FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Topic 2

Virtual Meeting

Thursday, April 29, 2021

12:31 p.m. to 2:53 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

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Susan Halabi, PhD

Professor of Biostatistics and Bioinformatics

Duke University Medical Center

Durham, North Carolina

Philip C. Hoffman, MD

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

Professor of Medicine

The University of Chicago

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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

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Founder, Patients for Affordable Drugs

Bethesda, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(12:31 p.m.)

Call to Order

DR. HOFFMAN: Good afternoon and welcome. I'd first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Amanda Turney. Her email and phone number are currently displayed.

My name is Philip Hoffman, and I will be chairing this meeting. I will now call the second 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 introductions.

Introduction of Committee

DR. STEVENSON: Good afternoon. 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 affiliation.

Dr. Halabi?

DR. STEVENSON: I'm sorry. We will come back to Dr. Halabi. She's still connecting.

Dr. Hoffman?

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

DR. STEVENSON: Dr. Lieu?

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

DR. STEVENSON: Dr. -- Mr. Mitchell?

MR. MITCHELL: You guys keep trying to give me letters after my name. I'm David Mitchell. I'm the consumer representative on the ODAC, and I am a cancer patient.

DR. STEVENSON: Karen Hoyt?

MS. HOYT: Hi. I am Karen R. Hoyt, and I'm the patient representative and hepatocellular carcinoma survivor.

DR. STEVENSON: Dr. Kunz?

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

DR. STEVENSON: Dr. Lewis?

DR. LEWIS: Hi. I am Mark Lewis, medical

oncologist, director of GI oncology at Intermountain Healthcare.

DR. STEVENSON: Dr. Weekes?

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

DR. STEVENSON: Okay. We'll go back to Dr. Halabi.

Dr. Halabi, if you can hear me, please introduce yourself and affiliation.

DR. HALABI: Yes. Sure. Good afternoon. I'm Susan Halabi, and I'm a biostatistician at Duke University.

DR. STEVENSON: Thank you.

Dr. Kraus?

(No response.)

DR. STEVENSON: Dr. Kraus, you may be on mute.

DR. KRAUS: Oh. Can you hear me now?

DR. STEVENSON: Yes, we can.

DR. KRAUS: Oh, ok. Good. Thank you.

Yes. Hi. Good afternoon. This is Albert

Kraus. I work in research and development, bringing medicines, hopeful new medicines, from the lab to the patient for Pfizer.

DR. STEVENSON: Thank you.

I will now introduce the FDA participants.

Dr. Pazdur?

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

DR. STEVENSON: Dr. Beaver?

DR. BEAVER: Hi. I'm 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. I'm Steven Lemery, a medical oncologist and the acting director of the Division of Oncology 3.

DR. STEVENSON: Okay. I'll hand it back to the chair.

DR. HOFFMAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite

strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during 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 042, trade name Keytruda, pembrolizumab, submitted by Merck Sharp & Dohme, indicated for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib.

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. Philip Hoffman, Christopher Lieu, and Colin Weekes.

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

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

Merck. For the second contract, his employer has received $375,000 to $425,000 with an additional $75,000 to $125,000 anticipated from the firm.

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 committee members and temporary voting members to disclose any public statements that they

have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Albert Kraus is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

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

Thank you, and I will hand it back to the Chair.

DR. HOFFMAN: We will proceed with the FDA's

introductory comments from Dr. Julia Beaver.

FDA Introductory Comments – Julia Beaver

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

I will be giving opening remarks to provide background on accelerated approval and set the stage for your discussions in this session. I 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 to expedite the delivery of promising drug products for serious or life-threatening illnesses that lacked satisfactory treatment, and cancer meets this serious and life-threatening requirement.

Like regular approval, accelerated approval still requires substantial evidence of efficacy and safety. However, for accelerated approval, the efficacy evidence can be based on an earlier endpoint reasonably likely to predict clinical benefit and needs to be an endpoint other than survival or irreversible morbidity.

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

over that of existing therapies, meaning over therapies that are approved under regular approval or set standards of care.

Because of the uncertainty associated with accelerated approval, confirmatory postmarketing trial or trials may be required to verify 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 these trials 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 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, though, 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 the Oncology Center of Excellence continuously evaluate the accelerated approval program to make sure the benefit to patients is maintained, and to increase transparency in the future, we may continue these public discussions 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 and 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 studies, the risk-benefit calculation for these indications may have changed in the contemporary treatment landscape and thus warrant further examination.

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

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

notable that both the small-cell lung cancer and urothelial indications have seen a changing landscape of disease treatment, meaning after these accelerated approvals were granted, alternative anti-PD-1 or 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 the treatment of patients with hepatocellular carcinoma.

There are some key issues for this session we would like the committee to consider. For hepatocellular carcinoma, an alternative checkpoint inhibitor, atezolizumab in combination with

bevacizumab, has demonstrated clear clinical benefit in an earlier line of therapy. 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 does not demonstrate clinical benefit and alternative therapies do, patients may not be served by continuation of the original accelerated approval. In addition, the response rate supporting the accelerated approval was low.

For this approval, FDA oncology took into consideration unmet need and the unusually long durable responses seen with immunotherapy. However, a discussion surrounding accelerated approval based on single-arm trials with low response rate 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. HOFFMAN: Both the Food and Drug

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

For this reason, FDA encourages all participants, including the Merck Sharpe & Dohme's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

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

We will now proceed with presentations from

Merck Sharp & Dohme, immediately followed by the FDA presentation.

Applicant Presentation – Scot Ebbinghaus

DR. EBBINGHAUS: Thank you, Dr. Hoffman.

Good afternoon, members of the committee, FDA. My name is Dr. Scot Ebbinghaus. I'm a medical oncologist and a vice president and therapeutic area head for oncology at Merck. I also led the team during the filing of the KEYNOTE-224 study.

Thank you for the opportunity to present the data that supported our accelerated approval of Keytruda for hepatocellular carcinoma and our progress towards confirming clinical benefit.

In 2018, the FDA granted accelerated approval for Keytruda, or pembrolizumab, for the treatment of patients with hepatocellular carcinoma, who have been previously treated with sorafenib, on the basis of results from a single-arm trial called KEYNOTE-224, a study evaluating pembrolizumab post-sorafenib in patients with hepatocellular carcinoma.

Our postmarketing requirement was to conduct and submit the results of one or more randomized trials to describe and verify the clinical benefits of pembrolizumab as compared to available therapy. Our original planned confirmatory trial was KEYNOTE-240, which was performed in a similar population as KEYNOTE-224. It was a randomized phase 3 study of pembrolizumab compared to placebo and best supportive care.

We are here today because our initial confirmatory trial, KEYNOTE-240, did not meet its endpoint. However, the FDA has agreed on two alternative PMR studies which have completed accrual and could provide confirmatory data within the next year. These studies are KEYNOTE-324 and LEAP-002.

KEYNOTE-394 is a phase 3 trial similar to KEYNOTE-240, but in an Asian population. LEAP-002 is a first-line trial comparing lenvatinib and pembrolizumab to lenvatinib and placebo. This design is consistent with comments from the FDA, both from yesterday and in the briefing book, that

a combination regimen may be used to confirm the benefits for monotherapy accelerated approval.

The FDA stated a filing based primarily on KEYNOTE-394 or LEAP-002 study results seeking to fulfill the PMR could support regular approval. We used our learnings from KEYNOTE-240 to optimize and power these studies appropriately.

To put this into context, I'd like to take you through the timeline of our hepatocellular carcinoma program relevant to today's discussion. When we started our HCC program in mid-2016, we simultaneously launched KEYNOTE-224 and KEYNOTE-240. At this time, there was no available therapy for HCC outside of sorafenib and no treatments that were known to be effective in the second line.

Pembrolizumab received accelerated approval in November of 2018 in second line HCC on the basis of ORR and DOR results from KEYNOTE-224. The results of KEYNOTE-240 read out shortly thereafter. During the enrollment period for KEYNOTE-224 and KEYNOTE-240, the TKI regorafenib and nivolumab

became approved for post-sorafenib in second-line therapy, and additional drugs have been approved since that time.

As you can see, there has been considerable evolution of the treatment landscape since we began clinical development of pembrolizumab in second-line HCC in 2016. Our two additional phase 3 trials, KEYNOTE-394 and LEAP-002, both of which could fulfill the PMR, are fully enrolled and will read out within the next year.

What you're going to hear today is that pembrolizumab remains an important option for the treatment of advanced HCC patients based on benefit-risk profile. The accelerated approval of pembrolizumab, based on KEYNOTE-224, still addresses a significant unmet medical need for HCC patients.

Pembrolizumab had an overall response rate of 17 percent in HCC patients that had been previously treated with sorafenib in KEYNOTE-224. The results were very consistent in KEYNOTE-240. Merck had several options for potential

confirmatory studies which can meet the postmarketing requirements to confirm the clinical benefits of Keytruda. The FDA has agreed that LEAP-002 and KEYNOTE-394 could serve as alternative studies that could confirm clinical benefit.

