FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Topic 1

Virtual Meeting

Wednesday, April 28, 2021

9:00 a.m. to 12:04 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICERS (Non-Voting)

Joyce Yu, PharmD

(April 27 and 28 Only)

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Susan Halabi, PhD

Professor of Biostatistics and Bioinformatics

Duke University Medical Center

Durham, North Carolina

Philip C. Hoffman, MD

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

Professor of Medicine

The University of Chicago

Section of Hematology/Oncology

Department of Medicine

Chicago, Illinois

Christopher H. Lieu, MD

Associate Professor of Medicine and Associate

Director, Clinical Research

Director, Gastrointestinal Medical Oncology Program

University of Colorado

Aurora, Colorado

David E. Mitchell

(Consumer Representative, April 28 and 29 Only)

Founder, Patients for Affordable Drugs

Bethesda, Maryland

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Albert L. Kraus, PhD

Global Regulatory Portfolio Lead, Oncology

Pfizer, Inc.

Guilford, Connecticut

TEMPORARY MEMBERS (Voting)

Andrea B. Apolo, MD

(April 28 Only)

Head, Bladder Cancer Section

Genitourinary Malignancies Branch

Director, Bladder Cancer and Genitourinary Tumors

Multidisciplinary Clinic

Center for Cancer Research (CCR)

National Cancer Institute (NCI)

National Institutes of Health (NIH)

Bethesda, Maryland

Colette Johnston

(Patient Representative, April 28 Only)

Moab, Utah

Ravi Madan, MD

(April 28 Only)

Clinical Director

Genitourinary Malignancies Branch

CCR, NCI, NIH

Bethesda, Maryland

Mohummad M. Siddiqui, MD, FACS

(April 28 Only)

Associate Professor of Surgery/Urology

Director of Urologic Oncology

University of Maryland Medical Center

Chief of Urology

Veterans Affairs Maryland Healthcare System

Baltimore, Maryland

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director, Oncology Center of Excellence (OCE)

Acting Director, Office of Oncologic Diseases (OOD)

Office of New Drugs (OND), CDER, FDA

Julia Beaver, MD

Chief of Medical Oncology, OCE

Deputy Director (Acting)

OOD, OND, CDER, FDA

Laleh Amiri-Kordestani, MD

(April 27 and 28 Only)

Director

Division of Oncology 1 (DO1)

OOD, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

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

My name is Philip Hoffman, and I will be chairing today's meeting. I will now call the first 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.

Introduction of Committee

DR. YU: Good morning. My name is Joyce Yu, and I'm 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: Can you hear me?

DR. YU: Yes.

DR. HALABI: Yes. Good morning. I'm Susan Halabi, biostatistician at Duke University.

DR. YU: Thanks.

Dr. Hoffman?

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

DR. YU: Dr. Lieu?

DR. LIEU: Hi. Christopher Lieu, medical oncologist at the University of Colorado.

DR. YU: Thank you.

Mr. Mitchell?

MR. MITCHELL: Hello. I'm David Mitchell. I'm the consumer representative on the ODAC. I'm also a cancer patient with multiple myeloma for 10 years.

DR. YU: Thank you.

Dr. Apolo will be joining us shortly, so we'll come back to her momentarily.

Ms. Johnston?

MS. JOHNSTON: Yes. Good morning. My name

is Colette Johnston. I am the patient representative and a past caregiver, and I work with the IRBs at multiple locations.

DR. YU: Thank you.

Dr. Madan?

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

DR. YU: Thank you.

Dr. Siddiqui?

DR. SIDDIQUI: Good morning. My name is Mohummad Siddiqui. I'm a urologic oncologist at the University of Maryland, as well as the Baltimore VA Medical Center.

DR. YU: Thank you.

Dr. Apolo, if you can hear me, I'll come back to you. Could you please introduce yourself by stating your name and affiliation?

DR. APOLO: Hi. My name is Andrea Apolo. I'm a medical oncologist at the National Cancer Institute in Bethesda, Maryland.

DR. YU: Thank you so much.

And Dr. Kraus?

DR. KRAUS: Yes. Hello. Albert Kraus. I work in oncology research and development to bring new medicines from the lab to the patient. I work for the Pfizer company.

DR. YU: Okay. And we'll introduce our FDA participants for this morning.

Dr. Pazdur?

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

DR. YU: Dr. Beaver?

DR. BEAVER: Hi. My name 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: Thank you.

Dr. Hoffman?

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

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of 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: 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 125514/supplement 17, trade name Keytruda, pembrolizumab, submitted by Merck Sharp & Dohme Corporation, indicated for the treatment of 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 used 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 Merck Sharp & Dohme's sBLA will be discussed.

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

Dr. Hoffman's waiver involves his employer's three research contracts funded by Merck, sponsor of Keytruda, pembrolizumab. For one of the contracts, his employer has received $150,000 to $200,000 with an additional $0 to $50,000 anticipated. For each of the other two research contracts, his employer receives $0 to $50,000 per year from the firm.

Dr. Lieu's waiver involves his employer's two research contracts funded by Merck, sponsor of Keytruda, pembrolizumab. For one of the contracts, his employer has received $300,000 to $350,000 with an additional $150,000 to $200,000 anticipated from Merck. For the second contract, his employer has received $375,000 to $425,000 with an additional $75,000 to $125,000 anticipated from the firm.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at 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 can be made 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 morning, 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 the 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 drugs for serious and life-threatening illnesses that lacked satisfactory treatment.

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

In oncology, this endpoint is most commonly response rate or progression-free survival, earlier endpoints that can be used for either regular or accelerated approval depending on the magnitude of the results, the safety data, and the 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 need to be carried out with due diligence. The majority of accelerated approvals have been for oncology products, and I'll now go over the oncology experience with accelerated approval.

Over the last three decades, there have been over 150 oncology accelerated approvals and 35 anti-PD-1 or PD-L1 antibody accelerated approvals, with close to half 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-1 or PD-L1 antibodies where accelerated approval had been granted, and results from confirmatory trial or trials did not meet their primary efficacy endpoint or only demonstrated a small benefit not deemed clinically meaningful.

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

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

Four antibody indications in small-cell lung cancer and in urothelial carcinoma, shown here, appropriately chose to voluntarily withdraw their indications in consultation with FDA.

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

While the four withdrawals were warranted, the remaining six indications that will be discussed during this three-day advisory committee meeting warrant further discussion and we hope to hear further advice. This session will discuss pembrolizumab 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 in a related setting may result in a changed benefit-risk profile compared to the time of the initial accelerated approval.

However, while for pembrolizumab, the confirmatory trial in the same disease setting did not confirm benefit, pembrolizumab has demonstrated overall survival benefit and received regular approval in the related second-line metastatic urothelial carcinoma setting.

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 objectives, the drug product should be re-evaluated in the context of currently available therapy, and if deemed to no longer benefit patients, the accelerated approval indication should be withdrawn.

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

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

For this reason, FDA encourages all participants, including the Merck Sharp & Dohme's

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

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

We will now proceed with presentations from Merck Sharp & Dohme Corporation, immediately followed by the FDA presentation.

Applicant Presentation – Scot Ebbinghaus

DR. EBBINGHAUS: Good morning, members of the committee and FDA. My name is Scot Ebbinghaus. I'm a medical oncologist and the therapeutic area head in oncology at Merck. Thank you for the opportunity to present the data that supported

accelerated approval of Keytruda for urothelial carcinoma and our progress toward confirming clinical benefit.

Merck is committed to evaluating Keytruda across a wide spectrum of tumor types, and Keytruda has demonstrated clinical benefit across multiple indications. Among 19 traditional approvals, 13 were originally traditional approvals, while six were initially accelerated approvals that have since verified clinical benefit.

Of the 10 remaining accelerated approvals, six have ongoing confirmatory studies and four had confirmatory studies that did not meet their primary endpoints. Of those four, we recently withdrew the indication for small-cell lung cancer after consultation with FDA, and we are here today to discuss the accelerated approval in cisplatin-ineligible bladder cancer in the first-line setting.

Merck's clinical development program in urothelial is comprehensive and spans all disease stages, from non-muscle-invasive bladder cancer to

the advanced setting. Merck received the initial approvals for Keytruda in advanced urothelial carcinoma globally in a subgroup of first-line patients and in the second-line setting based on the results of KEYNOTE-052 and KEYNOTE-045, which are shown in green, nearly four years ago.

As you can see on the left, also in green, Keytruda received traditional approval in the U.S. for patients with BCG-unresponsive, high risk, non-muscle-invasive bladder cancer based on the results of KEYNOTE-057.

KEYNOTE-361, in blue, represents the postmarketing commitment for KEYNOTE-052. As you will hear later in this presentation, long-term follow-up with KEYNOTE-052 in the context of the established survival benefit shown in KEYNOTE-045, and alternately the three studies in gray, are the proposals to confirm the benefit of pembrolizumab for the accelerated approval.

The accelerated approval was granted by FDA on May 18th of 2017 based on KEYNOTE-052. The indication was for use in a subgroup of first-line

patients who are not eligible for cisplatin-containing chemotherapy. In 2018, the indication was restricted to PD-L1 of CPS greater than or equal to 10 for cisplatin-eligible patients based on FDA review of data from KEYNOTE-052 and early data from the ongoing KEYNOTE-361 study. This was triggered by findings from an external data monitoring committee for KEYNOTE-361.

We are here because our initial confirmatory study, KEYNOTE-361, did not show a statistically significant improvement in PFS and OS for the pembrolizumab plus chemotherapy combination compared to chemotherapy alone. We are committed to fulfilling our postmarketing commitment and will work with FDA to evaluate the totality of evidence from our completed and ongoing studies.

The question before this committee is whether the current indication should be maintained. Another question is whether long-term follow-up data from KEYNOTE-052, in the context of the established survival benefit in second-line urothelial cancer from KEYNOTE-045, can confirm the

benefit of pembrolizumab in urothelial cancer, or if further confirmatory evidence from our ongoing development program is needed to confirm the clinical benefit.

The amended indication includes two populations in the front-line setting, cisplatin-ineligible urothelial carcinoma patients whose tumors express PD-L1 CPS greater than or equal to 10 and patients who are platinum ineligible regardless of PD-L1 status.

This slide outlines what you will hear today. First, you will hear from Dr. Balar that advanced urothelial carcinomas is incurable. Prognosis is poor. Many patients are considered ineligible for cisplatin or any platinum-based chemotherapy. Treatment options for these patients are limited and have not changed since the approval of anti-PD-1 or PD-L1 agents.

Pembrolizumab fulfills an unmet need in this indication under accelerated approval. Pembrolizumab demonstrated a clinically meaningful response rate and prolonged duration of response in

first-line cisplatin and platinum-ineligible patients, which is maintained over time. Pembrolizumab has a tolerable safety profile with a positive benefit-risk.

We will briefly present KEYNOTE-361 key findings to show that they are supportive of a continued positive benefit-risk ratio for pembrolizumab in urothelial carcinoma. Based on the unmet need that it addresses, we consider that the existing accelerated approval for pembrolizumab should be maintained, and the data from our development program will be able to provide confirmatory evidence for the benefit of pembrolizumab.

