FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Thursday, June 24, 2021

10:30 a.m. to 2:40 p.m.

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P R O C E E D I N G S

(10:30 a.m.)

Call to Order

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

My name is Philip Hoffman, and I will be chairing today's meeting. I will now call the June 24, 2021 meeting of the Oncologic Drugs Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting, and will begin with introductions.

Introduction of Committee

DR. CHEN: Good morning. My name is She-Chia Chen, and I am the designated federal officer for this meeting. Once I call your name, please introduce yourself by stating your name and affiliation. We'll first start with ODAC members.

Dr. Cristofanilli?

DR. CRISTOFANILLI: Good morning. This is Dr. Massimo Cristofanilli, breast medical oncology from Northwestern University.

DR. CHEN: Dr. Garcia?

DR. GARCIA: Good morning. Jorge Garcia, chief, Medical Oncology Division, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center in Cleveland, Ohio.

DR. CHEN: Dr. Halabi?

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

DR. CHEN: Dr. Hoffman?

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

DR. CHEN: Dr. Lieu?

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

DR. CHEN: Mr. Mitchell?

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

multiple myeloma patient.

DR. CHEN: Dr. Nieva?

DR. NIEVA: Hi. This is Jorge Nieva. I'm a medical oncologist at the University of Southern California, Norris Comprehensive Cancer Center.

DR. CHEN: And Dr. Rosko?

DR. ROSKO: Good morning. My name is Ashley Rosko. I'm an associate professor in the Division of Hematology at the Ohio State University and medical director of the Oncogeriatric Program.

DR. CHEN: Next are our temporary voting members.

Mr. Berlin?

MR. BERLIN: Hi. I'm Neil Berlin. I am the patient representative. I am a rectal cancer patient, and in my real life I'm the director of operations for summer camps in Maryland, for two summer camps in Maryland.

DR. CHEN: Dr. Cruz-Correa?

DR. CRUZ-CORREA: Good morning, a pleasure to be here. I'm a professor at the University of Puerto Rico, Medical Sciences Campus, and the

University of Puerto Rico Comprehensive Cancer Center. I'm a GI oncologist.

DR. CHEN: Dr. Kunz?

DR. KUNZ: Good morning, everyone. My name is Pamela Kunz, and I am a GI medical oncologist at Yale Cancer Center.

DR. CHEN: Dr. Lewis?

DR. LEWIS: Yes. Good morning. My name is Mark Lewis. I am a gastrointestinal medical oncologist and the director of GI Oncology at Intermountain Healthcare based in Salt Lake City, Utah.

DR. CHEN: Dr. Lurain?

DR. LURAIN: Good morning. I'm Kate Lurain. I am a hematologic oncologist to the HIV and AIDS Malignancy Branch at the National Cancer Institute.

DR. CHEN: Dr. Reidy-Lagunes?

DR. REIDY-LAGUNES: Good morning. My name is Diane Reidy-Lagunes. I'm a GI medical oncologist at Memorial Sloan Kettering Cancer Center.

DR. CHEN: We'll continue with temporary voting members.

Dr. Reiss Binder?

DR. REISS BINDER: Hi. I'm Kim Reiss Binder. I'm a gastrointestinal medical oncologist at the University of Pennsylvania.

DR. CHEN: Dr. Sanoff?

DR. SANOFF: Hi. Hanna Sanoff, also a GI medical oncologist at the University of North Carolina.

DR. CHEN: And Dr. Weekes?

DR. WEEKES: Good morning. I'm Colin Weekes. I'm a medical oncologist at Massachusetts General Hospital. Thank you.

DR. CHEN: Next is acting industry representative; Dr. Kraus?

DR. KRAUS: Yes. Good morning, everyone. I'm Albert Kraus. I work in research and development of cancer medicines for several decades; currently employed by Pfizer in Connecticut.

DR. CHEN: Finally, we'll go to the FDA participants.

Dr. Pazdur?

DR. PAZDUR: Hi. Richard Pazdur, director of the Oncology Center of Excellence, FDA.

DR. CHEN: Dr. Beaver?

DR. BEAVER: Hi. Julia Beaver, chief of medical oncology in the Oncology Center of Excellence and acting deputy director in the Office of Oncologic Diseases.

DR. CHEN: Dr. Kluetz?

DR. KLUETZ: Hi. This is Paul Kluetz. I'm deputy director in the Oncology Center of Excellence and acting supervisory associate director of the Office of Oncologic Diseases.

DR. CHEN: Dr. Lemery?

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

DR. CHEN: Dr. Fashoyin-Aje?

DR. FASHOYIN-AJE: Good morning. This is Lola Fashoyin-Aje, deputy director, Division of Oncology 3.

DR. CHEN: Dr. Casak?

