FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Topic 1

Virtual Meeting

Thursday, April 29, 2021

9:00 a.m. to 12:01 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICERS (Non-Voting)

Takyiah Stevenson, *PharmD*

(April 29 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

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)

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TEMPORARY MEMBERS (Voting)

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(Patient Representative, April 29 Topic 1 Only)

Mt. Pleasant, Michigan

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Diane Reidy-Lagunes, MD

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Colin D. Weekes, MD, PhD, FASCO

(April 29 Only)

Associate Professor of Medicine

Harvard Medical School

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(April 29 Only)

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OOD, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. REIDY-LAGUNES: Welcome. I would like to first remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Amanda Turney. Her email and phone number are currently displayed.

My name is Diane Reidy-Lagunes, and I will be chairing the first topic of today's meeting. I will now call the first topic of the April 29, 2021 meeting of the Oncologic Drugs Advisory Committee to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting and will begin with the introductions.

Introduction of Committee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliations.

Dr. Halabi?

DR. HALABI: Yes. Good morning. My name is Susan Halabi, and I'm a biostatistician at Duke University.

DR. STEVENSON: Dr. Lieu?

DR. LIEU: Good morning. I'm Chris Lieu, medical oncologist at the University of Colorado.

DR. STEVENSON: David Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm a consumer representative to the ODAC, and I am a multiple myeloma patient.

DR. STEVENSON: Dr. Kunz?

DR. KUNZ: Hi. Good morning. I'm Pamela Kunz, and I'm a GI medical oncologist at Yale Cancer Center.

DR. STEVENSON: Dr. Lewis?

DR. LEWIS: Good morning. This is Mark Lewis. I'm the director of gastrointestinal oncology at Intermountain Healthcare.

DR. STEVENSON: We'll come back to Dr. Hillard in just a moment.

Dr. Reidy-Lagunes?

DR. REIDY-LAGUNES: Hi. I'm Diane

Reidy-Lagunes. I'm a medical oncologist at Memorial Sloan Kettering Cancer Center.

DR. STEVENSON: Dr. Weekes?

DR. WEEKES: Hi. I'm Colin Weekes. I'm a medical oncologist at Massachusetts General Hospital.

DR. STEVENSON: Dr. Kraus?

DR. KRAUS: Yes. Good morning, everyone. My name is Albert Kraus. I work in research and development for Pfizer, and I'm the industry representative.

DR. STEVENSON: Dr. Hillard, if you can hear me, please introduce yourself.

(No response.)

DR. STEVENSON: Dr. Hillard, if you can hear me, please unmute.

(No response.)

DR. STEVENSON: Okay. We will come back to Dr. Hillard in just a moment. I will introduce the FDA participants.

Dr. Pazdur?

DR. PAZDUR: Hi. Rick Pazdur, director of

the Oncology Center of Excellence at the FDA.

DR. STEVENSON: Dr. Beaver?

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

DR. STEVENSON: Dr. Lemery?

DR. LEMERY: Hi. Steven Lemery. I'm the acting director of the Division of Oncology 3.

DR. STEVENSON: Okay.

I'm going to give Dr. Hillard just a moment, another moment, to connect. Please bear with us.

(Pause.)

(No response.)

DR. STEVENSON: Okay. We will come back later to continue the introductions. I'm going to hand it back to the chair.

DR. REIDY-LAGUNES: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal 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 very 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. Takyiah Stevenson will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to

special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest 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 024, trade name, Keytruda, pembrolizumab, submitted by Merck Sharp & Dohme, indicated for the treatment of patients with recurrent locally-advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1, combined positive score greater than or equal to 1, as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy, including fluoropyrimidine and platinum-containing chemotherapy, and if appropriate, HER2/neu-targeted therapy.

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

Confirmatory studies are postmarketing

studies to verify and describe the clinical benefit of a drug after it receives accelerated approval. Based on the updates provided, the committee will have a general discussion focused on next steps for this product, including whether the indication should remain on the market while additional trial or trials are conducted. This is a particular matters meeting during which specific matters related to Merck, Sharp & Dohme's sBLA, supplemental BLA, 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. Christopher Lieu and Colin Weekes.

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.

Dr. Weekes' waiver involves a research grant currently in negotiation by his employer with study funding and drug support anticipated from the firm. Dr. Weekes anticipates receiving salary support.

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 at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing 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 participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you, and now I'll hand it back to the Chair.

DR. REIDY-LAGUNES: Thank you.

We will proceed with the FDA introductory

comments from Dr. Julia Beaver.

FDA Introductory Comments – Julia Beaver

DR. BEAVER: Thank you.

Good morning, Chairperson 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 have provided similar remarks to introduce the other sessions in this three-day accelerated approval advisory committee meeting.

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

regulatory background and requirements for granting an accelerated approval.

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

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

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

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

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

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

approvals, with close to half of the 150 accelerated approvals already 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.

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

accelerated approval on the market.

In cases where withdrawal is appropriate, drugs have typically been removed voluntarily by the company through communication and consultation with FDA. The one exception to this voluntary withdrawal was bevacizumab for the treatment of patients with 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 FDA Oncology Center of Excellence continuously evaluate the accelerated approval program to make sure the benefit to patients is maintained, and to increase transparency in the future, we may continue public discussions of these evaluations on a more periodic basis.

Over the last six years, there has been an unprecedented level of drug development for the anti-PD-1 or 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 anti-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 trials, 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 dangling indications with the companies, recommending withdrawal or alternatively bringing the indication to a public discussion at this advisory committee meeting.

Four antibody indications in small-cell lung

cancer and in urothelial carcinoma, shown here, appropriately chose to voluntarily withdraw their indications in consultation with FDA. It is notable that both the small-cell lung cancer and urothelial indications have seen a changing landscape of disease treatment, meaning after these accelerated approvals were granted, alternative anti-PD-1 or 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 advisory committee meeting warrant further discussion and we hope to hear further advice. This session will discuss pembrolizumab for gastric or gastroesophageal carcinoma.

There are some key issues for this session

we would like the committee to consider. There were two trials that did not confirm benefit, one in the same treatment setting as the original accelerated approval, adding to the uncertainty. In addition, alternative anti-PD-1 therapy, nivolumab in combination with chemotherapy, has demonstrated clear benefit and been approved for an earlier-line setting. This change in available therapy results in a changed risk-benefit profile that differs compared to the time of the initial accelerated approval.

Accelerated approvals are meant to serve patients, and if postmarketing clinical trial data do not demonstrate clinical benefit and alternative therapies have, patients may not be served by continuation of the original accelerated approval. In addition, the response rate initially supporting the accelerated approval was low, on the order of 10 to 20 percent.

For the initial approvals, FDA oncology took into consideration unmet need and the unusually durable response rate seen with immunotherapy.

However, a discussion surrounding accelerated approval, based on single-arm trials with low response rates for this class of drug, is also warranted.

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

The percentage of drugs that do not ultimately confirm clinical benefit should not be viewed as a failure of the program but rather an expected trade-off to expedite drug development of promising agents for severe and life-threatening diseases like cancer. However, since the goal of accelerated approval is patient benefit, when postmarketing studies do not meet their primary objective, the drug product should be re-evaluated in the context of currently available therapy, and if deemed to no longer benefit patients, the accelerated approval indication should be

withdrawn.

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

DR. STEVENSON: Hello, everyone. This is Takyiah speaking. I'm going to go back to the introductions in just a moment.

(Pause.)

Okay. Dr. Hillard seems to have connected.

Dr. Hillard, if you can hear me, please introduce yourself and state your affiliation?

DR. HILLARD: Yes. Hi. This is Randy Hillard. Actually, I'm professor of psychiatry at the Central Michigan University. But again, I'm here as a patient.

DR. STEVENSON: Thank you very much, Dr. Hillard.

Okay. We will continue in just a moment.

Now, I'll hand it over back to the Chair to continue.

DR. REIDY-LAGUNES: Thank you.

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

For this reason, the FDA encourages all participants, including the Merck Sharpe & Dohme's non-employee presenters, to advise the committee of any financial relationships 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.

Applicant Presentation – Nageatte Ibrahim

DR. IBRAHIM: Good morning, members of the advisory committee and the FDA. I'm Nageatte Ibrahim, a medical oncologist and vice president of clinical research in late-stage oncology at Merck. Thank you for the opportunity to review the accelerated approval indication for Keytruda in third-line or later gastric cancer and our progress toward fulfilling the postmarketing requirement.

Keytruda, or pembrolizumab, has demonstrated clinical benefit and is approved in multiple tumor types. Of the 19 traditional approvals, six were accelerated approvals that have converted following verification of clinical benefit. Among the 10 accelerated approvals, six have ongoing confirmatory studies; four had confirmatory studies that did not meet their primary endpoints. We are here this morning to discuss the gastric cancer indication.

There are four approved Keytruda indications relevant to our discussion today. Accelerated approval for third-line or later gastric cancer based on the results from KEYNOTE-059 was granted in September 2017. In May 2017, Keytruda received a tumor agnostic indication for MSI-high/dMMR solid tumors, followed by a second tumor agnostic indication for TMB-high solid tumors in June 2020.

These biomarkers are enriched for response to Keytruda and occur with a varying prevalence in different tumor types. Although there is a potential for wide applicability of these tissue agnostic indications, including in gastric cancer, they unfortunately do not encompass every patient that may benefit from Keytruda.

Most recently, in March of this year, Keytruda was approved in combination with chemotherapy for the first-line treatment of esophageal and gastroesophageal junction, or GEJ, carcinoma, which accounts for about 30 percent gastric cancer.

The current indication for Keytruda in

third-line or later gastric cancer is for the treatment of recurrent locally-advanced or metastatic gastric, or GEJ, adenocarcinoma, with tumors expressing PD-L1 defined as a combined positive score greater than or equal to 1 and with disease progression on or after two or more lines of therapy. The FDA issued a postmarketing requirement in conjunction with this accelerated approval to describe the clinical benefit of Keytruda in a randomized trial in gastric cancer.

This is an overview of the pembrolizumab development program in gastric cancer at Merck. KEYNOTE-059 led to accelerated approval of pembrolizumab in third-line and beyond PD-L1 positive gastric cancer, and KEYNOTE-590 led to the approval in first-line esophageal and GEJ carcinoma.

Two randomized phase 3 studies in frontline and second line, KEYNOTE-061 and 062, had been completed and were intended to fulfill the postmarketing requirement associated with KEYNOTE-059, but they did not meet their primary

endpoints. These studies are not the focus of today's discussion.

Learnings from KEYNOTE-061 and 062 have informed the design of these four large randomized trials, looking at different combinations with pembrolizumab that could potentially fulfill the postmarketing requirement. A supplemental BLA for the first-line treatment of HER2-positive gastric cancer is currently under review at the FDA, based on the first interim analysis of KEYNOTE-811.

Here is what you will hear today. Patients with metastatic gastric cancer, who reached third-line treatment and beyond, have a very poor prognosis and limited treatment options. In KEYNOTE-059, pembrolizumab demonstrated clinically meaningful durable responses in the third-line-plus setting with a manageable safety profile. Based on learnings from KEYNOTE-061 and 062, our ongoing clinical development program in gastric cancer is well positioned to fulfill the postmarketing requirement in the next 1 to 3 years.

Today we ask the committee to consider the

unmet medical need and all available evidence when considering if pembrolizumab should retain its accelerated approval for third-line and beyond gastric cancer. We believe the evidence supports a positive benefit-risk assessment and retaining the accelerated approval until a confirmatory trial fulfills the postmarketing requirement.

Here is our agenda for today. Dr. Peter Enzinger from the Dana-Farber Cancer Institute will review the disease background and unmet medical need in gastric cancer; then Dr. Pooja Bhagia will review the efficacy and safety results of KEYNOTE-059 and describe the postmarketing requirement study. I will then come back at the end to provide some concluding remarks. In addition, Dr. Ronan Kelly from Baylor University Medical Center and Dr. Manish Shah from Weill Cornell Medicine will also be available to answer your questions.

I will now turn it over to Dr. Enzinger.