Now I will turn it over to Dr. Balar.

Applicant Presentation – Arjun Balar

DR. BALAR: Thank you, Dr. Ebbinghaus.

My name is Arjun Balar, and I'm the director of the GU medical oncology program at NYU Langone Health's Perlmutter Cancer Center. I'm a clinical investigator dedicated to advancing treatment options for patients with bladder cancer and was

the lead investigator for KEYNOTE-052, which tested the role for first-line pembrolizumab in cisplatin- and platinum-ineligible patients with advanced urothelial cancer.

I'll be describing the disease background and unmet medical need in advanced urothelial cancer. I'm a paid consultant for Merck, but have no financial interest in the outcome of this meeting.

Urothelial cancer is a common cancer in the United States. Advanced disease is frequent and typically incurable. Urothelial cancer disproportionately affects the elderly with a median age of diagnosis of 73, and is a carcinogen-induced malignancy. Patients often have co-existing medical conditions such as cardiovascular disease, impaired kidney function, which subsequently limits our treatment options.

Platinum-based chemotherapy is considered a standard of care. However, toxicity of first-line platinum treatment limits its extended use, and long-term survival with this therapy is uncommon.

According to real-world data, approximately 40 to 60 percent of first line platinum-eligible urothelial cancer patients are not eligible for cisplatin-based chemotherapy. And based on market, research data, approximately 20 percent of all first-line treated patients are ineligible for any platinum-based chemotherapy.

There are two prevailing approaches to clinically characterize and define the patients who are ineligible for cisplatin-based chemotherapy, so first I'll direct your attention to the column on the left. This is a standardized definition created for regulatory purposes, which defines cisplatin ineligibility as at least one of the following conditions: ECOG performance status of 2; impaired kidney function with a GFR of at least 30 but less than 60; grade 2 or worse peripheral neuropathy or hearing loss; or class 3 or worse New York Heart Association heart failure.

Now to the column on the right, this is a second, a group of clinical characteristics driven by both objective and subjective factors that

physicians use in clinical practice. These include advanced age; the presence of multiple medical comorbidities or other factors that may lead to poor tolerability of cisplatin-based chemotherapy; and the physician's clinical judgment.

There is no standardized definition for patients who are ineligible for both carboplatin- and cisplatin-based chemotherapy, and treatment decisions in this patient population are almost exclusively driven by clinical judgment and evaluation of clinical parameters.

In the first-line setting, for patients with an excellent performance status, adequate renal function, and fewer medical comorbidities, cisplatin-based chemotherapy is the preferred treatment option. In clinical practice, these are generally younger patients.

For patients who are not candidates for cisplatin and consistent with the literature -- this would be about 50 percent of the patients that I see in my practice -- the current clinical practice guidelines recommend carboplatin-based

chemotherapy or the PD-1 pathway inhibitors pembrolizumab or atezolizumab.

The recommendation for pembrolizumab or atezolizumab is specifically for patients with tumors that overexpress the PD-L1 protein. Maintenance therapy with avelumab is now recommended for patients who have completed first-line, platinum-containing chemotherapy and who have remained free of disease progression.

Among patients who are cisplatin ineligible, not all patients are offered carboplatin-based chemotherapy. There is a group of first-line, cisplatin-ineligible patients who are potential candidates for carboplatin-based regimens but refuse this treatment, but may be due to toxicity concerns. This represents approximately 20 percent of all first-line, cisplatin-ineligible patients based on market research data and reflects the need to have treatment options available for these patients.

For those patients, generally most advanced in age or medically frail who are not eligible for

any platinum-containing chemotherapy irrespective of PD-L1 expression status, the only approved treatment options are pembrolizumab or atezolizumab. This population is approximately 20 percent of the patients that I see in my practice, and before the advent of immunotherapy, such patients were counseled about best supportive care alone.

Prior to the accelerated approval of pembrolizumab and atezolizumab in 2017, there were no approved drugs for the cisplatin-ineligible patient population. Patients were routinely treated with carboplatin-based chemotherapy, which is associated with inferior outcomes relative to cisplatin-based chemotherapy, and treatment options were even more limited for patients who were not eligible to receive any platinum-containing chemotherapy.

Patients were not offered any treatment or were treated with single-agent chemotherapy, which is not approved in this setting and has very limited evidence available to support its use. No

new drugs have been approved in first-line, cisplatin-ineligible or platinum-ineligible urothelial cancer since the approval of PD-1 pathway inhibitors.

With the approval of pembrolizumab and atezolizumab in a subgroup of patients with advanced urothelial cancer, the proportion of patients who remained untreated -- and I'll direct you to the column on the left shown in gray -- has decreased from initially 39 percent, now down to 8 percent. Note that according to the literature, untreated patients have a dismal prognosis with a median survival of approximately 3.7 months from the time of diagnosis.

Pembrolizumab serves as a treatment option in advanced urothelial cancer, which is supported by the fact that approximately 40 percent of first-line patients receive immunotherapy, as shown now in green. According to claims data, pembrolizumab is prescribed in over 20 percent of first-line treated patients, which represents approximately 2700 new patients in the United

States annually.

This slide is intended to provide further detail in terms of the baseline characteristics of the first-line urothelial cancer patients, and it reflects how treatment patterns have changed with the approval of PD-1 1 pathway inhibitors, based on real-world data.

Prior to the approval of PD-1 pathway inhibitors, younger and fitter patients were more frequently treated, while older patients and patients with poor performance status, which are very common characteristics of patients with urothelial cancer, were frequently left untreated.

With the approval of PD-1 pathway inhibitors, the overall number of first-line, treated patients has increased, particularly among older and frailer patients who presumably were not considered adequate candidates for carboplatin-based regimens. This again speaks to the importance of having treatment options for the subset of patients for whom PD-1 pathway agents are approved.

To illustrate the type of patients who, in my judgment, are good candidates for first-line pembrolizumab, here are two examples from my practice who I routinely see in clinic. The first is a 79-year-old former smoker with hypertension, stage 3A chronic kidney dysfunction, and mild dementia. He initially presents with muscle-invasive bladder cancer with metastases to pelvic and retroperitoneal lymph nodes. He has an ECOG performance status of zero, but was initially very fearful of chemotherapy. His PD-L1 status score is 15.

The second example is an 86-year-old former smoker with coronary artery disease, hypertension, high cholesterol, and stage 3B chronic kidney disease. He's presenting with fatigue, gross hematuria, and acute renal failure with an estimated GFR of less than 15. He has a large locally-advanced bladder cancer, initially has nephrostomy tubes that are placed that are able to improve his kidney function to greater than 30 cc's per minute. He has an ECOG performance status of

2, but he's still interested in receiving treatment for his cancer.

In both cases, I recommended pembrolizumab, and now I will hand it over to Dr. Kang.

Applicant Presentation – Peter Kang

DR. KANG: Thank you, Dr. Balar.

My name is Peter Kang. I'm a medical oncologist and vice president of clinical research at Merck. I'm going to review the efficacy and safety data that support the first-line indication for pembrolizumab in a subset of patients with urothelial cancer, and the proposed option is to confirm clinical benefit.

One of the initial approvals for pembrolizumab in this disease was in the second-line setting. This traditional approval was based on data from KEYNOTE-045 that you're seeing on the screen.

In KEYNOTE-05, which was a randomized phase 3 trial, 542 patients, whose disease occurred or progressed after platinum-based chemotherapy, were randomized to pembrolizumab or investigator's

choice of chemotherapy. As shown here, pembrolizumab demonstrated statistically significant and a clinically meaningful overall survival benefit compared to active chemotherapy, thus providing level 1 evidence per NCCN guidelines.

Additional approval of pembrolizumab in the second-line setting came on the same day as the accelerated approval in the first-line setting. KEYNOTE-052 was a multicenter, single-arm, phase 2 study in treatment-naïve, cisplatin-ineligible patients with advanced urothelial cancer.

All patients received pembrolizumab every 3 weeks for up to 2 years. The primary endpoint of the study was objective response rate in all patients and in patients whose tumors expressed PD-L1, according to RECIST 1.1 in specified central review.

Between February 2015 and August 2016, a total of 370 patients received at least one dose of pembrolizumab. At the data cutoff, the minimum follow-up was two years since the last patient

enrollment.

Pembrolizumab demonstrated in the study a clinically meaningful response rate and long duration of response. The total study population response rate was 28.6 percent and the median duration of response was 30.1 month. In the PD-L1 CPS equals or greater than 10 subgroup, response rate was 47.3 percent and the median duration of response was not reached at that time, suggesting that the PD-L1 biomarker was associated with improved outcome.

With two additional years of follow-up the response rate remained consistent, and responses were well sustained with a median duration of response of now 33.4 months.

The Kaplan-Meier curves visually show the prolonged duration of response in patients with cisplatin-ineligible urothelial cancer. Notably, 52 and 57 percent of responses were estimated to be ongoing at the 24-month landmark in all patients on your left and CPS high subgroup on your right. Based on more mature follow-up data, 45 and

68 percent of responses were estimated to be ongoing at the 3-year landmark.

Subgroup analysis showed that elderly patients and patients with poor performance status derived similar efficacy with pembrolizumab and total study population. In addition, the current first-line indication for pembrolizumab include its use in patients who are not eligible for any platinum-based chemotherapy. As mentioned by Dr. Balar, clinical criteria such as advanced age, performance status, and presence of visceral metastases are frequently used by clinicians to determine platinum ineligibility.

Patients in KEYNOTE-052 who had poor performance status plus one additional relevant factor such as visceral met, or advanced stage, or renal dysfunction had consistent efficacy with pembrolizumab with 25.5 percent response rate as shown in the far right of this slide.

Now I'd like to discuss KEYNOTE-361, which was a confirmatory trial. 361 was a randomized phase 3 trial in patients with previously

untreated, locally advanced unresectable or metastatic urothelial cancer. As opposed to KEYNOTE-052, this trial only enrolled patients who were eligible to receive platinum-based chemotherapy. Patients were randomized to either the pembrolizumab plus chemotherapy combination arm, the pembrolizumab monotherapy arm, or the chemotherapy control arm in a 1 to 1 to 1 manner.

Randomization was stratified by PD-L1 status and investigators choice of chemotherapy, cisplatin, or carboplatin-based chemotherapy. The primary endpoints were PFS by RECIST per central review and overall survival for pembrolizumab plus chemotherapy combo versus chemotherapy alone comparison in all patients, and overall survival for pembrolizumab monotherapy versus chemotherapy in PD-L1 high in all patients.

The sequential statistical design was employed. As shown in blue color, PFS and OS for the pembrolizumab plus chemotherapy versus chemotherapy comparison had alpha initially allocated and were tested first. The formal

testing for all remaining hypotheses, shown in gray color, was done only if statistical significance for hypothesis number 2 was achieved.

Per the protocol, there were two interim analyses and the final analysis. The p-value boundaries at the final analysis are shown in the slide. Because hypothesis 2 did not achieve statistical significance, no further hypothesis testing was conducted.

