients who were not eligible for cisplatin therapy and had locally-advanced or metastatic urothelial carcinoma.

The primary endpoint was overall response rate. Duration of response was the secondary endpoint. The efficacy results of Cohort 1 are shown here. The overall response rate was 23.5 in the all-comers population and 28.1 percent in patients with PD-L1 high tumors.

As Dr. Beaver presented earlier, to receive an 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. At the time, there were no approved agents for this patient population, however, various chemotherapies were used off-label in this disease setting that led to slightly higher but short-lived responses.

Basically, the review of IMvigor130, not shown on this slide, also did not identify new safety signals, and safety was acceptable for this

patient population. Although the overall response rate of 23.5 percent was modestly [indiscernible] lower than the reported for chemotherapy used off-label in this disease setting, the FDA considered the longer duration of follow-up, the longer duration of response, in combination with an alternative toxicity profile, to constitute a favorable benefit-risk for an accelerated approval based on the available therapy at the time of approval. Based on these results, atezolizumab received and accelerated 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 this accelerated approval, IMvigor130 was an ongoing trial. This trial was designated as the confirmatory trial to confirm the benefit of atezolizumab.

This trial was evaluating atezolizumab either alone or in combination with platinum-based chemotherapy compared with chemotherapy alone. Patients who had not received prior systemic

therapy in the metastatic setting and were ineligible for any platinum-based chemotherapy were enrolled in the trial. The co-primary efficacy endpoints were investigator assessed progression-free survival and overall survival.

The external data monitoring committee's early review found that patients who had PD-L1 low tumors in the monotherapy arm of the IMvigor130 trial and another similar clinical trial, KEYNOTE-361 that was evaluating the efficacy of pembrolizumab in a similar patient population, had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy. Both studies were amended and stopped enrolling patients whose tumors had PD-L1 low status to the immunotherapy/monotherapy arm per the DMC's recommendation.

These results led to the restriction of the accelerated approval indication of atezolizumab in June 2018 for the population of cisplatin-ineligible patients without PD-L1 high tumors. Given the limited alternative effective therapies

for patients considered not eligible for both cisplatin and carboplatin, the accelerated approval indication for this population was maintained regardless of the PD-L1 status.

Subsequently, the primary efficacy results of IMvigor130 were reported. The final analyses of progression-free survival demonstrated a statistically significant improvement for the atezolizumab plus chemotherapy arm compared to the placebo plus chemotherapy arm. But in the context of an add-on therapy design, the FDA does not consider 1.9 months improvement in PFS to be clinically meaningful, particularly given the assessment interval of approximately every 2 months during the first year after randomization.

The concurrent first interim analysis of overall survival and the second interim overall survival analysis conducted in August 2020, with 85 percent overall survival events, also did not cross the interim efficacy boundary. The final analysis of overall survival is expected in 2022.

Now I will review other key trials that have

been conducted in urothelial carcinoma with atezolizumab. In the post-platinum, second-line setting, the results of Cohort 2 of the IMvigor210 trial formed the basis of initial accelerated approval of atezolizumab for this population. This accelerated approval was also based on durable response rate. However, the designated postmarketing confirmatory study, IMvigor211, failed to provide the confirmatory evidence of clinical benefit. Therefore, the post-platinum, second-line indication for atezolizumab was recently withdrawn from the market.

In the adjuvant setting, study IMvigor010 was a randomized study of either atezolizumab or observation, and enrolled patients with high-risk, muscle-invasive urothelial carcinoma, and included a subpopulation of cisplatin-ineligible patients. The primary endpoint was investigator-assessed, disease-free survival in the ITT population. At the final analysis for DFS, no benefit was observed for patients randomized to the atezolizumab arm.

In summary, given the totality of the data,

the clinical benefit of atezolizumab for treatment of patients with urothelial carcinoma remains to be shown.

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

While there were limited effective treatment options available for cisplatin-ineligible patients at the time of the FDA approval of atezolizumab in 2017, each patient may now be treated with gemcitabine plus carboplatin, followed by avelumab maintenance therapy in those without disease progression after chemotherapy, as avelumab maintenance therapy received regular approval in 2020 based on an overall survival benefit that was

shown for this regimen compared to chemotherapy alone.

Approximately 40 percent of patients enrolled in this study received prior gemcitabine plus carboplatin. Most patients would be expected to be eligible for avelumab maintenance following first-line chemotherapy, and recent guidelines recommend this regimen as one of the preferred treatment options for these patients.

In conclusion, atezolizumab received accelerated approval based on durable response rate for first-line treatment of patients who are not eligible for cisplatin. However, the confirmatory trial has not yet verified the clinical benefit. Furthermore, the benefit of atezolizumab has not been demonstrated in the second-line metastatic and adjuvant treatment setting.

Additionally, currently there is another available treatment option, carboplatin plus gemcitabine followed by avelumab maintenance therapy, that has shown a survival benefit in this patient population. However, FDA recognizes that

there is still an unmet medical need for treatment of patients who are unfit for chemotherapy.

Given the benefit of atezolizumab is not yet verified in the confirmatory trial in the same disease setting; and the benefit was not verified in the second-line metastatic setting and indication was withdrawn; and the adjuvant trial did not meet the primary endpoint; and the treatment landscape has changed, FDA is asking the advisory committee this question.

Should the indication for atezolizumab for the first-line treatment of cisplatin-ineligible patients with advanced or metastatic urothelial carcinoma be maintained pending final overall survival results from IMvigor130? Thank you.

**Clarifying Questions to Presenters**

DR. HOFFMAN: Thank you.

We will now take clarifying questions for the presenters, both Genentech and the FDA. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you've 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 we can move on to the next panel member.