Finally, you will hear how pembrolizumab is being used in real-world clinical practice and the benefits that it provides for patients. Today, we ask the committee to consider the unmet need and all available evidence when determining whether pembrolizumab should retain its accelerated approval for advanced HCC. We believe that the totality of evidence supports retaining the current accelerated approval.

Next, I'll introduce Abby Siegel, who will present our efficacy and safety data. She will also describe our ongoing clinical development program in HCC to address the postmarketing requirement for our accelerated approval in this space. After this, you'll hear from Dr. Richard Finn, a professor at UCLA who has been involved in many of the key recent trials in HCC and will

discuss his views about the place of pembrolizumab in the current treatment landscape. I will then return to make a few concluding statements.

We're also fortunate to have with us Dr. Mark Yarchoan, an assistant professor at Johns Hopkins who has expertise in liver cancer. He will be available to help answer your questions during the Q&A session.

Applicant Presentation – Abby Siegel

DR. SIEGEL: Thank you, Dr. Ebbinghaus.

My name is Dr. Abby Siegel. I worked with Dr. Ebbinghaus on the KEYNOTE-224 and 240 trials. Prior to joining Merck, I was assistant professor at Columbia University specializing in hepatobiliary oncology. Thank you for the opportunity to speak with you today. I will be showing data supporting our accelerated approval for pembrolizumab and our progress in our confirmatory studies.

As we know, liver cancer is the leading cause of cancer deaths around the world. It's actually the sixth leading cause of death in the

United States with the most rapidly increasing incidence rate and the dismal five-year survival for those with advanced disease of less than 3 percent.

Here you can see the current treatment landscape for advanced HCC. On the left, you can see sorafenib, lenvatinib, and atezolizumab and bevacizumab are now approved in the first-line setting. On the right are the approved second-line therapies.

Importantly, all of the fully approved second-line therapies are anti-angiogenics. The IO second-line therapies, shown in red boxes, are all accelerated approvals. You can also see that the IO therapies have relatively high response rates and prolonged durations of response. These characteristics are not typically seen with VEGF inhibitors.

Importantly, PD-1 monotherapy provides an important option over a PD-1 CTLA-4 combination due to the lower number of grade 3 to 5 adverse events. Further, the benefit of a PD-1 CTLA-4 combination

has not been verified in a confirmatory trial yet in HCC.

Next, we wanted to understand how these therapies are being used in current clinical practice. To better understand treatment patterns, we evaluated IQVIA open-claims data with close to 900 patients in first line and nearly 300 patients in second line to estimate the treatment distribution among all HCC patients in the United States.

The time period here reflects the most recent data available after the approval of atezolizumab and bevacizumab at the end of May of last year. As you can see on the left in the first-line setting, approximately 41 percent of patients initiated an FDA-approved anti-angiogenic tyrosine kinase inhibitor for advanced HCC. In the second-line setting, approximately 41 percent initiated a PD-1 inhibitor-based therapy. PD-1 inhibitors are clearly providing an important option in this setting.

Because it's a rapidly changing landscape, we also evaluated the data by month to understand how practice patterns are changing. This figure presents estimated treatment distributions for the patients, again, who initiated first-line systemic therapy each month from December 2019 to November 2020.

While the estimated proportion of patients initiating PD-1 containing regimens started to increase in early 2020, as we would expect, it has since reached a plateau at around 40 percent. Simultaneously, the estimated use of approved first-line TKI monotherapy among patients initiating first-line treatment decreased as we would expect, but also plateaued at around 40 percent.

These results support that while the uptake of atezolizumab-containing regimens in the first-line setting was rapid after the FDA approval, there remains a need for TKIs in this first-line setting.

Now that we've seen that many patients still receive a first-line TKI monotherapy treatment and need an option if they progress, let's explore the data from KEYNOTE-224, which supported our accelerated approval in second line. This was a single-arm, multicenter trial with 104 patients who were previously treated with sorafenib. Patients received pembrolizumab every 3 weeks until progressive disease and response rate was the primary endpoint.

You can see here that the response rate at the primary analysis, at 15 months median follow-up from the first dose to the data cutoff, was 17 percent and the median duration of response at this point was not reached. After another 16 months of follow-up, on the right, you can see that the median duration of response was now 21 months.

By Kaplan-Meier analysis, shown in the curve on the right, 77 percent of responders had a duration of response of at least 12 months. This longer term follow-up confirms the characteristic

prolonged duration of response that we see with IO agents.

We wanted to see how the safety profile of pembrolizumab in advanced HCC compared with the established safety profile of pembrolizumab, which is represented on the right by the reference safety data set. This is the basis for U.S. prescribing information for all indications.

As an immune checkpoint inhibitor, pembrolizumab is associated with immune-mediated events. These generally occur in about 1 out of 5 patients. They are mostly low grade, but occasionally they can be serious, life-threatening, or fatal. Immune-mediated adverse events can occur in any organ or tissue. The most frequently reported are hypo- and hyperthyroidism. Immune-mediated adverse events are usually manageable with hormone replacement, steroid use, and/or interruption of pembrolizumab.

As expected, in patients with advanced HCC, some categories of adverse events were higher primarily due to hepatic-related events in this

population. However, you can also see that immune-mediated adverse events were generally similar to the established safety profile, highlighting the overall tolerability of pembrolizumab in this patient population.

This is KEYNOTE-240, which was the initial study planned to provide confirmatory data for KEYNOTE-224. Our intent in describing the study to you is not to re-litigate its results, but to explain them enough so that you can see how it informs our other confirmatory trials.

KEYNOTE-240 had almost the same inclusion and exclusion criteria as KEYNOTE-224, except that it was randomized 2 to 1 against placebo. The study had dual primary endpoints of OS and PFS. One-sided type 1 error was controlled at 0.025 across overall survival, PFS, and ORR. OS was assigned an initial one-sided type 1 error rate of 0.023 and a PFS of 0.002.

As you can see, we were very encouraged by the overall survival analysis at a median time from randomization to data cutoff of 21 months. This

analysis showed a hazard ratio at our primary analysis of 0.78. The curves separate early and they remain separated. The difference in medians was about 3 months. A p-value of 0.023 is conventionally low, however, it did not meet the prespecified one-sided boundary for statistical significance, which in this case was 0.0174.

On the right with an additional 18 months of follow-up for median follow-up of 40 months, you can see that this hazard ratio was contained, which was encouraging and, again, suggested a clinically beneficial outcome for patients. In both figures you can also appreciate the tail on the KM curves; again, very characteristic of IO therapies, suggesting that some patients do very well with single-agent pembrolizumab.

At the primary PFS analysis for KEYNOTE-240, this was conducted at the time of the first interim analysis of OS, the hazard ratio was 0.78 with a p-value of 0.0186. Again, the p-value did not meet the threshold for statistical significance prespecified in the protocol, which was 0.002.

Similar to OS, however, the observed difference in PFS was maintained with long-term follow-up as shown in the figure on the right. The hazard ratio estimate was 0.7 and the pembrolizumab curve showed, again, the characteristic tail. Notably, here again, the KM curve for pembrolizumab was consistently higher than the placebo curve in both the primary analysis and the long-term follow-up; again, suggesting long-term benefit for some patients.

In KEYNOTE-240, the overall response rate was 18.3 percent and median duration of response in the pembro group was almost 14 months. This was almost identical to the ORR in KEYNOTE-224, which was 17.3 percent. The DOR in KEYNOTE-224 was not reached at the primary analysis.

This is a summary of adverse events in KEYNOTE-240. The placebo arm shows that the background rate of adverse events is notably high due to the underlying comorbidities in this HCC population. As expected, pembrolizumab has higher rates of some adverse event categories. The

overall rates and severity of immune-mediated adverse events in KEYNOTE-240 were consistent with the pembrolizumab reference safety data set and, as expected, higher in the pembrolizumab arm than in the placebo arm.

The types and frequencies of individual immune-mediated events seen in both KEYNOTE-224 and KEYNOTE-240 were also consistent with the pembro reference safety data set. The rate of hepatitis was slightly higher, as you can see. Immune-mediated events, including hepatitis, were generally manageable with hormone replacement, steroid use, and/or interruption of pembrolizumab.

In summary, the safety data from both KEYNOTE-224 and KEYNOTE-240 support the use of pembrolizumab in patients with advanced HCC.

In KEYNOTE-224, pembrolizumab demonstrated a favorable response rate, duration of response, and a manageable safety profile. KEYNOTE-240 was consistent with KEYNOTE-224 in terms of overall response rate and durability of response. It showed numeric improvements of OS and PFS compared

with placebo but did not reach prespecified p-values on the primary endpoints. However, the hazard ratio was maintained with additional follow-up.

Results for safety were generally consistent with the overall safety profile for pembrolizumab, and we did not see any new safety signals. We believe these data strongly support the benefit-risk profile for pembrolizumab in second-line HCC.

We learned several lessons from KEYNOTE-240. The positive trends in OS and PFS were encouraging, but in retrospect we believe our target hazard ratio for overall survival of 0.65 was too aggressive. Now that we have a better estimate of the treatment effect of pembrolizumab in advanced HCC, we have powered our subsequent studies more appropriately with this in mind. We will now turn our attention to discuss KEYNOTE-394 and LEAP-002.

