FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Topic 3

Virtual Meeting

Thursday, April 29, 2021

3:22 p.m. to 6:09 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICERS (Non-Voting)

Takyiah Stevenson, *PharmD*

(April 29 Only)

Division of Advisory Committee and

Consultant Management

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Professor of Biostatistics and Bioinformatics

Duke University Medical Center

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

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Colin D. Weekes, MD, PhD, FASCO

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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

(3:22 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 today's meeting. I will now call the third 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. Susan Halabi?

DR. HALABI: Thank you. This is Susan Halabi. I'm a biostatistician at Duke University.

DR. STEVENSON: 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, everybody. I'm Chris Lieu. I'm a medical oncologist at the University of Colorado.

DR. STEVENSON: David Mitchell?

(No response.)

DR. STEVENSON: David Mitchell?

(No response.)

DR. STEVENSON: Mr. Mitchell, can you hear me?

(No response.)

DR. STEVENSON: You may be double-muted.

(No response.)

DR. STEVENSON: Okay. I'll come back to Mr. Mitchell.

Dr. Sung?

DR. SUNG: Anthony Sung, hematopoietic stem

cell transplant physician at Duke University.

DR. STEVENSON: Karen Hoyt?

MS. HOYT: Hi. I'm Karen Hoyt, and I'm a patient representative.

DR. STEVENSON: Dr. Kunz?

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

DR. STEVENSON: Dr. Lewis?

DR. LEWIS: Mark Lewis, medical oncologist, director of gastrointestinal oncology and Intermountain Healthcare.

DR. STEVENSON: Dr. Weekes?

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

DR. STEVENSON: David Mitchell, if you can hear me, please introduce yourself.

(No response.)

DR. STEVENSON: I'm sorry. David Mitchell, can you hear us?

(No response.)

DR. STEVENSON: Okay. I'll come back to you

in just a moment.

Dr. Kraus?

DR. KRAUS: Yes. Hi. Good afternoon, everyone. I'm Albert Kraus. I work in oncology, research, and development, bringing medicines from the lab up through the patient and market. I work for the Pfizer corporation.

DR. STEVENSON: I will introduce the FDA participants.

Dr. Pazdur?

(No response.)

DR. STEVENSON: Dr. Pazdur, if you can hear me?

(No response.)

DR. STEVENSON: I'm sorry.

Dr. Pazdur, can you hear me? If not, I'll go to the next person.

(No response.)

DR. STEVENSON: Dr. Beaver?

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

DR. STEVENSON: Dr. Lemery?

DR. LEMERY: Hi. Steven Lemery, acting director, Division of Oncology 3.

DR. STEVENSON: Thank you.

Dr. Pazdur, can you hear me?

(No response.)

DR. STEVENSON: Okay. I'm going to try to go back to David Mitchell.

David Mitchell, can you hear me?

(No response.)

DR. STEVENSON: David Mitchell, can you hear me? Maybe check your personal phone to make sure you're not muted.

(No response.)

DR. STEVENSON: Okay. I will come back and continue to introduce the rest of the panel members.

DR. PAZDUR: This is Dr. Pazdur. Can you hear me now?

DR. STEVENSON: Yes. Hi, Dr. Pazdur. Yes. Thank you.

DR. PAZDUR: Okay. Good. I think you guys

muted me. Okay. Thank you.

DR. STEVENSON: Sure. Sorry about that. No problem.

DR. PAZDUR: Now let me introduce myself. This is Richard Pazdur. I'm the director of the Oncology Center of Excellence at the FDA.

DR. STEVENSON: Thank you so much, Dr. Pazdur.

David Mitchell?

(No response.)

DR. STEVENSON: Okay. We'll go back. We will continue. I will 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 the break. Thank you.

Dr. Takyiah Stevenson will read the Conflict of Interest Statement for the meeting.

DR. STEVENSON: I will try to go back.

David Mitchell, can you hear me? If you can, please introduce yourself.

MR. MITCHELL: Yes. I'm sorry. I think I managed to get reconnected. If you can hear me, I'm David Mitchell.

DR. STEVENSON: I can hear you.

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

DR. STEVENSON: Great. Thank you so much, and thank you for trying to reconnect.

I will continue with the Conflict of Interest Statement.

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 125554, supplement 041, trade name Opdivo, nivolumab, submitted by Bristol Myers Squibb Company, indicated as a single agent 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, sBLA, approved under 21 CFR 601.40, subpart E, accelerated approval regulations, with confirmatory trial or trials that have not verified clinical benefit. These updates will provide information on: 1) the status and results of confirmatory clinical studies for the given indication; and 2) any ongoing and planned trials.

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

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

Dr. Weekes' waiver involves his employer's research contract funded by Bristol Myers Squibb, sponsor of Opdivo, nivolumab. His employer receives $50,000 to $100,000 per year from the firm.

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

Copies of the waiver 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 may 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'll hand it back to the Chair.

DR. HOFFMAN: We will now proceed with FDA introductory comments from Dr. Julia Beaver.

FDA Introductory Comments – Julia Beaver

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

Diseases at FDA.

I will be giving opening remarks to provide background on accelerated approval and set the stage for your discussions in this session. I have provided similar remarks to introduce the other three 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 regulatory background and requirements for granting an accelerated approval.

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

threatening requirement.

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 clinical benefit. These trials would usually be underway at

the time of the accelerated approval; can be carried out in a different treatment setting, for instance, an accelerated approval as monotherapy in a refractory setting and a confirmatory trial in the same disease, but in an earlier setting in combination with chemotherapy; and need to be carried out with due diligence. The majority of accelerated approvals have been for oncology products, and I will now go over the oncology experience with accelerated approval.

Over the last three decades, there have been over 150 oncology accelerated approvals and 35 anti-PD-1 or anti-PD-L1 antibody accelerated approvals, with close to half converting to regular approval in a median of three years and only 10 withdrawals.

As discussed, accelerated approval indications may be withdrawn if postmarketing trials do not confirm clinical benefit or are not conducted with due diligence. FDA appreciates that a clinical trial that does not meet its endpoint or does not demonstrate a meaningful outcome does not

necessarily mean the drug is not effective. This failure to demonstrate meaningful efficacy rather than a true lack of efficacy can potentially be explained by differences in trial design, including endpoints, statistical testing, or biomarker selection.

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 public discussions of these evaluations on a more periodic basis.

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

The Oncology Center of Excellence evaluated these accelerated approvals and identified 10 indications for anti-PD-1 and 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 and has been discussed during this advisory committee meeting warrant further discussion and we hope to hear further advice. This session will discuss nivolumab 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 therapy, atezolizumab in combination with bevacizumab, has demonstrated clear survival benefit in an earlier setting. This change in available therapy results in a changed risk-benefit profile that differs compared to the time of the initial accelerated approval.

Accelerated approvals are meant to serve patients, and if postmarketing clinical trial data

do not demonstrate clinical benefit and alternative therapies do, patients may not be served by continuation of the original accelerated approval. In addition, the response rate initially supporting the accelerated approval was low.

For the initial approval, FDA oncology took into consideration unmet need and the unusually 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: Thank you.

Both the FDA 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 Bristol Myers Squibb Company'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 Bristol Myers Squibb Company.

Applicant Presentation – Mathias Hukkelhoven

DR. HUKKELHOVEN: Good afternoon. My name is Mathias Hukkelhoven, global head of regulatory and safety sciences at Bristol Myers Squibb. I would like to thank the committee members, as well as the FDA, for your time to discuss nivolumab and

the accelerated approval in patients with hepatocellular carcinoma, who have been previously treated with sorafenib.

Nivolumab was first approved in the U.S. in 2014 for the treatment of metastatic melanoma and has subsequently been approved by the FDA in 21 indications across 11 cancer types, which are noted on the slide. BMS is committed to the treatment of patients with hepatocellular carcinoma. We have a broad clinical development program evaluating nivolumab alone or in combination with other agents across different stages of disease, from the early disease setting to the metastatic setting.

Two of these studies, CHECKMATE-040 and CHECKMATE-459, have completed. There are three other phase 3 studies, CHECKMATE-9DX, CHECKMATE-74W, and CHECKMATE-9DW, which are currently ongoing and can potentially serve as confirmatory trials for the accelerated approval. You will hear more about these studies during the course of this presentation.

Nivolumab is a PD-1 inhibitor that received accelerated approval in September 2017 for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib. This indication was approved under the accelerated pathway based on tumor response rate and the durability of response.

Under this pathway, a postmarketing requirement to conduct and submit results of a multicenter, randomized trial to verify and describe the clinical benefit of nivolumab over standard therapy, in patients with advanced hepatocellular carcinoma, was agreed upon at the time of approval.

It is important to note that although it would be ideal for confirmatory trials to be conducted in the same setting, that may not be feasible. Confirmatory trials for accelerated approvals have historically been conducted in different lines of the same disease compared to the initial trial for conversion to full approval.

The accelerated approval was granted based

on a clinically meaningful benefit in 154 post-sorafenib hepatocellular carcinoma patients who received nivolumab in two cohorts of the phase 1-2 CHECKMATE-040 study. Durable responses were observed and the safety profile of nivolumab in HCC was generally consistent with that seen in other cancers.

The phase 3 CHECKMATE-459 study evaluating nivolumab versus sorafenib in first-line advanced hepatocellular carcinoma was intended to serve as the confirmatory trial for this accelerated approval. This study readout in 2019, and although there was encouraging separation seen in the Kaplan-Meier curves for the primary endpoint of overall survival, it did not meet statistical significance. Of note, the safety profile for nivolumab was favorable.

These are the topics we will discuss this afternoon. Since the approval of nivolumab for HCC in 2017, the treatment landscape has evolved. However, sorafenib still remains an important treatment option in the first-line setting for

certain HCC patients, and nivolumab represents a valuable treatment option for the advanced HCC patients that progress on or are intolerant to sorafenib.