Dr. Halabi, you have a question?

(No response.)

DR. HOFFMAN: Dr. Halabi, are you on?

DR. HALABI: Yes. Hi. Susan Halabi. Thank you, Dr. Hoffman.

First of all, I wanted to make one comment. I'm a little bit perplexed by the fact that the interim analysis results are presented, and I wanted to hear comments from the sponsor regarding DMC, what the DMC suggested with regards to presenting data while the trial is being monitored, because that will obviously jeopardize the conduct

and the final analysis of the study.

DR. FUCHS: Well, Dr. Halabi --

DR. HALABI: Yes?

DR. FUCHS: Sorry. Go ahead, please.

Should I answer now or should I wait for the next part?

DR. HALABI: Yes. Go ahead. I'll wait. Thank you.

DR. FUCHS: Of course, Dr. Halabi. This is Charlie Fuchs. Those interim analyses were planned as part of the prospective statistical analysis plan for IMvigor130. But let me also just turn to the statistician, Dr. Zheng, just to more specifically answer your question about the appropriateness of those interim analyses.

Dr. Zheng?

DR. ZHENG: This is Maoxia Zheng from Genentech statistics. Regarding the question of IDMC review, the IDMC, they do a periodical safety review of the study while the study's ongoing. In 2018, I think starting with the March review, they realized there was a problem with the atezolizumab

monotherapy in the PD-L1 low patient population.

So by that time, they informed our sponsor with their recommendation to stop the enrollment of the atezolizumab monotherapy arm for the PD-L1 high patient population. So we took the IDMC recommendation, also with the consultation with FDA, and informed the study to change that.

Regarding whether there's an impact on the study analysis, because the IDMC review is a blinded review, the study sponsor is not blinded -- is not unblinded at IDMC review, so there's no impact on the study.

DR. FUCHS: But Dr. Zheng, to specifically answer Dr. Halabi's question, those interim analyses that we're sharing were formally stipulated in the statistical analysis plan, correct?

DR. ZHENG: Yes.

DR. FUCHS: Thank you.

DR. ZHENG: We prespecified the first and the second interim analysis in the statistical analysis plan.

DR. HALABI: Thank you. That wasn't, really, my question because obviously that was created in the statistical analysis plan. My concern is more making the issue publicly available because anyone can potentially compute the conditional probability, and they can tell you most likely what the result was going to be for the overall survival.

So to me, it's more keeping the integrity of the trial and, frankly, I'm surprised that the DMC would allow that. But I'm going to move on to the next question.

Can you clarify why there is more grade 5 toxicity on the atezo arm compared to the control? I believe it was a 3 percent difference. Can you comment on that, please?

DR. FUCHS: Of course. Let me turn to Dr. Carter to review those events with you, within IMvigor130.

Dr. Carter?

DR. CARTER: Hi. Thank you, Dr. Fuchs and Dr. Halabi. I just want to be clear. Are you

talking about grade 5 events on the safety slide or were you talking about the early potential or early deaths?

DR. HALABI: Yes. I'm talking specifically -- my concern has to do with the death due to AE grade 5. That's what I'm referring to. It seems there are more -- I believe this was slide 33.

DR. CARTER: Yes. We can pull up slide 33; yes, ma'am.

DR. HALABI: Maybe you can walk us through why -- I mean, it sounded like there is some discrepancy, but maybe I'm not understanding that slide. So if you could comment on the death due to AE and the treatment-related grade 5 AE, those two rows, please.

DR. CARTER: Yes, and we can pull it up. Here we have the -- if you can see the slide right now -- IMvigor130.

DR. FUCHS: This is the slide you want, yes?

DR. CARTER: Yes, this is the slide I want, and this is the one you were pointing out. And I

do think it's important to note that there was a slight increase. And as any sponsor, and as we should do -- and we do a very good job trying to figure out what was the cause of disease.

In this, as you can imagine, there are advanced comorbidities, and we did an extensive evaluation. And all of those patients had deaths due to their comorbidities. And those were mainly cardiovascular deaths that we saw and those increased in grade 5.

Thank you. Do you have any more questions?

DR. HALABI: Thank you. I'm fine. You've answered my question.

DR. HOFFMAN: Okay. Dr. Madan?

DR. MADAN: Yes. I have a couple questions. I guess the first question I'd like to ask -- if I can clarify the question before us for the FDA; is it appropriate to do that now or do I have to wait until later?

DR. HOFFMAN: Probably later when we're ready to vote, but -- well, I don't know what you're going to ask, so I'm not sure.

DR. MADAN: I guess the voting question seems to be based on the indication of atezolizumab for first-line treatment of cisplatin-ineligible patients with advanced or metastatic urothelial carcinoma, based on the pending final results of IMvigor130.

But do we mean to interpret that to take into account the restricted accelerated approval indication that the FDA presented on slide 12, which brings up the PD-L1 status? Is that part of our question?

DR. AMIRI-KORDESTANI: Dr. Madan, this is Laleh Amiri from FDA. So the question is should the current indication be maintained or not? The question is for, basically, the current indication, which is the restricted indication.

DR. MADAN: Okay, good. Thanks for clarifying that. That does clarify one question I had.

Then I have a question for the sponsor regarding the subset analysis in those patients with a high PD-L1, expressing tumors where the

benefit was demonstrated. This was slide 27 in your presentation with about a little less than a hundred patients.

Can you comment at all if this was a prespecified endpoint and if there was any power to evaluate for this finding?

DR. FUCHS: Can we bring up slide 27?

I think, Dr. Madan, you're referring to this particular analysis by PD-L1 status, correct?

DR. MADAN: Correct.