Here we show the study design for KEYNOTE-394. This trial is fully enrolled. It's a very similar trial to KEYNOTE-240. It's a

second-line trial with 2 to 1 randomization. You can see that the inclusion criteria are almost identical to KEYNOTE-224 and KEYNOTE-240. However, all of the patients in KEYNOTE-394 are from Asia, where, as you know, hepatitis B is a more prevalent contributor to HCC etiology.

The response rate from previous studies with pembrolizumab looks very similar in all etiologies of patients with underlying liver disease. Further, PK studies have shown no difference in Asian patients treated with pembrolizumab.

For these reasons, we believe that KEYNOTE-394 is applicable to a Western population. KEYNOTE-394 is powered to detect a meaningful difference in overall survival with a larger sample size and an assumed true hazard ratio of 0.7 [indiscernible].

Next, I'd like to discuss LEAP-002. This is our first-line trial of lenvatinib and pembrolizumab compared with lenvatinib and placebo. But first I'd like to show you preliminary data from KEYNOTE-524. This is a phase 1B, single-arm

trial of lenvatinib plus pembrolizumab in the first-line setting, which led us to start LEAP-002. We were very excited also by these data, which showed a response rate of 37 percent and a median duration of response of over a year and overall survival in the front-line setting of over 22 months. This combination has received an FDA breakthrough designation.

It is interesting to note that KEYNOTE-524 was under FDA review at the time of the IMbrave150 approval. As you can see in the table on the right, our data were comparable with the atezolizumab and bevacizumab result, and these data give us confidence in LEAP-002.

Here is the schema for LEAP-002. It's a global phase 3 study, and patients were randomized 1 to 1 to lenvatinib plus pembro or lenvatinib plus placebo. Last patient was enrolled on April 28, 2020. The final analysis will be in 2022 with several interim analyses before that.

As with KEYNOTE-394, LEAP-002 has been discussed with the FDA and agreed upon as a

possible confirmatory trial for KEYNOTE-224. This is an add-on study design that will clearly demonstrate the contribution of pembrolizumab in the treatment of the HCC. As mentioned by Dr. Ebbinghaus, this design is consistent with the comments from Dr. Pazdur yesterday, that a combination regimen may be used to confirm the benefit for a monotherapy accelerated approval. It also has a hazard ratio of 0.75 or overall survival based on our understanding of the efficacy of pembrolizumab in HCC.

Now I will introduce Dr. Rich Finn, a professor at UCLA and a global expert in the HCC field. He will describe how pembrolizumab continues to play a role in clinical practice.

Applicant Presentation – Richard Finn

DR. FINN: Thank you very much, Dr. Siegel.

I'm Dr. Richard Finn, a medical oncologist from UCLA. I helped develop and participated in both KEYNOTE-224 and KEYNOTE-240, and it is a real privilege to be here today to present a clinical perspective on the accelerated approval of

pembrolizumab and its role in the treatment of advanced liver cancer. I'm a paid consultant for Merck, but I have no financial interest in the outcome of this meeting. My interest is in improving the care of patients with cancer, including breast and liver cancers.

I played a lead role in the accelerated and full approval of palbociclib in advanced ER-positive breast cancer, and I've had leadership roles in the development of most of the drugs approved for the treatment of HCC. This includes most recently leading the approval of atezolizumab and bevacizumab in the front-line setting.

The treatment landscape in advanced liver cancer has changed in the past several years. Atezolizumab and bevacizumab is now a standard of care for many patients in the front-line setting. However, given the known toxicity of bevacizumab, many of us estimate that about 15 to 20 percent of patients will not be candidates, and for that reason will receive single-agent tyrosine kinase inhibitors in the front-line setting.

Things we are concerned about in the liver cancer population include bleeding, which can be seen with bevacizumab, as well as hypertension, proteinuria, and ischemic event. Single-agent PD-1 inhibitors in the second line offer an alternative to TKIs for patients based on their adverse event and safety profile, higher response rate, and prolonged duration of response, which are unique to IO therapy.

Here you see the current thought process for a clinician dealing with a patient with advanced liver cancer. Patients who are eligible will receive first-line atezolizumab and bevacizumab. After progression, these patients have the option of second-line TKI.

Keep in mind, none of the currently approved drugs in the first- and second-line setting have been studied after atezolizumab and bevacizumab. Again, based on the toxicity profile of atezolizumab and bevacizumab, at least 15 to 20 percent of patients would not be eligible for

this treatment in the frontline, in which case they would get either sorafenib or lenvatinib.

Here we can see the actual exclusion criteria for the IMbrave150 study. These provide a bit more granularity to the population who cannot receive atezolizumab and bevacizumab. Because of the concerns around cardiovascular, bleeding, and clotting events, these patients were excluded. In addition, some patients who initially start on atezolizumab and bevacizumab will have to stop treatment because of toxicity. For them, the choice will be between VEGF receptor inhibitor or IO.

Now, for that 15 to 20 percent of patients who are not candidates for first-line atezolizumab and bevacizumab, or cannot tolerate it, sorafenib or lenvatinib are appropriate front-line options. At progression, we must make a decision either to continue with anti-VEGF therapy or give the patient an immunotherapy with either pembrolizumab or nivolumab or of nivolumab and ipilimumab, all of which currently have accelerated approvals.

Things that we consider when choosing IO therapy are response rate, duration of response, and side-effect profile from their first-line therapy. Toxicities including hand-foot-skin syndrome; diarrhea; anorexia; abdominal pain; hypertension; and proteinuria are seen with the TKIs, but these side effects are not as common or severe with single-agent IO, including pembrolizumab.

While IO-IO combinations such as ipilimumab and nivolumab may have a higher response rate, they are associated with a higher frequency of clinically significant adverse events, which are difficult for many patients with liver cancer being treated in the second line and can be a challenge for them to tolerate.

Let me give you a few examples from actual patients in the clinic that would be considered candidates for single-agent IO in practice. Factors that put each patient at increased risk for adverse events with atezolizumab and bevacizumab are highlighted in each example.

A 65-year-old patient with chronic hepatitis C, portal hypertension, a platelet count of 45 with recurrent varices that have been recently treated, the patient is Child-Pugh A with a large tumor, with right portal vein invasion and lung metastases. This patient gets lenvatinib but then progresses with increased size and number of lung metastases.

Another patient is a 67-year-old patient with chronic liver disease from non-alcoholic steatohepatitis. They are well compensated but has diabetes, coronary artery disease with a stent being placed within the last year. They're on aspirin, a statin, and beta blockers. This patient started sorafenib but eventually has progressive disease in the liver with enlarging lesions and the development of macrovascular invasion.

Another patient, a 58-year-old gentleman with hepatitis B, was found to have a very large liver cancer that had ruptured. They undergo transarterial chemoembolization to control bleeding and then starts lenvatinib. The patient has weight

loss, anorexia, and diarrhea, and eventually progresses with peritoneal disease and new liver lesions.

For all these patients, there is a need for a front-line TKI, and when they progress on their front-line therapy, I wouldn't hesitate to give them pembrolizumab monotherapy. What gives me the confidence to recommend pembrolizumab in these situations is because pembrolizumab has demonstrated a meaningful clinical benefit.

Here you see the studies that provide high-level evidence for drugs that have randomized data in the second-line setting. As you can see, regorafenib, cabozantinib, and ramucirumab, these studies all demonstrate an incremental improvement in overall survival that was statistically significant and supported the full approvals by the FDA. None of these were tested in the post-lenvatinib setting or post-atezolizumab and bevacizumab's approval, demonstrating the knowledge gaps that exist given the rapid changes in the treatment landscape over the past three years.

KEYNOTE-240 provided a median survival in the treatment arm of just under 14 months and a survival of 10.6 months in the placebo arm. The incremental benefit of 3.3 months with pembrolizumab is consistent with what we saw with the TKI. While not statistically significant, when coupled with the safety profile, these data are clinically meaningful and justify keeping the accelerated approval for pembrolizumab.

Most clinicians believe that the results of KEYNOTE-249 confirm the activity of pembrolizumab in advanced liver cancer, and these results are clinically meaningful. Specifically, a response rate of 18.3 percent, seen in this randomized phase 3 study, is consistent with the data that supported the accelerated approval in KEYNOTE-224, a high response rate with a long duration of response.

Acknowledging that the study did not reach its predefined statistical cutoff for positivity, the KM curve for 240 shows a clear separation between the pembro and the placebo arms, and they

remain separated throughout the course of follow-up. You can see from the long-term follow-up from KEYNOTE-240 that there is clearly a group of patients that do not progress over a period of years and maintain a long survival.

Pembrolizumab has an important role in the management of patients with advanced liver cancer, specifically those that do not get IO in the frontline and for patients who are looking for a different side-effect profile from the TKI.