Applicant Presentation – Peter Enzinger

DR. ENZINGER: Thank you, Dr. Ibrahim.

Good morning, everyone. My name is Peter Enzinger. I'm a medical oncologist at the Dana-Farber Cancer Institute and Harvard Medical School. I currently lead the Center for Esophageal and Gastric Cancer at the Dana-Farber Brigham & Women's Cancer Center.

I've participated in many clinical trials with pembrolizumab, starting with KEYNOTE-059 and was the highest enroller in that study. I'm a paid consultant for Merck and other pharmaceutical companies, but I have no financial interest in the outcome of this meeting. I will describe the disease background and unmet need in advanced metastatic gastric cancer and the role that pembrolizumab plays in filling that need in the third-line-plus setting.

Gastric cancer continues to be a serious problem in the United States. Treatment options are limited, and there remains a significant unmet need. There were an estimated $27,600 cases in 2020, and almost half of those patients will ultimately die of their disease. More than a third

had distant metastatic disease at diagnosis.

As you can see on the right, the 5-year survival rates remain very poor for these patients. Only about 5 percent of patients with stage 4 disease will be alive five years after diagnosis, which puts gastric cancer among the five most deadly solid tumors.

Part of the problem in gastric cancer is that patients are frequently too ill to receive treatment. Among the roughly 12,000 patients diagnosed with stage 4 disease, only about 18 percent will ultimately go on to receive third-line or subsequent lines of therapy, or roughly 2,200 patients annually. This speaks to the poor prognosis of this patient population.

Several biomarkers are important for defining the most appropriate treatment for patients with gastric cancer. The combined positive score, CPS, measures PD-L1 expression on tumor cells, lymphocytes, and macrophages. In KEYNOTE-059, CPS 1 or higher enriched for patients were more likely to respond to pembrolizumab.

Tumor mutation burden, TMB, is the number of mutations per genome in 10 or more mutations per megabase, and by the Foundation Medicine Companion Diagnostic is classified as TMB-high. TMB at less than 10 mutations per megabase is classified as non-TMB-high.

Microsatellite instability, MSI, refers to a high number of mutations in regions of repetitive DNA known as microsatellites. As a result of deficiencies in mismatch-repair pathways, tumors that are MSI-high are typically also TMB-high.

To appreciate how many patients can potentially benefit from treatment with pembrolizumab based on the third-line indication, it is important to consider the biomarker distribution in this population. Based on data from the total enrolled population in KEYNOTE-059, we know that about 57 percent of the third-line patients are PD-L1 positive with CPS greater than or equal to 1.

Within that overall study population, 85 patients were evaluable for TMB status,

including 51 who were CPS 1 or higher and 34 who were CPS less than 1. Within this TMB evaluable subset, testing for TMB demonstrated that 13 percent were TMB-high, and within that subgroup, 4 percent were also MSI-high.

After subtracting the TMB-high and MSI-high patients, 49 percent of patients were CPS 1 or higher, microsatellite stable, and non-TMB-high. When considering the 2,200 patients per year in the U.S. who received third-line-plus treatment, that leaves about 1,100 patients per year who are expected to have tumors that are microsatellite stable, non-TMB-high, and CPS 1 or higher, and therefore may benefit from the third-line indication for pembrolizumab.

Those data I just showed you are predicated on every patient having known TMB status. However, these data from an IQVIA Brandimpact survey show that in clinical practice in the U.S., only about half of gastric cancer patients are currently being tested for TMB. So although the data from KEYNOTE-059 suggest that about 13 percent of

third-line patients are TMB-high, less than 10 percent of gastric cancer patients are being identified as TMB-high in clinical practice.

In contrast to TMB testing, PD-L1 testing in the U.S. is more common. Physicians report about 80 percent of their patients with gastric cancer are tested, and 40 to 50 percent are PD-L1 positive. As you'll see from the KEYNOTE-059 data, CPS is an important biomarker in gastric cancer that independently enriches for response to pembrolizumab.

With that backdrop, let's take a look at the treatment landscape in gastric cancer, starting with the picture when pembrolizumab was first approved in 2017. At that time, standard front-line therapy was platinum-based chemotherapy. Ramucirumab with or without paclitaxel was approved in the second-line setting, and pembrolizumab was approved for patients with MSI-high tumors regardless of tumor location. The third-line-plus indication for pembrolizumab, based on KEYNOTE-059, is for patients with CPS 1 or higher.

Since approval in 2017, we have seen a significant increase in the use of pembrolizumab in the third-line-plus setting in the United States -- see the dark green line -- where it is now the most frequently prescribed agent. Importantly, the use of 5-FU containing regimens, shown in red, and ramucirumab plus paclitaxel in light green, the two most common chemotherapy regimens in the third line, has not decreased, indicating that pembrolizumab is addressing an unmet need, particularly for patients who cannot tolerate chemotherapy.

Use of irinotecan-containing regimens, the black line, has declined to less than 5 percent, and the use of trifluridine/tipiracil, Lonsurf, which was approved in 2019, remains limited, as shown in blue. These claims data are consistent with results from the U.S. Oncology Network electronic health record system.

This is the treatment landscape today. For most patients, the first-line standard of care remains platinum and fluoropyrimidine therapy,

although FDA recently approved the nivolumab chemotherapy combination that will likely become the front-line standard of care for many patients over the next couple of years.

In second line, most patients will still receive ramucirumab and paclitaxel, and for patients who have TMD-high or MSI-high status, pembrolizumab is an excellent option. Trastuzumab deruxtecan is also approved for HER2-positive patients.

In third line, pembrolizumab monotherapy remains the standard treatment for many PD-L1 positive patients. And although trifluridine/tipiracil has also been approved for these patients, it is not frequently used in the United States.

If pembrolizumab were not available in the third line for patients with CPS 1 or higher, it would leave a significant treatment gap. For example, if I have a patient with a CPS score of 1 or higher, who has not received prior checkpoint therapy, I prefer to treat them with pembrolizumab

because some patients will have a durable response, and pembrolizumab is well tolerated in most patients.

By contrast, trifluridine/tipiracil at best slows down the cancer without any major responses, and hematologic toxicity can be an issue. Irinotecan is unlikely to work after progression on two prior lines of conventional chemotherapy, and it can have significant side effects, especially in pretreated patients.

The reality is that third-line therapy in this disease is not very efficacious. With approved agents, response rates are low and overall survival is poor. The overall response rate with trifluridine/tipiracil is 4 percent with a median overall survival of about 6 months.

Of note, the activity of pembrolizumab in KEYNOTE-059 is similar to other agents approved in the third-line setting. The overall response rate of 13 percent is not considered low with respect to the options available for this patient population, and unlike chemotherapy, pembrolizumab has the

potential to achieve durable responses.

In conclusion, patients with metastatic gastric cancer continue to have a poor prognosis, particularly third-line patients who have limited treatment options. Chemotherapy is effective and required in the first-line and second-line settings. However, beyond second line, there is limited evidence that further lines of chemotherapy confer a survival advantage, and many patients cannot tolerate additional chemotherapy. For those who are eligible, cytotoxic chemotherapy yields negligible response rates and short duration of response with considerable toxicities.

The treatment landscape for third-line gastric cancer has not changed substantially since pembrolizumab was approved, and the very recent approval of nivolumab plus chemotherapy in first line will take time to impact the unmet need in the third line. So it remains critically important to have pembrolizumab available as a third-line immunotherapy option.

Now I will hand it over to Dr. Bhagia.

Applicant Presentation – Pooja Bhagia

DR. BHAGIA: Thank you, Dr. Enzinger.

Good morning, everyone. My name is Pooja Bhagia, and I am the clinical lead for gastric cancer at Merck. I will focus my presentation on the efficacy results from KEYNOTE-059 and the status of the ongoing studies to satisfy the postmarketing requirement.

Accelerated approval of pembrolizumab in third-line and beyond gastric and gastroesophageal junction cancer was based on the results of Cohort 1 of KEYNOTE-059. Cohort 1 tested pembrolizumab monotherapy in patients with two or more prior lines of chemotherapy regardless of PD-L1 status. Patients received 200 milligrams of pembrolizumab every 3 weeks until disease progression or intolerable toxicity up to a total of 35 cycles. The primary efficacy endpoint was overall response rate.

A total of 259 patients were enrolled in KEYNOTE-059 of whom 148 patients were PD-L1 positive at a CPS cutoff of 1 or greater.

Sixty-seven percent of patients were evaluable for microsatellite instability. Of those, 143 patients were PD-L1 positive and were not known to be MSI-high, meaning they were either MSS or had undetermined MSI or mismatch-repair status. Based on this population, KEYNOTE-059 was approved.

TMB was evaluated retrospectively. Due to a lack of available tissue, only 33 percent of the enrolled patients were evaluable for TMB status. Of the 143 patients in the labeled indication, six were TMB-high, 42 were non-TMB-high, and 95 patients had unknown TMB status.

The overall response rate with pembrolizumab monotherapy in the labeled indication was 13.3 percent, including two complete responses. Median duration of response was 9.9 months after 11 months of follow-up, ranging from 2.8 to 19.4 months, with 9 patients in response.

After an additional 48 months of follow-up, the upper range of the response duration is 50.4 months, with 2 patients still in response. As noted by FDA in the briefing document, in the

subset of hundred patients with known microsatellite stable tumors, the response rate was similar.

At FDA's request, Merck conducted a post hoc analysis to evaluate subgroups of patients based on TMB status in the not-known MSI-high, CPS greater than equal to 1 population. Among 95 patients who had unknown TMB status, the ORR was 15.8 percent with a median DOR of 15.7 months. We considered this population to reflect the current real-world situation, given the low rate of TMB testing.

Given the small sample size in the remaining subgroups, the confidence intervals are broad and overlapping, making it difficult to draw any firm conclusions about relative likelihood of response in these subgroups.

This swimmer's plot depicts the survival duration in all 19 responders in the labeled indication and is color coded based on TMB status. Nearly all of the 19 responders were alive at 1 year; 13 were alive at 2 years; and 7 were alive for more than 4 years. Six patients were still

alive as of the January 2021 data cutoff.

Only one responder had a PD-L1 positive MSS TMB-high tumor, as represented by the green bar. The blue bars represent patients with PD-L1 positive, not-known MSI-high, TMB unknown tumors. Most responders are in this group, and this group closely represents the real-world situation. The pink bars show the 3 responders with PD-L1 positive, MSS non-TMB-high tumors. Those three patients had long-term survival with pembrolizumab, including one who was still alive after 55 months. These data support maintaining pembrolizumab as an option for patients with PD-L1 positive tumors.

This slide summarizes the safety profile of pembrolizumab monotherapy in KEYNOTE-059 compared to the established safety profile of pembrolizumab, represented by the reference safety data set of approximately 2800 patients, which is referenced in the FDA approved labeling for all indications.

As an immune checkpoint inhibitor, pembrolizumab is causally associated with immune-mediated adverse events which occur in

approximately 1 out of 5 patients. These events can occur in any organ system and at any time after starting treatment. While these events are mostly low grade, they can be serious, life-threatening, or fatal. Most immune-mediated adverse events are manageable with hormone replacement, steroid use, or interruption pembrolizumab.

Although the rates of grade 3 to 5 AEs, SAEs, and deaths due to AEs were higher in KEYNOTE-059 done in the reference safety database, this reflects the comorbidities typical of the third-line gastric cancer population. Overall rates of adverse events leading to discontinuation were similar.

The immune-mediated AEs experienced in this population are generally consistent with the established pembrolizumab safety profile in the reference safety database. Immune-mediated AEs were generally low grade and non-serious, and none were life-threatening or fatal. Discontinuation rates were low, indicating a manageable safety profile in this population. There were no new

safety concerns identified.

I will now briefly discuss the design and results of the original PMR studies. I just want to clarify that these two studies were in earlier lines of treatment, which is different from KEYNOTE-059, which is a study in the third-line and beyond patient population.