DR. FUCHS: Yes. Let me turn to Dr. Zheng to answer your question about the statistical analysis plan around PD-L1 status.

DR. ZHENG: Maoxia Zheng from Genentech statistics. Let's pull up core slide number 19, which shows the hierarchical testing in the study. You can see the overall survival on the right side is tested in a hierarchical fashion.

We start on the top with atezolizumab versus chemotherapy, so that's positive. We go to atezolizumab monotherapy versus chemotherapy in the ITT population, and at the bottom we'll test

atezolizumab monotherapy versus chemotherapy in the PD-L1 high population.

So to your question, the testing between atezolizumab monotherapy versus chemotherapy in the PD-L1 high population, that's prespecified.

To your question in terms of whether this testing is adequately powered at the design stage, I have to say because this testing was added during the study as a protocol [indiscernible], although it's prespecified proper as a control, the power was not adequately powered at that time.

Now, based on the results we observed so far and back-calculated [indiscernible] the power, the power with this sample size added a target ratio around 0.67, as we observed, and the power is only about 50 percent.

DR. FUCHS: Dr. Madan, it's probably worth just pointing out -- that you may be aware -- that IMvigor130 was originally designed as a 2-arm study of chemotherapy with or without atezolizumab. The monotherapy arm was added later, given the interest in assessing that after obtaining the results of

the durable responses seen in IMvigor210.

DR. MADAN: Okay. That's very helpful.

Then one final point on this, since I'm not a statistician, so I appreciate your guidance, the hierarchical testing as I understand it is something you analyze if the overall study is positive. Am I understanding that correct?

DR. FUCHS: It's a stepwise fashion. So the study is positive for progression-free survival, as you saw, so that's positive. It then moves to overall survival in the intention to treat. As you saw, it's trending with a benefit in favor of chemotherapy plus atezolizumab with the additional data expected and final readout next year.

DR. MADAN: Okay. Thank you for taking my question.

DR. AMIRI-KORDESTANI: Thank you. This is Laleh Amiri from FDA. I would like to ask our statistician, Dr. Li [ph], to actually comment as well. Thank you.

(No response.)

DR. AMIRI-KORDESTANI: Dr. Li, are you

speaking? We can't hear you.

(No response.)

DR. AMIRI-KORDESTANI: Maybe Dr. Fiero will comment.

DR. FIERO: Yes. Hi. This is Mallorie Fiero, FDA statistics. The subgroup analyses that we're talking about are considered to be exploratory subgroup analyses and should be interpreted with caution. This is because the previous test for OS has not yet been found to be statistically significant, so any analyses performed thereafter are considered exploratory for us and are difficult to interpret at this point without further follow-up.

DR. HOFFMAN: Okay. Thank you.

Dr. Apolo?

DR. APOLO: Yes. Actually, my question was in line with exactly what we're discussing right now. Going back to slide 27 and interpreting the results that were presented, the primary endpoint was met with a PFS benefit. The OS benefit is still an interim analysis. So it's really, I think

at this point, very difficult to conclude the direction as to interpreting the subsequent endpoint.

But looking at the slide in the PD-L1 positive patients, where the label is currently indicated for, it's trending in the right direction. I understand this is a subset analysis having met the OS endpoint. So for the FDA -- and this is any statistical comments on this -- if the OS is not met, the PFS is met and the OS is not met, can you interpret this even if you wait another year for this arm that was added on later with the monotherapy atezolizumab?

DR. FIERO: This is Mallorie Fiero, FDA statistics. I think if OS is not found to be statistically significant, then we essentially have lost all of our alpha; all of our alpha is spent.

DR. APOLO: For the chemo, chemo plus atezo arm, right?

DR. FIERO: Yes, for the chemo plus atezo arm. All of our alpha would be spent if it was not found to be statistically significant, so we would

be concerned about making any false positive claims after that. So we would be very careful to interpret any analyses if OS did fail.

DR. APOLO: Yes. It's a difficult position to be in, in general, because it's a separate question. The combination of chemotherapy plus atezolizumab is not the same question as atezolizumab monotherapy in terms of the outcomes, but I understand the way that the trial was designed.

That was my first question, and my second question is for Genentech. Is there a backup trial in case it's difficult to interpret the final results of the IMvigor130 data in a year? I know there are a lot of trials ongoing that potentially the data could be used as confirmatory for this indication.

DR. FUCHS: Well, as you point out, we're continuing to garner more data and conduct more studies, looking at atezolizumab in urothelial cancer. IMvigor130 is designated as our confirmatory trial. The data set is not mature.

It has met its endpoint of progression-free, and next year we'll have the final data on overall survival.

I think when that data becomes available, we're obviously committed to sharing that with the FDA, with the scientific community, and with the patient advisory community to really fully understand the benefit of this agent in patients with advanced urothelial cancer.

The data so far, we would suggest, show a clinically meaningful response, durable response in the first line that approaches five years, and we are committed to following through with our commitment on 130. And depending on those results, we're open to working with the FDA on what additional studies should be pursued.

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

DR. HOFFMAN: Okay. This Dr. Hoffman. I apologize if I'm asking you to repeat something, but on the 210 study, the one that is specifically before us --

DR. BEAVER: Sorry. Dr. Hoffman?

DR. HOFFMAN: Yes?

DR. BEAVER: Sorry. Hi. This is Julia Beaver from FDA. I just wanted to follow up on the last question regarding if this trial does not confirm benefit, the FDA's thinking on that, if that would be ok.

DR. HOFFMAN: Yes.

DR. BEAVER: If the trial that we now have as a potential confirmatory trial does not have a favorable overall survival benefit, that would then be the third trial in this setting that would not have met either its endpoints or shown clinical benefit. And at that point, I think the FDA would not look favorably upon continuing the indication.