Here are the KM curves for pembrolizumab plus chemotherapy versus chemotherapy in all patients. The hazard ratios for both PFS and OS favored pembrolizumab plus the chemotherapy arm, however, neither of the prespecified significant thresholds were met.

It's important to note that this was an open-label trial, and the number of patients that went on to subsequent therapies without centrally verified disease progression may have compromised ability to detect significant differences in PFS, and high use of subsequent anti-cancer therapy in the control arm may also have impacted OS endpoint.

This slide summarizes overall response rate and median duration of response of pembrolizumab. The ITT population in KEYNOTE-361, shown in the middle column, shows that the pembrolizumab monotherapy arm from this trial reproduced the findings that were the basis for the accelerated approval from KEYNOTE-052, which is on your left.

Of note, the European Medicines Agency considered these data consistent with the results from KEYNOTE-052 and determined that benefit-risk ratio remained positive in this population. In addition, KEYNOTE-045, shown on your right, results are also consistent with findings from KEYNOTE-052 and 361, and raised a question as to whether all first-line, cisplatin-ineligible patients need to be treated with chemotherapy before potential treatment with anti-PD-1 agents.

Although not formally tested, the median overall survival for pembrolizumab monotherapy versus chemotherapy in ITT, as well as PD-L1 high-cell population was generally similar. The differences in the shape of the curve are due to

the different mechanisms of action of the two treatment approaches, which has been observed in other indications when comparing anti-PD-1 agents to active chemotherapy.

The safety profile of pembrolizumab in this trial was consistent with advanced bladder studies in KEYNOTE-052 and 045 and consistent with reference safety data set, which represent the established safety profile of pembrolizumab. Grade 3 to 5 AEs, SAEs, and deaths were higher for the bladder cancer studies compared to the reference data sets possibly because bladder cancer patients were older and generally more frail with multiple comorbid conditions.

The incidence of immune-mediated AEs with pembrolizumab in this trial was consistent with KEYNOTE-052 and 045 and with the reference safety data set. There were no life-threatening or fatal immune-mediated adverse events in KEYNOTE-361, and most of these adverse events do not require permanent treatment discontinuation.

Here we summarize the adverse events

observed in the pembrolizumab monotherapy arm and chemotherapy control arm in KEYNOTE-361. It's important to note that mean exposure was longer for pembrolizumab than chemotherapy, therefore, the time during which AEs could accrue was longer in the pembrolizumab arm. The incidence of all-cause grade 3-5 AEs was lower for pembrolizumab compared to chemotherapy by nearly 20 percent in spite of the longer exposure time.

With exposure adjustment, the differences in serious AEs and AEs leading to death were reduced and rates appeared similar. The number of drug-related deaths by investigator assessment was the same in both treatment arms.

This figure shows individual adverse events that occurred at least 10 percent of patients in either pembrolizumab monotherapy or chemotherapy arm for which there was a difference of at least 10 percent between arms. This graph reflects the fact that the safety profile of pembrolizumab is very different from that of chemotherapy. When looking at grade 3-5 adverse events, most of these

occurred in the chemotherapy arm; again, highlighting the difference between chemotherapy and pembrolizumab monotherapy.

Now I'd like to turn to the proposed confirmatory trials. We now have long-term follow-up data from KEYNOTE-052 showing that durable responses were sustainable and KEYNOTE-045 results demonstrating clear survival benefit over chemotherapy. We also have a comprehensive development program in this disease, and we have given thought to how to fulfill a postmarketing requirement. We have discussed alternative trials with FDA, but no final commitments have been agreed to.

Merck is proposing four options made up of five trials to confirm the clinical benefit of pembrolizumab in this disease. The first option, as shown in the slide, as suggested by FDA, is the data package of KEYNOTE-052 long-term follow-up data coupled with KEYNOTE-045 data.

Long-term follow-up data from KEYNOTE-052, approximately five years from the randomization,

expands the evidence of durable responses with pembrolizumab in the current first-line indication. In addition, KEYNOTE-045 clearly demonstrated superior overall survival outcome of pembrolizumab against active chemotherapy. This combined package represents very compelling and relevant data to this discussion.

Merck is proposing three other options. LEAP-011 is intended to build upon the efficacy of pembrolizumab in the same population as the current first-line indication. Because the study population includes patients who are ineligible for any platinum-based chemotherapy, a population for which anti-PD-1 therapy has become an accepted standard of care, pembrolizumab was selected as the control arm; that pembrolizumab monitored the arm may help verify the predictive clinical benefit of pembrolizumab in the accelerated approved indication.

KEYNOTE-866 and 905 evaluated the clinical benefit of perioperative pembrolizumab as a monotherapy and in combination with chemotherapy in

cis-eligible and ineligible muscle-invasive bladder cancer. As per FDA guidance, confirmatory trials may be conducted in a different but related population that can verify the predictive clinical benefit of the drug such as an earlier stage of the same cancer. Demonstrating clinical benefit in this earlier disease setting is relevant to the current indication in the metastatic setting because cancer biology is similar and most metastatic bladder cancers arise from muscle-invasive tumors.

These three trials are currently ongoing with interim analyses that are adequately powered for primary and key secondary endpoints at the initially allocated alpha to account for multiple interim analyses. Timelines for these studies fit within the historical precedent for a confirmatory trial.

In summary, first-line therapy for cisplatin- and platinum-ineligible advanced urothelial cancer represents a high unmet medical need. Prognosis is poor and treatment options

remain limited. Since 2017, pembrolizumab has been fulfilling this unmet medical need.

Although conducted in a different population, KEYNOTE-361 reproduced the response rate and very long duration of response that were the basis for accelerated approval of pembrolizumab. In addition, KEYNOTE-045 in a randomized phase 3 trial demonstrated a significant survival benefit as a second-line therapy. The safety profile of pembrolizumab in this disease is consistent with established profile of the product, and pembrolizumab offers a treatment option with a very different safety profile from that of chemotherapy.

I'd like to highlight that pembrolizumab has shown the highest level of evidence of clinical benefit across the full spectrum of urothelial cancer, starting from non-muscle-invasive bladder cancer to advance urothelial cancer, based on KEYNOTE-057 and KEYNOTE-045, resulting in traditional and regular approval. Access to pembrolizumab remains important for these patients,

and FDA approval should be maintained until postmarketing requirements are satisfied.

Thank you for your attention, and this concludes our presentation. We look forward to your questions.

DR. HOFFMAN: Thank you.

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

FDA Presentation – Laleh Amiri-Kordestani

DR. AMIRI-KORDESTANI: Thank you.

Good morning, Chairman and members of the committee. My name is Laleh Amiri-Kordestani. I am a hematologist/oncologist at the FDA. Today I will present FDA's perspective on the accelerated approval of pembrolizumab for the first-line treatment of patients with urothelial carcinoma who are not eligible for cisplatin therapy that was submitted by Merck, who I will refer to as the applicant for the rest of the representation.

Here is the outline of my talk. I will first summarize the key FDA concerns with this accelerated approval, then I will describe the

regulatory history of the initial accelerated approval of pembrolizumab, including the trial results that led to this approval and the result of the trial that was designated to confirm the benefit. I will then review the evolving landscape of treatment of patients with urothelial carcinoma.

Finally, I will conclude my presentation with a voting question. Should the indication for pembrolizumab for the first-line treatment of cisplatin-ineligible and carboplatin-ineligible patients, with advanced or metastatic urothelial carcinoma, be maintained pending conduct or completion of additional trials?

If your answer is yes, please discuss after the vote what trials may serve to confirm clinical benefit, including KEYNOTE-045.

The FDA concerns with this accelerated approval are the following. First, there is uncertainty regarding the efficacy of pembrolizumab for treatment of urothelial carcinoma, as the benefit was not confirmed in the confirmatory trial. Additionally, there is now another

available treatment option that has shown a survival benefit in this patient population. Third, there are some issues with the alternative trials that the applicant has proposed to confirm the benefit.

In May 2017, pembrolizumab received regular approval based on results of KEYNOTE-045. This trial demonstrated an overall survival benefit for pembrolizumab versus chemotherapy in the second-line treatment of patients with locally-advanced or metastatic urothelial carcinoma.

Additionally, based on results from the KEYNOTE-052 trial, pembrolizumab received accelerated approval for the first-line treatment of patients with locally-advanced or metastatic urothelial carcinoma who were not eligible for cisplatin.

In June 2018, based on the external data monitoring committee's findings of a decrease in overall survival, the first-line indication was restricted, as I will describe the details later.

Last year, the results of the confirmatory trial KEYNOTE-361 were reported, which did not confirm the clinical benefit in the first-line setting.

The KEYNOTE-052 trial was the basis of the initial accelerated approval. It was a phase 2, multicenter, single-arm trial. 370 patients with locally-advanced or metastatic urothelial carcinoma, who were not previously treated and were not eligible for cisplatin therapy, were enrolled to this trial. The primary endpoint of the trial was overall response rate assessed by a blinded independent review in the ITT and PD-L1 high subgroups. The duration of response was the secondary endpoint.

The initial and updated efficacy results of KEYNOTE-052 are shown here. The overall response rate was 29 percent in the all-comer population and 47 percent in the patients with PD-L1 high tumors. The median duration of response was not reached in the PD-L1 high subgroup or in all-comers in the initial submission. In the updated results with a cutoff of September 2018, the median duration of

response was 30 months in all-comers and still not reached in the PD-L1 high subgroup.

As Dr. Beaver presented, 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 drugs for this patient population, however, various chemotherapies were used off label in this disease setting that led to a slightly higher but shortest responses.

Additionally, the safety review of KEYNOTE-052, now shown on this slide, is not identified in the safety signals, and the toxicities appeared acceptable for the patient population.

FDA considered the longer duration of response in combination with an alternative toxicity profile constitutes a favorable benefit-risk over the available therapy at the time of approval for this unique patient population. Additionally, FDA considered the accelerated

approval pathway the most appropriate pathway in spite of the overall survival benefit demonstrated in the second-line setting, as the FDA considered the clinical benefit observed in the second-line setting does not necessarily represent or translate into a clinical benefit for the cisplatin-ineligible patient population in the first-line setting, and therefore there was residual uncertainty.

Based on these results, pembrolizumab received accelerated approval for treatment of patients with previously untreated locally-advanced or metastatic urothelial carcinoma, who were not eligible for cisplatin regardless of PD-L1 status. As noted earlier in Dr. Beaver's talk, accelerated approval may require confirmation of benefit.

At the time of this approval, KEYNOTE-361 was an ongoing trial. This trial was designated as a confirmatory trial to fulfill postmarketing requirements to confirm benefit of pembrolizumab for this indication. The trial was a randomized study, evaluating pembrolizumab either alone or in

combination with platinum-based chemotherapy compared with chemotherapy alone.

Patients with locally-advanced or metastatic urothelial carcinoma who had not received prior systemic therapy in the metastatic setting and who were eligible for any platinum-based chemotherapy were enrolled in this trial. Therefore, this trial included the cisplatin-ineligible patient population.