Here you can see the toxicity profiles of the anti-angiogenic drugs which have full approval in the second-line setting. As you can see, the toxicities are very different from what you see with pembrolizumab. Although immune-related adverse events can be seen with IO therapies, many patients tolerate single-agent IO better than tyrosine kinase inhibitors. As with the common adverse events for the VEGF targeting agent, the immune-mediated adverse events are well characterized, and management strategies are now familiar to the clinician community.

Again, while KEYNOTE-240 did not meet its primary endpoint, it confirmed the activity of pembrolizumab that was seen in the phase 1B KEYNOTE-224 study that supported its accelerated approval. When coupled with the differences in side-effect profile compared to the TKIs, this makes keeping pembrolizumab approved a priority because it is an important option for our patients.

I and other clinicians feel strongly that single-agent pembrolizumab fulfills an unmet need in clinical practice. As mentioned, at least 15 to 20 percent of patients will not receive atezolizumab and bevacizumab in the front-line setting, and for those patients, first-line TKIs have been shown to improve survival.

At progression, a decision whether to continue with a TKI or offering them and IO agent remains an important decision point. Pembrolizumab has shown that it can lead to meaningful tumor response and long-term disease control. Patients, like in the examples I described, depend on

pembrolizumab as a second-line option with a favorable safety profile.

It does not appear to be any benefit to removing access to pembrolizumab at this time while we wait for the results of confirmatory trials, which will read out very soon. Lenvatinib and pembrolizumab in particular show exciting data with response rates of 36 percent. Results of LEAP-002 are eagerly awaited. Thank you for the opportunity to present this clinical perspective. I will now pass it back to Dr. Ebbinghaus to summarize.

Applicant Presentation – Scot Ebbinghaus

DR. EBBINGHAUS: Thank you, Drs. Finn and Siegel.

I'd like to conclude today with key highlights that you heard. I want to reiterate that Merck is committed to evaluating pembrolizumab in hepatocellular cancer. We've initiated seven trials with monotherapy or combinations, and specifically have four ongoing phase 3 pembrolizumab-containing clinical trials across

multiple patient populations in hepatocellular cancer.

In conclusion, there remains an unmet need for patients who are not clinically suitable for atezolizumab and bevacizumab in first-line HCC and progress after a first-line TKI treatment. Pembrolizumab has shown clinical activity and a manageable safety profile, which is consistently observed over multiple studies.

The data from KEYNOTE-224 and KEYNOTE-240 are remarkably consistent with respect to ORR and DOR. Merck is committed to serving patients with HCC through a robust development program. Immunotherapy has already transformed the treatments in HCC, and we have two PMR studies fully enrolled, LEAP-002 and KEYNOTE-394, which will read out soon.

In the meantime, pembrolizumab fulfills an unmet need and should remain FDA approved for appropriately selected second-line HCC patients. Thank you for your attention, and this concludes the sponsor's presentation.

DR. HOFFMAN: Thank you.

We will now proceed with the FDA presentation from Dr. Steven Lemery.

FDA Presentation – Steven Lemery

DR. LEMERY: Good afternoon, Chairperson and members of the committee. Hello. My name is Steven Lemery, and now I will discuss the first of two applications for checkpoint inhibition for the treatment of hepatocellular carcinoma. This session will focus on pembrolizumab as monotherapy, and the following session will focus on nivolumab as a monotherapy.

Note that nivolumab in combination with ipilimumab has a separate accelerated approval in the second-line setting. This later combination regimen of nivolumab and ipilimumab is not considered a dangling accelerated approval indication and will be maintained as an immunotherapy treatment option at this time, regardless of the results of today's ODAC meeting.

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

treat a serious condition, provide 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 are underway to verify and describe the anticipated benefit, and such approvals may be subject to withdrawal if trials fail to verify benefit or if the risk-benefit assessment is not favorable.

As a reminder, pembrolizumab has received accelerated approval for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib. Here, I will highlight a few concerns relevant to the hepatocellular cancer indication.

First, the response rate of pembrolizumab in KEYNOTE-224 which supported approval is low, at 17 percent, albeit with some patients having long durations of response. Secondly, one study of pembrolizumab versus placebo in the second-line setting did not confirm benefit. The third topic is that the treatment landscape of hepatocellular

carcinoma is changing given the results of Study IMbrave150 that demonstrated an improvement in survival when atezolizumab and bevacizumab was compared to sorafenib.

Although there may be an argument that checkpoint inhibition may be appropriate after sorafenib in patients deferred from atezolizumab and bevacizumab due to the risk of bleeding, one potential limitation of this argument is that such patients were not physically studied in KEYNOTE-224, the study that was the basis for the accelerated approval of pembrolizumab.

Finally, we ask the committee to consider the ongoing alternative studies of pembrolizumab in HCC and whether they can confirm benefit. Furthermore, by maintaining the second-line monotherapy indication, is this considered an endorsement that may be an acceptable alternative to patients in lieu of receiving checkpoint inhibition in the first-line setting where there is a survival benefit for atezolizumab and bevacizumab?

Prior to discussing the effects of pembrolizumab, I will briefly discuss the current systemic changing landscape in advanced metastatic HCC. Sorafenib was approved in 2007, and for many years represented the only approved systemic therapy for advanced HCC based on improved survival versus placebo in the SHARP trial. In this setting, multiple drugs have demonstrated survival improvements after treatment with or progression on sorafenib, including regorafenib, cabozantinib, and ramucirumab.

In 2018, lenvatinib was approved for advanced HCC, joining sorafenib as an approved agent in the first-line setting. Although the second-line drugs were not studied after lenvatinib, they may be using in clinic off label. With the exception of pembrolizumab and nivolumab alone, or in combination with ipilimumab, the approved second-line drugs have VEGF inhibiting effects.

HCC is a complex disease to treat, and my presentation is simplified. Clinicians must

consider not only the cancer but hepatic function, sequelae of cirrhosis, and other patient factors. The vast majority of clinical trial data have been in patients with relatively preserved hepatic function with Child-Pugh A classification. Typically, such patients will not have hepatic encephalopathy and no ascites, or at worst, mild ascites. Patients with cirrhosis may have other complications such as portal hypertension and varices, which are considered when determining what treatment to offer patients.

To support approval of pembrolizumab, Merck submitted the results of Study KEYNOTE-224, which was an open-label, single-arm study that assessed the effects of pembrolizumab in patients with advanced HCC whose disease progressed on sorafenib or in patients who could not tolerate sorafenib.

KEYNOTE-224 enrolled patients with Child-Pugh A scores and excluded those with hepatic encephalopathy, clinically evident ascites, or esophageal or gastric bleeding within the past six months. The primary endpoint of KEYNOTE-224 was

overall response rate per RECIST 1.1 based on central review.

KEYNOTE-224 enrolled patients with a variety of risk factors for hepatocellular carcinoma. The population of Study 224 largely consisted of patients with Child-Pugh A5 scores. Additionally, only 17 percent of patients in the trial had vascular invasion, which is a high-risk feature in HCC, although 64 percent had extrahepatic disease.

FDA granted accelerated approval to pembrolizumab in 2018 based on the results of KEYNOTE-224, following the approval of nivolumab in 2017. The observed response rate in KEYNOTE-224 was 17 percent in 104 patients.

The response rate observed in the single-arm trial was low, however, some patients had long durations of response with at least half of the responding patients having responses of at least a year. Use of response criteria did not appear to have a notable impact on the results, with the response rates similar using a modified RECIST for HCC or immune RECIST.

As per the conditions of accelerated approval, FDA required that Merck conduct a study to verify the benefit of pembrolizumab. Merck proposed Study KEYNOTE-240 as a planned confirmatory trial. KEYNOTE-240 was a multicenter, multinational trial with 2 to 1 randomization of pembrolizumab versus placebo in patients with HCC who received prior sorafenib.

Note that this placebo-controlled study was designed prior to the approval of other drugs such as regorafenib in the second-line setting. Patients with esophageal gastric or variceal bleeding within the past six months were excluded. The study was designed with co-primary endpoints of overall survival and PFS with alpha split between them.

The baseline characteristics of Study 240 were generally balanced. Most patients were men, and like Study 224, the study enrolled patients with a variety of HCC risk factors, and a majority of patients had a Child-Pugh A5 score.

This slides shows the overall survival

results as described in Merck's section of the briefing document. The turquoise Kaplan-Meier curves are for pembrolizumab. The p-value and statistical significant thresholds shown are one-sided. The study did not demonstrate a statistically significant effect on overall survival given the alpha spending approach that was prespecified. Likewise, the results for PFS were not significant given the study's alpha spending approach. Again, the turquoise Kaplan-Meier curves are for pembrolizumab.

The other consideration of the pembrolizumab indication is a 2020 regular approval of atezolizumab and bevacizumab based on the results of Study IMbrave150. This study demonstrated an improvement in overall survival when atezolizumab and bevacizumab were compared to sorafenib in the first-line setting.

One consideration of this regimen is with respect to the risk of bleeding. IMbrave150 excluded patients if they had variceal bleeding within 6 months prior to treatment, untreated or

incompletely treated variceal bleeding, or a high risk of bleeding. Patients were also required to undergo an EGD within 6 months prior to treatment. KEYNOTE-224 also excluded patients with esophageal or gastric bleeding within the past 6 months but did not specify the other more restrictive criteria.