It's how many tries, you know, how many bites of the apple, so to speak, we would give to confirm benefit in the urothelial cancer space. So I think that is something to keep in mind. I don't know that we're asking for advice about alternative trials, additional trials.

DR. APOLO:

DR. HOFFMAN: Thank you. That's helpful.

DR. FUCHS: Dr. Hoffman, can I just speak to that as well? Perhaps I didn't understand the question if specifically it -- Dr. Apolo and perhaps your question as well -- is around the trials that were conducted in second line.

Can I just briefly speak to those as well?

DR. HOFFMAN: Yes, please.

DR. FUCHS: Thank you.

As you are aware, IMvigor210 had two cohorts. The one we've been emphasizing, speaking to specifically today, is the first-line cohort, but actually there was a second-line cohort as well that was published; that is patients who had progressed on first-line therapy.

In that cohort, the response rate in 210 was 14 percent with a median duration of response of 28 months, which led to the accelerated approval in the second-line setting. IMvigor211, which I think is the trial we're talking about, was a second-line study; that is patients who had progressed on frontline who were randomized to atezolizumab

monotherapy or second-line chemotherapy with a primary endpoint of overall survival, which was not technically a confirmation for the first line, but was, we believe, an important study.

Let me just ask Dr. Carter to briefly share the results of 211 with you.

Dr. Carter?

DR. CARTER: Thank you, Dr. Fuchs.

If I can get the slide pulled up on IMvigor211 just so I can give everybody a complete picture? IMvigor211 was a randomized, phase 3 trial, and it enrolled 931 patients, and it was our designated PMR for the second-line setting.

Here we see the primary analysis of IMvigor211, and the primary analysis was done in a hierarchical design where PD-L1 was the first overall survival we wanted to look at. Here we see the hazard ratio of 0.87 and the p-value was 0.4. This really was at the top of the hierarchy.

I think it's important for everybody to get the good picture on it and to look at the next slide, which is our intention to treat. Although

we weren't able to go down to the intention to treat, we did see a numeric improvement in this as well, overall survival of a hazard ratio of 0.82; so really looking at more of an 18 percent benefit over the standard chemotherapy there. Our response rate in these patients, as Dr. Fuchs said, ranged from 14 to 28 percent and 23 percent in the atezolizumab population there.

Now, I'll turn it back to Dr. Fuchs.

DR. FUCHS: Thank you, Dr. Carter.

I think, as rightly stated, IMvigor211 did not meet its stipulated endpoint. That said, if you look at that Kaplan-Meier curve, if we could return to it, I would suggest respectively that it's a Kaplan-Meier curve that is somewhat comparable to a separate checkpoint inhibitor in the second-line setting and actually did result in approval for the second line in 90 countries across the globe.

That said, we fully respect the position of the FDA on this. As well, we recognize in the second line that the treatment landscape had

changed with a full approval of another checkpoint inhibitor in second line, and as such, we did voluntarily withdraw last month the atezolizumab in second line. But we would still suggest that there is a clinically meaningful benefit for atezolizumab in the second line with a durable response.

DR. HOFFMAN: Okay. Thank you.

I was going to ask -- and apologies if I missed it -- about the duration of response for the responders in 210, the initial study. Could I just see that again or that slide? It would have been early on in the sponsor's section. I'm sorry. I just wanted to know about that, about the response rates.

DR. FUCHS: Of course. Is that slide 14 or thereabouts, in the original deck?

DR. HOFFMAN: Okay. Alright. That answers my question.

Next, Dr. Kraus?

DR. KRAUS: Yes. It's related to slide 19 and slide 22, but maybe 22 is the better one to put up. It's the statistical hierarchy. It's not

slide 19, but put up slide 22.

The question is this, and it's really for FDA and Dr. Fuchs and the sponsor to comment. I wanted to make sure I get clarity. I'm understanding this was the defined confirmatory study. I'm understanding it's successful for progression-free survival. I'm understanding that the overall survival is not mature.

Kind of siding with Dr. Halabi's question mark on why we're looking at interim data, often you don't see interim data. You just proceed until the final because that's when you have the event maturity that you need. And we're not yet at final maturity, which doesn't mean events in all patients. It means events in a reasonable proportion to have a solid answer.

There's a lot of discussion of what do we do if this fails. In the trialism world, it's been successful so far, and we're waiting for a year to get the adequate information to make it through assessment, rather than getting hypothetical about what could happen if it's positive, what could

happen if it's negative.

So I just want to get confirmation that if indeed -- this looks very promising, the 95th percentile confidence intervals with fewer events and final, 1 is the top end of it. So it's very possible this is positive.

So if this is positive, talking about it the other way, I would anticipate that would confirm a survival benefit in a positive trial, and then you could sort it out from there. But I guess the question would be, then do we believe it would have confirmed in that case from this trial?

If that's the case -- the reason I ask it this way is it's a very important industry question. If you're going to start reconsidering accelerated approval before a definitive trial is read out, this is complicated.

So the question is, as we look at this, as we go to confirmation, is this the one trial, to the sponsor and FDA? And two, is it correct that if indeed the OS is positive, this should confirm the benefit of accelerated approval?

DR. FUCHS: Well, Dr. Kraus, I can certainly start. As you point out, 130 is the stipulated confirmatory trial for the current accelerated approval indication, and we would hope that if we confirm a significant survival benefit in the chemotherapy plus atezolizumab arm, that would potentially serve for confirmation.

In the history of accelerated approvals, as you know, there have been circumstances where approval for a monotherapy has ultimately been confirmed by a combination, so there is precedent for that.