DR. CASAK: Good morning. I'm Sandra Casak, and I am the team leader for the GI malignancy team

in OOD.

DR. CHEN: And Dr. Saung?

DR. SAUNG: Good morning. My name is May Tun Saung. I'm the clinical reviewer in the Division of Oncology 3.

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. She-Chia Chen will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of the 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 the discussion of Biologics License Application, BLA, 761209, for retifanlimab injection, submitted by Incyte Corporation. The proposed indication used for this product is for the treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal, SCAC, who have progressed on or who are intolerant of platinum-based chemotherapy.

This is a particular matters meeting during which specific matters related to Incyte Corporation's BLA will be discussed.

Based on the agenda of today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Albert Kraus is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

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

issue. Thank you.

DR. HOFFMAN: We will now proceed with FDA introductory comments from Dr. Sandra Casak.

FDA Introductory Comments – Sandra Casak

DR. CASAK: Members of the advisory committee, of the Incyte team, public, and FDA colleagues, good morning. My name is Sandra Casak. I am a pediatric oncologist in the Office of Oncologic Diseases, and I am the cross-disciplinary team leader for the retifanlimab new biologics license application. I will refer to Incyte as the applicant for the remainder of the presentation.

The applicant is seeking accelerated approval of retifanlimab for the treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal who have progressed on or who are intolerant of platinum-based chemotherapy.

Retifanlimab is a programmed death receptor 1 or PD-1 blocking antibody. The applicant submitted results from POD1UM-202 to support their proposed indication. POD1UM-202 is

an ongoing, open-label, single-arm study of retifanlimab in patients with squamous anal canal cancer with disease relapse or progression after prior treatment. The primary endpoint is overall response rate as assessed by an independent central review. You will hear more details about the design of the trial in the upcoming FDA and sponsor's presentations.

FDA is bringing this application to the Oncologic Drugs Advisory Committee to enable public discussion of the results of POD1UM-202 and whether the evidence is sufficient to demonstrate the benefits of retifanlimab in patients with squamous anal canal cancer.

A key uncertainty regarding this application is whether the low response rate observed in a small number of patients in POD1UM-202 will translate into positive impact on progression-free survival or other clinical benefit, particularly in the context of an inconsistent relationship between low response rates observed in single-arm studies with immune checkpoints and clinical benefit in

confirmatory studies.

The accelerated approval program was designed to allow for earlier approval of drugs that treat serious conditions and that fill an unmet medical need based on an intermediate endpoint reasonably likely to predict clinical benefit, taking into account the availability, or lack thereof, of alternative treatments. As a condition of accelerated approval, FDA typically requires an additional study to verify and describe clinical benefit, converting the accelerated approval to a regular approval.

The FDA has approved seven antibodies directed against PD-1 or programmed death-ligand 1, PDL-1, across more than 75 indications in oncology. Of the first 76 approvals, 35 were initially granted approval using the accelerated approval pathway; 31 of these approvals were supported by single-arm studies with overall response rate as the primary endpoint.

As of June 1st, results of the confirmatory studies are unknown in 13 indications, and in 9 of

the indications, confirmatory studies successfully confirmed clinical benefit. In 9 of the of the indications approved, based on overall response rate, the confirmatory trials were not successful in meeting their objectives, and the response rate was between 10 and 20 percent in seven of these.

The table on the right summarizes the results of four single-arm studies with immune checkpoint inhibitors for which accelerated approval was granted based on a response rate between 10 and 20 percent, but with prolonged durations of response for which the confirmatory studies were unsuccessful and resulted in the voluntary withdrawal from the market of these indications.

The table on the left summarizes the results of five studies with immune checkpoint inhibitors for which accelerated approval was granted based on response rate and durable duration of response, for which the confirmatory study or studies were unsuccessful and were discussed in an oncologic advisory committee held on April 27 to April 29

this year.

After three days of lengthy discussions and the withdrawal of four indications from the market, one can infer that low response rate, even when some of these responses are durable, do not always translate into clinical benefit when a larger number of patients are studied in clinical trials.

Although we cannot discuss follow-up with respect to the advisory committee meetings, it is important to highlight that in instances where the advisory committee voted to maintain the indication, there were specific reasons, including additional trials to be read out, that will provide risk-benefit information.

For example, for the pembrolizumab hepatocellular cancer indication, the results of a randomized trial are expected this year, and the committee felt it appropriate to wait for those data. This contrasts with the current retifanlimab indication, where there will be a single study that will not read out until at least the end of 2024.

Given the uncertainty of modest response

rate and benefit discussed in these advisory committee meetings, it isn't clear if it's appropriate to maintain the status quo with respect to approvals based on low response rates in single-arm trials, especially considering that in many cases, randomized trials could have been initiated months or years earlier.