There are arguments in the briefing document that checkpoint inhibition may be an alternative to anti-VEGF-based therapy in patients at high risk of bleeding, including those with varices. However, it is not clear that these patients at a high risk of bleeding were adequately studied in KEYNOTE-224.

Additionally, prior to the regular approval of atezolizumab and bevacizumab, in March of 2020, FDA granted accelerated approval to nivolumab in combination with ipilimumab based on a response rate of 33 percent in a cohort of patients dosed in a nivo-1/ipi-3 arm, supported by similar response rates observed in other nivolumab-ipilimumab dosing arms.

Because this indication has accelerated

approval, it is not considered an available therapy for the purposes of the pembrolizumab indication, however, it provides another example of the development of combination regimens in HCC. Furthermore, as I stated before, the combination regimen of nivolumab and ipilimumab is not considered a dangling accelerated approval indication and will be maintained at this time, regardless of the results of today's ODAC meeting or FDA's assessment of the pembrolizumab or nivolumab monotherapy indication.

Given that Study KEYNOTE-240 was not successful, Merck is proposing two trials to potentially serve to confirm the clinical benefit of pembrolizumab. KEYNOTE-394 has a similar design to KEYNOTE-240, however, it is a larger study conducted solely in Eastern Asia, with differences between studies and risk factors among the population with hepatocellular carcinoma. Additionally, a subgroup of patients in KEYNOTE-394 will have received prior Folfox rather than sorafenib. KEYNOTE-394 also excludes patients with

esophageal or gastric variceal bleeding within the prior 6 months.

In addition, Merck is also proposing Study LEAP-002 as an alternative. This study will isolate the effect of pembrolizumab when added on to lenvatinib in the first-line, systemic setting. However, the result of this combination study may not be applicable to the use of pembrolizumab as monotherapy in the second-line setting, especially considering the potential for synergism or checkpoint inhibition and VEGF inhibition in the HCC.

Furthermore, if KEYNOTE-394 is not successful, it would represent two negative trials versus placebo in the second-line setting, which would appear to be more relevant to the use of pembrolizumab as monotherapy than the results of Study LEAP-002. Importantly, as shown on this slide, the results of these studies are expected to read out soon.

In the benefit-risk assessment, pembrolizumab's main effect observed to date is the

17 percent response rate in previously treated patients with HCC, with some patients having long durations of response. Reduction in tumor size may benefit some patients clinically, however, this does not mean that all responding patients will benefit.

This effect on response rate comes with a cost of the potential development of an immune-mediated adverse event. Atezolizumab in combination with bevacizumab is approved in the first-line setting, however, some patients may be deferred from this regimen, particularly those with a high risk of bleeding due to varices. An uncertainty is that these patients were not systematically studied in KEYNOTE-224 unless they had more severe liver disease, which would alter the risk-benefit assessment.

Given the changing landscape, it is worth considering how would we view an application submitted today for a single-arm trial of a checkpoint inhibitor therapy with a response rate of 17 percent in patients who had not received

prior atezolizumab and bevacizumab. Such an application would likely need to be based on the results of a study, with a population, a priori, that would clearly not be appropriate for treatment with bevacizumab, and would also have to address other approved drugs in the second-line setting or enroll patients without available therapy. Recall that for accelerated approval, a drug is approved on an early or intermediate endpoint and reasonably likely to predict benefit in the context of an advantage over available therapy.

Before I show the voting question, I will again show this slide of the ongoing trials of pembrolizumab in hepatocellular cancer. Again, Study 394 is similar to Study 240, but is larger and is being conducted solely in Eastern Asia. Although LEAP-002 will isolate the effect of pembrolizumab in combination with lenvatinib in the first-line setting, and we have allowed studies in different settings to inform results with accelerated approvals in the past, if KEYNOTE-394 is negative, it is unclear if LEAP-002 would be

relevant to the monotherapy setting, as there would not be one but two negative trials versus placebo in the exact same second-line setting.

Here is the voting question. Given the following: the low response rate of monotherapy in the post-sorafenib setting; treatment landscape has changed with an overall survival benefit of an alternative checkpoint inhibitor, atezolizumab, in combination with bevacizumab in the first-line setting; and that benefit has not been confirmed in the same post-sorafenib setting in KEYNOTE-240, should the indication for monotherapy use of pembrolizumab in patients previously treated with sorafenib be maintained pending conduct or completion of additional trials?

If the answer is yes, please discuss after the vote what ongoing or alternative trials, including whether KEYNOTE-394 in the same setting, may serve to confirm clinical benefit. Thank you.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you.

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

Dr. Lieu?

DR. LIEU: Hi. This is Chris Lieu from University of Colorado. I have one question for the Merck team, just a clarification in regards to KEYNOTE-394. I know that enrollment is complete. When do you expect final results or at least some sense of overall survival results to be available?

DR. EBBINGHAUS: Dr. Lieu, we expect that in

approximately June or July of this year. As you can appreciate, these final analyses, or these analyses, are event-driven analyses, so the precise timing can't be completely predicted. But we are currently running on our projections to have the final overall survival analysis results in June or July of this year

DR. LIEU: Thank you.

My next question is for the FDA. In regards to the thought that approximately 15 to 20 percent of patients with advanced hepatocellular carcinoma are not eligible or may have a contraindication to receive bevacizumab in that setting, my question is largely in regards to the clinically meaningfulness of that population size.

How does the FDA perceive the percentage of patients unable to receive atezolizumab and bevacizumab in the front-line setting?

DR. LEMERY: I don't think we typically look at a population size when we're thinking about whether a drug may address an unmet need. Sorry. This is Steven Lemery.

The one thing that we brought up in our presentation, though, is were those patients adequately studied. In general, a patient with a higher risk of bleeding or who may be deferred from bevacizumab probably has advanced cirrhosis rather than the majority of patients who had Child-Pugh A5 scores in KEYNOTE-224.

I think that's one of the things that we're bringing up. We don't say that it's just because you have a small population size, that a drug that addresses that small population size wouldn't address unmet need.

DR. LIEU: That's very helpful. Thank you --

DR. BEAVER: And --

DR. LIEU: -- very much. I have no further questions. Oh. Sorry. Go ahead.

DR. BEAVER: Sorry.

Steven, just to add -- this is Julia Beaver, FDA -- I think the key point is that if we were to view this accelerated approval in the contemporary treatment setting, despite the fact that was

provided regarding the number of patients that may not be receiving atezo-bev in the front-line therapy, we would need to consider atezo-bevacizumab as available therapy and recognize that there is no data for pembrolizumab treatment in patients not appropriate or not getting the atezolizumab-bevacizumab combination.

As we cannot create indications when patients have not been studied, in the current day, this accelerated approval would not be appropriate to grant.

DR. LIEU: That makes a lot of sense. Thank you very much. I have no further questions.

DR. HOFFMAN: Okay. This is Philip Hoffman. Maybe this is just a real-world question relative to the approval of the atezolizumab and bevacizumab. But if that's approved as a first line, is anyone verifying or monitoring that the combination itself is actually being used?

Could one, as the physician, say, "Well, I'd like to use first-line immunotherapy. There's an approval for atezo and bev. I think I'll skip the

bev because I think there's a contraindication in a particular patient"?

I don't know where that runs up against the insurers and such. I don't know whether the company has any thought about that. I realize that from a legal standpoint, we would be permitted to do it as a physician.

DR. EBBINGHAUS: Dr. Hoffman, since we have several very distinguished liver cancer experts, I'd like to call on Dr. Finn to address that question.

DR. FINN: Thank you. Richard Finn from UCLA. When I see a patient now, given the benefit of atezo-bev, I need to ask myself why am I not going to give this patient this regimen. That in mind, as I commented, about 15 to 20 percent of patients will not be candidates largely because of the bev's contribution. In practice, I do not use single-agent atezolizumab. It hasn't been labeled in that indication, and typically those patients would get a TKI.

Now, having the option of IO beyond

frontline, as we discussed, is a very important option for patients because of the response rate. And I respect the opinion that it is low, but when compared to the TKIs, where we have single-digit responses, given an overall survival proven advantage, which is ultimately the most important thing, for patients with bulky tumors and symptomatic tumors, having the option of something in second line that can give them a response that is long lasting is very important for us to discuss with our patients. Thank you.

DR. HOFFMAN: Okay. Thank you.

Dr. Kunz?

DR. KUNZ: Yes. This is Dr. Pamela Kunz from Yale Cancer Center. I have a question for the Merck team. I wondered if you could comment about KEYNOTE-394 and the patient population that's being studied in terms of it being an all East Asian population, and if that were to be a positive study, how that would apply more broadly to a western population. Thank you.

DR. EBBINGHAUS: Yes. I'll ask my

colleague, Dr. Siegel, to specifically address that question. I'll just quickly remind everyone that the eligibility criteria were quite similar between the two trials, but I'll have Dr. Siegel address that more specifically.

DR. SIEGEL: Thanks, Dr. Ebbinghaus.