DR. KRAUS: Thank you. And FDA?

DR. AMIRI-KORDESTANI: Yes. Thank you. I want to, again, basically comment that while the PFS was statistically significant, we don't view this result to be meaningful, so we don't consider the PFS benefit to confirm the benefit that is needed, basically. So if the overall survival result, the final overall survival result, turns out to be negative, then, basically, we don't consider this trial as a positive trial.

Another clarifying comment is that we already have 85 percent of the events needed for final overall survival data, however, you heard that, basically, the final result is expected next year.

So while these are interim analyses, very commonly in trials they actually build these analyses. They look at overall survival interim analysis. We have in the past actually even updated the drug label. For example, when interim analysis results are positive, then that's considered the final results. That's why they build these analyses. So it's not yet positive, so they need to look at the final result.

We have been following this closely because we don't consider the PFS benefit to be considered actually a positive or appropriate to confirm the benefit, even though it is statistically significant.

DR. KRAUS: Okay. I understand --

DR. AMIRI-KORDESTANI: If Dr. Beaver would like to add any comment; or if you understand,

then --

DR. HOFFMAN: I think we've covered this question sufficiently, if I may.

DR. AMIRI-KORDESTANI: Okay. Thank you.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: Thank you. My question is for the FDA. Actually, can we put up -- I know this is Genentech's slide -- slide 19? It helps me to ask my question. I've been getting caught up on understanding the dynamics of the statistics here, too. It's kind of a two-part question.

First is, when the accelerated approval was given and this plan was laid out for postmarket requirement, and IMvigor130 was designated as the trial that was going to be used to study the efficacy, was the plan to examine atezo plus chemo versus placebo, plus chemo overall survival outcome, or at that point, was that when this atezo monotherapy versus chemo was added on as the point of relevance since the accelerated approval was for atezo as a monotherapy?

Said another way, I'm just trying to

understand -- I'm getting kind of mixed up on the fact that this was like a staged trial where originally it was just a 2-arm trial, atezo/chemo versus placebo/chemo, and then atezo monotherapy was added on.

My question is, from the FDA's perspective in terms of demonstrating efficacy, is the overall survival of atezo/chemo versus placebo/chemo our focus, or do we have to kind of follow this graph all the way down to the last area, where atezo monotherapy versus chemo and the primary OS of the PD-L1 high patients is the OS of interest?

DR. AMIRI-KORDESTANI: Thank you for the question. This is Laleh Amiri from FDA. Just to clarify, for the postmarketing requirement of a study, it doesn't need to exactly ask the question about the benefit of the exact same indication. It can have, for example, add-on design or monotherapy replacement design.

So in order to accept the trial benefit or confirming the benefit, it doesn't need to be positive all the way to get basically the last

test. However, obviously if the trial fails to show the benefit in atezo combination to chemo, then the next test cannot be done. So then, basically, we can't view those anymore.

I hope I'm addressing your question.

DR. SIDDIQUI: Yes.

Then the other question is, too, in order to view the last outcome, primary OS, PD-L1 high, am I correct in understanding that first you would need the trial to demonstrate a positive result for the co-primary OS outcome, and then you would require it to demonstrate a positive result of the primary OS outcome of atezo versus placebo; and only then would you look at the PD-L1 high patient? Is that typically how the analysis would go?

DR. AMIRI-KORDESTANI: This is Laleh Amiri from FDA. This is how the sponsor had designed their statistical analyses, so we are going by the latest analysis plan. But the answer is yes, and I guess that's how it is written, so we can't modify it now. Yes.

DR. SIDDIQUI: Yes.

DR. AMIRI-KORDESTANI: But I can ask Dr. Fiero or others from the FDA stats team if they have any additional --

DR. FIERO: And just confirming -- this is Mallorie Fiero, FDA statistics -- that we can only formally look at that last hypothesis of OS for atezo versus placebo plus chemo only if the two outcomes proceeding it wins. So we do have to follow the prespecified hierarchical procedure.

DR. SIDDIQUI: Okay. This is actually --

DR. FUCHS: It's Genentech.

DR. SIDDIQUI: Go ahead. Sorry.

DR. FUCHS: But, Dr. Siddiqui, if I could just add, as I understand it, when the study was 2 arms, the chemotherapy plus the atezo arm was considered as potential confirmation for the accelerated approval; that is before the third arm was added. So it was agreed upon at that time.

DR. SIDDIQUI: That's helpful. Thank you.

Then this is actually for Genentech, then, also as follow-up. Based on the briefing material, am I placing the numbers correctly? You labeled

positive trend in OS for the atezo/chemo versus placebo/chemo for the interim analysis at 0.84. Now, the same interim analysis for the primary OS in the intention to treat, that was 0.99 at the moment, right? Am I placing the numbers correctly there?

DR. FUCHS: As you can see in this slide, we met the first outcome for progression-free survival, 0.82. The interim analysis of 0.84 is around the chemo plus atezo versus chemo alone; that's 0.84. The 0.99 that you're referring to is actually the intention-to-treat atezo monotherapy versus chemo; so no difference between atezo monotherapy and placebo, which we haven't gotten to because we're still waiting on the mature OS data for atezo/chemo versus chemo alone.

Does that answer your question?

DR. SIDDIQUI: Yes, I think so. Thank you. Those are all my questions.

DR. HOFFMAN: Alright. The final question, Dr. Rettig, please?

DR. RETTIG: Thanks. Yes. This is Matt

Rettig. Please leave up that slide, that same slide, slide 19. Can you bring up slide 19? Thank you.

So the way I see this is that the co-primary OS, the first OS event to be analyzed, if that's positive, presumably that could lead to the regulatory approval for the combination of atezo/chemo in the first-line setting.