While retifanlimab has not yet been approved, several of the concerns discussed at the ODAC held in April of this year are pertinent to this application. In POD1UM-202, the overall response rate, according to RECIST version 1.1, as assessed by independent review, is 14 percent; that is a total of 13 patients of the 94 enrolled in POD1UM-202 experienced responses with a lower bound of the 95 percent confidence interval as low as 8 percent.

The estimated median duration of response in the 13 responding patients is 9.5 months, with 7 of the 13 patients having a response lasting 6 months or more. However, the median should be interpreted with caution given the small number of responding

patients.

Importantly, a mere 9 of the 94, or 10 percent of patients, enrolled in the trial were HIV-positive, and two of them experienced a response. In addition, patients enrolled in POD1UM-202 tended to have non-bulky regional disease. For example, 4 of the 13 responders had non-bulky lymph node disease as the only target lesions.

From a safety perspective, the risk of retifanlimab appears generally consistent with the known safety of other approved PD-1 or PD-L1 therapies. Although uncommon, 6 percent of patients experienced grade 3 or higher events and resulted in treatment delay, discontinuation, and even death in at least one patient.

However, the safety database of POD1UM-202 is limited, and given its design as a single-arm trial, it is not possible to establish a causal relationship for the observed adverse events. The toxicity profile associated with retifanlimab will be discussed in more detail by both the applicant

and the FDA.

To summarize, Study POD1UM-202 yielded an overall response rate of just 14 percent with a 95 percent confidence interval, showing that the true response rate may be as low as 8 percent. Based on the briefing document, the applicant points to a large fraction of patients with durable, stable disease as indicative of the clinical benefit of retifanlimab. However, stable disease is not a reliable endpoint in a single-arm trial because it is not possible to assess whether any observed period of stable disease is due to a drug's effect or represents the natural history of a patient's tumor.

POD1UM-202 is a small, single-arm study in which only 13 patients had a response, and the response lasted more than 6 months in only 7 patients, and the small sample size contributes to the uncertainty on the characterization of the estimation of the retifanlimab effect.

Furthermore, due to the size of the study, a small number of patients who may disproportionately

suffer from anal canal cancer, like patients with HIV, blacks, and Hispanic or Latinos, have been enrolled in the study, which adds uncertainty to the study results as applicable to the population for which retifanlimab would be indicated if approved.

As mentioned before and discussed at the oncologic advisory committee meetings held in April, when assessing the relationship between low response rates observed in small, single-arm trials of monotherapy immune checkpoint antibodies and clinical benefit, there is uncertainty that these low rate of responses translate into clinical benefit.

As previously stated in this meeting, we are considering a low response rate in a single-arm trial. A benefit of single-arm trials is they can provide an early signal of the effects of a drug, and for drug with unprecedented or breakthrough effects, for example, certain drugs that target NTRK, ROS, ALK, or BRAF, single-arm trials may be sufficient to support regular approvals.

Single-arm trials can also be a means to provide access to an investigational drug while obtaining preliminary information about the drug's effect.

Although single-arm trials have been important to advance the treatment of diseases when substantial durable response were observed, unfortunately, in many development programs where there are uncertainties regarding a drug's effects, or a drug's effect is modest, this has led to an overreliance on single-arm studies to the potential detriment of patients.

For example, given the modest effect on overall response rate in POD1UM-202, it would seem that the randomized study should have been initiated earlier and certainly prior to enrolling as many as 90 patients in a single-arm trial. Indeed, published data have been available since as early as 2017 that described results of inhibition of the PD-1 pathway in advanced anal cancer.

As such, should we be reappraising the situations where single-arm studies are appropriate to support approval? And additionally, should

confirmatory studies be fully enrolled, or nearly fully enrolled, when an accelerated approval is granted?

A key uncertainty regarding the application is whether the low response rate observed in a small number of patients on POD1UM-202 will translate into a positive impact on progression-free survival or other clinical benefit.

The applicant is conducting a randomized, confirmatory trial of retifanlimab in combination with chemotherapy compared to chemotherapy alone in patients with squamous anal canal cancer, Study POD1UM-303 or InterAACT 2.

This may address uncertainties, however, as of May 25th, only 28 patients have been enrolled, adding additional concerns given the competitive landscape when other immune checkpoint inhibitors are also being studied in combination with chemotherapy.

At the end of the discussion period, the ODAC will be asked to vote on whether the

demonstrated effect of retifanlimab outweighs the risks of the drug in the proposed indication or whether an action should be delayed until data from the confirmatory studies, estimated to read out in the fourth quarter of 2024, are available.

This concludes my remarks, and I thank you for your attention.

DR. HOFFMAN: Thank you.

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

For this reason, FDA encourages all participants, including the sponsor'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 interests 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 Incyte Corporation.