Slide up, please. I think one way to address that question is to look at KEYNOTE-240, where actually we did have a relatively large percentage of patients from East Asia, not including Japan, although we did not have patients from China.

So you can see, on the right for instance, response rate by viral status, so hepatitis B, hepatitis C, and uninfected. This has been our primary surrogate for response, and you can see --

DR. EBBINGHAUS: Dr. Siegel, I'm sorry to interrupt. I'm not seeing your slide. I don't know if the slide is up or not.

DR. SIEGEL: Slide up?

DR. EBBINGHAUS: Thank you.

DR. SIEGEL: Can people see it now? Okay.

Sorry about that.

This is the East Asian population of KEYNOTE-240. You can see here, both on the left side, that the region, Asia without Japan versus Asia with Japan, response rates were [indiscernible], as were response rates by viral status.

I can say specifically with respect to your question around 394, it was mentioned by Dr. Lemery that we did elect Folfox, an oxali-based regimen. But that was only seen in 8 to 9 percent of patients; so really not seen in very many patients.

Finally, PK, that's not [indiscernible – audio distorted] going to differ between Asians and non-Asians, and we have some data to support that if you'd like to see it. So we have no reason to expect that efficacy would be different in the 394 population compared [indiscernible] to what we saw in 240.

DR. EBBINGHAUS: Dr. Finn would like to add some commentary as well.

Dr. Finn?

DR. FINN: Yes. Thank you.

As Dr. Siegel commented, with the IO agents across all of these studies that have been done, there's not been a demonstrated difference between etiology and region. In looking back across all the drugs approved in liver cancer, all of them are generally global studies now and stratify for these things.

The one thing to keep in mind is the approval of sorafenib. That was conducted after two phase 3 studies, one in North America in Europe, the SHARP study, and then an Asia-Pacific-only study; and the magnitude of benefit in both of those studies was exactly the same, a hazard ratio of about 0.68. Thank you.

DR. EBBINGHAUS: Thank you, Dr. Finn.

DR. HOFFMAN: Is that all for your question, Dr. Kunz?

DR. KUNZ: Yes. Thank you. That's all.

DR. HOFFMAN: Okay.

Dr. Weekes?

DR. WEEKES: I had the exact same question

as Dr. Kunz; at least one of my questions was the same question. My second question is for the liver cancer specialists.

In the setting where I agree that having IO options for patients in the second-line setting is important, I guess from a point of view of we've got pembrolizumab and we've got nivo in the same setting, from your point of view as treating these patients, is there any difference in using nivo versus pembro as monotherapy in the second-line setting for these patients? This would be for Dr. Finn.

DR. EBBINGHAUS: Yes, sure. Since we haven't heard from Dr. Yarchoan yet, I was going to ask him to comment first. But I could ask Dr. Finn and Dr. Yarchoan to both --

DR. WEEKES: Either is fine.

DR. EBBINGHAUS: -- comment.

DR. FINN: Hi. It's Richard Finn. I'll comment real quickly.

I have played a pivotal role in the development of both these agents. You saw I was

the lead accrue in the United States for the confirmatory 459 study, which you will hear about later, for nivolumab. I think the totality of the data with single-agent nivo and single-agent pembro in the phase 3 studies does confirm that these drugs are active and they have very similar single-agent response rates and very similar toxicity profiles. So really, it is physician choice there.

DR. EBBINGHAUS: Thank you.

Dr. Yarchoan, would you care to add?

DR. YARCHOAN: Hey. This is Mark Yarchoan. I'm a medical oncologist at Johns Hopkins, and I lead our HCC program here. Just because it's the first time I'm speaking, I'll just clarify for the record that my conflicts of interest, I have received research support from Merck in the past, but I have declined any personal compensation related to my participation in this meeting, and I have no personal financial interest in the outcome of this meeting.

I agree with Dr. Finn, really, that the

totality of the data does not seem to show any major difference between nivolumab and pembrolizumab as single agents. I will say that during COVID, sometimes the longer 6-week dosing availability of pembrolizumab was useful in select cases, but otherwise I think these agents are quite similar.

DR. EBBINGHAUS: Thank you, Dr. Yarchoan and Dr. Finn.

DR. HOFFMAN: Does that conclude your questions, Dr. Weekes?

DR. WEEKES: Yes. Thank you. I have no further questions.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Yes. Thank you. Susan Halabi. I have a few comments for the sponsor's clarification here.

For KEYNOTE-224, I haven't seen any survival data. Do you have that available?

(No response.)

DR. SIEGEL: Scot, can you hear us?

DR. EBBINGHAUS: Can you hear me?

DR. SIEGEL: Yes.

DR. HALABI: Yes.

DR. EBBINGHAUS: Okay. Sorry. My microphone seems to have been muted or unmated.

Yes, we do have overall survival data from KEYNOTE-240, and I'd ask Dr. Siegel to review that.

DR. SIEGEL: Sure.

DR. HALABI: Sorry. To clarify, the question was --

DR. EBBINGHAUS: Sorry; 224.

DR. HALABI: -- for KEYNOTE-224, yes

DR. EBBINGHAUS: Correct. Sorry.

DR. HALABI: Thank you.

DR. SIEGEL: Slide up, please.

You can see here the PFS and OS survival curves.

DR. HALABI: Okay. Do you have an explanation why this is a little bit lower than the other trials?

DR. SIEGEL: No specific explanation. I will say the patients were a teeny bit older. They were mostly recruited from Europe. But overall,

these data are quite consistent, we think.

DR. EBBINGHAUS: Yes. I agree. I think our interpretation is within the variability that you might see between two different studies. They're pretty comparable. The median overall survival was about 13 months in KEYNOTE-240, and it's 12.9 months here. So we interpret these to be really quite similar.

DR. HALABI: Okay. Then I have a next question. I know you've mentioned earlier about the LEAP trial, but the trial had two co-primary endpoints, so that when you talk about the interim analysis happening in June or July, is it going to be based on both endpoints, PFS and OS, or could you share this with the panel members?

DR. EBBINGHAUS: Just to clarify, when we were saying June or July, we were talking about the final overall survival analysis of KEYNOTE-394. The completion for LEAP-002 is expected about a year from now. But as you suggested, there certainly is an upcoming interim analysis, which will be considered the final analysis for

progression-free survival and the first interim analysis for overall survival, and that's upcoming actually in quite the near future.

DR. HALABI: Okay. Then I wanted to make one comment and, again, maybe this is out of place. But as a statistician I think, in my opinion, it's inappropriate to report p-values for KEYNOTE-240 with longer follow-up time because your primary analysis was completed.

I wanted to hear why this was done, unless I'm misunderstanding both slide 17 and 18, because you have the primary analysis and then you have long-term follow-up. And as you could tell, it was expected that the median is not going to change, but you have a tighter confidence interval around the hazard ratio.

So unless I'm misunderstanding that, you have more events with a longer term follow-up but that's really not your final analysis. Okay.

DR. EBBINGHAUS: Yes. Certainly. I can ask my colleague, Dr. Kuznetsova from our statistics department to comment further. Slide up, please.

Go ahead, Dr. Kuznetsova.

DR. KUZNETSOVA: Hi. I'm Olga Kuznetsova, Merck biostatistics. You're correct. We acknowledge the p-value that we provide as the long term for our analysis is just a nominal p-value not accounted for multiplicity.

You're right that at that time, with additional 18 months, we had a higher number of events; 352 events versus 284 is the final analysis. Therefore, as you noted, we have a higher precision of the hazard ratio. We also established that the hazard ratio was maintained with longer follow-up in spite of medication [indiscernible], especially on the placebo arm; that were alive already, that had already stopped this new medication.

DR. HALABI: Alright. Thank you.

DR. EBBINGHAUS: Thank you, Dr. Kuznetsova.

DR. HOFFMAN: Okay. Dr. Kraus?

DR. KRAUS: Yes.

DR. HOFFMAN: And I'll just remind everybody to please state your name for the record before you

ask questions.

DR. KRAUS: Yes. Hi. Albert Kraus. I noted that the confirmatory trial, randomized trial, just missed the statistical hierarchy. But combining that with the existing data from single-arm trials, it seems more evidence of benefit than many cases; many, many cases of accelerated approval.

I noted as well the short time frame of the two different confirmatory trials, and I heard FDA say that they'd be very concerned if some of those trials failed, which of course we all hope they wouldn't. But the thing that strikes me, FDA, is if indeed, say, trial 394 or week 002 succeeds, it seems there's an agreement that would confirm, and they're coming very fast.

So am I understanding right that if those trials read out positively for the agreed confirmation, that perhaps in 2-3 months you'd be confirming from the one or a year and a few months for the next? Is that true, Dr. Lemery?

DR. LEMERY: Hi. This is Steve Lemery.

This is one of the items that we're actually asking the committee about. As I mentioned before, KEYNOTE-394 is very similar to the other second-line study, and if that's positive, that would be a result in the same setting, in the second-line setting, albeit in a different population. However, we'll review the data to ensure that it makes sense to say, yes, that does confirm.