The external data monitoring committee's early review found that patients who had PD-L1 low tumor in the monotherapy arm of the KEYNOTE-361 trial and another similar trial, IMvigor-130 that was evaluating the efficacy of atezolizumab in a similar patient population, has decreased survival compared to patients who received cisplatin or carboplatin-based chemotherapy. Both the studies were amended and stopped enrolling patients since the tumors had PD-L1 low status for the immunotherapy/monotherapy arms per the DMC recommendation.

These results led to the restriction of the

accelerated approval indication in June 2018 for the population of cisplatin-ineligible patients without PD-L1 high tumors.

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

Subsequently, the final analyses of KEYNOTE-361, the confirmatory trial, were reported and demonstrated no benefit in either of the co-primary endpoints of progression-free survival or overall survival for pembrolizumab plus chemotherapy compared to chemotherapy alone.

In the next exploratory analysis, in a group of patients with PD-L1 high tumors in KEYNOTE-361 that corresponded to KEYNOTE-052, the overall response rate was 25 percent. As the confirmatory trial did not confirm the benefit of pembrolizumab for first-line treatment of cisplatin-ineligible patients, the applicant has proposed an alternative trial to confirm the benefit of pembrolizumab.

As we heard from Dr. Beaver's talk, the confirmatory trial can be performed in earlier disease settings rather than in the identical indication approved under accelerated approval. This promotes further drug development and also reduces patient accrual challenges to trials, evaluating an indication that has already been approved under accelerated approval.

LEAP-011 is a randomized phase 3 study of pembrolizumab plus lenvatinib versus pembrolizumab plus placebo, for previously untreated locally-advanced or metastatic urothelial carcinoma in cisplatin-ineligible patients whose tumors express PD-L1 and in patients ineligible for any platinum-containing chemotherapy, regardless of PD-L1 expression. However, this trial does not isolate the effect of pembrolizumab. Therefore, it will be challenging to use this trial to confirm the benefit of pembrolizumab.

KEYNOTE-866 is a randomized phase 3 study of perioperative pembrolizumab plus neoadjuvant chemotherapy versus placebo plus neoadjuvant

chemotherapy for cisplatin-eligible patients with muscle-invasive bladder cancer. However, this trial only enrolled the cisplatin-eligible population, and it will be challenging to use this trial to confirm the benefit of pembrolizumab in the cisplatin-ineligible population.

KEYNOTE-905 is a randomized phase 3 study of cystectomy plus perioperative pembrolizumab plus/minus enfortumab vedotin versus cystectomy alone in cisplatin-ineligible patients with muscle-invasive bladder cancer. This study's results will be available until 2027.

As we've heard from Dr. Beaver's talk, an important factor for consideration for accelerated approval is having an unmet medical need and the efficacy of the drug compared to available therapies. Since the trial has not confirmed benefit, before additional confirmatory trials are considered, the current unmet medical need and drugs that constitute available therapies should be reassessed to determine if the conditions for accelerated approval still exist.

While there were many close effective treatment options available for cisplatin-ineligible patients at the time of the accelerated approval of pembrolizumab in 2017, these patients may now be treated with gemcitabine plus carboplatin, followed by avelumab maintenance therapy in those without disease progression after the chemotherapy, as avelumab maintenance therapy received regular approval in 2020 based on an overall survival benefit for this regimen compared to chemotherapy alone.

Approximately 40 percent of patients enrolled in this study received gemcitabine plus carboplatin. The majority of cisplatin-ineligible patients would be accepted to the eligible for maintenance with avelumab therapy following their first-line chemotherapy. Recent guidelines recommend this regimen as one of the preferred treatment options for these patients. However, FDA recognizes that there is still an unmet medical need for treatment of patients who are unfit for any platinum-based chemotherapy or any

chemotherapy.

To summarize, the efficacy of pembrolizumab has not been confirmed for the first-line treatment of patients who are not cisplatin eligible. However, as mentioned earlier, the efficacy of pembrolizumab has been established in the second-line treatment setting for patients with urothelial cancer.

In the KEYNOTE-045 trial, pembrolizumab monotherapy demonstrated an overall survival benefit versus chemotherapy, and these results support regular approval of pembrolizumab for this indication. Additionally, pembrolizumab is approved for the treatment of non-muscle-invasive bladder cancer.

While the efficacy of pembrolizumab has not been confirmed for the first-line treatment of patients who are not cisplatin eligible, the efficacy of pembrolizumab is established in the second-line setting, and it has shown an overall survival in KEYNOTE-045. However, the treatment landscape has changed with the approval of avelumab

in the first-line maintenance setting.

The applicant has proposed alternative trials in different disease settings or populations, or the design doesn't [indiscernible] isolate the effect, and it is unclear which one of these alternative trials can confirm the benefit of pembrolizumab.

Given this, should the indication for pembrolizumab for the first-line treatment of cisplatin-ineligible and carboplatin-ineligible patients, with advanced or metastatic urothelial carcinoma, be maintained pending conduct or completion of additional trials?

If your answer is yes, please discuss after the vote what trials may serve to confirm clinical benefit, including KEYNOTE-045. Thank you for your attention.

Clarifying Questions to Presenters

DR. HOFFMAN: Okay. Thank you.

We will now take clarifying questions for the presenters, both Merck Sharp & Dome and the FDA. Please use the raised-hand icon to indicate

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

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

Dr. Lieu?

DR. LIEU: Hi. This is Chris Lieu, panel member. This is a question for Dr. Kang from the Merck team.

In regard to the confirmatory studies that you mentioned, you had mentioned that you're awaiting longer term follow-up from KEYNOTE-052. I was wondering if you could clarify exactly what endpoints and what type of data you are hoping to provide from that long-term follow-up to provide

confirmatory data to support the continued indication. Thank you.

DR. EBBINGHAUS: Yes. Dr. Lieu, this is Scot Ebbinghaus. I will have Dr. Kang address your question.

Dr. Kang?

DR. KANG: Peter Kang from Merck clinical. I would like to go back to the core deck, where updated duration of response data was presented.

Thanks for the question. It's a critical question. Initially, the accelerated approval data cut was September of 2016. Since then, what we presented in this presentation is the data based on the latest data cutoff, which essentially adds an additional four years of a follow-up.

So what the long-term follow-up from KEYNOTE-052 does is that it definitely adds certainty around duration of response, which was the essential element of the approval. So now the latest median duration of response is 33.4 months and, again, response rate remained consistent.

Back to you, Dr. Ebbinghaus.

DR. EBBINGHAUS: Thank you, Dr. Kang.

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

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: Thank you. This is Mohummad Siddiqui. This is also for the Merck team. I was hoping to get some clarification to make sure I'm understanding this well.

Based on the briefing document, and I think also in slide 13 of the FDA talk, it looked like in KEYNOTE-052, for the PD-L1 high expression versus low expression, the overall response rate was 43.5 versus 16.1 percent, but in KEYNOTE-361, that overall response rate seemed to be 25.4 versus 24.1 percent.

Do you have insights into why the ability of PD-L expression to stratify overall response rate did not pan out in KEYNOTE-361 versus 052?

DR. EBBINGHAUS: It's an important question that we've given a lot of thought to. I'll ask my colleague from our biomarker group, Dr. Rajasagi, to provide an answer.

DR. RAJASAGI: Mohini Rajasagi, Merck clinical biomarkers. Our view is that PD-L1 based enrichment is highly contextual and can vary based on several factors like patient population, baseline characteristics, anti-PD-L1 agents, and the PD-L1 ISP active.

The interpretation of PD-L1 predictive value has to be made in totality, and no single factor that I mentioned previously has been able to consistently demonstrate PD-L1 based enrichment in metastatic urothelial cancer trials within and between anti-PD-L1 agents.

Back to you, Dr. Ebbinghaus.

DR. EBBINGHAUS: Thank you, Dr. Rajasagi.

In summary, there were conflicting results, I think, with respect to PD-L1 enrichment between KEYNOTE-052 and KEYNOTE-361, which frankly don't have a good explanation. But I think it doesn't take away from the fact that there were durable responses in both groups, or shown with both studies, among patients who were PD-L1 high and among those who are not expressing as high a level

of PD-L1.

DR. SIDDIQUI: Thank you. I also had one more question for the Merck team, and this is, of all the studies that are proposed, the one that struck me as potentially most relevant was LEAP-011 in terms of the patient population's focusing on. However, I was having a hard time understanding how the pembro arm of the LEAP-011 add information that could not be obtained from KEYNOTE-052.

Am I correct in that the primary outcome was still overall response rate for that arm, as the proposed follow-up studies, or is there something additional that would be gained from the LEAP-011 pembro arm that could not be inferred from the long-term follow-up of KEYNOTE-052?

DR. EBBINGHAUS: I'll have my colleague, Dr. Kang, to provide a response to that.

DR. KANG: Peter Kang from Merck clinical. Slide up, please. I'll just go back to the core deck.

Again, the intention of the LEAP-011 very much is in line with our general approach at Merck,

which is always to try to improve upon activity on top of pembrolizumab as a standard care, and that's the objective of the study. The trial design is pembrolizumab plus lenvatinib versus pembrolizumab as a control arm. The strength of the study, as you mentioned, is the fact the trial's been conducted in exactly the same indication.

Another strength that would be very informative would be at the end of the trial, we'll have over 300 patients in the same population as the drug label being treated with pembrolizumab monotherapy. And what that will do is it will expand the existing body of evidence from 052, 045, and 361, which showed, as we have shown, consistent response rate and duration of response from almost 1,000 metastatic urothelial cancer patients treated with pembrolizumab monotherapy.

Back to you, Dr. Ebbinghaus.

DR. EBBINGHAUS: Yes, I agree, Dr. Kang. And I think in addition, as you pointed out on the slide, the endpoints of that study are progression-free survival and overall survival. So

while it will potentially serve to reproduce the OR and DOR that was observed in KEYNOTE-052, it can also provide progression-free and overall survival from a large randomized phase 3 trial, albeit not in comparison to something that doesn't have pembrolizumab.

DR. SIDDIQUI: Alright. Thank you.

DR. HOFFMAN: This is Dr. Hoffman. I had a question for the Merck team. I'm trying to figure out why the pembro-alone arm on 361 did not compare favorably with the KEYNOTE-052. And I'm just wondering if a fair number of these patients subsequently got immunotherapy after failing chemotherapy, and that that basically eliminates some of that lack of difference.

DR. EBBINGHAUS: Right. I'll have Dr. Kang address the question about second therapies following participation in the KEYNOTE-361 trial that was an important factor.

I'd like to point out, though, that the main difference in the outcome of the pembrolizumab monotherapy outcomes between KEYNOTE-052 and

KEYNOTE-361, with respect to PD-L1 enrichment, if you compare the outcome of the ITT population of KEYNOTE-052 and the ITT population for pembrolizumab monotherapy in KEYNOTE-361, they show very comparable response rates and durations of response.

But, Dr. Kang, could you perhaps review the post-study therapies to address Dr. Hoffman's question?

DR. KANG: Peter Kang from Merck clinical. In KEYNOTE-361, 48 percent of patients, so nearly half the patients in the chemotherapy control arm, eventually were treated with anti-PD-L1 or anti-PD-L1 agents. Perhaps more importantly, not an insignificant number of patients actually went on to receive second-line therapy from the chemotherapy arm before the verification of disease progression.