The question that we have been asked is really a different question, which is related to the monotherapy issue. I guess if you go to the second OS analysis of atezo versus chemo, right now the trend is that there's not really a difference, and largely the numbers are going to be driven by the PD-L1 low population, which is about three-quarters of the population. I just did a quick calculation on the back of the napkin there, the back of the envelope.

So the question that we're being asked today about continuing the accelerated approval for a monotherapy doesn't seem like it's likely to be addressed in this study, given what I've seen so

far on the data, the primary endpoint of overall survival, the co-primary OS for the combination atezo/chemo versus placebo/chemo, that may be met. But it seems to me implausible that the next OS analysis, atezo versus chemo, will be met given the very high proportion of patients with PD-L1 low tumors who have a detrimental effect of atezo monotherapy.

So I was wondering if both the FDA and the sponsor could comment on that.

DR. FUCHS: Who would you want to go first?

DR. AMIRI-KORDESTANI: I can start first. This is Laleh Amiri from FDA. I'm sorry if I actually didn't make it clear.

So if they win on the first test, which is basically the add-on atezo to chemo versus chemo, that confirms the benefit for us even in the current indication, which is a monotherapy indication.

So just to clarify, for the confirmation of benefit, we don't always ask for a trial to be exactly the same as the initial indication. It can

be an add-on design. It can be a replacement design. It can be a different setting. As long as it shows to isolate the effect and proves to be beneficial, which they show an overall survival benefit in this first test, that will confirm the benefit. They don't need to win in the atezo monotherapy versus chemo monotherapy to test the last, basically, test.

DR. RETTIG: I see. I guess to clarify my question, then, if the OS, the co-primary OS, is met for the combination of atezo/chemo versus placebo/chemo, and the subsequent analyses are not met -- let's assume that for a second -- are you saying that the approval would be for only the combination of atezo and chemo, or would it also be for atezo mono?

I think that's an important question because --

DR. AMIRI-KORDESTANI: Sure.

DR. RETTIG: -- we're not being asked about what would happen if the combination is positive; we're being asked about the monotherapy today and

should that accelerated approval be continued at this time.

DR. AMIRI-KORDESTANI: Thank you for your question. So overall survival --

DR. PAZDUR: Hey. This is Dr. Pazdur. Could I just butt in here, so to speak? You guys are making this way too complicated.

If they win on the first box, the atezo plus chemo versus placebo plus chemo, they get a new indication and they win; they convert their accelerated approval. The reason why we're converting the accelerated approval on the first box is because there's a precedence to convert on the basis of an earlier trial design as well as in combination chemotherapy.

So if they win on the first box, it's a twofer. If they get a new indication and an addition to that, they have their accelerated approval converted.

Any other questions? I don't know how much clearer I could make that.

DR. RETTIG: Well, that's helpful, because

that was never --

DR. PAZDUR: That's about as clear as I can get it. You get a twofer here. You get a new indication, and then in addition to that, you get your accelerated approval converted.

End of discussion. Okay?

DR. FUCHS: Dr. Rettig, I know your question was to both parties. Did that answer your question? Because I did want to clarify one thing that you mentioned.

Dr. Rettig?

DR. RETTIG: Yes. I'm happy to hear your --

DR. FUCHS: No. You mentioned something that I just wanted to clarify. This is on the third box; that is the primary OSITT for atezo monotherapy versus chemo, and you said the detrimental survival.

Could you just bring up slide 26? The hazard ratio, as you can see here, is 0.99, so there's no difference between atezolizumab monotherapy and chemotherapy with respect to

overall survival in an intention to treat. I just wanted to clarify the characterization of detrimental. And obviously the indication for monotherapy is, as you know, in PD-L1 positives in the cisplatin --

DR. RETTIG: Thanks for that clarification. I guess I was thinking of the second line, yes, so thank you for that. I have no further questions. Thank you.

DR. HOFFMAN: Okay. Thank you very much.

We'll now take a 10-minute break. Why don't we plan to reconvene at 2:45? Panel members, please remember that there should be no discussion of the meeting topic with anyone during the break. So we'll resume at 2:45. Thank you.

(Whereupon, at 2:34 p.m., a recess was taken.)

**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 our goals for today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

DR. PAL: Hi. My name is Dr. Monty Pal, Sumanta Pal. I'm a medical oncologist at the City of Hope Comprehensive Cancer Center. I specialize in kidney, bladder, and prostate cancer, and I've been on faculty here for a total of 12 years now.

I have in the past participated in a number of clinical trials, including several in the domain of bladder cancer. In addition to that, I will acknowledge that I've consulted with Roche, as well as with Merck, in the past, although I've had no consulting relationships with companies over the past 12-month period.

With that in mind, I'll keep my comments very brief. I wanted to really just offer some direct insights into why I feel that the current label for atezolizumab and cisplatin-ineligible patients should be maintained. I'm going to try to demonstrate this over the course of three relatively simple slides here. I've been in clinical all morning, so I apologize if this is data that's already been reviewed in the context of some of the previous discussions that have been ongoing today.

This is one of the most recent updates from the IMvigor130 study presented just several weeks ago at the AACR annual meeting. I wanted to make note of the fact that in this slide here, you see

the comparison of atezolizumab versus placebo with platinum gemcitabine in patients who are PD-L1 high, and this of course is at the crux of what we're discussing today.

I think that here the numbers are small but still appreciable with between 85 to 90 patients on each treatment arm. What you see here in my mind is a very striking difference in terms of overall survival with a hazard ratio of 0.67.