Dr. Thomas Abrams will discuss the unmet need that currently exists in the advanced HCC setting. Dr. Ashwin Sama will then present the efficacy and safety data for nivolumab from CHECKMATE-040 and highlight the clinical and meaningful responses observed in patients, as well as the acceptable safety profile. He will also present the study result from CHECKMATE-459 and the clinical activity of nivolumab seen in this first-line HCC study.

Dr. Ian Waxman will follow by providing an overview of the ongoing studies in the clinical development program for nivolumab in HCC that have the potential to serve as confirmatory trials and specifically discuss CHECKMATE-9DX, a phase 3 randomized study of nivolumab versus placebo in HCC patients following resection or local ablation, that is well suited to serve as the postmarketing

requirement for the nivolumab accelerated approval.

Finally, Dr. Anthony El-Khoueiry will provide his perspective on the clinical relevance of nivolumab and discuss why nivolumab should remain approved as a treatment option for patients with HCC post-sorafenib while awaiting further clinical data. In addition, Dr. Janet Wittes from WCG Statistics Collaborative will be available to answer your questions.

With that, I will turn it over to Dr. Abrams.

Applicant Presentation – Thomas Abrams

DR. ABRAMS: Hello. I'm Thomas Abrams, and I'm a senior physician with Dana-Farber Cancer Institute and an assistant professor of medicine at Harvard Medical School. I'm a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

Hepatocellular carcinoma is an aggressive tumor type associated with profound morbidity and early death. Worldwide, it is the sixth most commonly diagnosed malignancy. In the face of

rapidly rising rates of NAFLD and NASH, HCC incidence is predicted to rise in kind.

Last year in the U.S., HCC had a five-year survival rate of approximately 20 percent. It was estimated there were 43,000 new cases and 30,000 deaths related to HCC. As such, identifying and deploying effective treatments is critical in the face of this escalating health crisis.

HCC presents treatment challenges that are unique in oncology. Because nearly all those affected with HCC have underlying liver dysfunction from cirrhosis, treatment decisions must reflect the effects of progressive liver disease in addition to the effects of the cancer. Therefore, the treatment paradigm must include agents that can be safely and tolerably administered in patients with less than optimal liver function, marginal performance status, or substantial comorbidities.

HCC survival rates are extremely low. Since the disease is usually asymptomatic when confined to the liver, patients typically present only after symptoms such as abdominal bloating from ascites,

fatigue and pain, or bony fracture from metastases have emerged. By that point, patients have advanced incurable disease, and many have severely impacted qualities of life.

Most patients are diagnosed well beyond the point that surgery can be considered. Even among patients who go on to have curative resection, approximately half will recur. The median time to recurrence is less than 3 years. At the point of diagnosis, many patients often already have compromised liver function as calculated by Child-Pugh scores and are therefore better suited for first-line treatment with sorafenib.

The treatment landscape for advanced HCC patients has evolved rapidly. In 2018, lenvatinib joined sorafenib as an additional TKI option for first-line treatment of advanced HCC based on the REFLECT trial data, which showed lenvatinib was non-inferior to sorafenib.

In 2020, the combination IO anti-VEGF treatment of atezolizumab and bevacizumab was approved on the strength of the IMbrave150 data,

which showed superiority to sorafenib.

Current FDA-approved second-line options include regorafenib; nivolumab; pembrolizumab; cabozantinib; ramucirumab for patients with AFT of 400 or greater; and nivolumab plus ipilimumab. All these agents were studied following progression on sorafenib. For the Child-Pugh B population, NCCN guidelines recommend sorafenib in the first line and nivolumab in the second line.

This plot illustrates the treatment utilization percentages in the first-line setting, understanding that these data over most of 2020 reflect a shifting approval landscape. Atezo-bev captures 34 percent of the proportion of first-line starts, but lenvatinib and sorafenib together account for 43 percent of all starts.

Even if this data set underestimates the fraction of atezo-bev starts, I believe TKIs will continue to play an important role in first-line treatment of advanced HCC, based on the comorbidities and baseline characteristics of many advanced HCC patients. In fact, I don't expect the

atezo-bev usage to ever rise much past 50 percent.

Although literature suggests a Child-Pugh B prevalence of 22 percent, in my practice, nearly one-third of the patients are Child-Pugh B and a quarter are ECOG performance status 2. While there is considerable overlap between these two groups, it is by no means total.

As such, I estimate that between 35 and 40 percent of my patients with advanced HCC are ineligible for atezo-bev combination. For these patients, TKIs remain an important part of the first-line armamentarium.

Moreover, approximately 60 percent of HCC patients have esophageal varices. Varices confer a high risk of bleeding complications if they have not been endoscopically addressed. As such, patients were eligible for IMbrave150 only if they were evaluated for varices within 6 months of enrollment and had any symptomatic varices banded or sclerosed.

In the real-world setting, many patients are diagnosed with HCC without a known prior history of

cirrhosis. For these patients, it can take several weeks to have an EGD performed for variceal evaluation and treatment. Patients with rapidly progressive disease do not have the luxury of waiting to start active therapy.

Finally, I have reservations starting any patient with significant bleeding history over the previous 6 months on a bevacizumab-containing regimen. For these patients, sorafenib remains an important first-line option.

While the combination of atezo and bev is a highly effective treatment, there are bleeding risks that are associated with its use that need to be taken into account when choosing first-line therapy for HCC patients.

This figure shows that, overall, there is an increased rate of bleeding in the atezo-bev group with hemorrhagic events occurring in 25 percent of the atezo-bev group versus 17 percent in the sorafenib group. In a real-world setting, I'd expect the bleeding rates to be even higher given the strict eligibility criteria of the study. For

these reasons, it is critically important to properly select HCC patients for atezo-bev.

I would like to take you through this flow chart on how advanced HCC patients are treated in my clinic. When patients have good performance status, Child-Pugh A liver function, and no recent thromboembolic events or bleeding risks, they are treated with the atezolizumab and bevacizumab. If patients do not qualify for atezo-bev based on these criteria, they are treated with a TKI. If they have a good response and tolerate the TKI well, they are considered candidates to receive another TKI in the second line. If they rapidly progress or have toxicity from the TKI, then they are considered for IO therapy in the second line.

For IO therapy candidates, if a patient is younger, fitter, and has a good performance status, then I select a PD-1 CTLA-4 inhibitor. For the less fit patients who are unable to tolerate combination therapy, a PD-1 inhibitor is the treatment of choice. In my practice, this represents approximately a quarter of patients

eligible for second-line therapy. As such, nivolumab represents an important part of the therapeutic armamentarium.

I'll now pass it on to Dr. Sama, who will walk us through the CHECKMATE-040 and CHECKMATE-459 data for nivolumab in HCC.

Applicant Presentation – Ashwin Sama

DR. SAMA: Thank you, Dr. Abrams.

Good afternoon. My name is Ashwin Sama, and I'm the clinical development lead for HCC at BMS. As discussed in the unmet need presentation by Dr. Abrams, there are many patients who receive a TKI as first-line therapy, and nivolumab remains an important option for HCC patients post-sorafenib.

I'm now going to walk you through the efficacy and safety of nivolumab monotherapy in advanced HCC from the CHECKMATE-040 and CHECKMATE-459 clinical trials.

CHECKMATE-040 was a phase 1-2 study which evaluated nivolumab alone or in combination with other agents in advanced HCC. Cohort 1 included patients in the dose-escalation phase, which

evaluated 0.1 milligram per kilogram to 10 milligram per kilogram of nivolumab to identify a recommended phase 2 dose in advanced HCC. Cohort 2 tested the recommended phase 2 dose of 3 milligram per kilogram of nivolumab in advanced HCC.

The key eligibility criteria are shown on this slide. Unlike IMbrave150, which assessed atezolizumab plus bevacizumab versus sorafenib, there was no requirement for endoscopy or treatment of varices prior to enrollment to CHECKMATE-040, and patients taking daily NSAIDs, full-dose aspirin, or anticoagulants were eligible.

Overall, 262 patients were treated in Cohort 1 and 2 of which 154 were treated with nivolumab 3 milligram per kilogram post-sorafenib, which formed the FDA approval population. The primary endpoint of Cohort 1 was safety and tolerability, and overall response rate was the primary endpoint in Cohort 2.

CHECKMATE-040 showed a promising ORR of 14.3 percent and a median duration of response of

16.6 months with nivolumab in patients with advanced HCC post-sorafenib. The responses were deep, durable, and clinically meaningful, with ongoing responses in half the patients as seen in this swimmer's plot.

The median overall survival was 15.15 months based on a database logged in March 2017, which is favorable in the post-sorafenib population. Updated data show a 5-year survival rate of 12 percent in the post-sorafenib population, with some patients experiencing a long-term benefit, as seen by the tail of the Kaplan-Meier curve.

This figure shows any grade treatment-related adverse events seen in greater than 5 percent of patients treated with nivolumab monotherapy. No new safety signals were seen with nivolumab in HCC when compared to other tumors. Of note, the increase in AST, ALT, and bilirubin were manageable but established treatment algorithms. There were 5 treatment-related adverse events leading to discontinuation, and one patient experienced study drug toxicity leading to death.

This slide shows data from Cohort 5 of CHECKMATE-040, which evaluated nivolumab monotherapy in advanced HCC patients with a Child-Pugh score of 7 to 8. Patients were either sorafenib naïve, intolerant, or progressed on sorafenib. The primary endpoint was ORR by investigator assessment using RECIST 1.1.

The overall response rate in Cohort 5 was 10.2 percent by investigator assessment and the disease control rate was 55.1 percent; 4 out of the 5 responders had improvement in liver function from Child-Pugh B to Child-Pugh A, which lasted at least 6 months. No new safety signals were identified in Cohort 5, and nivolumab was tolerable in patients with Child-Pugh B cirrhosis.

Next, I'll go over the data from CHECKMATE-459, which was a randomized phase 3 study of nivolumab versus sorafenib in first-line advanced HCC. The key eligibility criteria included patients with histologically confirmed advanced HCC and were not eligible or progressed after surgical or local treatments. Patients were

systemic therapy naïve, Child-Pugh class A, and ECOG performance status zero to 1.