It amounts to be about 16 percent of patients in the control arm not only went on to receive second-line therapy, but earlier than the protocol would dictate. So that clearly had an

impact on the overall outcome.

Back to you, Dr. Ebbinghaus.

DR. EBBINGHAUS: Thank you, Dr. Kang.

DR. HOFFMAN: Okay. Thank you.

Dr. Madan?

DR. MADAN: Yes. I have a question for the Merck team with regard to the LEAP-011 trial. Are there any statistical assumptions you can share with us regarding the proportion of patients you anticipate to enroll who are PD-L1 positive and cisplatin ineligible versus those who were ineligible for all platinum chemotherapies?

DR. EBBINGHAUS: I'll actually have Dr. Kang to address that. The trial's ongoing in its enrollment, so we can actually share, obviously in a blinded fashion, what the trends have been so far in enrollment.

Dr. Kang?

DR. KANG: Peter Kang from Merck clinical. Again, the trial is being conducted in the same population with current drug approval. We obviously monitor in a blinded manner baseline

characteristics. Actually, the majority of the patients that are being enrolled in LEAP-011 at the moment is made up of platinum-ineligible patient population. At the end of the trial, we suspect that the majority of patients in LEAP-011 will be considered platinum ineligible, in addition to some patients who are considered cis ineligible but platinum eligible with PD-L1 high.

Back to you, Dr. Ebbinghaus.

DR. EBBINGHAUS: Thank you, Dr. Kang.

DR. MADAN: Just one follow-up question. Are there any specific statistical characterizations of what you're looking for in the patients who are ineligible for platinum therapies that are preset in the trial?

DR. EBBINGHAUS: This is Scot Ebbinghaus. I believe that we will perform, as would be typical in these types of trials, subgroup analyses to show consistency of the outcomes between patients with various characteristics. And obviously, that would be a very important subgroup analysis that we have not prespecified specific hypotheses in the

populations of patients who are ineligible for any platinum compared to those patients who are eligible for carboplatin-based therapy but may have a PD-L1 expression of greater than 10.

DR. MADAN: Okay. Thank you for your time.

DR. HOFFMAN: Dr. Apolo?

DR. APOLO: Hi. This is Dr. Apolo. My question is for the KEYNOTE-361 study that you have discussed, and there have been several questions about this trial because it did have a monotherapy pembrolizumab arm.

Would you consider the KEYNOTE-361 a longer follow-up as a confirmatory -- also one of the ones as a confirmatory for survival benefit with monotherapy pembrolizumab? This is for the Merck team.

DR. EBBINGHAUS: This is Scot Ebbinghaus. Our sense is that we have pretty much final information on KEYNOTE-052 in terms of the comparison of chemotherapy to pembrolizumab as a monotherapy. Of course, for essentially all Merck trials, we follow patients very long-term, even

after the final analyses of these studies.

So we can certainly provide long-term data on KEYNOTE-361 to further supplement the overall body of knowledge on the durability of the responses that were observed, and we'd certainly be open to do that, both for the scientific community in terms of publications and presentations, and in terms of discussions with the FDA to satisfy the totality of evidence for the durability of the responses in this unmet need population.

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

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Yes. Hi. Susan Halabi. I have a couple of follow-up questions. Actually, Dr. Apolo alluded to one of them. The first one has to do with the follow-up time for 361. Also, I'm curious to hear from the sponsor on the number of events. I may have missed that, in terms of the number of events for your analysis for the KEYNOTE-361. So that's my first question.

Then the second question, I may have missed

that one, too. I haven't seen any data presented for PFS for the other trial, and I was wondering if you have this information. I've seen only PFS for, I believe, KEYNOTE-361.

DR. EBBINGHAUS: Okay. Just to be clear, Dr. Halabi, you're asking about the follow-up time and number of survival events from KEYNOTE-361, and then if we could show progression-free survival data from KEYNOTE-052.

Those are the questions?

DR. HALABI: Yes, please.

DR. EBBINGHAUS: Okay.

One of our statisticians was having difficulty with audio, but I was going to call on Dr. De Lucca from our biostatistics to talk about the number of events that were observed for the final analysis of KEYNOTE-361, if he's still on; if not, his backup, Dr. Gause.

DR. GAUSE: Hello. This is Christine Gause for Merck biostatistics. In KEYNOTE-361, the combo versus chemo comparison for overall survival, we had 508 events. For the PFS combo versus chemo

comparison, we had 493 events. For the monotherapy versus combination therapy for overall survival, we had 472 events, and then for monotherapy versus chemotherapy in PFS.

DR. HALABI: Thank you. So in other words, are you planning to continue following all the patients or this is the final follow-up, just to clarify?

DR. EBBINGHAUS: That was the final formal analysis of the study, and there will be no additional formal analyses for inferential or hypothesis testing. However, as mentioned, we will continue to follow patients on the study for longer-term outcomes.

Then to get back to your other question, I'd like to have my colleague, Dr. Kang, show you the progression-free survival data from KEYNOTE-052.

DR. HALABI: Okay. Thank you.

DR. KANG: Peter Kang from Merck clinical. Slide up. The slide shows PFS data with pembrolizumab and chemotherapy in all patients and choice of carbo subgroup. I think what you're

looking for is PFS data from KEYNOTE-052, shown in the left-most graph. I think the take-home from this data for us was, along with overall survival and response rate and duration of response data, it was general consistency between KEYNOTE-052 and 361.

Back to you, Dr. Ebbinghaus.

DR. EBBINGHAUS: If you look at the pattern of the progression-free survival curve from KEYNOTE-052, it's quite supportive of the durability of responses, showing that there's a tail on the curve and a fraction of patients that likely derive long-term benefit.

DR. HALABI: Thank you.

DR. HOFFMAN: Dr. Kraus?

DR. KRAUS: Yes. Thank you. Albert Kraus, industry representative. I have a comment and question about slide 25 from the Merck presentation, if you could put that up, perhaps. This is the trial 361, PFS and OS, Kaplan-Meiers.

The comment is -- because this is something I think we face and will face more of with very

highly effective targeted therapies. The hazard ratio for progression-free survival, the 95 percent confidence interval excludes 1, suggesting a benefit despite the statistical parameters that restricted alpha to not show it, and in survival, it barely exceeds 1, suggesting a benefit.

This is in the milieu of what we heard before, that there was 48 percent subsequent PD-1 -- PD-L1 use after progression, essentially making the OS an evaluation of combination versus sequential therapy in substantial part, not is the combination effective. The second part is on PFS, you noted a number of dropouts. I think we said 16 percent of the control arm, who then went to receive PD-1's or PD-L1's before they ever progressed.

So I bring this up because this is something with highly targeted agents we face, that in an open-label trial, for many patients there are trials that stop because so many patients in a control arm stop.

So I'm just wondering -- and it's a question

for Merck and a question for FDA. I think we can expect to see these kinds of problematic, experimental situations that might occlude truth because of, obviously, the patient knowledge, physician knowledge, and desire to get people off a control arm or move them to a subsequent therapy for their own benefit, which makes sense. However, it complicates the data understanding and the measurement. It reduces the chance that you're measuring a treatment effect.

I'm wondering if both FDA and Merck could comment on that and how they think we should be looking at that as we go forward, because this study is not just one study with nothing around it. There's tremendous positive evidence in the second line of a survival benefit and other evidence in non-muscle-invasive of significant benefit.

So I'll stop there, but if we could get a comment from FDA and Merck on that, that would be helpful.

DR. AMIRI-KORDESTANI: Thank you. Actually, Dr. Boyar [ph], a statistician from FDA, can

comment on this.

FDA STATISTICIAN: Hi. This is [indiscernible] from FDA statistics. Unfortunately, given the current design of the study and the results that we obtained, it's very difficult to conclude any statistical significance, based on the results that we see. I think both FDA and the applicant have agreed that there is no statistical significance achieved here, so it is very difficult to interpret the results from a stats perspective.

One more other quick comment that I would like to mention is regarding the previous question which was asked, which is that the final results for the KEYNOTE-361 trial, the formal analysis has already been conducted, so any further follow-ups will be considered exploratory in nature.

Finally for the KEYNOTE-052, even though we are looking at PFS, when we are looking at PFS, I would like to stress that PFS in a single-arm trial is also difficult, is not interpretable, and should be looked at with caution as well. Thank you.

DR. EBBINGHAUS: So from the Merck perspective, we certainly agree that the circumstances of the post-study therapy, and patients who went on to subsequent therapies without confirmed disease progression by independent central review, can potentially explain, in part, why the trial showed favorable observed differences between the treatment and the control arm but didn't quite reach statistical significance.

I think it may be worthwhile to ask for a clinical perspective from our clinical bladder cancer experts. We actually had Dr. Matt Galsky who came with us to provide some potential clinical interpretation of the outcome of the totality of evidence, including what you've observed from KEYNOTE-361.

Dr. Galsky, would you have any comments to share with the committee?

DR. GALSKY: Matt Galsky, medical oncology at Mount Sinai, and I have served as a consultant for Merck. I agree with what the committee member

said about the impact of subsequent treatment. I think I would just highlight a couple of things about the discussion today.

One that isn't being debated is the efficacy of pembrolizumab in metastatic urothelial cancer. Of course, we've heard that there's level-one evidence that pembro will improve survival in patients with metastatic urothelial cancer who've progressed despite prior platinum-based chemotherapy; so why we accept its standard of care in that context.

I think also what's not being debated is whether or not there is activity of pembro in patients with metastatic urothelial cancer who haven't had platinum-based chemotherapy; that is whether there is some mechanistic reason why prior exposure to platinum would make the drug work better. Because we see durable responses with pembro similar to what's observed in patients with metastatic urothelial cancer that has progressed despite prior platinum-based chemotherapy in the chemotherapy-naïve setting, and now in two very

large data sets in KEYNOTE-052 and KEYNOTE-361. In fact, response proportions in the chemotherapy-naïve setting are similar to maybe even a little bit higher.

So clearly what's being debated is the relative benefit of front-line pembro versus carboplatin-based chemotherapy in cisplatin-ineligible patients, or pembro versus no treatment in patients who aren't optimal candidates for chemotherapy at all.

I really see this as a question about patient physician choice. Some patients want the chance at a durable response with immune checkpoint blockade without having to be subjected to the potential side effects with chemotherapy. I personally would hate to have payers telling my patients and me that the patient has to receive chemotherapy prior to having a chance to receive immune checkpoint blockade. And so immune checkpoint.

So immune checkpoint blockade might not be the optimal first-line treatment for all patients,

or even most in fact, with metastatic urothelial cancer, but I do feel strongly that it should be a choice available to those patients who want to pursue that approach. Thank you.

DR. EBBINGHAUS: Thank you, Dr. Galsky.

DR. KRAUS: Thank you. I appreciate the clarity.

DR. AMIRI-KORDESTANI: The FDA team would like to add another comment. Generally, we see this crossover in many trials, and they don't affect progression-free survival, but they may affect overall survival.

I don't know if Dr. Bloomquist, our stat team lead, can add comments here.

DR. BLOOMQUIST: Sure. And thank you, Dr. Kraus, for the question.