KEYNOTE-061 compared pembrolizumab monotherapy to paclitaxel in the second-line gastric cancer setting. Overall survival and progression-free survival were the primary endpoints. In the CPS greater than equal to 1 population, the hazard ratio for overall survival was 0.82, which did not cross the prespecified one-sided p-value boundary of 0.0135 but showed a trend in favor of pembrolizumab.

Of note, the shape of the curve is consistent with the different mechanisms of action and has been observed before when comparing an anti-PD-L1 agent to active chemotherapy. Pembrolizumab demonstrated durable responses, as noted by the tail of the curve.

KEYNOTE-062 was a 3-arm study comparing pembrolizumab monotherapy and pembrolizumab plus chemotherapy to chemotherapy in the first-line gastric cancer setting. Overall survival and progression-free survival were the primary endpoints.

For the comparison of pembrolizumab monotherapy with chemotherapy, the hazard ratio for overall survival was 0.91, and for the comparison of pembrolizumab plus chemotherapy with chemotherapy, the hazard ratio for overall survival was 0.85, which did not cross the prespecified one-sided p-value boundary of 0.008, but it showed a positive trend in favor of pembrolizumab.

The key learnings from KEYNOTE-062 are that in earlier lines of gastric cancer, chemotherapy is required, and the hazard ratio assumptions for chemotherapy plus pembrolizumab, based on our understanding from melanoma and lung studies, were too aggressive for gastric cancer. Therefore, a larger study is required.

Now I would like to briefly share the

results of KEYNOTE-590 that supported the recent approval of pembrolizumab plus chemotherapy as first-line therapy in esophageal and gastroesophageal junction carcinoma. This was not a PMR study for the gastric program, but it provides supportive evidence of the activity of pembrolizumab plus chemotherapy in gastrointestinal cancer.

Pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in overall survival compared with chemotherapy. A survival benefit was also observed in the prespecified subgroup of patients with adenocarcinoma, which includes gastroesophageal junction cancer and is histologically similar to gastric cancer.

The learnings from KEYNOTE-061 and 062, along with these data, give us confidence that our ongoing PMR studies with chemo-pembro combo in early lines of therapy will be successful.

That brings me to the option and timing of additional ongoing studies in gastric cancer. We

have several large ongoing phase 3 trials. Three of these studies are in the first-line setting and KEYNOTE-585, on the far right, is in the neoadjuvant/adjuvant setting.

We have discussed the three KEYNOTE trials shown here with FDA. These studies will isolate and define the clinical benefit of adding pembrolizumab to standard-of-care chemotherapy in gastric cancer. In June 2019, FDA acknowledged that data from any of those studies could potentially fulfill the postmarketing commitment for KEYNOTE-059. LEAP-015 recently started enrollment and has not yet been discussed with FDA for its potential to fulfill the PMR.

KEYNOTE-859 is a randomized study of pembrolizumab plus chemotherapy versus chemotherapy in first-line metastatic gastric cancer. The primary endpoint is overall survival. This study is similar to KEYNOTE-062 but is much larger and does not include a pembrolizumab monotherapy arm. Enrollment is over 95 percent complete.

KEYNOTE-811 is a randomized study of

pembrolizumab added to standard of care in first-line metastatic, HER-2 positive, gastric cancer. The results from the first interim analysis, based on response rate and duration of response, are currently under review at FDA. The study will continue and analyze the primary endpoint of progression-free and overall survival at the next analysis. Enrollment is over 90 percent complete. LEAP-015 is combining pembrolizumab with lenvatinib and chemotherapy in metastatic gastric cancer in the first-line setting.

Finally, KEYNOTE-585 is a randomized study of pembrolizumab added to standard of care as neoadjuvant and adjuvant therapy in resectable gastric cancer. The primary endpoints are pathologic complete response, event-free survival, and overall survival. This study is fully enrolled. The timelines for study completion fit within historical precedent for confirmatory trials, and interim analyses have the potential to confirm the benefit of pembrolizumab in gastric

cancer even sooner.

In summary, pembrolizumab demonstrated clinically meaningful durable responses with a manageable safety profile in the CPS greater than or equal to 1 population in the third-line and beyond setting with an overall positive benefit-risk assessment. This is a heavily pretreated patient population that often cannot tolerate or is unlikely to benefit from additional chemotherapy.

Based on the learnings from KEYNOTE-061 and 062, we are confident that the three ongoing phase 3 trials, investigating the combination of pembrolizumab with chemotherapy in earlier lines of treatment, will confirm the benefit of pembrolizumab in gastric cancer. Thank you, and now I will hand it back to Dr. Ibrahim.

Applicant Presentation – Nageatte Ibrahim

DR. IBRAHIM: Thank you, Dr. Bhagia.

In conclusion, patients with third-line and beyond metastatic gastric cancer have a poor prognosis and limited treatment options. Despite

the emergence of first-line immunotherapy with chemotherapy and the tumor agnostic approvals of pembrolizumab for MSI-high and TMB-high tumors, there remains an unmet need for an immunotherapy option with a manageable safety profile in the third-line and beyond setting. Use of a chemotherapy is limited by toxicity, and the MSI-high and TMB-high indications cover only a small subset of the gastric cancer population.

Merck is committed to fulfilling the postmarketing requirement of the accelerated approval based on KEYNOTE-059. Our ongoing trials will demonstrate the clinical benefit of adding pembrolizumab to standard-of-care chemotherapy in earlier lines of gastric cancer. These studies could fulfill the postmarketing requirement consistent with FDA guidance and regulatory precedent and as indicated by FDA in their presentation.

Pembrolizumab should remain an improved option for third-line and beyond gastric cancer patients until additional confirmatory data are

available. Pembrolizumab provides a chemotherapy-free option, and there is a substantial body of evidence that support its activity in gastrointestinal malignancies. Thank you for your attention. We look forward to your questions.

DR. REIDY-LAGUNES: We will now proceed with the FDA presentation from Dr. Steven Lemery.

FDA Presentation – Steven Lemery

DR. LEMERY: Good morning, Chairperson and members of the committee. My name is Steven Lemery, and I will be presenting FDA's position on the existing accelerated approval of pembrolizumab in the third-line gastric cancer setting. I will also be presenting at the two subsequent advisory committee meetings today. Although many of the points that I will make will be repeated throughout the three meetings, this repetition is necessary because each meeting should stand on its own merits.

Recall from Dr. Beaver's presentation that accelerated approval may be granted for drugs that

treat a serious condition, provides for a meaningful advantage in the context of available therapies, and are based on an effect on an earlier endpoint that is reasonably likely to predict benefit.

Ordinarily, confirmatory trials that are underway to verify and describe the anticipated benefit in such approvals may be subject to withdrawal if trials fail to verify benefit or if the risk-benefit assessment is not favorable.

My presentation will address the following issues. The first is the low response rate of pembrolizumab in patients with microsatellite stable disease. The second is that two separate studies do not confirm benefit. And the third is whether a monotherapy indication is appropriate, given these results and given the evolving treatment landscape of gastric or gastroesophageal junction cancers.

Importantly, FDA agrees that there is a role for checkpoint inhibition in gastric cancer. However, FDA questions whether the current

monotherapy indication in the third-line-plus setting has a favorable risk-benefit profile and meets the criteria for continued marketing, especially in the context of the recent approval of nivolumab in gastric cancer.

Furthermore, by maintaining the third-line monotherapy indication, is this an endorsement that this may be an acceptable alternative to patients in lieu of receiving checkpoint inhibition in the first-line setting where there has been a demonstrated overall survival benefit?

Before I discuss the pembrolizumab results, I will briefly discuss the treatment landscape for unresectable or metastatic gastric cancer. This is a simplified version and presented for the purposes of the public discussion.

Today we will be discussing the third-line accelerated approval of pembrolizumab, in red on the bottom right, in the PD-L1 CPS greater than or equal to 1 subgroup. In the first-line setting, patients will typically receive doublet chemotherapy, including either 5-FU or capecitabine

in combination with a platinum. More recently, and importantly, nivolumab was approved in the first-line setting, and I will discuss this later.

Upon progression on the first-line setting, patients may also receive paclitaxel with ramucirumab, ramucirumab alone, or a different cytotoxic drug. In the third-line setting, trifluridine with tipiracil is approved.

Finally, I would like to point out that the response rate for pembrolizumab in MSI-high disease appears to be higher, especially with this patient population, and should be considered separate from patients with microsatellite stable disease. We want to make clear that the accelerated approvals in subgroups such as MSI-high will not be affected if a third-line gastric cancer indication is withdrawn.

Pembrolizumab received accelerated approval for the gastric cancer indication based on results of Study KEYNOTE-059, a multi-cohort study in patients with gastric or gastroesophageal junction cancer. Specifically, for approval, the results

were considered for the third-line-plus cohort, which is identified in red. Patients in this cohort could receive no prior checkpoint inhibitor therapy. The primary endpoint was overall response rate per central review.

FDA may consider overall response rate with data on duration of response in single-arm studies as supportive of an approval because tumors generally do not shrink in the absence of therapy and, hence, represent the direct anti-tumor effect of the drug.

Ultimately, pembrolizumab received accelerated approval in the third-line-plus setting in a subgroup of patients with PD-L1 CPS score of 1 or greater. Pembrolizumab received this accelerated approval in 2017 based on a response rate of 13 percent observed in Cohort 1 of Study KEYNOTE-059, along with durability of these responses. As described in labeling, more than half of responding patients experienced a response of at least 6 months.

Given the unprecedented effects of

checkpoint inhibition in patients with MSI-high tumors, for this ODAC, FDA requested an analysis of response rate in KEYNOTE-059 in the subgroup of patients with PD-L1 positive tumors and known microsatellite stable disease, because about a third of the patients in KEYNOTE-059 were not tested for microsatellite instability.

In KEYNOTE-059, the response rate in the known microsatellite stable population was 11 percent. For comparison, the response rate for MSI-high tumors in the second bullet are those described in product labeling for the MSI-high indication from different clinical trials. I will reiterate that the MSI-high indication will be maintained irrespective of any decision on the gastric cancer indication.

Although I will not get into too much detail regarding tumor mutation burden, the vast majority of patients with gastric cancer appear to have TMB-low disease, and the response rate in these patients in Merck's analyses described in the briefing document and evident from both KEYNOTE-

059, and additional patients with gastric cancer in a non-KEYNOTE-158 data set in the TMB-high accelerated approval application, appear to be even lower at 6 to 7 percent, although with a higher response rate in patients with TMB-high disease.

Remember that continued marketing under accelerated approval should be based on a belief that a drug produces an effect that is reasonably likely to predict benefit. This should be a science-based decision.

As per the conditions of accelerated approval, Merck was to conduct and submit the results of one or more randomized trials to verify and describe the clinical benefit of pembrolizumab, based on a clinically meaningful improvement in overall survival in patients with PD-L1 positive microsatellite stable disease. Study KEYNOTE-061 was identified during the review of the application as a study that, if positive, could confirm benefit. KEYNOTE-062 was a second potentially applicable study in gastric cancer.

This slide shows a simplified design of the

two studies in gastric cancer applicable to the current monotherapy indication. KEYNOTE-061 was a second-line study versus paclitaxel with primary endpoints of overall survival and PFS in the group of patients with PD-L1 CPS score of 1 or greater.

Note the paclitaxel monotherapy control arm. Although there is not a comparative effectiveness requirement for regular approval, in current practice, patients frequently receive ramucirumab combined with paclitaxel, as this regimen has demonstrated improved survival compared to paclitaxel alone.

KEYNOTE-062, on the right, was a first-line study with 3 arms, including a monotherapy pembrolizumab arm, a combination pembrolizumab chemotherapy arm, and a chemotherapy-alone arm. KEYNOTE-062 tested multiple hypotheses for PFS or survival in patients with tumors that were PD-L1 CPS 1 or greater or PD-L1 CPS of 10 or greater.

This slide summarizes the results of Study KEYNOTE-061 and the monotherapy superiority comparison of KEYNOTE-062 in the PD-L1 CPS greater

than or equal to 1 groups. The Kaplan-Meier curves for survival for the monotherapy comparisons are shown on the left with pembrolizumab in blue and crossed in both trials, indicating non-proportional hazards.