Applicant Presentation – Michael McGraw

DR. MCGRAW: Good morning, Mr. Chairman, members of the advisory committee, and the FDA. I'm Michael McGraw, executive director of regulatory affairs at Incyte. We're pleased to be here today to share the data supporting accelerated approval of retifanlimab for the treatment of locally advanced or metastatic squamous carcinoma of the anal canal.

The proposed indication is for patients who have progressed on or are intolerant of platinum-based chemotherapy. Squamous carcinoma of

the anal canal that has progressed on platinum-based chemotherapy is a rare and serious disease with no approved therapies. As such, retifanlimab was granted orphan drug designation for the treatment of anal cancer and fast-track designation for our proposed indication.

This application was also granted priority review. These designations are granted for drugs that are intended to treat serious conditions and fulfill an unmet medical need. Likewise, the accelerated approval pathway is intended to provide earlier access to potentially valuable therapies where there's been a demonstration of effect on a surrogate endpoint that's reasonably likely to predict clinical benefit. This pathway allows for remaining questions to be answered with future studies.

Advanced anal cancer is a prime example of why this pathway is important. Patients with platinum refractory anal cancer have no approved options despite their dire prognosis. Approval through this accelerated pathway would make

retifanlimab available to patients years earlier than what would be possible under the regular approval mechanism.

Retifanlimab is anti-PD-1 monoclonal antibody that shares a similar mechanism of action within this well-established class, and the retifanlimab data generated demonstrate that the nonclinical pharmacology and clinical efficacy and safety profile are consistent with other PD-1 inhibitors. Anti-PD-1 therapies have proven to be an exceptionally important advance in oncology with almost half of the FDA approvals granted as accelerated approval.

It is important to note that anal cancer shares the same biology with other tumors that are caused by HPV infection. Chronic HPV infection has a unique biology that shapes the tumor immune microenvironment in ways that favor potential benefit from immunotherapy, and the POD1UM-202 results are entirely consistent with the experience in cervical and head and neck cancer for the currently approved anti-PD-1 therapies.

In these HPV-driven malignancies, an initial response rate, considered modest by chemotherapy standards, has consistently predicted for survival benefit in confirmatory studies. This reflects the fact that responses to immunotherapy are usually quite durable, and the accelerated approvals in these indications were granted because of the prolonged duration of response.

Unlike other tumors discussed in the FDA briefing document, this consistent pathology makes HPV-driven cancers ideal targets for anti-PD-1 therapy and supports that the results of POD1UM-202 are reasonably likely to predict clinical benefit in our confirmatory study, POD1UM-303.

Although there are no FDA-approved therapies for these patients, PD-1 inhibitors are used off-label based on their inclusion in the NCCN guidelines. However, access is frequently restricted. In fact, access to this treatment option is dependent on where patients receive care and their insurance coverage. Based on healthcare claims data and survey research, a significant

proportion of physicians experience reimbursement challenges, preventing many patients in community settings from ever receiving a PD-1 inhibitor. Thus, there is a wide disparity in how Americans with anal cancer are treated.

As you can see from these data, off-label use of PD-1 inhibitors is not a substitute for regulatory approval. A labeled indication for retifanlimab in anal carcinoma would improve access to needed therapy for all patients, including for those patients who are treated outside of large academic centers. Approval would also greatly expand the knowledge base with rigorously collected pre- and post-approval data.

Additionally, approval would allow dissemination of the most current disease and treatment information to patients in the form of proper product labeling, and would facilitate educational efforts, not only in a drug class, but also in anal cancer in general, which, unfortunately, has been understudied.

The data we will share today demonstrate

that retifanlimab has a positive benefit-risk profile and fulfills the criteria for accelerated approval. This is a rare cancer with a poor prognosis and a significant unmet need. The POD1UM-202 results demonstrate a meaningful advance for patients who have no approved therapy.

The results are reasonably likely to predict improvement in long-term outcomes, based on a similar experience with PD-1 inhibitors in other previously treated HPV-driven malignancies. Lastly, our phase 3 confirmatory study, POD1UM-303, is already underway and is expected to provide practice changing results for patients with earlier disease in approximately four years time.

With this information in mind, let me provide the agenda for the rest of today's presentation. First, Dr. Marwan Fakih will review the significant unmet medical need. Dr. Mark Cornfeld will then present the clinical data from the retifanlimab development program. Dr. Fakih will then return to provide his clinical perspective, and Dr. Cornfeld will conclude with

the benefit-risk.

We also have additional responders to help answer any questions. All external presenters have been compensated for their time. Thank you. I'll now turn the presentation to Dr. Fakih.

Applicant Presentation – Marwan Fakih

DR. FAKIH: Thank you.