Patients were randomized 1 to 1 to nivolumab or sorafenib and treated until disease progression or unacceptable toxicity. The primary endpoint was overall survival and key secondary endpoints included overall response rate and progression-free survival.

At the time of the primary analysis in June 2019, with the minimum follow-up of 22.8 months, nivolumab showed a median overall survival of 16.4 months compared to 14.7 months with sorafenib. The hazard ratio was 0.85 with a p-value of 0.075, which did not reach the prespecified significance level of 0.042. Note that this observed hazard ratio was slightly higher than the critical hazard ratio of 0.84 per protocol design.

As shown here, nivolumab and sorafenib performed similarly for the first 8 months followed by a maintained separation in the Kaplan-Meier curves. Updated data from April 2020 with a

minimum follow-up of 33.6 months confirmed the separation in the Kaplan-Meier curves between 24 and 33 months with reduced censoring, showing continued benefit of nivolumab over sorafenib.

Exploratory analyses was conducted to understand reasons overall survival in CHECKMATE-459 failed to demonstrate statistical significance. These post hoc analyses are described in more detail in the briefing book.

One important factor was a longer than anticipated time to separation of the Kaplan-Meier curves, which reduced the statistical power from 90 to 50 percent. The longer delayed separation in turn requires a longer follow-up to appropriately capture the treatment effect. This delayed treatment effect was potentially due to the higher proportion of subsequent systemic therapy used in this sorafenib arm, including higher IO therapy used.

When CHECKMATE-459 was designed, there was no approved second-line treatment options. During the conduct of the study, many second-line options,

including regorafenib, nivolumab, pembrolizumab, cabozantinib, and ramucirumab became available, as seen in Dr. Abrams' presentation. Subsequent therapy may have therefore confounded the overall survival results.

The overall response rate with nivolumab was 15 percent versus 7 percent with sorafenib, and the odds ratio was 2.41. Of note, the response rate observed with nivolumab monotherapy in CHECKMATE-459 was similar to CHECKMATE-040. There were more complete responses with nivolumab compared to sorafenib. Responses were durable with median duration of response of almost 2 years in both arms.

As shown in the tornado plot here, nivolumab had lower treatment-related adverse events compared to sorafenib. The most common treatment-related adverse events reported in greater than 10 percent of patients for nivolumab or sorafenib are shown here, and these demonstrate a differentiated safety profile for nivolumab compared to sorafenib. There were lower grade 3-4 adverse events and lower

treatment-related adverse events leading to discontinuation with nivolumab compared to sorafenib. There were 4 deaths in the nivolumab arm and 1 death in the sorafenib arm due to study drug toxicity.

The benefit of nivolumab versus sorafenib was also shown by measuring health-related quality of life, which was an exploratory endpoint. This figure represents the mean change from baseline in quality of life in the nivolumab and sorafenib arms using FACT-Hep. FACT-Hep measures the effects of HCC and its treatment on quality of life. Overall, nivolumab showed a better quality of life compared to sorafenib, with nivolumab allowing for a maintained quality of life while sorafenib led to worsening.

In summary, nivolumab monotherapy showed deep and durable responses in CHECKMATE-040 with responses also seen in Child-Pugh B patients. Overall survival did not meet statistical significance in CHECKMATE-459 despite a separation in the Kaplan-Meier curves, with some patients

deriving long-term benefit. The overall response rate in CHECKMATE-459 was consistent with CHECKMATE-040.

Safety was similar to the known safety profile of nivolumab monotherapy in other tumors and favorable compared to sorafenib. Quality of life, which was an exploratory endpoint, was improved with nivolumab compared to sorafenib.

With that, I'd like to hand it to Dr. Ian Waxman, who will discuss the nivolumab HCC clinical development program and the ongoing studies with nivolumab and HCC that may serve to fulfill the PMR.

Applicant Presentation – Ian Waxman

DR. WAXMAN: Good afternoon. My name is Ian Waxman, and I'm the development lead for GI cancers at BMS, and I'll start with an overview of the comprehensive development program already in place for nivolumab in HCC. This program includes not only the completed studies just discussed by Dr. Sama, but also three ongoing phase 3 trials as described on this slide, each of which has the

potential to serve as the alternative confirmatory trial.

The first is a study of adjuvant nivolumab monotherapy versus placebo in the early disease setting; the second is a study of nivolumab combined with ipilimumab versus TKI in the first-line metastatic setting; and the third is the study of nivolumab combined with TACE with or without ipilimumab in the intermediate setting.

The adjuvant study, known as CHECKMATE-9DX, is uniquely positioned to characterize the clinical activity of nivolumab monotherapy, and it's therefore particularly well suited to serve as the PMR for this accelerated approval.

This study is also the first of the three studies to have completed enrollment, and is likely to be the first to provide data with final analysis projected to occur in 2023, and the potential for an interim readout in the first half of 2022.

We welcome the committee's feedback on the use of CHECKMATE-9DX or one of the other ongoing studies in HCC as the confirmatory trial for this

accelerated approval.

Details of the 9DX study design are shown here. This is a study of 530 patients with early-stage HCC, who had already undergone resection or ablation and are at high risk of recurrence. Patients were randomized in a 1-to-1 fashion to receive either nivolumab monotherapy or placebo for a total treatment duration of up to one year.

I highlight here the use of placebo as the comparator since, unlike in the metastatic setting, there is currently no active therapy utilized as a standard of care in the adjuvant setting. The primary endpoint of the study is recurrence-free survival with a key secondary endpoint of overall survival.

CHECKMATE-9DX, as just described, is well, suited to serve as the postmarketing study for the current second-line accelerated approval for a few reasons. First, it's important to point out that per the FDA guidance on clinical trial endpoints, disease-free or recurrence-free survival can

sometimes serve as the primary endpoint for traditional approval either as a direct measure of clinical benefit or as a surrogate known to predict clinical benefit, and this endpoint has already been used to support traditional approval across multiple solid tumor adjuvant indications.

Further acknowledgement of the potential acceptability of an RFS endpoint was received in the form of FDA feedback for the 9DX study, with the agency stating that a robust improvement in RFS could support approval if the effect size was of a large enough magnitude to indicate clinical meaningfulness. And we're confident that a clinically meaningful RFS improvement will be observed with nivolumab in early-stage HCC.

This is based on the size of the benefit already shown in phase 3 adjuvant studies of nivolumab across other solid tumors and also on the compelling activity recently demonstrated in the neoadjuvant HCC setting. Finally, given the statistical design of 9DX, we're confident that it can clearly characterize this anticipated clinical

benefit.

I'll now turn over the presentation to Dr. El-Khoueiry to provide his own thoughts on nivolumab's place in the second-line treatment landscape, but before doing so, I'd like to conclude with a few key points.

First, the CHECKMATE-040 study has demonstrated robust efficacy for nivolumab after sorafenib based on the occurrence of responses with both depth and durability, along with a safety profile differentiated from that of TKIs.

Second, nivolumab as a later-line treatment option continues to address the significant unmet need despite the approval of atezo-bev, given that sorafenib remains the preferred first-line therapy for a sizable patient population.

Positive results from the CHECKMATE-9DX study, or one of the other ongoing studies in HCC, could support conversion of our second-line accelerated approval to full approval, especially when considering the durability of responses seen in CHECKMATE-040 and the encouraging activity seen

in CHECKMATE-459, and more broadly with this class of agents in HCC.

With that, I'll turn the presentation over to Dr. El-Khoueiry to share his clinical perspective and to provide some closing remarks.

Applicant Presentation – Anthony El-Khoueiry

DR. EL-KHOUEIRY: Hello. My name is Anthony El-Khoueiry, and I'm an associate professor of medicine at the University of Southern California Norris Comprehensive Cancer Center. I was the lead investigator for the CHECKMATE-040 study. I'm a paid consultant of the sponsor, but I have no financial interest in the outcome of this meeting.

Despite the evolving landscape of HCC therapy, a subset of patients will still be treated with a TKI in first line due to contraindications to one or more of the components of the combination of atezolizumab and bevacizumab.

The majority of the patients treated with sorafenib will eventually discontinue treatment either due to progression or intolerance, making nivolumab monotherapy a valuable option in these

patients. In addition, patients with intolerance to sorafenib may not be good candidates for treatment with another TKI in the second-line setting. Approximately 35 percent of patients receive nivolumab in the second-line setting currently.

Nivolumab has been studied and shown to be efficacious independent of ideology. It has also shown benefit in Child-Pugh B and elderly patients. Given the favorable safety profile and the potential for durable response translating into meaningful clinical benefit, all IO-naïve patients going into the second-line treatment should have the option to use nivolumab.

When evaluating second-line monotherapy options, we can see that nivolumab has a favorable benefit-risk profile given its level of efficacy and safety. This is extremely important, as second-line patients often have poorer performance status or worsened liver function with multiple comorbidities after first-line treatment. When looking across trials, nivolumab tends to have a

lower rate of grade 3 and 4 all-causality events compared to TKIs. Nivolumab has efficacy independent of AST level, unlike the activity of ramucirumab, which is limited to patients with AST of 400 or higher.

Here I provide the treatment course for one of my patients. This is an 88-year-old Asian man with chronic hepatitis B, hypertension, COPD, and myocardial infarction in 2018. He was incidentally diagnosed with HCC in March of 2019 when he presented with unrelated back pain. Multiphase CT and MRI noted a right liver lobe mass with arterial enhancements and venous washout, with an AST above 4,000.

He was treated with Y90 radioembolization in June of 2019. Despite the evidence of response in the treated lesion, CT scan in August of 2019 noted the development of multiple new liver lesions consistent with HCC. He was then started on sorafenib at 400 milligrams daily with poor tolerance related to fatigue, diarrhea, and grade 3 hand-foot-skin reaction. Sorafenib was

subsequently decreased to 400 milligrams every other day within 2 to 3 weeks.