The statistical test for superiority in these trials were negative. The PFS hazard ratios, including the lower bound of the 95 percent confidence interval, was above 1; the same thing with the chemotherapy arm in both trials. These results include a small number of patients with MSI-high tumors with results that appear to have greatly favored the pembrolizumab arm. We believe that a more relevant group of patients for the third-line indication are patients with microsatellite stable disease.

Here are the Kaplan-Meier curves for the comparison of pembrolizumab plus 5-FU cisplatin versus 5-FU cisplatin alone in the PD-L1 CPS greater than or equal to 1 group. The pembrolizumab chemotherapy arm is in orange. Although the p-value was just under 0.05, this

result was not statistically significant. Like the pembro-chemo arm in KEYNOTE-062, all of Merck's ongoing trials in gastric cancer are combination trials and not monotherapy trials.

As stated previously, the treatment landscape of gastric cancer is changing. Earlier this year, FDA approved trastuzumab deruxtecan in HER-2 positive disease. Previously and more relevant for unselected population of gastric cancer, in 2019, FDA approved trifluridine/ tipiracil in the third-line setting, based on a modest improvement in survival versus placebo.

Although the applicant's section in the briefing document stated that this should be reserved for patients with low-volume disease, this should not imply that pembrolizumab is more effective in patients with bulkier high-volume disease. Furthermore, we want to make clear that the indication for trifluridine/ tipiracil is for the third-line treatment of gastric cancer and does not limit use to patients with low-volume disease.

Additionally, approximately two weeks ago,

FDA approved nivolumab in combination with fluoropyrimidine and platinum-containing chemotherapy for the treatment of patients with gastric, gastroesophageal junction, or esophageal cancer, effectively establishing a new standard of treatment. The trial supporting the approval was conducted in the first-line metastatic setting, and approximately 70 percent of patients had gastric cancer.

Shown here are the results in the ITT population, which are only tested after the biomarker-positive population, and based on PD-L1 demonstrated statistically significant effects. Importantly, as more and more patients are treated with checkpoint inhibitor therapy in the first-line setting, fewer will receive single-agent checkpoint inhibitor therapy in the third-line or greater settings.

As a reminder to the committee, the pembrolizumab accelerated approval was granted for an immuno-oncology naïve population, as there are currently no data showing the effectiveness of

pembrolizumab in the gastric cancer population that was previously treated with an immuno-oncology drug.

As I stated before, it is important to consider if by maintaining the third-line monotherapy indication, whether this is an endorsement that this may be an acceptable alternative for patients in lieu of receiving checkpoint inhibition in the first-line setting and there has been a demonstrated overall survival benefit.

To further highlight, in the changing landscape of the treatment of gastric cancer, Merck is proposing four potential randomized-controlled trials to confirm benefit. These are all large trials that may further define the role of checkpoint inhibition in patients with gastric cancer. A unifying theme among all four trials is that they're assessing pembrolizumab in combination with chemotherapy.

Studies 859 and 811 differ in that 859 is in a HER-2 negative population, whereas 811 is in the

HER-2 positive population. Study 585 is a perioperative trial of pembrolizumab and chemotherapy in patients with resectable disease. Finally, LEAP-015 is assessing pembrolizumab, TKI lenvatinib, and chemotherapy in the first-line advanced setting. All are due to be completed in 2024 unless they are stopped early for futility or efficacy based on interim analyses.

Although these are all potentially important trials, the relevance to the third-line indication is not clear because of the two negative trials of pembrolizumab monotherapy in gastric cancer and the low response rate of pembrolizumab as monotherapy.

Now I come to the risk-benefit assessment for the current third-line indication. Pembrolizumab's main effect observed today is a response rate of 13 percent or 11 percent among the hundred patients with no microsatellite stable disease. Some patients have experienced responses of long duration. Furthermore, pembrolizumab's effects are via a different mechanism of action compared with the other available drugs,

trifluridine and tipiracil, which have demonstrated a modest improvement in survival in the third-line-plus setting.

Countering the low response rate observed in KEYNOTE-059 are the risks of immune-related adverse effects and lack of benefit for most patients. Although most patients tolerate anti-PD-L1 therapies, serious immune-related effects such as pneumonitis, myocarditis, or nephritis can occur in a subgroup of patients and can sometimes cause long-lasting morbidity. Additionally, treatment of these conditions with long-term steroids can be challenging for patients.

With accelerated approvals, we must also consider uncertainties. Remember that accelerated approvals are based on early or intermediate endpoints, and typically additional information is requested to verify and describe the benefit. For pembrolizumab, two trials of monotherapy have not yielded successful results when compared to chemotherapy.

Most relevant to the third line approved

indication is the second-line trial, KEYNOTE-061 versus paclitaxel, which was negative. Remember that paclitaxel was administered without ramucirumab, and the expected efficacy of paclitaxel alone in the second-line setting is expected to be modest.

For example, the data supporting the use of paclitaxel provided in the treatment guidelines include two references to non-randomized studies in esophageal cancer and one negative study versus irinotecan in gastric cancer.

Second, there are uncertainties with respect to the selection of patients. Clearly, microsatellite instability is an important marker to predict benefit. Recall that KEYNOTE-061 and KEYNOTE-062 did not exclude patients with MSI-high disease.

Another question is whether a different PD-L1 CPS score would be more optimal. Although the PD-L1 CPS 10 or greater subgroup in KEYNOTE-062 appears to show a nominally larger effect in the monotherapy analysis, this was not necessarily

replicated in the pembrolizumab chemotherapy versus chemotherapy analysis. At this time, any consideration of selection based on a different CPS score would be considered exploratory.

Although TMB stratified responses in the applicant's data sets, the TMB indication is under accelerated approval, and testing is not universal in practice. At the end of the day, for the current application, we are limited to selecting patients based on PD-L1 CPS of 1 or greater, which may not be optimal.

When we see applications of a low response rate in a single-arm trial, it can be difficult to accurately quantify risk and benefit. A subset of responding patients may clinically benefit. For example, tumor shrinkage might improve pain, relieve a GI obstruction, or shrink a disfiguring cutaneous lesion; and it's just hard to characterize these more direct effects given limitations in PRO instruments or limitations in clinical trials.

Therefore, we are ultimately left with

uncertainties with respect to the benefit compared to the known toxicity profile of pembrolizumab. Remember that to support accelerated approval, scientific data should be provided that a drug's effect is reasonably likely to predict benefit.

In summary, the current accelerated approval of pembrolizumab in PD-L1 CPS 1 or greater gastric cancer is based on a low response rate, albeit with some patients having long durations of response. This comes with a cost of serious toxicities in a subgroup of patients, and there are uncertainties with respect to clinical effects based on unsuccessful monotherapy studies in the first- or second-line settings.

Added to this, the treatment landscape of gastric cancer has changed. Even before the results of CHECKMATE-649, establishing the use of nivolumab in the first-line setting, the number of patients who received third-line therapy in the U.S. are limited.

Given the negative randomized trial of pembrolizumab as monotherapy, including one against

paclitaxel in the second-line setting, it appears that the optimal use of checkpoint inhibition will be in combination regimen. This is underscored by Merck's four ongoing trials, which are all investigating the use of these combination regimens.

When new results conflict with the prior accelerated approval, the drug product should be re-evaluated in the context of currently available therapy, and the indication withdrawn if the drug no longer will provide a favorable risk-benefit profile to patients.

Given the changing landscape, it is worth considering that it is unlikely that FDA would approve an application today for accelerated approval of a checkpoint inhibitor based on a response rate of 13 percent in patients who had not received prior checkpoint inhibitor therapy. Recall that for accelerated approval, a drug is approved on an early or intermediate endpoint reasonably likely to predict benefit in the context of an advantage over available therapy, which would

include nivolumab.

Furthermore, this legal requirement of a treatment effect that is really likely to predict benefit is an important standard to consider. This is not the same as observing any treatment effect on a CT scan.

Prior to introducing the question, I will again show this table which summarizes the ongoing pembrolizumab trials in gastric cancer. Study 859 is in patients with HER2-negative disease; 811 is in HER2-positive disease; 585 is in the perioperative setting; and LEAP-015 is in combination with lenvatinib and chemotherapy.

All have estimated completion dates in 2024. To be clear, FDA does have a long history of using trials in different settings to verify and describe an effect of an accelerated approval, and this concept has been discussed in the prior advisory committee meetings during the previous two days. However, the consideration here is different given the two negative monotherapy trials.

Now we will come to the voting question.

Given the following, the low response rate in the third-line setting changed the treatment landscape with nivolumab approval in the first-line setting based on an improvement in survival, two trials with monotherapy comparisons in the first- and second-line settings that did not confirm benefit, and that ongoing trials will not assess the monotherapy effect, should the indication for the monotherapy use of pembrolizumab in the PD-L1 CPS greater than or equal to 1 gastric or GE junction adenocarcinoma, in the third-line or greater setting, be maintained pending conduct or completion of additional trials? Thank you.

Clarifying Questions to Presenters

DR. REIDY-LAGUNES: We will now take clarifying questions for the presenters, both Merck, Sharp & Dohme and the FDA. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a

specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge at the end of your question with a thank you, and follow-up your question with "That is all for my questions" so that we can move on to the next panel member.

I'm Diane Reidy. I'm going to start with the first question. My question is for either Dr. Bhagia or Dr. Ibrahim from Merck, and it's essentially a follow-up to Dr. Lemery's presentation.

You noted, Dr. Ibrahim, that this is a chemotherapy-free treatment option; but again, the requirement to fill the FDA requirements for drug approval as a single agent were contingent on the positive results of 061 and 062. So can you please comment on the awaiting trials and how we can make sense of this?

DR. IBRAHIM: Yes. So 061 and 062 were the original studies set as the postmarketing

requirement for the accelerated approval. When those did not meet the primary endpoint, there were follow-up discussions with the FDA. I will turn it over to Dr. Bhagia to succinctly review the relevance of our ongoing studies.

Dr. Bhagia?

DR. BHAGIA: Pooja Bhagia, Merck clinical. We learned from our original PMR trials -- that was KEYNOTE-062 and 061 -- that chemo combination is essential for patients who have earlier lines of gastric cancer. So these patients are chemo naïve and a monotherapy trial may not be feasible for these patients.

I want to point out that KEYNOTE-059 is a study in third-line and beyond gastric cancer patients. These patients are heavily pretreated, and many of these patients are unable to tolerate chemotherapy or have toxicities from prior chemotherapy and, hence, they can't tolerate. Hence, as we saw from our presentation with the durable responses that we saw in 059, pembrolizumab is an appropriate option.

Going to our ongoing PMR studies, I can show you the slide that has our four ongoing studies.

Can you please show the slide that has the four ongoing studies from the core deck? As that slide is being pulled up, I'll describe those four studies.

The four ongoing studies are, as we described, studies combining pembrolizumab with standard of care, and this is, again, based on a learning from KEYNOTE-062 that chemo-pembro combo is essential in these earlier lines of treatment. As you can see, the effect of additional pembrolizumab can be isolated from these trials. These trials can complete as soon as within the next 1 to 3 years and can confirm the benefit.

Moreover, I want to point out the recent results from KEYNOTE-590 and CHECKMATE-649, which were in earlier lines of treatment. And these trials showed that in early lines of treatment, combining immunotherapy with chemotherapy is the correct strategy.

Back to you, Dr. Ibrahim.

DR. IBRAHIM: Thank you, Dr. Bhagia.

I would like Dr. Manish Shah to give his clinical perspective and issues with conducting a monotherapy study in third line and beyond in today's landscape.

Dr. Shah?

DR. SHAH: Hi. Yes. Manish Shah, Weill Cornell New York. Thank you.

I think that it's really an important point that many of us who treat GI cancers, and gastric cancer specifically, realize that there is a benefit of a checkpoint inhibitor in the third-line setting. We've treated patients with pembrolizumab as per the indication and have had patients with durable responses. We're aware of the ATTRACTION-2 data, which was a randomized study done in Japan that compared nivolumab to that supportive care, and there was a substantial benefit with nivolumab, which is essentially hitting the same target.