Admittedly because of the numbers, that confidence interval crosses over a threshold of 1.0, but I would suggest that nonetheless this is a meaningful difference. And I would suggest that, again, for one like myself who see these patients day to day in clinical practice, there's a preponderance of individuals that we characterize as platinum ineligible or cisplatin ineligible, who are really borderline in terms of functional status and performance status, and this represents a very, very critical option for them.

I think what's really critical in this discussion as well is the duration of response.

It's really impressive to see here the median duration of response with atezolizumab 29 months. What we don't often acknowledge is that when we look at response rates, PFS, we don't acknowledge the fact that amongst those individuals who garner benefit, the benefit's very substantial. I can attest to many patients who have cisplatin-eligible disease receiving atezolizumab and doing well for extended durations of time, often measured in years, and I can assure you that this wouldn't be the case with platinum-based chemotherapy.

This is a slide, again, that I think really speaks for itself in terms of adverse events, which you can see here is a significant difference amongst those patients receiving chemotherapy versus those individuals receiving atezolizumab, a marked difference in terms of grade 3-4 adverse events favoring atezolizumab monotherapy.

This really speaks to the importance of quality of life within this population. Again, this is a frail group, and I think that that really needs to be taken into account. I appreciate the

opportunity to convey my thoughts to ODAC and happy to entertain any questions later. Thank you.

DR. HOFFMAN: Thank you.

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

DR. CHISOLM: Hello. Thank you for the opportunity to speak today. My name is Stephanie Chisolm, and I'm the director of education and research at the Bladder Cancer Advocacy Network or BCAN. BCAN does receive some grant funding in support of our programs from Genentech.

I know you realize that more than 17,000 people are expected to die this year from bladder cancer, and prior to the initial approval of checkpoint inhibitor medications, there have been no new treatments approved for our community in decades. There is a group of patients for whom standard of care is either not effective or safe because of other concerns. Obviously, you've heard a lot about this. For patients with advanced

disease, there are few options, really, beyond getting your affairs in order.

Behind all the statistics that are shared in this form, I just want to remind you that for every N that's discussed, there's a real person, a member of our bladder cancer community, along with the others that care about them, and that the statistics are really just representing people with the tears wiped away.

So we definitely encourage more exploration into the benefit, but we do want to remind you that these are all people. These individuals and families need more options when standard of care does not work or puts them at additional risk. Patients want the opportunity to receive a treatment that provides a durable response when other treatment options are not open to them.

So on behalf of the bladder cancer community, we want to emphasize the critical need for the FDA to fully examine and approve all viable options for treating and managing this devastating disease. Thank you for your time.

DR. HOFFMAN: Okay. Thank you. I don't think we have anything further.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We'll now take any remaining clarifying questions for all the presenters thus far.

Please use the raised-hand icon to indicate that you have a question, and remember to put your hand down after you've asked your question, and the same recommendations as before.

Are there any other additional questions that we didn't cover before the break?

(No response.)

**Questions to the Committee and Discussion**

DR. HOFFMAN: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will proceed with the questions to the committee and panel discussion. I would like to remind public observers that while this meeting is open for

public observation, public attendees may not participate except at the specific request of the panel.

Today's question is a voting question. The question is, should the indication for atezolizumab, for the first-line treatment of cisplatin-ineligible patients with advanced or metastatic urothelial carcinoma, be maintained pending final overall survival results from IMvigor130 trial?

Dr. Joyce Yu will provide instructions for the voting.

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

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will

be no discussion in the breakout room. You should select the radio button, that is the round circular button, in the window [inaudible – audio gap] -- 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 to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

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

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

(No response.)

Mr. Mitchell, I think I saw your hand raised for a moment. Did you have a question?

MR. MITCHELL: No, I don't have a question.

DR. YU: Okay. I'm sorry.

Dr. Hoffman?

DR. HOFFMAN: Okay.

If there are no questions or comments concerning the wording of the question, we'll now begin the voting on question 1. I read it a moment ago.

DR. YU: Okay. Thank you.

We'll now move voting members into the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. YU: The voting has now closed and is complete. The vote results are 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 state the reason why you voted as you did, if you want to.

The vote is 10 yeses, 1 no, [inaudible - audio gap] abstentions. Thank you.

DR. HOFFMAN: Just to repeat, because Dr. Yu's sound is going in and out a little bit, the vote was 10 yeses, 1 no, and no abstentions.

Dr. Madan, do you want to go first, please?

DR. MADAN: Yes. This is Ravi Madan, National Cancer Institute. I voted yes, to wait for the final results. I'm optimistic that the data will continue to support the best care for our patients with bladder cancer. Thank you.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: Yes. This is Mohummad Siddiqui, and I voted yes as well. The interim analysis on the primary overall survival endpoint for IMvigor130 looks promising, so I felt it was very reasonable to wait until the final analysis comes out.

DR. HOFFMAN: Dr. Rettig?

DR. RETTIG: Yes. I also voted yes for some of those same reasons. There's still potential for there to be an overall survival benefit of the

combination.

I should point out I remain a little bit confused because, according to what Dr. Pazdur stated, if the primary overall survival analysis of the combination is met, that is the combination is better than chemo alone, then there will be an approval for the combination as well as the monotherapy, even if the monotherapy comparison does not meet its endpoint.

So I remain befuddled by that, but I will accept that as a fact.

DR. HOFFMAN: This is Dr. Hoffman. I voted no. I realize that I may be a bit inconsistent between the morning and the afternoon, but I found compelling the FDA noting that while the progression-free survival was a positive test, that it may not necessarily be a meaningful difference.