I think if KEYNOTE-394 is negative, then we have a different situation here. Then we have a situation where if the other study is positive, you have a study that's positive with another checkpoint inhibitor, with a VEGF inhibitor. We've seen that already with atezo-bev. We've seen a successful trial with improvement in survival.

So the question is, is then there is some, in essence, synergy where you have both drugs together and you need both drugs together? I think that's an important study, clearly. But if 394 is negative in the exact same setting as the accelerated approval, then we'll have two negative

studies, randomized-controlled studies, to get placebo in the second-line setting, and that's a different situation.

DR. KRAUS: Yes, I understand. But that's to be seen in months yet. Thank you.

DR. LEMERY: Yes, 394 will be in months. The other one I think will take about a year or so, from what we saw on the slide.

DR. HOFFMAN: Okay. Ms. Hoyt?

MS. HOYT: Hi. This is Karen Hoyt. I'm a patient representative, and I would like to hear Merck describe or discuss what some of the ongoing or alternate trials look like. And then perhaps the FDA might address what they would do as a response to controlling these new trials. Would they be randomized controls or what would those look like, please? Thank you.

DR. EBBINGHAUS: Ms. Hoyt, could I clarify your question? Were you talking specifically about KEYNOTE-394 and the LEAP-002 study that we're talking about for confirmatory trials, or the broader development program, what we're doing

looking forward?

MS. HOYT: I'm looking at the broader development looking forward. Some of the closing statements that were made, I just made some notes. And one of them was about the ongoing or alternative trials, and that would be of great interest to me, and to other patients.

DR. EBBINGHAUS: Okay.

MS. HOYT: Thank you.

DR. EBBINGHAUS: Right. We have a slide from our core deck. If we could bring that slide up, please?

So as you can see, we have a pretty extensive program in hepatocellular cancer that includes our studies in treatment refractory disease in the second-line setting; first-line metastatic or advanced setting; intermediate stage disease; and adjuvant disease.

All of the trials that you can see in the right-hand column are randomized-controlled trials that have been carefully designed, discussed with the FDA, and agreed upon that if they show a

clinical benefit, would have been adequately designed to demonstrate the benefit of pembrolizumab alone or in combination in certain settings.

Our KEYNOTE-394 study is a study of pembrolizumab in the post-operative treatment setting for patients who had resected hepatocellular cancer. This is a randomized, double-blind, placebo-controlled study because there's currently no treatment in the adjuvant setting.

In the intermediate stage disease setting, we're combining pembrolizumab with lenvatinib and transarterial chemoembolization and comparing that to transarterial chemoembolization alone. And then you've heard quite a lot about LEAP-002 and our two studies in the second-line setting, so I won't describe those further.

MS. HOYT: Thank you. That's all for my questions.

DR. HOFFMAN: Okay. Thank you.

I think we'll take a break now for

10 minutes, and then we'll follow up with the open public hearing. Panel members, please remember that there should be no discussion of the meeting topic with anyone during the break, and we will resume at 2:20. Thank you.

(Whereupon, at 2:11 p.m., a recess was taken.)

Open Public Hearing

DR. HOFFMAN: We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial 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, speak only when recognized by the chairperson. Thank you for your cooperation.

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

MS. WOODS: My name is Andrea Wilson Woods, and I'm the president and founder of Blue Faery: The Adrienne Wilson Liver Cancer Association. While my charity has received educational grants and support from Merck and I have personally consulted for some pharmaceutical companies, I am not being paid for my testimony today. I am representing HCC patients, their caregivers, and any person who may be at risk for liver cancer.

Founded in 2002, Blue Faery's mission is to prevent, treat, and cure primary liver cancer, specifically hepatocellular carcinoma, also known as HCC, through research, education, and advocacy. I started Blue Faery after losing my younger sister Adrienne to HCC. I raised Adrienne from the time

she was 8 years old until her death at the age of 15.

On May 16, 2001, one month after her 15th birthday, Adrienne was diagnosed with stage 4 liver cancer. At that time, there was no treatment for advanced HCC. Adrienne died 147 days after her diagnosis.

It would be another seven years before the drug sorafenib was widely available for HCC patients. You, the FDA, approved sorafenib even though the median survival increased by less than 3 months and the side effects are horrific. Almost every patient I have spoken to over the last 10 years stopped taking sorafenib because their quality of life was ruined by non-stop diarrhea and peeling, painful, and blistering skin due to hand-foot syndrome.

However, in the last few years, many targeted and immunotherapy drugs have been approved for people suffering from advanced HCC. Whether they are first line, second line, or third line, the vast array of therapies available for HCC

patients gives them three things they didn't have before: choices, time, and hope.

I've been working with HCC patients for more than a decade. I know numerous patients who have lived many years with an advanced liver cancer diagnosis. They lived longer because they had more choices. If one therapy failed, or stopped working, or decreased their quality of life, patients had other options. While some people may not benefit from immunotherapy, many do.

On behalf of HCC patients and in memory of my sister Adrienne, I implore you, please don't take away Keytruda as a choice of treatment for people with advanced HCC. Thank you so much.

DR. HOFFMAN: Thank you.

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

MR. NAGY: My name is Neil Nagy. I am not representing anybody but myself. I'm not being paid by anybody to be here.

In 2015, I had a back pain, and my pain management doctor sent me for a CT scan and MRI that showed two masses, one in my liver and one in my spine. My cardiologist told me that I had stage 4 HCC and statistically had 6 months to live, and there is no treatment other than a drug that would possibly extend my life a little bit.

I have three daughters and seven grandkids. When they found out this, they all came to visit me and gathered around me, presumably to say goodbye. I'm an artist, and two galleries gave me retrospectives, which is pretty cool because that usually happens only after an artist dies. It was like going to my own funeral.

I was given Nexavar. It was not well tolerated at all by me. At the same time I had a round of chemo, radiology, several operations for my back, and it was a pretty raggedy time for me. Dr. Finn at UCLA got me a ticket to a clinical trial, Keytruda, and my tumor shrunk almost immediately after being on the trial, so I guess I got the real thing. It was a double-blind trial.

It stabilized. The tumor lost its blood supply. Two years into the trial, when it was over, I was stable and released. I thought it was over with, and I continued to be monitored by UCLA. And after a year, the tumor started to grow again, so I went back on Keytruda treatment through UCLA. The tumor growth immediately stabilized, and my alpha 1 beta protein went from 202 at the time that it was discovered, down to about 20 now, and it's stable.

I will continue, I suppose, on the Keytruda until I'm better. So that's it. This is not the end of my story. Thank you, Dr. Finn, and Merck, and UCLA.

DR. HOFFMAN: Thank you.

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

DR. JAVLE: My name is Milind Javle. I'm a medical oncologist and professor at MD Anderson Cancer Center, and I'm also the chair of the NCI

task force for hepatobiliary cancer. I have no financial relationships with the sponsor for this testimony.

I'm very honored to speak about this disease because this disease, even in 2021, is associated with a very poor five-year survival of less than 5 percent. It's an area of great unmet need, and as clinicians, we target two different diseases. One is hepatocellular cancer and the second is the underlying liver disease with varices, cirrhosis, and portal hypertension, as a result of which many patients are really not candidates for bevacizumab and atezolizumab first-line therapy due to risk of bleeding. They get first-line sorafenib or lenvatinib, and typically after 4 months get second-line access to TKIS, which again are complicated by toxicity because of their VEGF-related effects.

So therefore in the second-line setting, a single-agent checkpoint inhibitor like pembrolizumab presents an attractive option. As clinicians, we are very excited that this agent was

approved based on the KEYNOTE-224 trial with 17 percent response rate, which was sustained. The follow-up trial, in our interpretation, almost exactly replicated the results with the same response rate, which was also sustained.

Unfortunately, the study was negative because the bar for OS and PFS in our view was too high, and then the placebo arm sustained some noise and interpretation because these patients actually see second-line TKI on nivolumab.

The drugs are still valid. This agent is effective in the second-line setting. And as a clinician, I hope that FDA will continue its approval, at least until the completion of the follow-up phase 3 trials, which are still pending in this setting. Thank you very much for allowing me to advocate on behalf of my patients.

DR. HOFFMAN: Thank you.

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

DR. ENG: My name is Dr. Kathy Eng. I'm a professor at Vanderbilt-Ingram Cancer Center. I'm an expert in GI malignancies, but I predominately treat metastatic colorectal carcinoma. I am not receiving any payment for today and have received payment once before for a PARS CME event.

I just want to put things in perspective because greater than 65 percent of all patients are going to be greater than the age of 55 years of age. Forty-four percent of patients will have regional or metastatic disease, and this is the fifth leading cause of cancer death, where 72 percent of patients will succumb to this disease.

The incidence of new cases will disproportionately impact the minority patient population, notably blacks, Asian-Pacific Islanders, American Indians, and Hispanics, where it's going to be that 17.6 to 21.7 of 100,000 individuals will be diagnosed. It's an unmet need.

I understand that it failed to meet its prespecified endpoints of progression-free survival

and overall survival, but keep in mind that with prolonged follow-up, the response rate has been maintained and, in fact, there continues to demonstrate an early splay in KM curve for 12 months, and 24 months, and 36 months for overall survival, resulting in a hazard ratio of 0.77; so 23 percent benefit and improvement of likelihood of survival with pembrolizumab.