So I think at this point, a third-line monotherapy study, it wouldn't be feasible. There isn't equipoise versus best supportive care. Then

one might argue that perhaps you should do a study versus a chemotherapy backbone, and I would argue that that actually isn't the same population. Patients have to get from first line, to second line, to third line.

The IQVIA slide, slide CG-17, please? That study, that real-world example demonstrates that chemotherapy in the third-line setting is less and less effective, and people are not using it. What we see here is the black line, topoisomerase inhibitors, going less than 5 percent. Lonsurf, which was recently approved, is also less than 5 percent. That's because most patients aren't able to get cytotoxic therapy with significant side effects in the third-line setting.

So I think for the treatment, there's a clear unmet need, but importantly, from a clinical trial standpoint, there isn't equipoise that we could do a study in the third-line setting, testing monotherapy. Thank you.

DR. IBRAHIM: Thank you, Dr. Shah.

DR. REIDY-LAGUNES: Thank you.

I have a question from Dr. Lieu.

DR. LIEU: Hi. This is Chris Lieu. I have a question for the Merck team, maybe specifically Dr. Bhagia. In regards to KEYNOTE-061 and 062, does Merck have any sense of the later lines of therapy that may have impacted overall survival, and particularly the use of immunotherapy in later lines of therapy following the completion of that study?

DR. IBRAHIM: Yes. Dr. Bhagia, if you'd like to answer the question regarding subsequent therapies in KEYNOTE-061 and 062, please.

DR. BHAGIA: Pooja Bhagia, Merck clinical. Can I please see the slide that has subsequent therapy from KEYNOTE-061?

So while that slide is being pulled up that describes subsequent therapy, and specifically the immunotherapy from KEYNOTE-061, I want to point out that there was a higher rate of immunotherapy.

Slide up, please? As you can see on this slide, the rate of immunotherapy was almost 10 percent in the paclitaxel arm, and there was no

subsequent immunotherapy in the pembrolizumab arm. And even overall in terms of any subsequent therapies, it was approximately 60 percent in the paclitaxel arm, which was higher than the pembrolizumab arm, which was about 45.9 percent.

Back to you, Dr. Ibrahim.

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

DR. IBRAHIM: Thank you.

DR. REIDY-LAGUNES: Thank you.

The next question is from Dr. Weekes.

DR. WEEKES: Yes. This is for the Merck team. Can anyone who's on their team discuss the relationship between chemotherapy and PD-L1 expression in gastric cancer?

DR. IBRAHIM: Sure. In gastric cancer, PD-L1 is not as defined as in other tumor types. I will have Dr. Cao review with you how we have come in terms of the biomarker in gastric cancer, to start to answer your question.

Dr. Cao?

DR. CAO: Alex Cao, Merck, clinical

biomarkers. Our data have shown that PD-L1 CPS is a clinical biomarker that is predictive of pembrolizumab efficacy in gastric cancer, and it is not predictive of the chemotherapies in gastric cancer.

Back to you, Dr. Ibrahim.

DR. IBRAHIM: Yes. I'd like to call on Dr. Peter Enzinger to give his clinical perspective of CPS utility in the clinic.

Dr. Enzinger?

DR. ENZINGER: Hi. Peter Enzinger, Dana-Farber Cancer Institute. I don't think, really, there is any PD-L1 effect on regular chemotherapy. So basically we think that this is an independent effect and the chemotherapy works equally or not well in PD-L1 positive and PD-L1 negative patients. So I do think that that's an independent mechanism. Thank you.

DR. IBRAHIM: Thank you.

DR. REIDY-LAGUNES: Thank you. The next question is from Dr. Hillard.

DR. HILLARD: Yes. Just to clarify, have

there been no statistically significant positive studies completed since the original accelerated approval?

DR. IBRAHIM: As we reviewed today, we went over KEYNOTE-061 and 062 and those results that didn't meet the postmarketing requirement. We have KEYNOTE-590 that was just recently approved. We'll review that. I'll ask Dr. Ronan Kelly to come to the podium and give us his clinical perspective, and we're continually waiting for the other studies to read out. As noted, we have an application under review at the FDA for KEYNOTE-811, which is in HER2-positive gastric cancer based on our results.

Dr. Kelly?

DR. KELLY: Yes. Thank you. Dr. Ronan Kelly from Baylor University Medical Center. I'm a paid consultant by Merck for this meeting, but I do not have any financial interest in the outcome of this meeting.

It's really a great question. It's been a phenomenal year, I would say, for gastric and

esophageal cancer. We were waiting for many years for positive studies, but this year alone, we've seen four positive phase 3 trials, and we actually had our own plenary session at ESMO for the first-ever time, where four studies were selected in gastric and esophageal cancer.

I think it's really important for us to understand that we've actually learned the lessons from prior trials that haven't met the endpoint because gastric is not the same as melanoma and lung cancer that may be exquisitely sensitive to single-agent PD-L1 inhibition in earlier stage disease.

What we've learned is, in those early stages, we should combine with chemotherapy because that's where we're seeing synergies. However, when patients get into the third-line setting, they really cannot tolerate chemotherapy. What we've seen is patients are weak, they're frail, and we only have two approved options. We have pembrolizumab or we have the Lonsurf drug. And unfortunately, Lonsurf has a lot of toxicities, and

it has a response rate of 4 percent, which means if we do not have the option of pembrolizumab, we really do not have any options. Maybe hospice is the only option in patients in the third line.

I will just say one other thing about the approval of nivolumab in the first-line setting. That has just happened two weeks ago. What about all the patients with gastric cancer that have moved beyond first-line therapy now in the United States? They should have the option of receiving a checkpoint inhibitor in the third line because we've shown that the duration of response in those that respond is much better than what you would get with chemotherapy.

So really a great year, phenomenal results, multiple FDA approvals coming, but we've learned on the lessons of previous years. Thank you very much.

DR. IBRAHIM: Thank you, Dr. Kelly.

DR. REIDY-LAGUNES: Dr. Kraus, next question?

DR. KRAUS: Yes. Thank you. I think it was

predominantly covered by Dr. Kelly because I think Dr. Lemery from FDA asked the question about the role of monotherapy as opposed to combination, as is not uncommon that combination produces better activity in many cases.

But I was going to direct it to Merck and to Dr. Enzinger because I got the sense that Dr. Kelly was emphasizing that there may be a number of patients -- I don't know how many exactly -- that aren't good candidates because of comorbidities and performance status that might be served well by a monotherapy. But I was wondering if Dr. Enzinger could provide some perspective in that regard as well.

DR. IBRAHIM: Yes. Dr. Enzinger, if you'd like to give your clinical perspective on the use of monotherapy in later lines for gastric cancer.

DR. ENZINGER: Absolutely. Peter Enzinger, Dana-Farber Cancer Institute. I think it's important for everybody to understand that we give chemotherapy when it works, and that's why we give chemotherapy in combination with immunotherapy in

the front-line setting. But the problem is that the chemotherapy loses its effectiveness. The patients become refractory to chemotherapy, and that's why we don't give chemotherapy in this third-line setting because, simply, chemotherapy doesn't add any additional benefit. It only adds substantial toxicity. Instead, we give immunotherapy.

You can see from the IQVIA data that I showed you earlier that oncologists are voting with their feet. They are all using pembrolizumab, and the reason they're using pembrolizumab is that there are no good alternatives. Lonsurf had a very low response rate, it has toxicity and, importantly, no durable responses. Irinotecan is toxic. It doesn't really work in refractory disease, and the other agents have all been exhausted.

So it is critically important to understand that there is a big difference between treating patients in the front-line setting and in the third-line setting. And I think it's quite clear

that these agents are effective. I mean, we've got four positive studies that show this. The FDA has acknowledged this and has given broad approval.

Unfortunately, there are patients who won't benefit from this. These patients started their journey two years ago. And I think it's really unfair not to allow these patients who can't benefit from front-line therapy not to benefit from immunotherapy in the third-line setting. Thank you.

DR. KRAUS: Thank you. No further questions.

DR. REIDY-LAGUNES: Thank you.

We have a comment from Dr. Lemery from the FDA.

DR. LEMERY: Yes. Let me start, and we'll see if anyone else would like to jump in as well. We've had this situation before where drugs have been taken off the market in the accelerated approval setting, and there have been programs set up for the limited number of patients who still would potentially be able to receive that drug.

So I think our decisions here for whether to keep a drug or not should be based on data. And the data here are based on a particular response rate in an application, as well as negative -- or I should say unsuccessful studies in monotherapy use of pembrolizumab.

It's generally not a situation where a drug is removed from accelerated approval and patients are just completely left without anything so to speak. I think it's problematic just to say, okay, the indication's withdrawn and there's nothing.

Dr. Pazdur, do you want to add anything?

DR. PAZDUR: Yes. Can you hear me?

DR. LEMERY: Yes.

DR. PAZDUR: Yes. I think Steve is correct. We've been down this pathway before, and the way we handle this is by an expanded access program and a treatment protocol. Here again, even if action is taken, there is some period of months basically before the indication is actually removed from the market.

So the numbers of patients that are caught

in this limbo, so to speak, can be handled by a treatment protocol by single-patient INDs, et cetera, or by just delaying the removal of the drug for several months here. So we're cognizant that we don't want to leave people and patients in the lurch here without a therapy.

But I think a major point here -- and I'd like to get this across because I don't want to get lost in the weeds here with, really, what our major issue is with this application, and that is the changing landscape -- as Steve mentioned, is we firmly believe that there is a role for checkpoint inhibitors in gastric cancer here, in this disease. We believe that it's in the front-line therapy where survival has been shown. Okay. End of discussion.

The issue here where you have this third-line indication could actually have unintended consequences. First of all, will people assume that, well, even if somebody got treated with nivolumab in the first-line therapy, let's try pembrolizumab in the third-line setting. Well,

there's no data on those patients, and those patients would really have to be studied. But that's an entirely different risk-benefit after one has received a checkpoint inhibitor.

The other unintended consequences, and I think Steve alluded to this, is basically would somebody say, "Well, I have two options here. One is the first-line therapy and one is the third-line therapy, and they're both FDA-approved indications. Maybe I'll choose the third-line therapy."

That would be obviously wrong because we have a survival advantage shown in the first-line therapy and we have no advantage, other than a small response rate demonstrated, in this third-line therapy.

It is incumbent upon us and the integrity of this program that when we have an accelerated approval, and they have failed to demonstrate confirmatory trials, that we take a look at should we continue this indication here. We have to ask ourselves the question, the fundamental question, would we grant this indication at this time if we

were going to reassess this indication? Because that's really what we're asked to do, because many of these trials that are listed on the potential confirmatory trials are going to be available not for years here, so to speak.

So we have to reassess the situation, and would we grant this indication at this time? And the definitive answer is no. For a single-arm trial, we have patients, basically, that have a survival advantage in the first line. If somebody wants to come into the third line, they have to show that patients have progressed on a first-line therapy that included a checkpoint inhibitor.

Here again, I want to emphasize to a patient community out there, we firmly believe in the role of checkpoint inhibitors in this disease. We have been cognizant in what is the appropriate setting for that, and it currently is in the first-line setting. This third-line setting, which has not demonstrated the clinical benefit despite two negative trials, we would handle those small numbers of patients through a treatment access

program. We can delay the removal of this indication by several months to allow patients to receive the drug if needed, and those that are responding to continue on a treatment protocol, or a single-patient IND, or Merck can alternatively give the drug gratis to these patients.

So that's my point, and that's the essence of why we're bringing this to this committee.

DR. IBRAHIM: Is it ok if we respond? This is the sponsor. I think we can address all those points, Dr. Pazdur. Is it ok if we respond?

DR. REIDY-LAGUNES: Yes, please. I would ask you to respond.

DR. IBRAHIM: Okay.

So you brought up three issues. I'd like to take them one at a time, and I'd also like to call on a couple of our advisors to help me with two of the points.