In November of 2019, a CT scan showed progression again in the liver, and AST reached over 65,000. He was then referred to me, and I started him on nivolumab on 11-18 2019, which led to a partial response on first scan in January 2020 and a dramatic decrease of AST to 454. He continued on treatment with excellent tolerance and a deepening response, reaching complete response by modified resistance September of 2020.

Given the complete response and the fact that he had been on treatment for one year, we held treatment in November of 2020 and placed the patient on surveillance. Follow-up CT in January 2021 revealed maintained response, and he continued to stay off treatment with a normal alpha-fetoprotein.

This example highlights the significant potential benefit of single-agent nivolumab in the treatment of patients with advanced HCC and reinforces the need for nivolumab as a

post-sorafenib treatment option for these patients. And with that, I will conclude our presentation. Thank you for your consideration.

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 nivolumab monotherapy application for the treatment of hepatocellular carcinoma.

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 therapy, and are based on effect on an earlier endpoint that is reasonably likely to predict benefit.

Ordinarily, confirmatory trials are underway to verify and describe 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. Importantly, there are legal standards with respect to the criteria for both accelerated and regular approvals, and it is important to carefully assess whether data in applications meet these standards.

Nivolumab has received accelerated approval as a single agent and in combination with ipilimumab for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib. As a reminder, for the purposes of the meeting today, we are only addressing whether the indication for nivolumab as a single agent should be maintained and that the indication in combination with ipilimumab will not be affected by any FDA action on the monotherapy indication.

Like the prior presentation, I will highlight a few issues that are relevant to the nivolumab hepatocellular cancer indication.

First, the response rate of nivolumab in CHECKMATE-040 which supported approval is low at 14 percent, albeit some patients have long

durations of response. Secondly, CHECKMATE-459, which compared nivolumab to sorafenib in the first-line setting, did not confirm benefit. The third topic is that the treatment landscape of HCC is changing given the results of Study IMbrave150 that demonstrated an improvement in survival when atezolizumab and bevacizumab were compared to sorafenib.

Fourth, we will ask why is it appropriate to maintain the monotherapy indication considering the accelerated approval of nivolumab and ipilimumab and the ongoing development of ipilimumab and nivolumab. Finally, we ask the committee to consider the ongoing studies of nivolumab, including a study to assess nivolumab in combination with ipilimumab, as well as your other studies.

As a reminder, here is the treatment landscape in advanced HCC. Again, atezolizumab in combination with bevacizumab has recently received regular approval in the first-line setting, and the other two available drugs in the first-line setting

are sorafenib and lenvatinib. The data for the available therapies in the second-line or later settings are all following prior treatment with sorafenib.

Nivolumab received accelerated approval for HCC in 2017 and pembrolizumab received accelerated approval in 2018. The nivolumab-ipilimumab indication was based on a separate accelerated approval that was granted in March of 2020.

We consider statements of favorable risk-benefit of nivolumab versus other approved therapies in the second-line setting as problematic because the other drugs have demonstrated improvements in overall survival and BMS has not compared nivolumab to these drugs and such a trial could be conducted.

To support the accelerated approval of nivolumab as a single agent, BMS submitted the results of Study CHECKMATE-040, which was an open-label, multi-cohort study that assessed the effects of nivolumab in patients with advanced HCC, whose disease progressed on sorafenib or in

patients who could not tolerate sorafenib.

For approval, the relevant cohorts of CHECKMATE-040 enrolled patients with Child-Pugh A liver function and excluded those with hepatic encephalopathy or clinically evident ascites. Patients with Child-Pugh B liver function were enrolled in a separate cohort of Study CHECKMATE-040. The primary endpoint of CHECKMATE-040 was ORR per RECIST 1.1 based on central review.

For the monotherapy approval of CHECKMATE-040, most patients had hepatitis B or C as a risk factor for HCC, and close to 70 percent of patients had Child-Pugh A5 scores, indicating relatively preserved hepatic function. Therefore, although there was not a specific exclusion criterion for bleeding, it is unlikely that the trial enrolled a notable number of patients who are at high risk.

FDA granted accelerated approval to nivolumab as a single agent in 2017 based on a response rate of 14 percent for nivolumab in the

indicated population. However, some patients had long durations of response with at least half of responding patients maintaining their responses for at least a year. Use of response criteria did not appear to have a notable impact in results with response rates similar using modified RECIST for HCC or immune RECIST.

As per the conditions of accelerated approval, FDA required that BMS conduct an additional study to verify the benefit of nivolumab. BMS proposed CHECKMATE-459 as the planned confirmatory trial. CHECKMATE-459 was a multicenter, multinational trial with randomization of nivolumab versus sorafenib in patients with HCC who received no prior systemic therapy and were not amenable to surgery or local regional therapy, or who progressed after local regional therapy.

The trial enrolled patients with Child-Pugh class A liver function and with a variety of HCC risk factors. The trial excluded patients with evidence of portal hypertension with bleeding, or esophageal or gastric varices within the past

6 months. However, an EGD was not required at screening. The primary endpoint of the study was overall survival.

This slide shows the overall survival results from Kaplan-Meier curves for CHECKMATE-459. The study did not demonstrate a statistically significant effect on overall survival for nivolumab when compared to sorafenib. The point estimate for the hazard ratio was 0.85 favoring nivolumab, but with a two-sided p-value of 0.075. PFS was similar between arms with an estimated hazard ratio of 0.93.

Remember that the Kaplan-Meier observations in a particular trial are point estimates, and as such, that any conclusions regarding trends should be interpreted with caution.

Here I'll provide FDA's position on the quality-of-life analyses that were described by the applicant in their presentation; for example, that improvements in quality of life were observed for nivolumab over sorafenib.

We only considered the analysis to be

exploratory, as overall survival and PFS benefits were not established for nivolumab, and the trial was not specifically designed to measure differences in symptoms caused by the patient's cancer.

Furthermore, attrition due to progressive disease, treatment discontinuation, or death resulted in a large proportion of absent patient-reported outcomes data beyond month 4. Therefore, it is difficult to draw meaningful conclusions from the longitudinal data from only the small number of patients.

Finally, these differences may be influenced by the adverse event profile of sorafenib, which is generally reversible upon discontinuation, whereas a small subset of patients on nivolumab can have severe immune-related toxicities with persistent morbidity upon treatment discontinuation.

Another consideration for the nivolumab monotherapy indication is the 2020 regular approval of atezolizumab and bevacizumab based on the results of Study IMbrave150. This study

demonstrated an important improvement in overall survival when atezolizumab and bevacizumab was 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. They also excluded patients with untreated or incompletely treated varices with bleeding or a high risk of bleeding. Patients were also required to undergo an EGD within 6 months prior to treatment.

There are arguments in the briefing document that checkpoint inhibition may be an alternative to anti-VEGF-based therapies in patients with a high risk of bleeding, including those with varices. However, to highlight a potential difference in risk-benefit, the independently reviewed assessed response rate for nivolumab was 6 percent among 49 patients with Child-Pugh B cirrhosis studied in a different cohort than CHECKMATE-040.

Additionally, prior to the regular approval of atezolizumab and bevacizumab, in March of 2020,

FDA granted accelerated approval to nivolumab in combination with ipilimumab. This was based on a 3-arm, randomized dose-finding study with patients in all 3 arms receiving both nivolumab and ipilimumab at different doses or schedules. Major eligibility criteria were like those of the monotherapy cohort of CHECKMATE-040, with patients having disease progression after prior sorafenib, Child-Pugh A scores, ECOG of zero or 1, and patients could have hepatitis B, C, or no infection.

Shown here are the results of the nivo 1-ipi 3 regimen that was submitted for the March 2020 accelerated approval. The response rate was 33 percent, which was like the response rate in the other nivo-ipi arm. The addition of ipilimumab also appeared to increase the rate of immune-related adverse events compared to nivolumab alone, based on non-randomized cross-cohort comparisons.

Although a nivolumab and ipilimumab indication would not, per se, block a hypothetical

new nivolumab monotherapy application if it were submitted today instead of 2017, we believe the combination regimen to be highly relevant given the low response rate for monotherapy, the negative randomized trial to date in the first-line setting, and the continued development of nivolumab and ipilimumab by BMS in the advanced setting.

Given that the CHECKMATE-459 trial of nivolumab versus sorafenib was not successful, BMS is proposing three trials to potentially confirm the clinical benefit of nivolumab.

CHECKMATE-9DW, shown in the red box, is investigating the effect of nivolumab combined with ipilimumab in the first-line advanced setting. This trial would appear to be more appropriate to verify and describe the nivolumab and ipilimumab accelerated approval rather than the nivolumab monotherapy accelerated approval.

CHECKMATE-9DX is investigating the use of nivolumab following definitive surgery or radiation in earlier stage disease, which may be less applicable to the second-line advanced setting.

CHECKMATE-74W is assessing the effect of nivolumab and ipilimumab, or nivolumab alone, when combined with transarterial chemoembolization in patients with intermediate stage disease.

Note that the primary analysis here is also the comparison of nivolumab, ipilimumab, and TACE versus TACE alone. Also note that this study will not be complete until 2026, which would potentially require an additional five years to assess whether this study could be used to verify the effect of the nivolumab monotherapy indication.

In the benefit-risk assessment, nivolumab's main effect observed to date is a 14 percent response rate in previously treated patients with HCC, with some patients maintaining long response duration. Reductions in tumor size may benefit some patients clinically, however, this does not mean all responding patients will benefit. This effect in response rate comes at a cost of potential development of immune-mediated adverse events.

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 specifically studied in CHECKMATE-040 unless they had more severe liver disease, which could alter the risk-benefit assessment.

For example, the response rate assessed of nivolumab in a cohort of patients with Child-Pugh B cirrhosis was 10 percent among investigators and 6 percent among the independently assessed response rate, which is typically what is used for regulatory decision making.