Dr. Amiri is correct. PFS typically will not be effective by crossover. Typically, a small majority of patients will switch to alternative therapy if they're still seeing benefit; let's say stable disease.

In terms of overall survival, yes; of

course, we do see crossover possibly affecting the results, however, it's been the position that we typically want to see results based upon the ITT without the effects for crossover here. In this case, they were not able to show statistical significance, and we have to interpret this as a failed trial, OS. This was not shown via a level that rolls out chance findings in this case.

DR. KRAUS: Thank you, Dr. Bloomquist.

DR. HOFFMAN: Okay. Let's take our last question before the break, and then if there are others, we'll do that after the open public hearing.

Mr. Mitchell?

MR. MITCHELL: Yes, thank you very much, Dr. Hoffman.

My question is, to what extent does avelumab fulfill or meet the unmet need that was present at the time accelerated approval was granted to pembrolizumab? Can patients be served effectively with avelumab, the population we're looking at, in the absence of pembrolizumab?

DR. EBBINGHAUS: Mr. Mitchell, I'll have one of our urothelial cancer experts to address your question.

Dr. Balar, the question is about does avelumab fulfill the unmet medical need.

DR. BALAR: Thank you, Dr. Ebbinghaus.

Arjun Balar, medical oncologist, NYU Langone Health. I think the JAVELIN bladder 100 study is an important trial, but I think it's important to recognize that that trial does not, really at all, address the first-line untreated metastatic urothelial cancer patient population.

Importantly, that trial addresses a population that has already been treated with first-line platinum-based chemotherapy, has had a good outcome to platinum-based chemotherapy, and then subsequently transitions to maintenance immunotherapy.

Now, it does raise the question of is there a group of patients that need treatment with platinum-based chemotherapy, and that answer would be yes. And there are some patients who do present

with very aggressive features, and those patients should receive carboplatin-based treatment. But there are patients who are cisplatin ineligible by virtue of their disease characteristics, and there are some patients who are cisplatin ineligible by virtue of their baseline health characteristics such as advanced cardiovascular disease, other health conditions, and so forth.

So it's important for both clinicians and the patients to have their choices; for instance, patients who are very advanced in age -- late octogenarians, nonagenarians -- for whom platinum-based chemotherapy could pose a significant safety risk in terms of treatment. And for those patients, immunotherapy is, in many instances, the only viable safe treatment option. Thank you.

DR. EBBINGHAUS: Thank you, Dr. Balar.

MR. MITCHELL: Thank you very much.

DR. HOFFMAN: Let's take a break. Let's reconvene at 11:05. At that point we'll do the open public hearing, and then if there are

additional clarifying questions, we'll do that subsequent. So we'll reconvene at 11:05. Thank you.

(Whereupon, at 10:48 a.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're representing for the record.

DR. ZUCKERMAN: Yes. Thank you very much. Can you hear me?

DR. HOFFMAN: Yes.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our center is a non-profit think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products. I'm trained in statistics, clinical trial design, epidemiology, and public health, and was a faculty member and researcher at Yale and Harvard, and a fellow in bioethics at Penn. I've also worked at HHS.

The details today for Keytruda and Tecentriq differ but in both cases are statistical, and research analyses support the FDA findings that the data do not confirm the indication. And that's

especially important because both drugs cause substantial adverse events and because an alternative treatment has shown clear benefit.

FDA grants accelerated approval with requirements for postmarket, randomized-controlled trials to evaluate overall survival, but the randomized clinical trials conducted did not show benefit. So how can FDA continue to offer accelerated approval for any drugs in the future if postmarket randomized-controlled trial results are ignored?

Most of you on this panel are clinicians and you're used to trying different types of treatment in hopes that something will work and sometimes that does work, but the rules for FDA approval are different. Shouldn't cancer patients be eligible for free treatments in clinical trials instead of paying for treatment that isn't proven to work and that has risks?

Can other studies be used to confirm the indication? FDA explained the problems very clearly. It would not be appropriate to use

studies with data based on patients who aren't for the same indication, which is PD-L1 high and not-cisplatin eligible or platinum eligible.

Let's face it. Merck is not a start-up company. They should conduct well-designed studies. If less appropriate studies are accepted as alternatives, doesn't this create disincentives for all companies so that they no longer do the well-designed studies they have agreed to do?

Our analysis agrees with FDA that neither progression-free survival nor overall survival were clinically meaningful or statistically significant. So what's the justification for keeping the indication for years while awaiting data that might or might not support approval in the future?

FDA also has pointed out that real-world data must meet scientific standards to confirm meaningful benefit. Most important, patients deserve treatments that provide meaningful benefits that outweigh meaningful risks, and they need to be able to trust that FDA approval confirms that.

As a cancer survivor myself, I know that

patients want hope. So what's the ethics of your decision today? FDA approval means rigorous evidence. It isn't supposed to be based on wishful thinking, or speculation about crossover data, or post hoc manipulation of data. I respectfully urge you to listen to what the FDA scientists have told us repeatedly in their memo; the evidence does not support continued approval and using other studies can't provide the data needed.

In conclusion, patients have suffered from taking cancer drugs that aren't proven to work. Other treatment options are proven to work. Physicians can still choose whatever treatments are on the market, but those treatment decisions shouldn't be based on the mistaken belief that either Keytruda or Tecentriq are proven effective for advanced urothelial carcinoma. Thanks very much for the opportunity to speak today.

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

DR. MAMTANI: My name is Ronac Mamtani, and I am a bladder cancer oncologist and cancer epidemiologist at the University of Pennsylvania. I'm not receiving any compensation by the sponsor for this presentation.

I'd like to describe, number one, how the treatment of patients with advanced bladder cancer has evolved with the approval of the immune checkpoint inhibitors in the frontline setting and, number two, why I believe retaining the indication for anti-PD-1/L1 agents in the frontline setting is critical for some patients who are cisplatin or anti-platinum ineligible.

Now, prior to 2017 for patients who are unable to receive cisplatin-based chemotherapy, the preferred treatment was carboplatin-based chemotherapy or clinical trial participation. The median survival for patients treated with carboplatin-based chemotherapy is only 9 months. These regimens are associated with severe toxicity in approximately 10 to 15 percent of patients, mainly hematologic adverse events. Now, some of

these patients refuse these treatments because of tolerability concerns and limited long-term efficacy.

Before the advent of the immune checkpoint inhibitors, there were no other treatment options for these patients. Now even more difficult to treat, and without any approved treatment options before the checkpoint inhibitors, are patients who are ineligible for both cisplatin and carboplatin-based chemotherapy. These patients are medically frail and are typically offered best supportive care alone. Approximately 1 in 5 patients in my practice fall within this group, and this group has a dismal prognosis.

The approval of the anti-PD-1/L1 agents in 2017 represent a pivotal change in the first-line treatment landscape of bladder cancer patients. Once these treatment options became available, we observed a clear shift in the treatment patterns of bladder cancers in our practice and nationally.

For the first time, we were able to offer alternatives to patients who are eligible for

carboplatin-based chemotherapy but did not want to be exposed to chemotherapy-related side effects. We were also able to offer effective treatment options to patients that were otherwise left untreated. Now, we acknowledge that response rates are lower for anti-PD-1/L1 agents when compared to chemotherapy, but with these agents, for the first time we have witnessed long-term survival in a subset.

In summary, the approval of the checkpoint inhibitors in 2017 as a first-line treatment option remains a pivotal moment for the bladder cancer community. Since 2017, there are no new treatment options in the first-line setting. There remains a high unmet medical need in cisplatin- and platinum-ineligible patients that these drugs fulfill. Withdrawing effective and tolerable treatment options is potentially detrimental to this vulnerable population that would otherwise be left with carboplatin-based chemotherapy or no cancer therapy.

As clinicians, we would like to be able to

continue offering our patients the option of chemotherapy or anti-PD-1/L1 agents and allowing them to make informed treatment decisions based on the available clinical evidence. Thank you very much.

DR. HOFFMAN: Thank you.

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

DR. CHISOLM: Thank you for the opportunity to speak today on behalf of the bladder cancer community. My name is Stephanie Chisolm, and I'm the director of education and research at the Bladder Cancer Advocacy Network or BCAN. I do want to point out that BCAN does receive some grant funding in support of our programming from Merck.

I'm here today on behalf of the more than 83,000 people who will be diagnosed with bladder cancer this year alone. The sad reality is that over 17,000 will die from this disease, and until the checkpoint inhibitor medications were approved

a few years ago, there were few options for some of those patients who weren't eligible for chemotherapy, beyond getting their affairs in order.

I think that that's really a challenge, and I wanted to just briefly share the story of two members of our community who were diagnosed with advanced urothelial carcinoma who benefited from access to immunotherapy.

The first is Bob, who had symptoms of urgency and frequency from age 38 to 48 and was treated for benign prostatic hyperplasia until he was finally diagnosed at 48 with stage 4 bladder cancer.

I've seen Bob's scans. He had 42 tumors that had metastasized to his liver. He was told to get his affairs in order. There was nothing that could be done. He had two teenage boys at the time in high school and going into college, and he sought a clinical trial on a yet-to-be-approved immunotherapy.

Bob contacted us because he volunteered to

drive from New Jersey to Chicago to help man our booths at the ASCO meeting. He wanted to be in the facility, in the room, when his doctor from Memorial Sloan Kettering presented, pre-approval, for the immunotherapy he had been receiving.

I've seen his scan after his treatment. There's no evidence of disease, and the result of this new classification of treatment is really important for somebody who had no other option. He was told to have his bucket list and get his affairs in order, and I'm really proud and happy to say that he's on his third bucket list so far.

The other patient is Gail, who was diagnosed with advanced bladder cancer. Because of a heart condition, she's not eligible for chemotherapy. She talked about her experience as one of just seeing all the known treatment doors closing in front of her, and the only treatment that was available to her was immunotherapy with Keytruda.

Six months into treatment, Gail retired from her job at the University of Washington. She's an avid walker, she does Qigong, and is very active in

raising awareness of this disease with BCAN, all the while having minimal side effects from walking through that last treatment door that was available to her.

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

DR. HOFFMAN: Thank you.

We're just going to take one minute before we continue.

(Pause.)

DR. HOFFMAN: Speaker number, actually, 4 -- but it says speaker number 3 on the screen -- your audio is there. Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? And please state your name and any organization you're representing for the record.

MR. BURTCHELL: My name is Steven Burtchell. I've received no compensation for speaking this

morning. I'm a 74-year-old white male, and I have benefited from Keytruda itself, so I guess I'm a cancer survivor.

A little bit about me, I spent 22 years in the Navy, in aviation, and earned two master degrees in the Navy, and I joined Paul Davis Restoration in '92 and was with them for 25 years; and now for my journey.

In late 2017, I was diagnosed with cancer in situ of the bladder along with prostate cancer. The bladder cancer was most likely from smoking for 45 years. I treated it with BCG every 2 months until the cancer was discovered in my bladder, and further in my prostate and lymph nodes, throughout the pelvic area.