The first point regarding patient access, Merck is committed to ensuring that our patients have access to medicines. We believe that regulatory approval is the best way to provide

access for patients. We maintain that resuming this indication will ensure patient access to medication that may help them.

The expanded access program that you had mentioned, that is not generally an appropriate mechanism for providing an approved drug to patients for an unapproved use, and that would require further discussions between us and the FDA.

DR. PAZDUR: Ma'am, we would allow that. We have control over that at the FDA.

DR. IBRAHIM: Yes. So our concern is that that would impose some administrative burden for the physicians and could actually delay and restrict access. Not all centers may be able to participate. I will have Dr. Enzinger further comment on that, but before that, I also want to address the other two issues that he will also speak to.

The second one is regarding retreatment. I just want to clarify that our indication is in third line. These patients studied in KEYNOTE-059 did not have prior immunotherapy. Now, as you are

aware, the majority of our KEYNOTE studies, we do allow retreatment as a second course for patients that have had stable disease or better, i.e., a response, at the investigator discretion, pending what other available therapy is.

What we are here advocating for, for patients, is that there's going to be a long time before an adoption of a front-line combination regimen with immunotherapy, and that there is a subset of patients that need third-line treatment or that for some reason cannot tolerate the front-line combination regimen.

We do acknowledge and recognize that this population is small and will get smaller over time, but we don't think that we are here today. That is why we are advocating to keep the indication and to not restrict or have any cumbersome mechanism that could hinder access to the patients who need it.

For the third point, regarding that this may generate confusion where a patient may delay front-line treatment for third line, that's a patient and physician decision, right? That's a discussion

between them, and our experts speak to that and how that decision is made. But by no means are we saying delay your upfront treatment and reserve it for third line. That is not our message. That is not the intention.

Now, I would like to hand it over first to Dr. Enzinger to touch upon these key points as well.

DR. ENZINGER: Yes. Peter Enzinger, Dana-Farber Cancer Institute. I must say an expanded access program sounds very nice, but the reality is that our patients are incredibly sick and that weeks matter. It requires all this administrative approval that really delays treatment.

Having personally had many patients on expanded access programs, it takes weeks often to get patients on these studies. You get insurance blockages. The patient has to provide information. Our patients just don't have the time for that. Therefore, I don't think the expanded access program is the way to go.

I would just say that for my patients, again, I think that we are not advocating that patients who already received a checkpoint inhibitor should get another one. We don't think that that works. I think we all agree that the setting to give checkpoint inhibitors in the future is in the frontline, but unfortunately some patients haven't had that chance yet. And I think that it is those patients who deserve an opportunity, the same opportunity that the new front-line patients have, to receive a checkpoint inhibitor. Thank you.

DR. IBRAHIM: I'd like Dr. Kelly to add, if that's ok, and there are a couple of other people.

DR. KELLY: Thank you. Ronan Kelly, University Medical Center. I also think it's really important for us to think about gastric cancer in the United States. It's not a common tumor, so the majority of our medical oncologists throughout the community are not aware of the gastric cancer data; so they may or may not have heard about the first-line approval. We are going

to have to do a lot of work in educating people. They keep up to date with the breast cancer data, the lung cancer data, but the gastric data, they're not keeping up to date with this information.

So my concern is it's been a wonderful year, as I said. We've got first-line indications, but there will be doctors that aren't aware of the indication, and patients can go through their treatment cycles and make it to the third line without ever having a checkpoint inhibitor.

What's the population we're talking about? 2,200 patients. If you then break that 2,200 down into 57 percent or CPS greater than 1, you're looking at just over a thousand. Let's give those patients a chance.

I don't think the company's thinking keep indefinite third-line approval, but for the next foreseeable future, my concern would be if those patients don't have access to that drug, they -- as we've shown, if we can pull up the slide on the slide on the swimmer's plot, please, there is a duration of response that we just do not see with

chemotherapy, and that's real. We've all had those patients.

Slide up, please. You can see here in light blue, this is the real world. This is what we're faced in 2021 in gastric in the United States. We do not know the TMB status on the vast majority of patients. We do have the PD-L1 status. And you can see here that there is a durable response in a population of patients. Let's give those patients a chance in the third line, even if they've missed out on the first-line indication because that's so new. That's my concern. Thank you very much.

DR. IBRAHIM: Thank you, Dr. Kelly.

DR. PAZDUR: Could I make a response to that?

DR. REIDY-LAGUNES: Yes, please, Dr. Pazdur.

DR. PAZDUR: Okay. First of all, I think it's relatively naïve to think that patients or physicians, and medical oncologists, will not be aware of this first-line approval. I have firm belief -- let me just tell you this -- in the marketing department of all of these large

pharmaceutical companies to get the word out as free here, so to speak. So to keep an indication on the market because you don't believe that the physicians will be educated on this is, really, an unreasonable argument to me.

The second thing I'd like to bring up regarding expanded access is plugs for our program that we initiated in the Oncology Center of Excellence. And thank you for giving me this opportunity to plug this program because it has implications outside of this.

We have a special program just to help physicians with this certain situation that is manned between the business hours of Monday through Friday to walk people through expanded access, and we've handled many, many of these and are facilitating this process. So we really actually have a special program to facilitate -- and hence, the word, "project facilitate" -- the single-patient INDs.

Really, what I'm talking about, though, is not a single-patient access program but primarily a

treatment protocol that could easily be done. And we've done this, let me tell you, on numerous occasions, numerous occasions, where we have a transition here between going from an approved drug and removing a drug from the market, with specialized pharmacies, et cetera, to shift the drug if it was an unapproved drug or the drug was actually being taken off. But here you really have the drug still maintained on the market.

So there has been sufficient experience with this, with the FDA and the pharmaceutical companies working on these withdrawals of these indications. We could leave it at that.

DR. LEMERY: This is Steven Lemery. In some cases, companies that just provided the drug, if the drug is not going off the market and it's clearly approved for many uses, I think that's been a situation as well. That's a company decision of course, but that has clearly been the case in other situations.

DR. PAZDUR: I'm sure since Merck is concerned about the welfare of these patients,

they'd be happy to give this drug free to them. Right?

DR. REIDY-LAGUNES: I want to make sure we have time for the advisory committee to answer their questions as well, but I do have one question for the FDA.

In June 2019, the FDA did indicate that the three ongoing phase 3 studies could be considered as confirmatory studies, 859, 811, and 585. Given the changing landscape, can you just share with us what does that mean given that we do have these two confirmatory single-agent studies that are negative, but in the context of where we are today, what happened in June '19 and how that plays at all with the current situation?

DR. LEMERY: Sure. I can start, and then, Dr. Pazdur, you can add anything if you feel fit.

When we review these trials, as has been in the two days in the prior advisory committee meetings, we are able to take a different setting and grant a regular approval if the study is positive, for example, in that other setting. As

Dr. Pazdur mentioned yesterday, you get a twofer. You get an approval in that first-line setting, plus you convert the later-line setting.

In most cases, if these studies are positive and if it's an easier call, we acknowledge there may be some uncertainty regarding in one setting it's the combination, in another setting it's the monotherapy, but at least that other study was positive. So there's an acknowledgement at that time that maybe these other studies could be used.

Now we're having to reassess these applications in the setting of these negative trials. And we're doing that for not just this application, but we're doing this for other applications as well, and saying does it really make sense, especially in the negative studies that are more akin to these other approvals that are on the market at the moment.

So we are reassessing does it make sense to consider these other studies in light of the two negative studies -- or not negative, but unsuccessful studies in monotherapy.

DR. PAZDUR: And they could get additional indications for these trials if they are positive irrespective of whether they are used to maintain the accelerated approval. But here again, I think as Steve mentioned, the whole reason why we're having this ODAC is really to assess this treatment landscape. We have to ask ourselves the question, given the current landscape at this time, does it make sense to have a third-line indication out with these two negative trials when we have a positive first-line study?

And we really think that patients should be treated with a first-line therapy, and we can't make any determination of what the effect would be of a third-line indication if patients were treated with first-line nivolumab. Those patients simply have not been studied.

DR. REIDY-LAGUNES: Thank you.

We do have to move on to the break, so additional clarifying questions can certainly be asked after the conclusion of the OPH. It's a 10-minute break. Panel members, please remember

that there should be no chatting or discussion of the meeting topic with anyone during the break, and we will resume at 11:06.

(Whereupon, at 10:57 a.m., a recess was taken.)

Open Public Hearing

DR. REIDY-LAGUNES: 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 relationships 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 please begin and introduce yourself? Please state your name and your organization you're representing for the record.

MS. EIDELMAN: My name is Andrea Eidelman, and I am the CEO of Debbie's Dream Foundation: Curing Stomach Cancer. We are the largest patient advocacy group for stomach cancer, and I have not received compensation from the sponsor for my presentation here today.

I am here because this issue goes to the heart of the mission of the Debbie's Dream Foundation. Our founder, Debbie Zelman, founded the organization in 2009 after one year of being diagnosed with stage 4 incurable stomach cancer. Debbie was just 40 years old, a mother of three, a practicing attorney, and a wife and daughter of a prominent physician.

Debbie found through her own personal journey that there had not been a new treatment in

gastric cancer in over 30 years. She founded the organization to change this landscape. Her goal was to fund research and provide more treatment options for stomach cancer patients.

We are now in 2021, not 2009, and as a patient advocate, one of the greatest unmet needs of our stomach cancer community is around the fact that patients still run out of treatment options pretty quickly. During my time here, I have seen patients struggle through the same journey as Debbie, and have personally interacted with patients that are taking Keytruda. For many, this medication has made an extraordinary impact.

I am here today to support to keep the accelerated approval for Keytruda. The reasons why is that patients benefited in the third line that have not had IO in the past. It is also shown to be good for third-line patients that can't tolerate additional chemotherapy like older patients, which is a large part of our patient population. Keytruda satisfies one of those unmet needs arising from the lack of options, and it has proven to

benefit many patients.

Thank you for your time. Do you have any questions for me?

(No response.)

MS. GERMANO: I have not received compensation from the sponsor for my presentation today. My name is Terry G.

Good morning, and thank you for having me. In February of 2018, two months before my 80th birthday, I was diagnosed with stage 4 esophageal cancer that had already spread to the liver. The tumor blockage was in the GI junction, part of my esophagus, and I was placed on a feeding tube due to my inability to swallow.

Forty days post-diagnosis, I finally had my first Folfox chemotherapy treatment. Amazingly after the fourth treatment, my tumor shrunk to half its size. I continued with 10 more rounds of Folfox, and then followed that with 22 daily treatments of radiation.

Almost a year into my whole journey in March of 2019, I began immunotherapy. I began receiving

treatments of Herceptin every 3 weeks. Unfortunately, though, about 4 months later, just after 6 treatments, the CT showed signs of tumor reappearing. The suggestion was to do more radiation and pair it up with a different immunotherapy other than Herceptin. That's when I was introduced to Keytruda.

Having gone through a year of heavy-duty treatment at 80 years old, I mentioned to my oncologist and radiologist that I just couldn't physically handle both radiation and Keytruda, and I opted for just Keytruda. It only took a few treatments for the CT to show that I was undetectable, and to this day I still am.

I just turned 82 last week, and I just finished my 30th treatment of Keytruda. I tolerate it very well and only have had some mild side effects along the way. During the first year, I experienced leg sores, but mitigated them with a topical steroid. And more recently, I have had an itchy rash on my entire body, excluding my legs. Again, though, I have been able to manage it with a

steroid.

I am so pleased with the results I have gotten these past two years with Keytruda. I may not be alive today if not for this immunotherapy drug. Our family has been familiar to this disease for the past 27 years, with one of my two daughters having Lynch syndrome. She has battled colon cancer twice already, the first being stage 3 at age 28, stage 1 at 39, and as well as thyroid cancer at 24.

Finally, I would be remiss if I didn't mention Mario, my late husband. Unfortunately and ironically, he passed 11 years ago of stage 4 stomach cancer that had already spread to his liver. The time frame between his diagnosis and his passing was 8 weeks. Mario opted to forego any treatment, but was strong until the very end and with not one complaint.