Given the changing landscape, it is worth considering how we would view a nivolumab application with a 14 percent response rate for second-line HCC indication today if it was submitted anew, with knowledge of IMbrave150. In other words, would it be reasonable to approve the second-line therapy knowing that atezolizumab and bevacizumab is an available therapy in the first-line setting?

Recall that for accelerated approval, a drug is approved on an earlier or intermediate endpoint that is reasonably likely to predict benefit in the context of an advantage over available therapy.

Furthermore, we will again highlight that FDA has granted accelerated approval to nivolumab in combination with ipilimumab, and this is the regimen that BMS is developing in the advanced setting in CHECKMATE-9DW. This is based on an approximate doubled response rate compared to nivolumab when administered alone.

As such, given the negative randomized trial in the first-line setting, does it make sense to maintain the current monotherapy indication given that the combination indication will be maintained at this time?

Before I show the voting question, I will again show this slide of the ongoing nivolumab trial. CHECKMATE-9DW is a 2-arm trial and not a 3-arm trial, and therefore it will be better to assess the accelerated approval of nivolumab and ipilimumab that was discussed in the last slide.

I will reiterate that the nivo-ipi approval will be maintained pending the results of the confirmatory trial, regardless of the decision taken for the monotherapy indication. CHECKMATE-9DX and 74W have monotherapy arms but are in different settings.

Finally, I would again like to state that there are legal standards regarding approval, and the decisions regarding regulatory actions are based on data submitted in applications to the FDA.

Now we come to the voting question. Given the following, the low response rate of monotherapy in the post-sorafenib setting; the treatment landscape changing with a survival benefit of alternative checkpoint inhibitor, atezolizumab, in combination with bevacizumab in the first-line setting; the negative monotherapy trial, or the unsuccessful monotherapy trial, versus sorafenib in the first-line setting; and the combination indication for nivolumab and ipilimumab will be maintained with the response rate higher with combination than compared to monotherapy, given

those, should the indication for monotherapy use of nivolumab in patients previously treated with sorafenib be maintained pending conduct or completion of additional trials? Thank you.

Clarifying Questions to Presenters

DR. HOFFMAN: Okay. Thank you.

We will now take clarifying questions for the presenters, both Bristol Myers Squibb Company and the FDA. Please use your 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.

I'm going to start. Dr. El-Khoueiry said

that one of the reasons for continuing this indication was that patients in the first line may have a contraindication to bevacizumab or atezolizumab. I was wondering whether there was some contraindication that might be present for atezolizumab that would still allow a patient to subsequently have nivolumab. I'm not entirely sure what was meant there.

DR. WAXMAN: Hi. This is Ian Waxman from BMS. I'll ask Dr. El-Khoueiry to clarify his statement.

DR. EL-KHOUEIRY: Yes. I appreciate the question. That is correct. If there is a contraindication to atezolizumab, that contraindication would usually stand for nivolumab as well. So it's really patients who have a contraindication to bevacizumab who would not get that combination of atezo-bev in first line and would in turn potentially benefit from nivolumab in second line.

DR. HOFFMAN: Okay. I had one other question. This would probably be for any of the

members of the company. As we heard at the end of the FDA presentation, if the second-line indication for nivolumab plus ipilimumab is going to be maintained for now, and the response rates are higher, why would we maintain the indication for the single agent?

DR. WAXMAN: Hi. This is Ian Waxman again. The benefit-risk profiles for nivolumab monotherapy and for the ipi-nivo combination are quite different, with each option being preferred for very distinct patient populations, as was already mentioned by Dr. Abrams.

To help ensure access for patients better suited for nivolumab monotherapy, we believe the current indication should also be maintained. I'll ask Dr. Abrams if he has any additional commentary to provide.

DR. ABRAMS: Thank you for the question. I would just add that the ipilimumab-nivolumab combination is really reserved for the fitter patients who failed TKI in the first line. The patients who would be considered for nivolumab

monotherapy have more comorbidities and generally have more marginal performance status. So they are really two different patient populations.

DR. HOFFMAN: Okay. Thank you. That's all for my questions.

Dr. Kraus?

DR. KRAUS: Yes. Thank you. Albert Kraus. I have a question, and it relates to the Study 459 results on survival; I guess slide 12, if you could put that up, 12 to 13.

The question is this, while you're putting it up. It was very close. It unfortunately didn't show statistical superiority. I did want to highlight for members around the ODAC table, we've been dealing with so many studies in the last six. ODACs and three days. This is a monotherapy superiority trial against an active drug, and that's a harder hurdle than beating placebo in a combination against the background or in isolation.

So I'll preface with that. But the question is around slide 12, which is, the results, the original and the extended, you mentioned you had

more subsequent therapy after the treatment period before death in the sorafenib arm. But you also had 20 percent immuno-oncology drug treatment in the control group after progression, which of course can influence result.

I'm wondering if you give a little more perspective on that because those are things that are hard to change because of the importance of the therapy, but certainly can impact the results.

DR. WAXMAN: Could we pull the slide up that Dr. Kraus had requested, the survival curves from the 459 study? I don't see it on the main screen. And while that's being pulled up for the audience to review, I will ask Ashwin Sama from our clinical group to also comment on the use of subsequent therapy in the study.

I'm sorry. I'm still not seeing the slide come up.

(Pause.)

DR. WAXMAN: We may be having a technical issue with the slides being presented. But, Ashwin, why don't you go ahead and speak to the

usage of subsequent therapy?

DR. SAMA: Ashwin Sama, clinical development, BMS. Slide up.

As I mentioned in my presentation, during the conduct of the study, many second-line options became available, including nivolumab. As we can see in the subsequent therapy slide, about 20 percent of patients got subsequent IO therapies, and there were another 10 percent, or 11 percent of patients, who got investigational agents, sometimes in a blinded study. So we could not clearly identify what agent the patient got.

So there are 20 to 30 percent of patients who got a subsequent IO therapy in the sorafenib arm.

DR. KRAUS: Thank you.

DR. HOFFMAN: Okay.

Dr. Lemery, did you have a comment?

DR. LEMERY: Yes. I want to actually make two comments. One is our first comment about whether the comparison was to placebo versus active control. I think that's acknowledged, but I think

it's dangerous, when a study is not positive, to say exactly why it's not positive.

There are many reasons why studies are not positive, including some of the things that have been mentioned as far as crossover. But these are sort of post hoc considerations, and I think it's dangerous to just ascribe positive results when a study's negative. I think that's not an acceptable situation.

With the comparison of nivo, ipi to nivo, for the most part, it's the same eligibility criteria for the enrollment of patients into both types of treatments, whether nivo alone or nivo-ipi. Nivo did have a separate cohort of Child-Pugh B. It was a smaller cohort, and the response rate was lower, especially when you compare the independently reviewed responses in both groups.

So I think, again, you have a situation where the eligibility criteria were similar for both. So there is not a data-driven decision as to why you would pick one versus the other in a

particular patient, and I think it's important to convey that message.

Dr. Beaver, Dr. Fashoyin-Aje, do you want to add anything?

DR. PAZDUR: Well, I was just going to ask that question to you guys. Was there a difference in the eligibility criteria between the single-arm nivo versus the combination of nivo and ipi? And if that wasn't true, if there was none, do we have adequate information [inaudible – audio gap] that tolerate ipi or nivo?

Because here again, we can't contrive or just make up an indication here, so to speak, to say that we're going to retain this indication, because we probably should even change the indication if we maintain it to those that cannot maintain and cannot tolerate this combination, and how do we characterize that patient population and has it been studied. Because if it hasn't been studied, we have no idea about the efficacy of that population.

Here again, we can't contrive indication off

the fly here, so to speak, because we want to. Is the data there in the single-arm nivo study of patients that could not tolerate ipi-nivo? That's what we're being asked here.

Could I see that data from BMS? I'm asking, you retained this indication for patients that cannot tolerate nivo and ipi. Okay. Were those patients studied? Because, obviously, anyone should give a patient population, a patient, a combination here because it has a higher response rate.

If you're advocating that there are some patients that cannot tolerate it -- and I firmly believe there are; believe me, I do -- were those patients studied and what is the response rate here?

That's a fair question to ask. You're asking us, really, to give you a new indication here for patients that cannot tolerate nivo and ipi, right?

DR. WAXMAN: This is Ian Waxman. I think the eligibility criteria that involves the

monotherapy Study 459 and 040, as well as the combination Study 9DW, are kept broad enough to allow the physicians to make decisions about which patients they think fit well into each one.

I will ask Dr. El-Khoueiry to provide his thoughts here.

DR. PAZDUR: I want to know what the response rate is in this patient population that cannot tolerate nivo and ipi, the combination. You're asking for that indication.

DR. WAXMAN: Right. So we don't have those exact data in front of us today --

DR. PAZDUR: Don't you think you should, if we're going to grant that indication?

DR. WAXMAN: What we do know is the Child-Pugh B data, which is representative of those less fit patients who would not be getting ipi-nivo but would be getting nivolumab monotherapy, and in that population, can I ask Dr. El-Khoueiry to speak about the types of results that he's seen?

DR. PAZDUR: Yes. I'm not that interested in personal observations. I'm interested in the

data that you have, not anecdotal experience. You're advocating for a new indication for patients that cannot tolerate the combination. Please provide me the response rate for those patients from your data pool, the data that you studied, not anecdotal information.

DR. WAXMAN: So all I can respond is that we do have patients included in the 040 and 459 studies who would not have been good candidates for ipi-nivo. We do not have data necessarily analyzed specifically in those subgroups to share today.

DR. PAZDUR: Because generally, if practice of medicine would allow people to lower doses, et cetera, we could go down multiple different routes here of giving people multiple different indications for people that think that they cannot tolerate a therapy just based on kind of they feel like it, so to speak.

I realize that there are people that cannot tolerate that combination because it probably is more toxic to some people. However, what's the data of the response rate in that population?

Because people have a right to know that if this is going to remain on the market. That population has to be studied. We cannot just make up indications on the fly.