Hi. I'm Marwan Fakih, professor of medical oncology and therapeutic research at the City of Hope Cancer Center in California. I appreciate the opportunity to provide the background on squamous carcinoma of the anal canal, as well as discuss the urgent need for an approved therapy to treat our patients.

Anal cancer is a rare, HPV-driven, life-threatening disease with an annual incidence of approximately 9,000 cases per year in the United States, approximately 2,000 of whom will eventually become refractory to the available treatments. While rare, the incidence and its associated death has increased by 3 percent per year for the past decade, particularly in HIV-positive patients who

are at the greatest risk.

About 30 percent of patients with anal cancer will present with unresectable metastatic disease that is not curable or will develop metastatic disease following chemoradiation. These patients can initially be treated with platinum-based chemotherapy but will inevitably progress within a year or less. There are no approved treatment options for patients who have progressed on platinum-based chemotherapy despite the poor prognosis.

In addition to short survival, patients with advanced anal cancer experience diminished quality of life due to significant disease burden. Patients commonly experience locoregional progressive disease with or without distant metastases, resulting in pain due to sacral involvement, symptomatic adenopathy, and destruction of the anal canal.

These symptoms are compounded further by chronic toxicities related to their prior chemoradiation. As a result, tumor shrinkage or

preventing tumor progression can provide meaningful palliative benefits and is certainly one of the goals I have for my patients.

The first-line standard of care for unresectable, locally advanced or metastatic anal cancer is platinum-based chemotherapy. The Kaplan-Meier curve shown here is from the phase 2 InterAACT study, which established carboplatin with weekly paclitaxel as a preferred treatment as per NCCN guidelines.

Unfortunately, the benefits of first-line chemotherapy are limited, and all patients will ultimately develop progressive disease, as shown here. Once progressed on first-line therapy, the outcome is dismal, and the estimated progression-free survival at 6 months is less than 15 percent.

Despite the severity of this disease, there are no approved therapies for patients with advanced anal cancer following progression on platinum-based therapy. A limited number of salvage chemotherapy regimens have been used after

platinum. These studies were characterized by small sample size and lack of central review assessment, and given their retrospective nature, are not reliable. Therefore, none of these have been endorsed in clinical practice and should not be considered as a standard of care.

In addition, some prospective clinical trials have evaluated immunotherapy agents. Pembrolizumab and nivolumab have been endorsed for use in this setting based on the limited data which you see here. As noted by Dr. McGraw, inclusion in guidelines does not mean that these therapies are available to all Americans, particularly those with limited resources or who lack access to a cancer center.

This is an unfortunate reality for too many, particularly those being treated in the community setting. And while these PD-1s or anti-PD-1s have been associated with clinical activity, none have led to drug approval or standard of care for patients. Note that HIV-positive patients are poorly represented in these studies, despite being

the population at greatest risk for developing the disease.

Immunotherapy is a promising option for treatment for advanced anal cancer based on the underlying biology and favorable experience with PD-1 inhibitors and other HPV-driven squamous cell cancers, like cervical and oropharyngeal cancer as shown in this slide.

Despite the relatively modest overall response rate, these responses are extremely durable and translated into meaningful prolonged survival, as you can see in randomized studies of pembrolizumab, cemiplimab, and nivolumab.

To summarize, patients with locally advanced or metastatic anal cancer have a very poor prognosis and there are no approved or widely available, and effective treatments for patients who have progressed on first-line platinum-based chemotherapy.

Anti-PD-1s are the most promising salvage therapy option and have regularly demonstrated durable responses in HPV-driven squamous cancers,

leading to a prolonged overall survival.

It is biologically plausible that this should extend to anal cancer as well, since it shares the same biology as cervical cancer and HPV-driven head and neck cancers. Our patients urgently need approved options. The Incyte retifanlimab program represents the first comprehensive assessment of these promising therapies in anal cancer.

Thank you. I will now turn the presentation to Dr. Cornfeld.

Applicant Presentation – Mark Cornfeld

DR. CORNFELD: Thank you.

My name is Mark Cornfeld, and I am vice president of immuno-oncology drug development at Incyte. I will describe the results of POD1UM-202, demonstrating how treatment with retifanlimab resulted in clinically meaningful benefit with an acceptable safety profile in patients with previously treated squamous carcinoma of the anal canal.

You will see that retifanlimab provides

durable, independently confirmed tumor responses in 14 percent of the study population in RECIST stable disease in another third. Thus, almost half of the POD1UM-202 study population benefited from retifanlimab.

Both response and stable disease were associated with prolongation of progression free and overall survival, and the efficacy of retifanlimab is comparable to what has been seen with other PD-1 inhibitors in the setting of previously treated HPV-driven malignancy and continues to evolve with our longer follow-up.