Dr. Richard Joseph from Mayo Clinic Jacksonville was my oncologist. He prescribed dense-dose chemo, which included cisplatin, and after one round, I started having renal failure. My creatinine level went from 1.3 to 6.2, and I do have kidney disease, stage 3. Dr. Joseph, who ran the clinical trial for Keytruda at Mayo, then put

me on 5 doses of Keytruda, 1 every 3 weeks. He said it had a 20 percent chance of success or remission.

I tolerated Keytruda extremely well. I had absolutely no side effects whatsoever. After the cancer had been eradicated by blood/urine work and CT scans, I had robotic-assisted surgery at Mayo in early July of 2019 to remove the bladder and prostate. Mayo told me I had a 50/50 chance that I would be in remission after 5 years, and I'm getting blood and urine samples and CT scans every 4 months.

My summary is I have Medicare and TRICARE for life that has covered all of my costs so far, except for $500. The total cost I've rung up that they have paid for is over $550,000 worth, so I guess I'm on my way to be a million-dollar man.

Keytruda at the time was my only option after failing chemo. I think I was lucky. It worked for me. I ran into Dr. Richard Joseph, who's been by my side the whole time. It worked, and I'm here speaking to you this morning. If

anything, I would urge you to maintain Keytruda as an option for other patients who can't tolerate cisplatin. It may be their only chance for survival. Thank you for the opportunity to speak with you this morning.

DR. HOFFMAN: Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. CODERO: Good morning. My name is Wilma Cordero. I'm married to Esteban Cordero, who is being treated for bladder cancer by Dr. Arjun Balar from NYU Langone. I'm going to start talking, and then Esteban will join in.

Esteban is going on. 90 years old. We've been married for 60 years, happily. We are not receiving any compensation for speaking today. Esteban was diagnosed with bladder cancer, and when we finally reached Dr. Balar, after numerous meetings with other doctors and was scraping for hopefully removing the cancer, we determined with

Dr. Balar that Keytruda would be the only viable option for his treatment. He's been treated with Keytruda now for almost two years.

Esteban, would you go on and just explain how you're feeling and how you reacted to the treatment?

MR. CORDERO: Well, I feel great, [indiscernible] the fact -- the urine; better than ever, really, no signs of any sickness, any blood, cancer. It disappeared completely, practically, is what I feel, and I feel it is what it is.

I live a complete normal life, eat well, have fun, go to the movies, walk a lot, enjoy my children and grandchildren, and plus your great grandchildren, eventually.

(Laughter.)

MR. CORDERO: Well, that's there; as well as can be.

MS. CORDERO: As you can see, Keytruda has been really a miracle for us. The main reason we agreed to speak today is because we want Keytruda to continue to be available to any patient who

needs it. We feel it is a miracle drug --

MR. CORDERO: Yes, it is.

MS. CODERO: -- and has enabled us to continue having a normal, fulfilling, happy, enjoyable life together. Thank you very much.

DR. HOFFMAN: Thank you.

Will speaker number 6 begin and introduce yourself? Please state your name and any organization you represent for the record.

DR. HOIMES: Good morning. This is Christopher Hoimes, Dr. Hoimes. Today I represent myself, and statements should not be taken to represent those of a current or former institution. I've not received any compensation for speaking today. Notable conflict of interest includes remuneration for consultation in speaking with Genentech Roche through the year 2018. As PI of many trials, my institution does receive research funding from industry, including Genentech Roche and Merck.

I trained at Yale University and held faculty positions at Yale and Case Western Reserve

School of Medicine. As a bladder cancer oncologist at Duke, I see over a dozen new patients per month and is the focus of my translational and clinical investigative research.

The patients that fit the accelerated approval label have few options, which include best supportive care, palliative, endoscopic, resection, radiation, and systemic treatments that include gemcitabine and carboplatin combination; or monotherapy with a cytotoxic agent such as gemcitabine; and more recently can consider pembrolizumab, thankfully, in patients who are platinum ineligible or for those who are PD-L1 positive and cisplatin ineligible.

These patients have significant disease-related symptoms and/or medical comorbid conditions that would meet inclusion criteria for the trial cohorts but would have been excluded from many disease-related concerns. Most notable is exclusionary criterion around stable pain regimens or stability of symptoms sufficient for trial.

These patients frequently have recurrent

hospitalization for symptom management and are simply not represented on our recurrent trials. They are, in fact, ECOG performance status zero over 1 and appropriate for trial if only their hematuria and cystalgia related to the primary tumor was controlled, or if their abdominal cramping and back pain from bulky retroperitoneal mass could be addressed.

They require significant resources from multidisciplinary teams to stabilize symptoms before we can consider a systemic therapy trial. Once they are stabilized with palliative endoscopic resection, antibiotics for urinary tract super infection, setting of tumor, have radiation to the bulky adenopathy, they may then have been screened and enrolled on a trial and should be accounted for when generalizing results from these trial cohorts of KEYNOTE-052 and 361 trial to our everyday population.

In the real-world setting, in fact, with this first-line accelerated indication, we're now able to use systemic therapy in parallel with

symptom management. In my clinic, nearly 1 in 6 fit this setting of systemic therapy and aggressive symptom management and may have had notable improvement in performance status, indicating a clinical response with improved symptoms, avoidance of inpatient resources, and overall disease control.

A dozen have had at least an imaging partial response, including several with over 2 years of complete remission and off therapy on surveillance. Again, I am of course specifically discussing the patients at hand today with regard to the accelerated approval label.

What may not be captured in the discussions today, and important to highlight, is that our real-world patients are not adequately represented in the cohorts of these trials. Knowing this population and how this disease behaves with a relentless tempo and causes much disruption to the urinary system and beyond, I recognize the extraordinary efforts of the investigator teams encouragement of subjects in these cohorts of

cisplatin or platinum ineligible to get to a symptomatically and medical optimized state fit enough for trial enrollment.

That optimized state, however, unravels pretty quickly, and it's tough to hold with any systemic therapy, especially if there have been systemic therapy delays while addressing symptoms separately.

I do also recognize that there are many patients who aspire to be on such a trial, but systemic therapy with standard-of-care model suppressive agents like gemcitabine monotherapy or carbo/gem carry too much risk with little reward and die trying symptom management and optimization.

When one has gross hematuria, obstruction, and urinary tract super infection in the setting of locally-advanced or metastatic peritoneal cancer, giving a one- or two-drug regimen of carbo/gem or the systemic therapy options to palliate, as you know, these have DLT and black box warnings of severe myelosuppression, both neutropenia and thrombocytopenia, resulting in severe infection or

bleeding, and is not in many patients' best interest from a disease or palliation standpoint. Perhaps we consider perspective change, one that is less about platinum eligibility status and consider how myelosuppression risk and intolerance embodies this group, a patient's perspective.

I am anxious about a time where we may again be faced without a systemic therapy option for this niche of a disease state. Because these patients simply couldn't be captured on a trial to understand the true performance and benefit in this challenging disease setting, I ask that the ODAC and FDA recognize with me that pembrolizumab, in fact, has activity in these patients where there remains a high unmet need in a population of patients who are vulnerable with significant disease-related symptom burden and comorbid conditions.

On behalf of my patients, their caregivers, and similar patients around our country and territories, I ask that ODAC and the FDA maintain pembrolizumab in a setting as an option for our

patients. Thank you kindly for the opportunity to speak today.

Clarifying Questions to Presenters (continued)

DR. HOFFMAN: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

We can now take a few remaining clarifying questions if there are any that have not already been answered in the prior discussions. I will point out that we're a little pressed for time, so if there are any additional questions, I hope we can keep them brief.

Dr. Kraus, I think you have your hand up.

DR. KRAUS: My apologies. I forgot to lower it after the last one, so no further questions.

DR. HOFFMAN: Okay. Anyone else?

(No response.)

DR. HOFFMAN: Okay.

The committee will now turn its attention to -- I'm sorry.

Dr. Siddiqui, did I miss you here?

DR. SIDDIQUI: Yes. Thank you. If I could, I had been hoping to ask the FDA one question.

The FDA told us about the accelerated approval requirements, for unmet need in particular, may have shifted over time since the emergency use of first authorized. Understanding that Keytruda in this setting was first indicated for cisplatin ineligible but also, then, all chemotherapy, or more specifically platinum-drug ineligible patients as two groups, it seems like the cisplatin group now has an approved therapy, so that unmet need has changed. However, the all-platin group remains an unmet need, and to me that's like the crux of this issue.

My question for the FDA is, in this setting, can emergency-use authorizations be adjusted to hone in on the smaller population that remains unmet? Then secondly, in a population where there is no great standard of care, for a postmarketing requirement follow-up, a demonstration of efficacy, what are your standards for accomplishing demonstration of benefit?

Is it still standards of overall survival, which would require a randomized trial of placebo versus intervention? Or as kind of what is being discussed here, is further follow-up with durable overall response rate and duration of response over a longer period of time something that could be accepted as a postmarketing requirement for demonstrating benefit?

DR. AMIRI-KORDESTANI: Thank you. I'll start, and then I'll ask Dr. Beaver to also comment.

Regarding maybe starting with your second question, we have actually in some cases accepted more longer follow-up of the same trial to be used for the confirmation of benefit when we felt, for example, randomization was not possible, absolutely was not possible, in some instances. But generally, as was discussed, a randomized trial with a survival endpoint -- not overall survival but also like progression-free survival -- in the majority of cases have been used for confirmation of benefit.

Regarding your first question, I think you're commenting on the initial accelerated approval. Also, basically you're commenting on the two bullets that, basically, the restricted indication includes patients that are not eligible for cisplatin-containing chemotherapy and they are PD-L1 high, or they are not eligible for any platinum chemotherapy.

I think your question is basically around the second bullet, and please clarify if that's the case.

DR. SIDDIQUI: That's exactly right.

DR. AMIRI-KORDESTANI: Okay. That's basically a good question. What you're asking is, is it possible to further restrict the indication, for example, because there is no available therapy for patients that basically are not eligible for any platinum-containing chemotherapy, and then keep the drug available for that subset of the population; basically just maintaining the entire indication.

I think, basically, you cannot discuss about

it, but I just want to point out that, generally, the postmarketing studies haven't really also studied the exact indication, so we don't necessarily need to get confirmation of benefit for the exact indication to be able to convert accelerated approval indication. I just want to clarify that.

Dr. Beaver, would you like to add any comments?

DR. BEAVER: Sure.

Hi. This is Julia Beaver, FDA. Yes. Just to add on, first of all, this is not an EUA. That's different. Emergency use authorization is different from accelerated approval. The requirements for accelerated approval have been the same since 1992. Those requirements for accelerated approval have not changed.

What has changed in this case is that there has been a confirmatory trial that did not verify benefit. So at that point, we are re-evaluating the conditions for accelerated approval at this current time point because this had a confirmatory

trial that did not verify benefit, and the question is, are those still met?

So we're asking the committee to discuss if there is still unmet need for the population currently approved under the accelerated approval as the indication currently stands now, and that's the discussion that we would like to hear, both components of that indication. That is the advice and discussion we'd like to hear from the advisory committee meeting.