DR. WAXMAN: I think the data that are quite relevant are the safety data. And we know that there's a side-effect profile associated with ipi-nivo that is just not going to be appropriate for many second-line post-sorafenib patients.

DR. PAZDUR: But what is the efficacy data, Dr. Waxman? That's what I'm after. It's a risk-benefit analysis and making a regulatory decision. What is the response rate?

You're asking us to change this indication; basically that this remains on the market. And usually what is done for patients that can't tolerate a given regimen, the practice of medicine -- not a regulatory decision, but the practice of medicine -- is to reduce doses, and that falls into the practice of medicine, not new indication.

DR. WAXMAN: If I can just clarify, we're

not asking for a new indication in any way. We're asking this indication remain --

DR. PAZDUR: By the virtue of this discussion, you're asking for a new indication.

Again, why would somebody maintain this indication? I think Dr. Hoffman addressed that in his question, is why would somebody want to take a single-agent nivolumab when you have much higher response rates? Who are those people, and then what is the efficacy in that population? People would have a right to know that.

(No response.)

DR. PAZDUR: Okay. So you can't answer my question. Thank you.

DR. HUKKELHOVEN: This is Matt Hukkelhoven from EMS. Let me be very clear that we are not asking here for a new --

DR. PAZDUR: Well, I'm asking it. I'm asking if this remains on the market, because that's the argument that you're making here.

DR. HUKKELHOVEN: No. I think it's up to the physician to determine whether a patient would

be most suitable to receive monotherapy or combination therapy. What we are asking is to consider the second-line indication to retain for the monotherapy.

DR. PAZDUR: And I want to know what the response rate is for those patients that can't tolerate this. It's a risk-benefit decision, and physicians need to know what the efficacy is in this. Although it may not be a written difference in indication, we might consider writing the indication differently. We certainly could do that, but what would be the efficacy data?

I think this data does not exist, so let's just bring this conversation to a close.

DR. HOFFMAN: I think, Dr. Pazdur, you've made your point. We should probably continue with the clarifying questions from the committee, if we may.

Dr. Halabi, you have a question?

DR. HALABI: Yes. This is Susan Halabi. Actually, one of them was asked by Dr. Pazdur, but I had other questions.

I haven't seen any survival data -- and maybe I missed that -- for CHECKMATE-040, Cohort 5. I would also like to see the progression-free survival if you have any data on that. And then I have some other questions.

DR. WAXMAN: Hi. This is Ian Waxman.

DR. HALABI: Yes.

DR. WAXMAN: So let's address this one first, then we can come back to the others, if that's preferred. I'll ask Ashwin Sama first to speak to the survival data for the Child-Pugh B cohort, Cohort 5, and as well, the PFS data if we have that to share.

DR. SAMA: Ashwin Sama, BMS clinical development. We have not shared the Child-Pugh B survival data. This was a single-arm study, so we presented the overall response rate. The median overall survival in Cohort 5 was 7.59 months, and the median progression-free survival was 2.4 months. The historical survival for Child-Pugh B HCC patients is about 4 months.

DR. HALABI: Okay. Thank you.

The next question has to do more with the CM-459. I mean, clearly this is a situation where the proportional hazard assumption hasn't been met, and it definitely had an adverse impact on the power of the trial.

One thing, I'm just curious because it seems even with taking into account the analysis you presented based on the piecewise hazard, even though this is exploratory analysis, it doesn't look to me that there is a benefit, even when you take into account the proportional hazard assumption hasn't been met.

Can you comment on that, please?

DR. WAXMAN: I'm going to ask Kalyanee Appanna from our statistics group to provide comment.

DR. HALABI: Thank you.

DR. APPANNA: Kalyanee Appanna, head of oncology biostatistics, Bristol Myers Squibb. We did check the proportional hazard assumption for the overall survival analysis, and we are looking at the treatment by time interaction test. We did

obtain a p-value of 0.23, suggesting the valuation of the proportional hazard as you mentioned.

In order to get meaningful insight into the magnitude of the benefit, as you saw in the briefing book, we calculated a piecewise hazard ratio, and for the first 8 months we had a hazard ratio of close to 1, as you saw in the briefing book, and after 8 months, it was 0.72.

Now, what we also did is we used the math [indiscernible] combo method to calculate the hazard ratio given that this method had the flexibility of accommodating different types of non-proportionalities and perhaps would be more robust in this case. Using that, we got a hazard ratio of 0.76 with a 95 percent confidence interval, ranging between 0.63 and 0.93 with a nominal p-value, if we can add there, of 0.012.

DR. HALABI: Thank you. I'm trying to understand how does this relate to the PFS since I haven't seen the Kaplan-Meier for PFS, but I think I've got the general idea.

Then the last question had to do with the

ongoing trials. A lot of them, the results are not going to read out it seems until 2023, and I was wondering when is your first readout or interim analysis plan; if the sponsor could share that with the panel members?

DR. WAXMAN: Yes, I can share that. For both the 9DX adjuvant study and the 9DW metastatic study, we expect final analysis in 2023. Each of those has a built-in interim analysis. Of course, they're event driven, so we can't predict the exact timing, but those would be expected to occur potentially in 2022.

DR. HALABI: Okay. Thank you.

Which part of '22? Can you say which quarter, more or less, q1, q2, or the end?

DR. WAXMAN: For the 9DX adjuvant study, since that study is completely enrolled and we're able to track events in a pooled fashion, we're estimating the first half of 2022.

DR. HALABI: Alright. Thank you.

DR. HOFFMAN: Thank you.

Dr. Weekes?

DR. WEEKES: Yes. This is for the BMS team. Can you expound upon how the ongoing studies relate to the second-line setting? Thanks.

DR. WAXMAN: Yes, I can address that first. As we've heard from the FDA --

DR. HOFFMAN: Sorry. Please state who's speaking.

DR. WAXMAN: This is Ian Waxman from BMS again. As we've heard, earlier-line studies can and have successfully served as PMRs for late-line accelerated approvals in the past. We think that the 9DX study is particularly well positioned because of its ability to characterize the benefit of nivolumab monotherapy not obscured by a combination, for example, in the same disease, although not in the same line. And we have confidence that those data will be relevant because in tumors where we have late-line metastatic data, in addition to adjuvant data, we've seen benefit in both of those settings.

DR. WEEKES: And how about the other two?

DR. WAXMAN: The 9DW study would add to the

body of evidence, showing that nivolumab or a nivolumab combination offers clinical benefit versus an active comparator in the first-line metastatic setting. Those data in combination with the 459 monotherapy data showing encouraging activity and the 040 data showing durable responses could potentially serve to fulfill the PMR.

The TACE study, 74W, is well positioned because it does allow for characterization of nivolumab monotherapy because one of the arms is a combination of nivo plus TACE and the comparator arm is TACE alone.

We can pull that slide up. It's a bit of a complex study design, so it may be easier to see it. But because we're able to characterize in the 74W study the nivolumab contribution, we think that this is also an acceptable postmarketing study to consider.

DR. WEEKES: Thank you.

(Pause.)

DR. STEVENSON: I'm sorry, everyone. The chair is reconnecting. Please bear with us a

moment.

(Pause.)

DR. STEVENSON: Hello. This is Takyiah Stevenson speaking. As the chair is reconnecting, it looks like, Dr. Lemery, you have a comment to make. Please state your name and your comment if you have a comment to make.

DR. LEMERY: Hi. This is Steven Lemery. Actually, I was raising my hand for Dr. Fashoyin-Aje, who would like to make a comment.

DR. STEVENSON: Go ahead.

DR. FASHOYIN-AJE: Yes. Hi. Good afternoon. I'm Lola Fashoyin-Aje. I'm a medical oncologist at FDA. I just did want to make some comments to extend the discussion that occurred when Dr. Pazdur raised the question about the data supporting maintaining an approval for nivolumab in the context of an approval for the combination with ipilimumab.

I think an equally important question, really, is that in considering whether single-agent nivolumab addresses an unmet medical need for a

bevacizumab or anti-VEGF ineligible population, which the applicant and the representatives from the applicant have raised a number of times, we would really need to evaluate that population in a well-designed and well-executed trial that demonstrates benefit in the context of a favorable benefit-risk assessment.

This bevacizumab ineligible population just was not specifically studied in the CHECKMATE-040 trial or in the CHECKMATE-459 trial; nor is that population the subject of investigation in any of the ongoing trials that are being proposed as potential confirmatory trials for this indication.

I think another important point to consider as we make inferences about the population studied in the 040 trial is that that trial was initiated in 2012, before the first approval of immune checkpoint inhibitors, which occurred in 2014. So it is unlikely that investigators would have been enrolling patients in that trial with clinical characteristics that portend a worse prognosis, as may be the case in 2021. So I think it's important

to have that in context as you consider these issues.

I just want to also reiterate what Dr. Pazdur said, which is that the testimony regarding the clinical experience is really important context to have, and we always appreciate having that. But our regulatory decision making is based upon scientific assessed questions, and we just don't have the data to carve out that population.

So it would really be incumbent upon BMS to really show us the data that supports maintaining this indication in the context of the available therapy. Thank you.

DR. WAXMAN: This is Ian Waxman. Can I add a comment?

DR. HOFFMAN: Yes.

DR. WAXMAN: Thank you. I just wanted to note that with the availability of ipilimumab and nivolumab in combination in the second-line setting, I think what you raise is an important question, but it's important beyond just nivolumab

because it is an option for all patients, regardless of which second-line agents, including other IO therapies, they're potentially given. It's not unique for nivolumab.

DR. HOFFMAN: I think we've covered the clarifying comments.

We're now going to take a 10-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topic with anyone during the break, and let's resume at 5:20. Thank you.

(Whereupon, at 5:09 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, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

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 Bristol Myers Squibb, and I have personally consulted for some pharmaceutical companies, I am not being paid for my testimony today. I am representing HCC patients and their caregivers.

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 endured 5 and a half rounds of useless chemotherapy. She 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. Most of the patients I've 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 past 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: choice, time, and hope.