Let's examine the underlying rationale for the study. There is a strong scientific basis for therapeutic use of checkpoint inhibitors in refractory squamous carcinoma settings, particularly those that are driven by chronic viral infections like HPV. Like cervical cancer, squamous anal cancer is preceded by integration of HPV into the host genome, and this triggers carcinogenesis through expression of the E6 and E7 viral oncoproteins.

In addition to promoting oncogenesis, HPV shapes the tumor microenvironment in ways that allow tumor growth but that will also favor response to a PD-1 inhibitor. T cells become reactive against tumor cells expressing HPV antigens, but due to chronic exposure, they will eventually become exhausted and non-functional, in part due to the upregulation of the PD-1/PD-L1 axis. It has been shown that HPV-driven tumors have an abundance of exhausted PD-1 positive T cells that are specific for HPV viral antigens, and these are the targets for retifanlimab.

This response to immunotherapy is also exceptionally broad in terms of antigen spreading, which promotes durable tumor control. This is unlike other tumor types where the antigen is recognized by T cells are heterogeneous and in many cases subclonal.

We had already seen promising activity with retifanlimab in cervical cancer, so this served as further proof of concept for initiating the POD1UM-202 trial. Let's look at the study design.

POD1UM-202 is an ongoing phase 2 study in adults with advanced anal cancer who have progressed after prior exposure to platinum, and therefore have no approved therapeutic options. In the absence of a standard of care or an acceptable control for comparison, the study has a single-arm, open-label design.

All of the patients had an ECOG performance status of 0 or 1 in RECIST measurable disease, and since patients with HIV represent a group of particularly high-risk for developing anal cancer, we made a special effort to include them in accordance with ASCO guidelines and also FDA's input on how they should be monitored during treatment.

The primary endpoint is objective response rate as adjudicated by an independent central reviewer. The sample size of 94 is large for an orphan disease and allows meaningful assessment of the risk-benefit of retifanlimab, including biologically important patient subsets.

The secondary endpoints were duration of

response, disease control rate, overall survival, and progression-free survival. We also conducted exploratory efficacy analyses, which will be shared today, as well as an exploratory assessment of quality of life, since this can frequently be impacted in advanced anal cancer.

We recruited a population with advanced disease that is highly representative of what is seen in clinical practice. The study was conducted in the United States and Europe, with the majority of participants coming from France and the UK. The median age was 64 years and there was a female predominance. The patients were predominantly white, though information on race could not be collected for a quarter of the study population due to local privacy regulations.

Moving to baseline characteristics, approximately 10 percent of the study population were HIV-positive, which is also consistent with the epidemiology of the disease. Nearly all the patients had received prior radiotherapy, most in the form of chemoradiation, and all but 3 patients

had received prior platinum-based therapy with exceptions allowed per the study entry criteria.

Eighty-two percent of study patients had distant metastases with more than one measurable tumor focus identified in the majority. Liver metastases were common, as was locoregional disease. Baseline hypercalcemia was also present in 12 percent of patients which is consistent with the advanced nature of their disease.

Turning now to the efficacy results, the primary endpoint of objective response rate per independent reviewer was 13.8 percent and included 1 complete response and 12 partial responses. An additional 33 patients had stable disease as their best response, which brings the overall disease control rate to almost 49 percent. Though stable disease represents a lesser degree of disease control than RECIST response, it is still clinically relevant, as will be shown in our subsequent analyses.

All the responding patients had received prior platinum and radiotherapy, and the

investigator-assessed response rate was similar at 15 percent, though there were additional complete responses when assessed locally.

Importantly, responses were observed regardless of gender, age, race, HIV status, presence or absence of liver metastases, or tumor PD-L1 expression. In addition, none of the responders had tumors within this match with their phenotype. In fact, every subgroup of interest appeared to benefit from retifanlimab, which allows the results to be generalized to standard practice.

Durability of response was assessed after all responding patients had been followed for a minimum of 6 months from the time of their initial response, at FDA's request. The estimated median duration of response was 9.5 months. As would be expected for an effective immunotherapy, these responses to retifanlimab are considerably more durable than what can be anticipated from salvage chemotherapy.

Turning to our additional analyses, 46 percent of patients had a decrease in the target

tumor burden, based on the independent review, which is promising for this refractory cancer. These were not insignificant tumors either. The median sum of diameters for purposes of RECIST assessment was more than 5 centimeters for responders and those with stable disease. However, this is an underestimate of the total tumor burden, since RECIST restricts the number of lesions that can be followed and discourages selection of large, complex masses, since these are typically more difficult to measure reliably. In addition, lymph nodes are assessed using the short access of their measurement.

Non-target disease is also not considered in the RECIST assessment of measurable tumor burden. In our study population, persistent disease in the anal rectum was often considered non-target due to the radiotherapy that all patients had received earlier in the course of their disease.