In closing, I want to say thank you for having been blessed to have both the immunotherapy drugs and the doctors available to my family and myself. Being on Keytruda has allowed me to have a

quality of life that I am familiar with and has extended my life as well. Our family and I are so grateful. Thank you from the bottom of my heart.

DR. REIDY-LAGUNES: Speaker number 3, can you please begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. ZUCKERMAN: Yes. Hi. 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.

Today, I'm speaking from my perspective as a scientist who left Harvard more than 30 years ago to come to Washington DC to work in the House of Representatives. I worked as a congressional investigator for the subcommittee that conducts oversight over HHS, and that's when I first learned about the laws and regulations governing the FDA. I was responsible for several oversight hearings that attracted enormous media attention because we

found that patients had been harmed when the FDA was not following the law pertaining to FDA approval. Again, that was a long time ago.

The law is very clear. Drugs and biologics must be proven safe and effective, and that's defined as having benefits that outweigh the risks for most patients. FDA's memoranda provided to this committee for this meeting, and for each of these indications over the last three days, have made it clear that the data do not support that.

This advisory committee has looked at the data, seen reasons for optimism when looking at non-significant trends, and recommended that the FDA keep drugs on the market that don't meet the standard specified by law. That's your right to do that since you're advising the FDA based on your perspectives, your experiences, and your interpretations of the data.

So I want to thank the FDA scientists who carefully analyze the data and presented their finding. You did a great job. I'm here to urge the FDA to follow in your footsteps and follow the

law, and rescind approval for these indications until the company's complete randomized clinical trials that prove that the benefits outweigh the risks.

I especially want to thank Dr. Pazdur for explaining how the FDA's expanded access program can fill in the gaps for patients who need access. That's a program we've strongly supported at our center.

The companies agreed to complete confirmatory trial as part of the accelerated approval of their drugs, and I strongly urge the FDA to hold them to it. All of these companies are leaders in their field and absolutely capable of conducting the research needed to prove whether or not their drugs have benefits that outweigh the risks for the exact specific indications they were previously approved for.

The companies also have the ability to make expanded access quick and easy. Let's face it. If they don't have the expertise and resources to do the studies and to help with expanded access, who

does?

If the data don't confirm the initial accelerated approval, the companies should work with the FDA to design trials to narrow the indication to figure out which are the patients most likely to be helped and which are the ones most likely to be harmed.

That's it. I don't want to use any more of my slides, and I just want to thank you for the opportunity to speak today.

DR. REIDY-LAGUNES: Speaker 4, can you please begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. KLEMPNER: My name is Samuel Klempner. I'm a GI medical oncologist at Massachusetts General Hospital in Boston, Massachusetts, and I'm speaking on behalf of myself. I have not received any compensation for this presentation, although in the spirit of full transparency, as someone focused in gastric esophageal, I have received advisory compensation from Merck, BMS, and other industry

partners in the field of gastric cancer.

I'm really speaking on behalf of myself, but more on behalf of the gastroesophageal patients who are here in my clinic today. In fact, right now I'm between two advanced cancer patients, one of whom is going to be waiting an extra few minutes. But for the last eight years, I've exclusively focused on caring for gastric and esophageal cancer patients and been lucky enough to see our toolkit expand several times, thanks in part to this committee and the larger FDA.

Having been through cancer with my mother when I was in my 20's and a medical student, I can speak to how reassuring it is as a son and as a caregiver to hear an oncologist talk about having multiple available agents to offer a patient during their journey.

I do know that the gastric and esophageal treatment landscape is changing and will continue to change over the years, but the reality for this disease is that, unfortunately, the timelines for our patients are not measured in years. In fact,

if you took a cross-sectional snapshot of the U.S. gastric and esophageal population right now, several thousand patients on current first-line therapy and second-line therapy, a large portion of them will have passed away over the next 6 to 9 months.

I'd like to recognize ODAC and the FDA more broadly for their role in understanding the aggressive disease that is gastric esophageal adenocarcinoma, then helping to increase the number of available agents. But I would also really like to point out the urgent existing need to maintain our current toolkit.

As practitioners, we deal on the frontline with implementing new approvals and recognize that broad implementation takes time. Looking at my own clinic since the recent front-line pembrolizumab and nivolumab approval, nearly all my patients currently receiving 5-FU and platinum are not receiving a current PD-L1 based on the approval timelines.

I know this not to just be true for my

clinic, but it's particularly true of smaller community practices. I'm lucky enough to practice in a large academic center where we have maximal resources, and change can happen more quickly. But 75 to 80 percent of our patients are actually cared for in the community where we anticipate a further lag before front-line chemo plus PD-L1 is more widely adopted.

All of these IO-naïve patients will continue to progress through first- and second-line therapies, and we will remain a pool of candidates for current third-line pembrolizumab approval. I do have concerns about jeopardizing the toolkit and available options for these patients that continue to be IO-naïve in the first- and second-line setting currently.

Anyone who's been touched by this disease really can understand the morbidity and the cumulative burden of therapy. It's really a relentless disease, and striking a balance of quality and quantity is increasingly important as we go through lines of therapy. And the current

third-line pembrolizumab approval for PD-L1 positive patients has hit this balance for many of my own patients.

As I think you can see, as practice patterns and market research clearly bears out, when a PD-L1 positive patient coming in the third time or later is given a choice between pembrolizumab or chemotherapy, the data really has spoken for itself in terms of the prescribing patterns.

In the last few moments, I really just want to speak to the difficulty of conducting validation studies in the third-line or later populations. The previous speaker made some excellent points, and I fully recognize that no trial is perfect. But when KEYNOTE-059 was designed and initiated, we did have a significantly lesser understanding of what factors may impact PD-L1 responsiveness. What we did know was that there was a huge unmet need in the patient population desperate for more options.

In the years since, we've learned a lot, but third-line activity of pembrolizumab remains in PD-L1 positive patients. I imagine this is quite

clear to the committee, that the evolving landscape and anticipated increase in first-line chemo and PD-L1 will make conducting another third-line PD-L1 trial essentially impossible.

As a clinical investigator and strong believer in trials, I completely understand the rationale and desire for additional data in the third-line space, but I also recognize that this will just not be possible. So we're left with existing data and existing patient population, and we just want to maintain our maximal therapeutic options.

So on behalf of myself and my own patients, and many others, I'm simply advocating for your help in. maintaining the maximal available options for our patients as the landscape continues to evolve. Thank you for the time.

DR. REIDY-LAGUNES: Will speaker 5 please begin and introduce yourself? Please state your name and any organization you're representing for the record.

MR. BEAL: Good morning. My name is David

Beal. I'm a patient of Dr. Enzinger. I have received no financial, whatever, compensation. I met Dr. Enzinger on July 1, 2014. I was given approximately six months to live.

I'm sorry. I'm very emotional. I prepared for this, and it's not working. I am a patient who lives in rural New Hampshire, and my local doctor, when I was diagnosed on May 1st of 2014, told my wife and I that he would provide palliative care for us. I'm a CPA, and I had no idea what palliative care was.

Thanks to Dr. Enzinger, he guided my country physician for 18 months until this trial came along. During my first visit with Dr. Enzinger, he spent an hour with me. And his final words to me were, "You have one job. Your job is to stay alive until I can find a treatment for you," and Keytruda saved me.

I'm sorry. This isn't very productive. I'd just like to point out to the panel as a whole that all these trials include only one thing, people like me. We're numbers on a sheet of paper when

you analyze the trials and their effectiveness. But as the previous doctor just said -- who I've never met and I don't remember his name, from Mass General -- it doesn't make any sense to me, as a layperson and as a patient, for you to take any possible treatment for a patient off the table when it works, even for 10 or 15 percent of the people in the trial.

I expected to know Dr. Enzinger for one Christmas. We have happily met every 3 weeks for 7 Christmases.

My time's up. If anybody wants to ask me a question, I'd be happy to. But I'm so proud to know Dr. Enzinger and all the people at Dana-Farber. My grandchildren thank you and my daughters thank you.

It doesn't make any sense to me to take a treatment off the table that works for some of us. Does it work for everybody? No. But you know what? There's nothing that works for anybody, because to me, and all the different treatments I've had, and all the different nurses I've talked

to, the cancer, all cancers seem to treat everybody just a little differently.

Keytruda works for some of us, and it makes no sense to take it off the table. I'm still on it. I was in full remission after 18 months in the trial. I went back --

DR. REIDY-LAGUNES: I just want to thank --

MR. BEAL: I'm sorry.

DR. REIDY-LAGUNES: No. On the contrary, we do have to move on, but I just wanted to thank you so much for reminding us, those of us who are oncologists, what we do every single day and why we do it. It was a beautiful statement.

MR. BEAL: I'm sorry, and what I –

Clarifying Questions to Presenters (continued)

DR. REIDY-LAGUNES: On the contrary, I want to thank you and all of the speakers today. It was very helpful for us.

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

We will now take the remaining clarifying

questions for all the presenters thus far. Please use the raised-hand icon to indicate that you have a question, and remember to put your hand down after you have asked your question. 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. As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "This is all for my questions," so we can move on to the next panel.

I would say, as you probably have noticed, we are a little bit behind, so I would ask the committee members to keep the questions brief as possible, and I'm going to start with Dr. Halabi.

DR. HALABI: Hi. Susan Halabi. I think someone else answered my concern, but I would like briefly to ask the sponsor if they have any data on potential confounding treatment, post-progression,

from the trial that they could share with us. Thank you.

DR. IBRAHIM: Sure.

Dr. Bhagia, would you like to review the subsequent therapy from our studies? You can do 061 and 062, and 059.

DR. BHAGIA: Pooja Bhagia, Merck clinical.

Can I please see the slide that has the 061 subsequent therapies, showing both the arms, the pembrolizumab arm and the paclitaxel arm?

While that slide is being pulled up, I just want to point out that in KEYNOTE-061, the immunotherapy was about 10 percent in the paclitaxel arm as subsequent therapy, and there were no patients that received immunotherapy in the pembrolizumab arm.

Moreover, as you will see on this slide, when it's shared, the total number of any subsequent therapy was also higher in the paclitaxel arm, as is now projected on this screen, which was approximately 60 percent of the patients, and this was lower in the pembrolizumab arm at

45.9 percent.

Back to you, Dr. Ibrahim.

DR. IBRAHIM: Thank you.

DR. HALABI: Thank you.

DR. REIDY-LAGUNES: Thank you.

Dr. Mitchell has a question.

MR. MITCHELL: It's Mr. Mitchell. I wish it was Dr. Mitchell.

DR. REIDY-LAGUNES: Okay. Mr. Mitchell. Sorry about that.

MR. MITCHELL: A question for the folks from Merck. In the slide that showed the four trials that could possibly serve as confirmatory trials, the year of completion was 2024. But one of the representatives from Merck said there might be data as soon as 1 to 4 years.

Is it possible that there would be confirmatory data from those trials as soon as a year from now?

DR. IBRAHIM: Yes. If you can pull up the slide from the core deck for the four studies?

All the studies have interim analyses built

in, and these are all event-driven. So depending on how quickly the study enrolls, how quickly these events accumulate, that will dictate and trigger the first analysis; so yes, it can be much sooner.

For example, we mentioned KEYNOTE-811, which did have an interim analysis that is under review currently with the agency; so a much earlier time point, but still waiting for the final analysis. So yes, to answer your question, we can have data much sooner than the 1 to 3 years that we're quoting.

MR. MITCHELL: Thank you.

DR. IBRAHIM: Thank you.

DR. REIDY-LAGUNES: Thank you.

We have a question from Dr. Pamela Kunz.

DR. KUNZ: Hi. It's Dr. Kunz from Yale Cancer Center. I have a question for Dr. Lemery. There were a number of comments made throughout that if this approval were removed, that there will be a lag in patients not being able to access third-line therapy. Dr. Lemery mentioned a delay and removal for several months.

Can you please speak to that and if there's precedent to that?

DR. LEMERY: Yes. My understanding is with one of the drugs that was removed, it did take some time to actually take it off the market. I'm not sure if that was due simply to this or other operational factors. Maybe I'll ask Dr. Beaver or Dr. Pazdur if they have experienced it because they've dealt with more withdrawals than I have.