I've been working with HCC patients and caregivers 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 beg you, please don't take away Opdivo as a choice of treatment for people with advanced HCC. Thank you for your time.

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 are representing for the record.

MS. PICKARD: My name is Bonnie Pickard. I'm a caregiver and I have no financial connection to anybody. In March 2019, we were stunned to learn at age 63, my husband had stage 4 inoperable HCC with portal vein clot and tumor; prognosis 3 to 6 months with no cure; treatment, keep the cancer at bay.

My husband was working a job he loved as an electro optics engineer in the defense industry and wasn't thinking of retiring. I was still working as an RN. Our first grandson was only 11 months Life changed.

Managing the HCC is a balancing act with treating without worsening the underlying liver disease. Initial treatment was Y90 radiation beads and a systemic med which worked for 10 months before scans showed progression. Our doctors were excited to offer Opdivo immunotherapy option, and

told us for some people this could provide years. I personally know of miracle responses of years.

Opdivo gave us seven more months, longer than the original prognosis, and provided a bridge of time until the next treatment, which was an Avastin-Tecentriq combination that was just FDA approved.

Immunotherapies are a beacon of hope in a bleak HCC treatment landscape and are just emerging. They offer hope of time, better quality of life, and with less side effects. A few short years ago, there was only one med option throughout, sorafenib, which is poorly tolerated by many. My husband could not tolerate a full dose of it, and quality of life was affected.

We are grateful that now, thanks to research trials and FDA expedited approvals, there are more options. Immunotherapies are key because every immune system is different, and HCC is so unique, MDs can't yet predict who will respond and are still learning the best way to use immunotherapy, but responses are improving.

For us, time is moments. Family trips are planned with trip insurance, as we can't predict how my husband will be feeling. Imagine your spouse saying, "I dreamed I don't have cancer." We live between scans and next treatment.

Thanks to FDA expedited approvals and immunotherapy options like Opdivo, my husband has had time with our grandson who is now 3 and his grandad's shadow. They have Yoo-hoo happy hour, as you can see on the screen. We now have a granddaughter who turns 1 in June. Our younger daughter just got engaged, and he hopes to be able to walk her down the aisle.

These moments would not be possible without the time of hope drugs like TKIs and immunotherapies like Opdivo are providing. If this is your spouse, child, or parent, you want that option to try that med, which offers hope for the next birthday, Christmas, or walking a daughter down the aisle.

I implore you, please do not rob your own family members, and anyone living with HCC, of the

time and hope Opdivo is offering by making it unavailable. I urge you to continue the wonderful work the FDA is doing with expedited approvals, which is expanding treatment options, and hope, and quality of life for advanced HCC patients like my husband. Thank you.

DR. HOFFMAN: Thank you.

Open public hearing 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.

MS. CRYER: Thank you very much. My name is Donna Cryer. I am the founder and CEO of the Global Liver Institute. I am also a liver patient. And in addition, although I'm only speaking on behalf of the Global Liver Institute today, I do serve on the executive committee of the Clinical Trials Transformation Initiative; the board of directors of Sibley Hospital within the Johns Hopkins medicine system; and for over a decade, I have served as an FDA patient representative, so I

understand the challenges before you all today, and I thank for your diligence.

As far as disclosures, the Global Liver Institute does receive educational grants from BMS and many companies in the hepatology and gastroenterology space. However, we have not been paid for this testimony today and have no financial stake in the outcome of this hearing.

I'll be making brief remarks. My written responses have been submitted for the consideration of all of those involved here, so I will focus my remarks on three things, the importance of innovation to the mission of GLI, which compels us to testify here today. The Global Liver Institute is a patient-led, patient-driven organization whose board and government structure is majority patients and patient families.

This is simply an indication to give some context of which our liver cancer's work and community sits as we provide scalable models to lead liver health advocacy in the United States and across the globe.

So I speak to you today not only as certainly an individual patient, and a patient who has mentored and spoken with many liver cancer patients who are directly affected by this issue, but the Liver Cancer Council, which has over 30 members -- including Mayo Clinic; Mount Sinai; Moffitt; University of Texas Southwestern Medical Center; the Cancer Support Community; Prevent Cancer Foundation; the Association of Community Cancer Centers; Triage Cancer -- enjoys participation from both the National Cancer Institute here in the United States, as well as in Egypt.

So it is within that context and within that backing that I say to you today the following comment on the serious and urgent nature of hepatocellular carcinoma, as stated so well by Dr. Abrams earlier, and speak in very strong support about maintaining access to monotherapy indication for Opdivo as a treatment for advanced HCC patients.

I see my time is up, so I will simply end

there and thank you, particularly as the FDA has embarked very soon in Black Cancer Family Week. We do not have Black Cancer Family Week unless we have options for black patients, who are particularly underserved in the liver cancer space. And so I thank you for your time today.

DR. HOFFMAN: Thank you.

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

DR. EL-RAYES: Hello. This is Bassel El-Rayes. I'm a medical oncologist who treats patients with liver cancer, and I was one of the investigators on CHECKMATE-040. I have no financial conflicts to declare.

I wanted to talk today about the impact that nivolumab has in patients with HCC. It definitely provides a therapeutic option that allows patients to have prolonged disease control, which is something we haven't seen prior to the advent of

immune therapy.

In addition, nivolumab offers a treatment option that is relatively safe with lower impact on quality of life and the available TKIs in the second-line setting. Even in the advent of immune therapy in the frontline setting with atezolizumab and bevacizumab, there is still a subset of patients who are not candidates for this therapy and who would benefit from potentially immune therapy in the second-line setting. Those are patients who have contraindications to bevacizumab, and in my practice I find that those patients do benefit from nivolumab in the second-line setting.

This is basically my conclusion. Thank you.

DR. HOFFMAN: Thank you.

Speaker number 6 --

MR. SCHROETER: Yes?

DR. HOFFMAN: -- your audio is connected now. Please introduce yourself and state your name and any organization you're representing for the record.

MR. SCHROETER: Yes. My name is Gary

Schroeter, and I am a cancer patient, liver cancer. For full transparency, I work with Bristol Myers Squibb as a patient ambassador. However, Bristol Myers Squibb is not connected or compensating me for participating today, and I've chosen to do my presentation strictly on my own. I did want to thank the ODAC for allowing me the opportunity to relate my personal experience with nivolumab and with the Opdivo drug.

As I said, my name is Gary Schroeter. I was diagnosed with liver cancer in February of 2013. At the time, I was told my life expectancy was probably around 12 months. As the former boxer and poet laureate, Mike Tyson, once said, "Everyone has a plan until they get punched in the face."

Well, getting the news of having hepatocellular carcinoma at age 57 was definitely my punch in the face, but with the help of my support group, we decided to try and fight the disease. I just had one caveat, and that was I'd be able to lead an active lifestyle.

I began my treatment of the disease by

taking Nexavar. It kept the cancer stable for about a year before it became ineffective. During that time, I did some research, and the immunotherapy drugs looked to have the brightest future for treating me and the cancer, so I applied for and was blessed to be accepted to take part in a clinical trial for the nivolumab at Emory's Winship Cancer Institute. I also have to add that I was blessed to get a great doctor, who without him, I would not be on this call today.

Now, after my first cycle on the Bristol Myers Squibb drug, Opdivo, my tumor shrank roughly 70 percent, and best of all, the cancer was not growing or spreading to my other organs. During my time on and off nivolumab, I've experienced very few side effects, and I've been able to remain active, which includes playing golf one to two times a week with my friends and playing tennis two and sometimes three times a week.

Best of all, the nivolumab has allowed me to walk my daughters down the aisle, and my wife and I are enjoying our first grandchild, who turns 3 in

August.

So to sum it up, my experience with Opdivo has been extremely positive, and I feel that it should be made available to treat liver diseases to anyone that it can possibly help. Thank you all so much for your time and your attention.

DR. HOFFMAN: Thank you.

Speaker number 7, your audio is connected now. Will speaker number 7 please begin and introduce yourself? And state your name and any organization you're representing for the record.

DR. KELLEY: Thank you. My name is Katie Kelley, and I'm a GI medical oncologist at UCSF. I'm an investigator on several BMS-sponsored trials, which my institution receives research funding. I do not receive any personal compensation from BMS, and I'm not being compensated for my comments today.

I'd like to share some real-world experience on nivolumab in advanced HCC patients who are not optimal candidates for anti-angiogenic therapy. Many patients with advanced HCC have absolute or

relative contraindications to anti-angiogenic therapy. These include refractory bleeding, non-healing wounds, and greater degrees of hepatic dysfunction. Patients with these conditions generally are excluded from clinical trials.

Next, I'll show several examples.

GI bleeding is a common challenge in HCC. The first patient is a 74-year-old female with chronic hep B, who was diagnosed with multifocal HCC and duodenal invasion, complicated by a massive upper GI bleed and multiple intra-abdominal abscesses. She was not a candidate for anti-angiogenic therapy, so started first-line nivolumab.

She had a partial response around 14 months, during which time she recovered fully from the bleeding and abscesses. She then started lenvatinib at progression and has been doing well now for over 6 months.

Another example is this 25-year-old male with non-viral HCC diagnosed in 2013, who was treated with multiple liver-directed therapy

followed by multiple systemic therapy regimens, including sorafenib, several clinical trials, and ramucirumab.

He had worsening hepatic dysfunction over time and recurrent variceal bleeding. He started nivolumab in 2015 with subsequent complete response, now ongoing for over 5 years with improvement in liver function back to Child-Pugh A. This graph shows his hospitalization largely for bleeding events while on prior therapy before nivolumab, after which he had no further variceal bleeding.

Hepatic dysfunction is another prevalent contraindication to most HCC treatment options. This next case is a 70-year-old male with Child-Pugh B7 cirrhosis, diagnosed with metastatic. HCC after prior Y90. He started first-line sorafenib, which was contraindicated by symptomatic encephalopathy and rising bilirubin.