Overall, approximately 60 percent of the study population had locoregional disease defined as pelvic, rectal, anal, or local lymph node tumor

deposits.

Spider plots are another way of looking at the durability of tumor control. Here you see the change in the measurable tumor burden over time for patients who were assessed as having an ICR response. The solid portion of the lines refers to data from the primary analysis, and the dotted lines indicate additional data that became available at the time of the follow-up analysis for durability last October. You can see that the tumor control was quite durable, in some cases exceeding 1 year, as is typical with immunotherapy.

Here is the corresponding spider plot for patients with best response of stable disease. Again, you can see the tumor control in these patients, though less dramatic, still remains quite stable over a protracted period of the time. This represents clinical benefit, too, and our ongoing follow-up of study population, though not shown here, reinforces this conclusion.

The composite spider plot demonstrates that treatment effects are well maintained over the

entire duration of observation for both the responding population, as well as those with stable disease. The median progression-free survival is added here for reference, and you can see the median PFS for all patients with disease control is 7.4 months, which is considerably longer than the historical experience.

Here you see the Kaplan-Meier curve for overall survival with a median of 10.1 months in the overall population, as of the cutoff date just over a year ago. Though not a controlled comparison, the median overall survival of patients with both RECIST response and stable disease was not reached and was longer than the 7.7 months for patients with progressive disease. Notably, all of the responding patients were still alive at the time of the primary analysis, which suggests that a survival benefit may emerge in randomized studies like the ongoing confirmatory study, POD1UM-303.

The swim-lane plot illustrates the clinical course for the 46 patients with ICR-assessed response, shown in green, or stable disease, shown

in gray, as of the primary data cutoff last June. You can see that many patients remained ongoing when this analysis was conducted, as indicated by the arrow at the end of the bars, and this benefit persists with our more recent follow-up.

Liver metastases are typically viewed as being poorly responsive to immunotherapy, despite their importance as a frequent site of metastasis in advanced anal cancer. In this regard, it is noteworthy that meaningful reduction in liver tumor burden was seen in 24 percent of our study population and included major reduction in bulky liver metastases in 2 patients. Note that not all of these patients were classified as having had a RECIST response.

To summarize the efficacy seen in POD1UM-202, retifanlimab elicited clinically meaningful, durable tumor responses. The durability of these responses, the disease control rate, and the overall survival compare favorably to what can be expected from salvage chemotherapy, and responses were demonstrated across all patient

populations of interest, including patients with liver metastases, those who were HIV-positive, and those with PD-L1 non-expressing tumors.

Overall response rate and stable disease were both associated with prolongation of progression-free survival and overall survival, and additional evidence for benefit was shown in our exploratory analyses.

Taken as a whole, these data strongly suggest that the clinical benefits of retifanlimab were experienced by a large proportion of the POD1UM-202 study population, and there are consistent with what has been achieved with PD-1 inhibition in other refractory HPV-driven cancers, including cervical and head and neck cancer, where PD-1 inhibitors are already approved.

Turning now to the safety profile, a total of 521 patients with advanced solid tumors, including the 94 patients with anal cancer, received at least one dose of retifanlimab and are included in the all-cancer population. The all-cancer population includes patients with both

treatment refractory and less advanced solid tumors, and represents the complete experience of retifanlimab monotherapy that was submitted to FDA for review. The median exposure and number of infusions was similar in both groups of at 4, and there were a handful of patients that had received treatment for more than one year at the time of the analysis.

Overall, the safety profile was as expected for the disease under study and also for the PD-1 inhibitor class. Treatment toxicity could be managed within the well-established guidelines that are familiar to oncologists.

Most severe and serious adverse events were related to causes other than treatment; in particular, complications of the underlying malignancy, and these events also rarely led to discontinuation of retifanlimab. There was only one death attributed to retifanlimab throughout our program, and this was a case of suspected tumor hyperprogression.

We will be focusing on the immune-related

adverse events since these are the events of interest for the PD-1 inhibitor class. Immune-related events were generally mild to moderate in severity and reflect the known immune toxicities of PD-1 inhibitors. No previously unrecognized immune-related toxicity was reported in either the anal cancer or the all-cancer population.

There were 2 events leading to treatment discontinuation in the initial analysis of the anal cancer study, which was skin reaction and pneumonitis. Through routine pharmacovigilance, we've identified two additional discontinuations, one due to immune hepatitis and the other due to immune enterocolitis, and both of these are well described in the literature. The overall incidence of infusion reactions was low, with none being severe or resulting in a change of management.

Let me review the immune-related events in a little more detail. The most common events, accounting for nearly half of the immune-related AE, were either thyroid or skin reactions. These were generally mild and manageable with

immunosuppression or endocrine replacement as per the established treatment guidelines.

Again, we see that rates in the anal cancer patients are comparable to the all-cancer population and also consistent with what has been reported for the PD-1 inhibitor class as a whole.