This is a convenient schedule for patients along a q3-week or q6-week of dosing. I know that it was criticized earlier regarding the patient population for KEYNOTE-394, which will be reported soon, but it's important to keep in mind that this trial must be conducted in Asia, specifically to finish enrollment given this current study design.

For patients in the second-line setting, only anti-VEGF agents are available if you remove this drug. For cabozantinib, there are toxicities; for regorafenib, it was approved based upon prior tolerances of sorafenib; ramucirumab requires an AST greater than 400; and the doublet nivo and ipi, high toxicities.

Regarding concerns about bleeding due to varices, I think many of us are familiar with treating with IO therapies and are very comfortable in that setting, especially since I treat colorectal cancer where we have large tumors. Historically, there's been no notable bleeding concerns.

In regards to looking at recent data regarding HCC, the largest increase still remains among those greater than 65 years of age based upon the most recent CR data review. So HCC patients are sorely in need of treatment options given the associated mortality, and they need these options based upon accessibility, convenience of treatment schedule, and reduced toxicities, especially in the era of the pandemic.

Keeping in mind the need of quality, as exemplified by this year's ASCO theme, Equitable Care for All Patients, we need to take into account our underserved minority and remote patient population. Decreasing treatment options is not the approach to improve community outreach, and I

do not believe that discontinuation of pembrolizumab for accelerated approval as a second line, where continuity of care is important, is in the best interest of the patient. Thank you.

DR. HOFFMAN: Thank you.

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

If there are any additional clarifying questions for the presenters, we can take them, although I don't see any hands up. It seemed like we finished before the open public hearing portion. I'll give it a few seconds to see if any hands go up; otherwise we'll move along.

(No response.)

Questions to the Committee and Discussion

DR. HOFFMAN: Okay. Not seeing any, 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'll 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 I will read it. It's in your packet as well. We'll read it again. It's been read earlier.

Should the indication for the monotherapy use of pembrolizumab in patients previously treated with sorafenib be maintained pending conduct or completion of additional trials?

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 question has already been read to the record -- all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window 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 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. HOFFMAN: Okay. Not hearing any, are there any questions or comments about the wording of the question? If not, we'll move on to the actual vote.

(No response.)

DR. STEVENSON: 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 result 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 the list, and each voting member will state their name and their vote into the record. You can also state the

reason why you voted as you did, if you want.

There are 8 yeses, zero noes, zero abstentions.

DR. HOFFMAN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record, and you may also provide justification for your vote, if you wish to. We'll start with Dr. Weekes.

DR. WEEKES: Hi. This is Colin Weekes. I voted yes. My rationale for voting yes is that although the results are not statistically significant, I believe they are clinically significant, bore out by the persistent benefit demonstrated in the overall survival curves.

In addition, I do believe that with the results of the 394 study that is to be reported within the next six months, we will be able to have a definitive answer as to whether there is truly benefit or not of single-agent pembrolizumab in the second-line setting. So I do think at this time it does make sense to continue with the accelerated

approval of pembrolizumab in this setting.

DR. HOFFMAN: Okay. Thank you.

Dr. Halabi?

DR. HALABI: Yes. Susan Halabi. I also voted yes pretty much for the same reasons that my previous peer mentioned. I think there is clinical benefit here, although statistically it did not exceed the boundaries for the primary endpoints of OS and PFS. Given the timeline with regard to the ongoing trials, we may have answers sooner than later.

Also, the last reason is because it seems the benefits from the treatment outweigh the risks for the patients, considering the other available treatments. Yes, that's it. Thank you.

DR. HOFFMAN: Okay. This is Dr. Philip Hoffman, and I voted yes. I agree that although the statistics on the confirmatory study did not meet the specified endpoint, the results seem remarkably similar to the earlier study. And while the response rate is relatively low, the duration of responses -- and this is true of immunotherapy

in general. The responses are often remarkably long.

I was also persuaded by the unmet need question, that there are still a fair number of patients who are not going to be suitable for treatment with bevacizumab up front because of the bleeding risk or occasionally clotting risk, and that there remains the need to be able to use a checkpoint inhibitor in the second line, pending any further trials that are running.

Mr. Mitchell?

MR. MITCHELL: Thank you, Dr. Hoffman.

I'm David Mitchell. I voted yes. Basically what everyone has said already I'm generally in agreement with. The totality of the research shows impact. The safety profile is well established. We're only a few months away from results in 394. We should wait and see if it's confirmatory. Thank you.

DR. HOFFMAN: Thank you.

Ms. Hoyt?

MS. HOYT: Thank you. I voted yes. I'm so

happy to see a robust HCC development. Fourteen months is a long time to the life of a liver-disease patient. I think it fulfills an unmet need for long-term disease control. I'm excited to see the research and the scientists, and I was really encouraged today to hear about the tumor response. Liver disease patients are happy to see any kind of response, so thank you for this opportunity today.

DR. HOFFMAN: I'm sorry. Can I just trouble you to state your name and your vote into the record?

MS. HOYT: I thought I said. I'm sorry. I may have been still muted. Karen Hoyt. I voted yes.

DR. HOFFMAN: Yes. We got the vote. I just needed the name to go with it.

MS. HOYT: Oh, I'm sorry.

DR. HOFFMAN: No, that's fine.

MS. HOYT: It must have been a slippage of time. Thank you.

DR. HOFFMAN: Dr. Lieu?

DR. LIEU: Yes. This is Chris Lieu, and I voted yes. I certainly will echo the comments that have been made. Again, the results from the KEYNOTE-240 study, I think that there's clinical benefit, as was stated there.

With the confirmatory study of KEYNOTE-394, this will either clearly support the continued indication or may simply prove that pembrolizumab may not be effective enough to reach prespecified statistical boundaries, and we'll know this within one month. So I think that we'll get the answers soon enough.

I think the key point, really, here is that we assume that 15 to 20 percent of patients cannot receive bevacizumab in a front-line setting. Is it reasonable to continue an indication in an immunotherapy-naïve population in the second-line setting where an overall survival benefit may exist? And I believe that answer to be yes, again, until we have the results from the other confirmatory study. So at this time I support the current indication for pembrolizumab as written.

DR. HOFFMAN: Okay. Thank you.

Dr. Lewis?

DR. LEWIS: Yes. This is Mark Lewis. I voted yes. I voted yes because, in my mind, there was an enormous drought in the therapeutic landscape for HCC between the SHARP trial bringing in sorafenib, and then what I view as the paradigm shift, the IMbrave150 with atezolizumab and bevacizumab.

I also think it was stated very elegantly by Dr. Javle during the open public hearing that so often there are comorbidities attendant to HCC from a vascular perspective that render it unsafe or at least relatively contraindicated to give bevacizumab, and I think the protocols regarding anti-VEGF agents are appropriately circumspect.

As such, I share Dr. Lieu's view that with the imminent maturation of KEYNOTE-394, it seems to me premature to withdraw the approval at this time until we have seen those data.

DR. HOFFMAN: Okay. Thank you.

Dr. Kunz?

DR. KUNZ: Yes. This is Pamela Kunz, and I voted yes for many of the reasons stated. The two main reasons that I voted yes include the need to await the KEYNOTE-394 results and the fact that 15 to 20 percent of patients cannot receive bevacizumab in the first-line setting, thus creating an unmet need. Thank you.

DR. HOFFMAN: Okay. Thank you, everybody.

I think that it's clear that the committee has consensus around this, and people have clearly stated the reasons, the need for something for people that can't get bevacizumab; and the awaiting for Trial 394, which should be coming out shortly; and the consistency of responses, and some responses being durable. And the safety aspects compare favorably with that of some of the TKIs that are also available.

Before we adjourn this topic, I think, Dr. Lemery, did you want to make a comment?

DR. LEMERY: Yes. I just want to thank the committee -- this is Steven Lemery -- for their deliberation. We'll see what the results of 294

are.

Actually, I did want to have Dr. Fashoyin-Aje, the OCE's associate director for science and policy, to address disparities in the OCE, to address one point, though.

DR. FASHOYIN-AJE: Thank you, Dr. Lemery.

I guess I wanted to make a comment to Dr. Eng's point about these therapies being available for patients who are minorities who badly need treatment options. I wanted to note that I was glad to hear Dr. Eng mention the need to address unmet medical need for patients who are underrepresented in clinical trials, and note that many of the trials, including the trials that were discussed here, do not reflect the patient population who will be using the drug post-approval.

So I just wanted to put a plug in for continuing to evaluate measures that we can implement to address these populations. Thank you.

Adjournment

DR. HOFFMAN: Okay. Thank you.

We will now adjourn the topic. We will reconvene at, let's say, 3:05 Eastern time for the third topic. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break.

I think I said 3:05, so that's about 13 minutes. Thank you. Well, actually, I'm sorry. I was just given heads up to do 30 minutes, so 3:22 is when we'll reconvene; at 3:22.

(Whereupon, at 2:53 p.m., the meeting was adjourned.)