He next started second-line nivolumab, after which the encephalopathy resolved and bilirubin normalized. As shown in this graph, he experienced

a prolonged partial response for around 12 months before progressing.

There are many other relative or absolute contraindications to anti-angiogenic therapy. This last case is another with a non-healing wound, which receive nivolumab and had a complete response to therapy, ongoing now for three years.

In conclusion, relative or absolute contraindications to anti-angiogenic therapies are very common in real-world advanced HCC, and systemic therapy options with level-1 evidence are quite limited for our patients with these comorbidities.

Immune checkpoint inhibition with nivolumab monotherapy has demonstrated acceptable safety in patients with Child-Pugh B hepatic dysfunction, and a subset of patients who are not candidates for anti-angiogenic therapies can derive meaningful benefit. 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.

I think we completed our clarifying questions for the presenters.

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

DR. KRAUS: Yes, I did. Thank you, Dr. Hoffman. I'll be very brief, as we're late on time.

Certainly the facts and specific situations are always different in the considerations that ODAC faces, and that FDA faces. Certainly, I just want to emphasize that that the flexibility confirmatory trials being of varying types and often earlier lines, combination or monotherapy, are emphasized.

But the second, and probably more important point -- and I applaud FDA, oncology in particular, for being very good about this over the years -- is, since we have two hepatocellular carcinoma considerations that have certain similarities, it's very important for regulated industry to have a consistent playing field and a consistent assessment of behavior and outcome in

same situations.

I'm not saying these are the same situations, however I am just noting the importance of that consistent playing field as we make a consideration for ODAC. Thank you. That's all.

DR. HOFFMAN: Thank you.

Dr. Waxman, do you have your hand up?

DR. WAXMAN: No. I no longer have a comment. Thank you.

DR. HOFFMAN: Okay.

Questions to the Committee and Discussion

DR. HOFFMAN: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will proceed with the 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

we'll display that in a moment.

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

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

yes, no, or abstain. You should not leave the "no vote" choice selected.

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

Dr. Kraus, you have your hand up. Did you have a question?

DR. KRAUS: No. I'm sorry. I forgot to pull the hand down.

DR. STEVENSON: Oh, no problem at all.

DR. HOFFMAN: Okay. We will now begin the voting on question 1.

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 votes into the record. You can also state the reason why you voted as you did, if you want to.

There are 4 yeses, 5 noes, and zero abstentions.

DR. HOFFMAN: This is Dr. Hoffman. I voted yes because I think there's still an unmet need for

second-line immunotherapy, because there will always be some patients who are poor candidates for bevacizumab or who are not tolerating or responding, of course, to sorafenib.

I do take Dr. Pazdur's point about maybe a bit too much wiggle room in terms of deciding between nivolumab itself or nivolumab plus ipilimumab. And I guess, theoretically, a clinician could say, "Well, I'm going to give nivo, and the dose of ipi I'm using is zero," but I wouldn't want to have to tangle with the insurance companies about that.

So I think that, based on the clinical information I've heard, I would say to retain this indication pending further study.

Next is Dr. Sung.

DR. SUNG: Yes. My name is Anthony Sung, and I voted no. The reason I voted no was because of the negative randomized trial. And, again, as Dr. Hoffman alluded to, I think I might have found Dr. Pazdur's line of inquiry more compelling. I just think the data is not there, and it does not

sound like there is a trial that is currently planned that will help yield more data.

One of the industry representatives asked about consistency, and I would note that yesterday I voted yes, while today I voted no. I would say, at least in my mind, the reason I voted yes for the drug under discussion yesterday was because there was a potential signal, a biomarker signal, that could help distinguish who would respond.

Because I do think that there are patients who benefit from nivo monotherapy. I just think that the data shows that the benefit is not there for the population as a whole. And I would encourage BMS, or other members of the pharmaceutical industry, to dig a little bit more deeper, especially in these drugs which have low response rates, to try to identify biomarkers that could identify which subjects may benefit from these drugs.

But again, while I believe that there may be individuals who benefit, I don't think the data is there for the population as a whole. Thank you.

DR. HOFFMAN: Thank you.

Dr. Halabi?

DR. HALABI: Susan Halabi. I voted no, and the main reason is while we all acknowledge there is an unmet need and there may be a subgroup of patients who may benefit – [inaudible – audio gap] -- looking at the totality of the data in terms of objective responses, I think -- and I wasn't convinced -- that there is really a big clinical benefit to the patients, and also taking into account the quality of life and the missing data, and the fact that this was totally exploratory.

Then the final point that I wanted to mention is I'm looking at the opportunity cost for the patients, and I believe, as we discussed earlier today, that even though this may not be maintained, a group of patients will have access to nivo. And maybe I misunderstood that, but this patient will always have access through the expanded access program. Thank you.

DR. HOFFMAN: Thank you.

Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell, and I voted yes. This was a very close call. Over the last 90 minutes, I was on both sides of this, closer to Dr. Hoffman part of the time, closer to Dr. Sung the rest. But I came down in the end, yes, because I feel there is an unmet need that was compelling.

There is evidence of effectiveness, but I do think the FDA should look very closely at the interim analyses for CM-9DX and CM-9DW studies as early as possible next year. And I fervently hope there's going to be clear data in the future that supports Opdivo as second-line monotherapy.

DR. HOFFMAN: Okay. Thank you.

Dr. Weekes?

DR. WEEKES: Hi. It's Colin Weekes. I voted no. I don't think the randomized data support the continued approval as a population. I did not feel that the proposed studies will shed light into the second-line setting, and the time needed to get those results I think are not close

enough to warrant further approval.

DR. HOFFMAN: Thank you.

Ms. Hoyt?

MS. HOYT: My name is Karen Hoyt, and I voted yes. I, too, understand, and I listened carefully to everyone speak today, and I considered carefully Dr. Pazdur's questions about the data. I want to applaud the research by the sponsor and the oversight by the FDA.

As a patient advocate, for a decade I ran a website for liver disease, and I was a lucky one. I got the tumor -- the transplant. In a way, my tumor became a golden ticket, and I was able to build a bridge to transplant.

I've been in relationship with so many HCC patients that my heart goes out with a great urgency. I encourage and I applaud the research, and continued research and oversight through continued trials so that the HCC death rate can be reduced. And I appreciate the chance to speak on behalf of patients today. Thank you.

DR. HOFFMAN: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu, and I voted yes. I share, I think, the difficult decision that's been described by multiple others on the committee. I think I fell more on the line of Dr. Hoffman in regards to unmet need.

I'm going to make the point that this indication is certainly more complicated than our prior discussion, and that's mainly because the confirmatory study that does not reach statistical significance is in a completely different line of therapy. There is a late but somewhat believable separation that occurs, but the lack of statistical significance is certainly problematic.

Again, the issue largely being, in patients that cannot receive bevacizumab in the front-line setting, is it reasonable to continue an indication in an immunotherapy-naïve population where an overall survival benefit may exist? I do believe that the answer at this time is yes, but certainly a confirmatory study is needed.

This is complicated as well because I see

CHECKMATE-9DX, that study, as the only viable alternative, and of course that's another completely different line of treatment that does not necessarily relate well to the second-line setting.

Certainly, if 9DX is positive, it would support continued indication. But as Dr. Weekes had mentioned, there's reservation regarding the timing of the study for the readout. And of course if that study is negative, I would certainly support removal of the indication at that time. Thank you.

DR. HOFFMAN: Thank you.

Dr. Lewis?

DR. LEWIS: Yes. This is Mark Lewis, and I voted no. And even though we ended up on different sides of the fence, I share Dr. Lieu's sense that this was an extremely nuanced and difficult decision.

You know, when I am trying to perform a risk-benefit calculus, I need both a numerator and a denominator, and both of the quantities were not

clear to me here, which is the main reason I voted no.

As a clinician, I have to tell you, there's a certain je ne sais quoi, when I look at a patient in front of me, as to whom I think will tolerate an immunotherapy doublet. And part of learning that Gestalt, that only comes with practice and experience, and that is, again, a part of being a doctor. It's part of being an oncologist.

The problem is here, trying to distill that Gestalt down into data, and specifically into eligibility criteria. As I said in a previous discussion, one of the reasons I think we're convening today is to prevent these accelerated approvals from dangling ad infinitum, and I couldn't see any upcoming data -- even acknowledging that CHECKMATE-9DX is going to be important, I couldn't see any upcoming data that are going to specifically address the risk-benefit calculus around nivolumab as monotherapy here.

So many other schemas are wonderful and scientifically rigorous, but are predicated on

doublet therapy. So that's why in the end I came down on a no vote.

DR. HOFFMAN: Okay. Thank you. Dr. Kunz?

DR. KUNZ: Yes. Thank you. This is Pamela Kunz, and I also voted no; lots of great discussion here at the end of the day, and I agree that this was an incredibly difficult decision, and I fell in the no column.

I think the two things that really led to that decision for me were that there really are no postmarketing trials planned that specifically address efficacy of monotherapy in the second-line setting. Then secondly, I agree with comments made around needing additional data for the ipi-nivo ineligible population, as challenging as that is. Thank you.

DR. HOFFMAN: Okay. Thank you.

Clearly, we have a split vote here and some people taking into account the unmet need and some good clinical results, and others correctly concerned about the lack of firm data from a confirmatory trial. I just want to ask if there

are any final comments from the FDA before we adjourn.

DR. LEMERY: Sure. This is Steven Lemery. It's been a long day, and we just want to thank the committee for their careful deliberation for all the sessions, and the open public speakers and patients for contributing today, and I wish everyone a good evening.

Does anyone else from FDA have any comments?

(No response.)

Adjournment

DR. HOFFMAN: I'd like to also thank everyone who prepared so thoroughly, the sponsors and the scientists at the FDA for a very thorough job, and also for the technical staff of the FDA that managed to put this all together with remarkably few hiccups. It's a feat, so I appreciate that.

I think we'll now adjourn the meeting and thank everybody for their participation.

(Whereupon, at 6:09 p.m., the meeting was adjourned.)