As Dr. Amiri mentioned, there are cases for postmarketing requirements follow-up on clinical benefit where FDA can use various endpoints to confirm clinical benefit. This can be from overall survival and gold standard; in some cases this can be from PFS, progression-free survival; or in some cases it can be for a longer term duration of response and overall response rate if that longer follow-up for duration of response is deemed to be a clinical benefit.

So that is definitely something that is a possibility, in general, for confirmation of

benefit. Thank you.

DR. HOFFMAN: Mr. Mitchell, do you have your hand up?

MR. MITCHELL: I do. Very quickly, is there anything that prevents pembrolizumab from being used off label in the absence of accelerated approval for the group we're talking about, based on clinician and patient decision to do so?

DR. HOFFMAN: Well, I can probably answer that. I think the answer is no. There's nothing that specifically prevents it except getting approvals through insurance companies and so on. But I'll allow anybody else to comment.

DR. EBBINGHAUS: This is Scot Ebbinghaus from Merck. I agree with what Dr. Hoffman said. In the United States, physicians can prescribe medicines that are approved in other indications, however, access to those treatments may end up being substantially limited and, really, the best way to ensure that there's access is to maintain FDA approval.

DR. HOFFMAN: Right.

Our last comment is from Dr. Apolo.

DR. APOLO: Hi. My last comment, or I guess question, is if we decide that this indication should be removed, just to emphasize what was said by the FDA, does this mean that the indication is lost for not only cisplatin-ineligible patients that are PD-L1 high but also ineligible patients regardless of PD-L1 status? The question is for FDA.

DR. AMIRI-KORDESTANI: Thank you for the question. The question that we have as part of the voting question actually asks for the entire indication, but I hear that you're raising the same comment. You're asking if you would vote yes for one bullet but not for the other one. I wonder if the advisory committee members could actually then discuss this, if that's how they feel about this, so we can take that into consideration.

I don't know if, Dr. Beaver, you have any additional comments.

DR. BEAVER: Julia Beaver, FDA. No. I think Dr. Amiri said that correctly. We're looking

for your input on that. You can feel free to discuss that. The voting question is, though, related to the broader indication but, yes, we would like discussion on that point.

Questions to the Committee and Discussion

DR. HOFFMAN: Okay. That could be part of someone's justification regarding their vote. We're not going to separate the questions at the moment for voting purposes.

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. We 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, and the question specifically is, should the indication for pembrolizumab for the first-line treatment of cisplatin-ineligible and carboplatin-ineligible

patients with advanced or metastatic urothelial carcinoma be maintained pending conduct or completion of additional trials?

Dr. Joyce Yu will provide the instructions for voting.

DR. YU: Yes. 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, which you have, and all questions and discussion regarding the wording of the vote question are complete, then the chairperson will announce that the voting will begin.

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

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

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

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

(No response.)

DR. YU: Okay. I don't hear any questions.

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.

DR. YU: Okay. If there are no questions or comments concerning the wording of the question, then we will 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 closed and is now complete. We're waiting for the vote results to display, and then I will read the vote result into the record.

(Pause.)

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

The vote total is 5 yeses, [inaudible] noes, zero abstentions.

DR. HOFFMAN: Thank you. We'll start at the top of the list.

Dr. Siddiqui?

DR. SIDDIQUI: Mohummad Siddiqui. I voted no. The reason why I voted no is I felt that the initial accelerated approval for the two indications, the data has emerged regarding the first indication for cisplatin-ineligible patients who now have an alternate therapy available.

For the second indication, the patients that have no platinum-based therapies available to them, I think it's worth noting that there is a window where I feel like I would advise that the FDA could consider continued accelerated approval. It's just that the question as posed did not allow me to kind of tease those pieces out, but I think that that still remains an unmet need population.

The only thing about that population and accelerated approval in that population is that it's not clear to me what kind of confirmatory follow-up trial would demonstrate efficacy ultimately and whether just continued follow-up of KEYNOTE-052 is sufficient or whatnot. But since that's a little bit outside of the scope of what we

focused on, I think mentioning that that was my thought process is where I'll stop.

DR. HOFFMAN: Thank you.

Dr. Apolo?

DR. APOLO: Yes. I voted yes, and the reason is pembro is active for second-line treatment of patients with platinum-refractory urothelial carcinoma. And I would argue that pembro is also active in the first-line treatment setting for patients that are cisplatin ineligible that are PD-L1 high. Is it superior to carbo-platinum based chemotherapy in the first-line setting? So far we do not have data supporting this, but the data does show activity and durable benefit.

I personally favor chemotherapy in the first-line setting, followed by either immunotherapy maintenance or second-line therapy. However, there is also a small population of patients that cannot receive any kind of chemotherapy and are platinum ineligible. And as a treating medical oncologist and bladder cancer

specialist, I vote to keep pembrolizumab available as a treatment option for patients in the first-line setting that are PD-L1 high.

In terms of a confirmatory trial, the options aren't great, but I would say LEAP-011 may be the best trial for confirmation of the results because it is in the same settings.

DR. HOFFMAN: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes, Dr. Hoffman. Thank you.

I voted no. This was a hard decision for me as a patient, but I am concerned that while the clinical experience and the anecdotes are encouraging and positive, the data aren't there. I feel strongly for the safety and well being of patients like myself that we have to rely on data. I don't see it, so therefore I voted no.

DR. HOFFMAN: Alright. Thank you.

I'm Dr. Hoffman. I voted yes. I felt that the clinical information from the urologic oncologists was compelling about the patients who are not eligible for chemotherapy, whether

cisplatin or carboplatin based, and that the toxicity for most patients is low, and some patients do get remarkably long periods of remission with pembrolizumab.

I also think that a significant number of crossover patients into immunotherapy from KEYNOTE-361 tells me it's another point in favor of the value of immunotherapy and abolishes some of that apparent negativity.

Then finally, the fact that there is avelumab available as a maintenance is further indication that if the checkpoint inhibitors are effective, but for that, you have to get to at least stable disease or partial remission to be eligible for maintenance therapy. So the fact that it's available to me does not exclude keeping pembrolizumab available for the first line.

Dr. Madan?

DR. MADAN: Yes. Ravi Madan. I voted no because of the inclusion of the cisplatin-ineligible patients in the question. I feel like we have some data, at least in that population when

they received carboplatin, and it didn't support the indication as it stands.

In terms of looking at patients who are platinum ineligible, I feel that, again, there is lacking confirmatory data at this point. We have many phase 2 data from other treatments that show response rates in this range, and this kind of falls in that category.

In terms of confirmatory trials, I was optimistic that LEAP-011 could provide some confirmatory data but, again, it's going to provide single-arm evidence that will leave some questions open. I hope for patients who fit this category, that there will be confirmatory data with this or other similar treatments in their near future to confirm and affirm the benefits and safety in this population.

DR. HOFFMAN: Thank you.

Dr. Halabi?

DR. HALABI: Yes. Susan Halabi. This has been a very hard decision for me. The data is definitely perplexing, but I think even though

there was no confirmation from KEYNOTE-361, the trend does indicate prolongation of survival in OS and higher ORR rates. That was pretty much consistent, and not only in first line but also second line.

I think the other reason why I voted yes was the unmet need in carboplatin-ineligible patients. Also, as others alluded to, I hope that LEAP-011 may be the best confirmation, even though this trial is not going to read out until 2023. Thank you.

DR. HOFFMAN: Thank you.

Ms. Johnston?

MS. JOHNSTON: Yes. I have to echo the concerns. This was a very difficult vote, but as a patient advocate and as a caregiver for somebody who would have qualified for this drug and unfortunately is no longer here to do that, I had to vote yes because I don't want to see people being limited for access to this by their insurance, and I don't want to see them going into medical bankruptcy because of that, which we do

know happens.

Also, I feel if we remove the option, it is going to take a very vulnerable population -- take that away from them. And we don't see a lot of research in this particular cancer. So to have something taken away at this point, I simply wasn't willing to be responsible for. But I do have to say with that, I am concerned about the data, and I do hope that 011 provides for us what we'll need. And I did vote yes.

DR. HOFFMAN: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu, and I voted yes in favor of maintaining the current approval. This is going to echo a lot of what everybody has said, but my main reason for voting yes is that I think that there's a clear unmet need in patients who are platinum ineligible, who obviously have incredibly limited options.

The 052 data is compelling. This is strengthened by the overall survival benefit seen in the second-line setting. I'll say in regard to

the use of avelumab in the maintenance setting, I think that this indication really could be the treatment of choice in patients that are carboplatin eligible. But my concern regarding the unmet need is patients who are unable to receive platinum-based chemotherapy at all.

So if we rescind this approval, then those patients would be potentially left with no available treatment options. I think as you've heard on this call, this does bring up the issue of potentially revising the indication to specifically address this patient population.

Regarding the confirmatory study of 361, again, my concern is that this evaluates a population that is cisplatin eligible and really doesn't necessarily help answer the question about the population that I'm addressing.

Having said that, when you look at the alternative proposed confirmatory studies, the LEAP-866 or 905 studies, none of these studies are going to provide the data that is needed in isolation, and I think it's also really clear that

a randomized study in this setting is going to be impossible to conduct.

I do believe that the totality of the potential data derived from 052-045 in the pembro-only group, the LEAP study may further support either the full approval in this setting or potentially show data that recommends removal of the indication. But I was mainly concerned about keeping pembrolizumab available to patients unable to receive platinum-based chemotherapy.

DR. HOFFMAN: Thank you.

Dr. Yu, just to clarify -- I think there was a hitch there -- read the vote back into the record again.

DR. YU: Okay. Thank you.

Will you summarize the panel discussion? I can read.

DR. HOFFMAN: Well, I don't want to repeat everything that has been said. As we see, I think the issues of the continued unmet need in platinum-ineligible patients and some immaturity of the data still, and not wanting to remove a

potential value drug, we know that the drug is useful in other settings, second line, and maintenance, and we have seen some long benefits in patients who were platinum ineligible and tolerated this very well.

The people that voted no rightly would want to see more mature data and further confirmatory data about effects on overall survival, and we look forward to seeing those accumulate in the coming years.

DR. YU: Thank you, Dr. Hoffman.

This is Joyce Yu, the DFO. Can everyone hear me?

DR. HOFFMAN: Yes.

DR. YU: Okay. I will re-read the vote totals for the record. The vote is 5 yeses, 3 noes, zero abstentions.

Thank you, Dr. Hoffman.

DR. HOFFMAN: Okay. Before we adjourn this topic, are there any last comments from the FDA?

DR. AMIRI-KORDESTANI: No. Thank you so much, Dr. Hoffman.

Adjournment

DR. HOFFMAN: Okay. We will reconvene at 12:40 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 second topic should plan to rejoin sufficiently before 12:40 Eastern to ensure that you're connected so that we can reconvene on time.

Thank you very much for everyone's participation this morning

DR. YU: Bye, everyone. Thank you so much.

This is Joyce Yu, the DFO. Thank you for attending the morning session. The chat will be closing the meeting room temporarily for the next session. Everyone will be disconnected from the room and from the phone, so please log back in only if you are a designated attendee for Topic 2. Thank you so much.

(Whereupon, at 12:04 p.m., the morning session was adjourned.)