Before I hand the mic over to them, though, I just want to comment on one thing, just to clarify based on the prior answer from Merck regarding the interim analyses. Some of those interim analyses aren't necessarily what we expect for a full regular approval. They may be based on surrogate endpoints and could support an accelerated approval and not a full approval. These studies actually would depend on what the interim analysis was, what the results are, and whether an earlier analysis would support a regular approval.

Dr. Pazdur, do you have anything to add to

Dr. Kunz's question about delaying the timing of withdrawing the accelerated approval from the market?

(No response.)

DR. FASHOYIN-AJE: Steven?

DR. LEMERY: Yes?

DR. FASHOYIN-AJE: Can you guys hear me?

DR. LEMERY: Yes.

DR. FASHOYIN-AJE: This is Lola Fashoyin-Aje. I can maybe chime in before Dr. Pazdur has an opportunity.

I was just going to mention that we do have experience with providing access to therapies that have been previously withdrawn from the market. One recent example is the drug olaratumab, which was withdrawn from market. It was indicated for the treatment of soft-tissue sarcoma.

In that case, it took, I would say, approximately a year, or even longer than that, from the time when we initiated discussions about withdrawal to when it was ultimately withdrawn. And we worked with the company very closely to

ensure that patients had access to treatment, including patients who had recently initiated treatment with the drug.

DR. LEMERY: Yes.

DR. FASHOYIN-AJE: So there is a mechanism for that, so I think that's something that can be easily addressed.

DR. PAZDUR: Yes. I'd like to just chime in. Yes, we would use our discretion on that point and allow maximum availability of the drug while we were negotiating with the company via negotiation of the withdrawal of the indication, so there is flexibility here.

The other point I'd like to make sure that the members of the committee realize, there were four other applications or indications by the companies that make PD-L1 drugs that were withdrawn, and we've had discussions with all of them on this same topic of withdrawal and ensuring the continued availability of the drug.

So we're doing this with the four other indications where they have been withdrawn, and

these companies are stepping up to the plate to ensure that the patients receive these drugs in a timely fashion even though the marketing indications may be removed. So there are discussions on these four indications that have been previously removed.

DR. IBRAHIM: I'd like to clarify my response to Dr. Kunz -- or Mr. Mitchell. Sorry.

KEYNOTE-859, actually its first interim will readout for overall survival, and it could be as early next year. So according to Dr. Lemery's response, that would be for a full approval. So each study is variable, and it depends, but we're confident. And based on the results you're aware of with CHECKMATE-649, this is a similar study, same size, similar population, so we are anxiously awaiting that study to read out.

Questions to the Committee and Discussion

DR. REIDY-LAGUNES: Thank you.

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

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

Today's question is a voting question, and Dr. Takyiah Stevenson will provide the instructions for the voting.

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

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular

button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

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

(No response.)

DR. REIDY-LAGUNES: I will read the voting question. Given the following: low response rate

in third-line setting, a treatment landscape of 13 percent; the treatment landscape has changed with nivolumab approval in the first-line setting on improvement in overall survival; two trials with monotherapy comparisons in the first- and second-line settings do not confirm benefit; and ongoing trials will not assess the monotherapy effect.

The voting question is the following. Should the indication for the monotherapy use of pembrolizumab in PD-L1 CPS greater than or equal to 1 in gastric and GE junction adenocarcinoma, third line or greater, be maintained pending conduct or completion of additional trials?

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

Is there any question about the wording of the question?

(No response.)

DR. REIDY-LAGUNES: Thank you.

Go ahead, Takyiah.

DR. STEVENSON: If there are no questions, we will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

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

(Pause.)

DR. STEVENSON: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down a 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. There are 2 yeses; 6 noes; and zero abstentions.

DR. REIDY-LAGUNES: James Hillard?

DR. HILLARD: Yes. I'm the patient representative, and I was impressed that we -- it's going to be very difficult to come up with monotherapy trials, and we already have nivolumab, which I think has been shown to be effective. On

the other hand, the existing trials are things that will at least give us some indication of the added value of Keytruda.

Particularly, like the KEYNOTE-811 study, I'm a prolonged survivor with HER2 positive. So again, should I relapse, I would be eligible for that study. But prior to its completion, I would like to have the opportunity to try this therapy should I relapse.

DR. REIDY-LAGUNES: Thank you.

DR. HILLARD: Bye-bye.

DR. REIDY-LAGUNES: Susan Halabi?

DR. HALABI: Yes. Susan Halabi. While I do recognize that there is an unmet need, the reason why I voted no is because I found the data not compelling. As was presented, the response rate was low, and then when we look at the risk-benefit ratio, definitely the risks I think outweigh the benefits to the patient.

Also, the fact that the patients will have access to the expanded program also persuaded me for that vote. Then finally, because of the

changing landscape, I wasn't convinced that the monotherapy by itself is going to work with the drug itself. It's not going to work with chemotherapy. I haven't seen much data on that.

A final comment, I really want to commend the FDA for evaluating the whole accelerated approval process. I think that we all need to step back and critically evaluate the strength of the data. Thank you.

DR. REIDY-LAGUNES: Thank you. I had an error.

Dr. Hillard -- or, sorry, Mr. Hillard, could you confirm your vote for the record?

DR. HALABI: Yes. I voted no.

DR. REIDY-LAGUNES: Great.

And James Hillard, can you state your name and the vote, for the record?

DR. HILLARD: Yes. James Hillard, and I voted yes.

DR. REIDY-LAGUNES: Great. Thank you.

David Mitchell, can you state your name and vote for the record

MR. MITCHELL: My name is David Mitchell, and I voted no. I'll take a minute here because this one was really hard.

As a patient with incurable cancer, who's now being given all three major classes of drugs to treat my disease in combination, these issues really cut close to home. My vote was largely based on the changing treatment landscape. Neither Merck, nor the FDA, nor any of the clinicians I heard today believes checkpoint inhibitors should be given first line, and then third line.

We have proven benefits in first line. We have unproven benefits in third line. We need to get pembro to patients with chemo in first line, not delayed to third line. As long as the FDA expanded access programs are effective and efficient to ensure access for the patients who are already past first line, the patients who were described as being in limbo, we can withdraw approval and delay taking the drug off the market, and those folks should be protected.

Someone said it's only about a thousand

patients we're talking about now. Every one of them is important. But in several months, there will be fewer. And between the FDA processes for withdrawal and the company's ability to ensure access, we can protect all of them.

For the patient who is Dr. Enzinger's patient, we're not taking Keytruda off the table. We're going to move it to the place in treatment where it's most effective and proven to work. To protect the safety and well-being of patients, we have to base decisions on data. The data don't support maintaining the indication for third line. Thank you.

DR. REIDY-LAGUNES: Thank you.

Dr. Colin Weekes, can you state your name and vote for the record?

DR. WEEKES: Yes. This is Colin Weekes. I voted no. I voted no because I do not believe the data supports continued use of single-agent pembrolizumab in the third-line setting. I do think that changing landscapes were important and its appropriate use is in the first-line setting

with chemotherapy.

I would say, although I do agree this is very much an unmet need, I think the FDA's approach to delay and working with the sponsor to make sure that all patients who may be caught in this conundrum of not having appropriate exposure to pembrolizumab will be able to do so in an appropriate way to both meet the needs of the patients who have not received access to pembrolizumab, who should; and then as well as the fact that the data just do not support its continued use in the third-line setting.

DR. REIDY-LAGUNES: Thank you.

My name is Diane Reidy-Lagunes. I voted yes, and this was also incredibly hard for me. I actually changed it last minute. I think I did so because in the third-line setting, for those patients that haven't had a PD-L1, I believe the data on 059. I think for those of us who use these therapies often, there is a tail of the curve, and it would be terribly devastating for a patient to not receive the therapy.

Recognizing there are access programs with disparities of healthcare and differences in the way that patients are treated throughout our country, I was nervous that they may not be able to get that. But I think that the potential 859 could have shown an overall survival benefit, but being able to test this in the third-line setting was just going to be too difficult to do.

Having said that, I think that, as my colleagues said, 061 and 062 really did prove that single-agent therapy really does not seem to pan out as compared to combination.

Dr. Christopher Lieu, can you state your name and vote for the record?

DR. LIEU: This is Chris Lieu, and I voted no. I believe the accelerated approval of pembro in the third-line setting was appropriate based on the modest response rate in KEYNOTE-059 and the clear unmet need. But the landscape, as others have mentioned, has clearly changed, and it is highly likely that by third-line therapy, patients will have received some form of immune checkpoint

therapy previously.

Of note, as noted previously, KEYNOTE-061 and 062 are troubling in terms of their lack of positive data, although the data from KEYNOTE-590 are obviously extremely encouraging and also further supports the fact that patients with GE junction cancer will likely have received immune checkpoint therapy, as well as gastric cancer in the front-line setting.

So at this time I don't believe the indication should continue as written. But as also stated previously, given the issue that patients may be in second-line therapy without having received immunotherapy, I think there should be strong consideration given to delaying the removal of this indication, at least for several months, because of this issue. Thank you.

DR. REIDY-LAGUNES: Thank you.

Dr. Mark Lewis, can you state your name and vote for the record?

DR. LEWIS: Yes. This is Mark Lewis. I voted no, and I'm actually going to reiterate many

of Dr. Lieu's points.

I think the landscape of both therapeutics and even companion diagnostics just looks so different now, thankfully, than when the accelerated approval was first granted. I think the timing of this meeting is really providential, coming after the seismic CHECKMATE-649 data and subsequent approval. I think we are going to see immunotherapy move earlier in treatment lines.

Frankly, the main reason I voted no -- and it is not to cast a deaf ear on the unmet needs of the patients who I feel so much for. As a medical oncologist, that's always my first concern, is patient care and meeting those needs.

My main concern is that none of the pending studies, as best I could tell, would definitively answer the question of either monotherapy or the position in terms of lines of therapeutic sequencing of this agent. And given that, I couldn't see any other outcome beyond that this accelerated approval would remain essentially approved ad infinitum. I think one of proponents

for it said, well, for the foreseeable future, and that's not a temporal endpoint that I think is acceptable to this committee, and thus I voted no.

DR. REIDY-LAGUNES: Thank you.

Dr. Pamela Kunz, can you state your name and vote for the record?

DR. KUNZ: Yes. Dr. Pamela Kunz, and I voted no. The benefit of going last, I think all of my colleagues made excellent points. I'd like to just emphasize one; that my main reason for voting no is around the changing landscape. I do, however, believe there is a bit of a gap in terms of patients that are currently on second-line treatment, and also would strongly endorse a delay in removing this from the market for 6 to 12 months.

DR. REIDY-LAGUNES: Thank you.

In summary, our panel has recommended that the accelerated approval and landscape has changed, which is why the group majority have said no, and that we also have given strong recommendations to consider a delay in the removal of the approval.

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

DR. LEMERY: Hi. This is Steven Lemery. I guess I'll start. We thank the committee for their careful deliberation. We want to express that, FDA, we want to take our actions in a patient-centric manner, so we'll think carefully about the approach to go forward in order to work as best we can for the benefit of the patients.

Adjournment

DR. REIDY-LAGUNES: Thank you.

If there are no further comments, we will now adjourn the first topic and break for lunch. We will reconvene at 12:10 Eastern time. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members.

Additionally, those panel members participating in the second topic should plan to rejoin at 12 Eastern -- well, that's 12 now -- to ensure you're connected before we reconvene at 12:10.

DR. STEVENSON: Hello? Dr. Reidy?

DR. REIDY-LAGUNES: Yes?

DR. STEVENSON: This is Takyiah Stevenson. Actually, we will have to reconvene at 12:30 to give the full 30-minute break. Yes. I'm sorry.

DR. REIDY-LAGUNES: That's ok. Thank you.

DR. STEVENSON: Thank you.

DR. REIDY-LAGUNES: Thank you, all.

(Whereupon, at 12:01 p.m., the meeting was adjourned.)