But more importantly, I'm concerned about the fact that a second-line trial was a negative trial that led to the withdrawal of the drug from that indication. It sort of goes against most oncologic history where something shows benefit and

a later line, more advanced disease; then it's moved progressively earlier to show that it's equally effective or better. I was struck by the fact that this is the opposite of that, so I voted no.

Dr. Lieu?

DR. LIEU: This is Chris Lieu. I voted yes. Like you've already heard, I certainly don't think that the story of the 130 study is complete, and we do need a final readout of the overall survival outcomes.

To second what Dr. Hoffman has stated, I think the results of the 211 and 01 studies in the second-line setting and the adjuvant setting really are troubling, and they certainly lend credence to the concerns raised during the meeting.

I am intrigued by the hazard ratios seen within the PD-L1 positive patients as well as the cisplatin-ineligible patients, but of course these numbers are rather small, with only half of the events reached in those cohorts.

I honestly believe that continuation of this

approval should be contingent on the final overall survival analyses when they're met in the next several months to a year, and obviously indication should be withdrawn if that primary endpoint is not reached. Having said that, I do believe we should allow the data to mature prior to making that decision. Thank you.

DR. HOFFMAN: Thank you.

Dr. Sung?

DR. SUNG: I voted yes for the reasons many of the other panelists gave. I would just suggest, as with Dr. Lieu's comments, I'm very intrigued by the different results in the PD-L1 high patients, and I wonder if down the line that may serve to help distinguish therapy choices.

DR. HOFFMAN: Thank you.

Ms. Johnston?

MS. JOHNSTON: Yes. Colette Johnston, and I voted yes. I felt that the data did support that continuing was in the best interest of the very small patient population. They have so many limited resources and so many limited options, and

I think this leaves open one option for the clinicians and the patients. So I feel confident with a vote of yes.

DR. HOFFMAN: Thank you.

Dr. Apolo?

DR. APOLO: Hi. I voted yes. My feeling from looking at the data and the discussions today is that atezolizumab is an active agent for patients with metastatic bladder cancer, both in the first-line setting and I would argue the second-line setting, too.

The trial designs, several of the phase 3 trials that were discussed today, are complicated, and they can be difficult to interpret because although these may be positive in terms of numbers, the studies may still be negative due to the hierarchical design.

We await for the longer follow-up to assess the benefit of atezo plus chemo versus chemo in the first-line setting that will lead to approval of the monotherapy atezo, and I think the interim analysis of the monotherapy atezo looks promising.

There's also a small population of platinum refractory patients that would lose this approval if the indication is withdrawn. So as a treating medical oncologist, I vote to keep atezolizumab available as a treatment option for our patients with urothelial carcinoma that are cisplatin ineligible PD-L1 high and that are platinum ineligible.

DR. HOFFMAN: Alright. Thank you.

Dr. Graff?

DR. GRAFF: Yes. I voted yes. We'll know soon enough the results of the overall survival of the phase 3 study, and there aren't enough harms to really pull it and confuse patients and doctors.

DR. HOFFMAN: Dr. Halabi?

(No response.)

DR. HOFFMAN: Let's go to Mr. Mitchell, and then we'll get back to Dr. Halabi.

MR. MITCHELL: I'm David Mitchell. I voted yes. The data are very encouraging, and we don't have to wait long to learn the results of the 130 trial.

DR. HOFFMAN: Thank you.

Dr. Halabi, are you on now?

DR. HALABI: Yes. Sorry about that.

Susan Halabi. I voted yes. As I stated earlier, while I expect to see interim results from the data monitoring committee, unfortunately now the hazard ratio from the interim analysis for overall survival is in the public domain, and there is definitely some likelihood -- I would say more than some likelihood -- for the results to be positive, and one can never underplay the role of chance. Thank you.

DR. HOFFMAN: Okay. Thank you.

Obviously, the committee felt overwhelmingly optimistic that the final data on this trial will pan out positively, and their votes reflect that. I've already stated my slight reservations about it.

I want to give a moment for Dr. Kraus, who is a non-voting member of the committee but asked for a moment to speak to the committee about something important.

You want to go ahead, Dr. Kraus?

DR. KRAUS: Yes. Well, it wasn't as much reference here as to when we have votes and then talk about different confirmatory designs, and we haven't been doing that separately. But here I would say I'm encouraged by the vote to wait for definitive data from the definitive trial to make the decision.

I would say the complication that's being noted is something we face heavily in oncology drug development. A perfect example is eGFR agents. I was involved with Erbitux colorectal cancer approvals. We found out it was an active drug, and we also found out it worked in half the patients, not the other half some years later; and didn't have the definitive data and had to kind of daisy wheel back to restricting the indication to the patients where it worked better, as we learned more.

I think we may see more and more of this with all the great workups that cancer patients are getting because we do trials. And I mention it

here because the PD-L1 high versus not is kind of the complicating factor, and that's complicated designs. No one knew this going in. So designs went a certain way, and then we see data and we say, well we can't look at that data because of the conclusions.

But the data is the data, but it's also true statistically that you shouldn't look at it and it's not in the hierarchy. But we get faced with these tough questions, and this sounds like we're going to have to weigh it out. So we're trying to figure out how to design better, but hindsight's always 20/20; it's sometimes hard. But that's all I'll say.

Thank you, Dr. Hoffman.

**Adjournment**

DR. HOFFMAN: Alright. Thank you.

We will now adjourn the meeting, and we will reconvene tomorrow, April 29th, 9 o'clock Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members.

Additionally, the panel members participating in the first topic tomorrow should plan to rejoin at 8:15 a.m. Eastern time to ensure that you're connected before we reconvene at 9 o'clock. Thank you very much for your participation this afternoon.

(Whereupon, at 3:12 p.m., the afternoon session was adjourned.)