Of particular interest with the safety in patients with HIV, since this is a population at high risk for anal cancer that has historically been excluded from clinical trials, the 10 percent HIV positivity rate in our study slightly exceeds the frequency in the general anal cancer population; so POD1UM-202 provides a basis for decision making in these patients who clinicians are now routinely seeing.

All HIV-positive patients continued their retroviral therapy during the study, and in general they fared quite well. The safety profile was consistent with the general population experience, and of note, there were no opportunistic infections reported in this group. Additionally, we did rigorous assessments of CD4 counts and viral load,

and no patient experienced loss of HIV control during the study.

In summary, the safety profile of retifanlimab is acceptable in advanced anal cancer and the wide variety of tumor types that we studied in our clinical development program. Our overall experience in more than 500 patients is also consistent with what has been reported for the PD-1 inhibitor class.

Immune-related adverse events were manageable, and discontinuations due to these events were infrequent, and treatment was well-tolerated in all patient subsets, including those who were HIV-positive.

Of particular importance for this disease is that we did not observe myelosuppression. This is impactful because these patients are almost universally exposed to pelvic radiotherapy and chemotherapy as part of their primary treatment. Thus, salvage chemotherapy, which is widely used, becomes difficult to administer because of the myelosuppressive complications that are frequently

associated with it.

I'll turn now to the confirmatory study, which was designed with FDA's input and is already underway. This study is being scientifically supported by the International Rare Cancers Initiative, which successfully conducted the previous groundbreaking InterAACT trial.

The study will provide confirmatory evidence for the efficacy of retifanlimab in platinum-refractory disease while also establishing the benefits of earlier treatment. Study results are expected in about four years.

POD1UM-303 is a blinded, phase 3 study in surgically unresectable locally advanced or metastatic anal cancer. Our design has a 1 to 1 randomization to standard-of-care chemotherapy, with the addition of either retifanlimab or placebo for one year. We plan to enroll 300 patients who will be stratified by PD-L1 expression, geographic region, and the extent of their disease. There is a controlled crossover to retifanlimab after ICR confirmation of progression, which will facilitate

recruitment in the United States.

Due to the rarity of this disease and the need for crossover, progression-free survival is the primary endpoint with a targeted hazard ratio of 0.67. Overall survival is a key secondary endpoint. We expect the crossover data to be of great interest, too, since this population will closely resemble the POD1UM-202 patients.

POD1UM-303 is currently underway with the first patient dosed in November of last year. Current enrollment is 32 patients. The study is being conducted worldwide, and we have instituted several measures to increase minority participation in the United States. Study completion is projected for 2024, with submission of the study report in the second half of 2025.

Thank you. I'll now invite Dr. Fakih to share his clinical perspective on the data.

Applicant Presentation – Marwan Fakih

DR. FAKIH: Thank you, Dr. Cornfeld.

As mentioned, anal cancer is a rare and, unfortunately, understudied cancer. Despite

increasing rates and high mortality, regimens that were developed decades ago remain the mainstay of treatment, and there are no approved agents once the cancer progresses on chemotherapy. Response to second-line chemotherapy is anecdotal at best, and treatment is associated with serious toxicities.

Current PD-1 inhibitors, while showing evidence of effectivity, have not been approved for anal cancer, and off-label use is restricted, particularly for patients treated in the community setting, some of whom, unfortunately, die from their disease without the opportunity of being treated with anti-PD-1 agents.

The clinical benefits of retifanlimab in POD1UM-202 were considerable and extended beyond patients who were described as having a response to RECIST guidelines. The study population was very representative of the patients we see every day in clinical practice, and they clearly had advanced refractory disease.

The disease control rate of 49 percent will have a major clinical impact on these patients, as

demonstrated by median progression-free survival of 7.4 months, greatly exceeding historical expectations.

Responses in the liver were also noteworthy, since these have been associated with poorer responses to immunotherapy and other tumor types such as melanoma and non-small cell lung cancer. This study also provides meaningful data for decision making in patients with anal cancer who are HIV-positive.

Putting these results from POD1UM-202 in context, the efficacy of retifanlimab is consistent with what has previously been seen in checkpoint inhibitor trials of previously treated HPV-driven malignancies, including those where PD-1 inhibitors are now approved for use in cervical and head and neck cancers.

From my perspective, the retifanlimab safety profile is favorable and aligns with other approved anti-PD-1 agents. I am very comfortable that clinicians who are currently using these drugs will know how to manage these side effects and manage

the safety profile of retifanlimab. Additionally, the safety data that have been generated for patients with HIV are informative.

Taken together, the POD1UM-202 data supports accelerated approval of retifanlimab. Retifanlimab demonstrates meaningful activity and an acceptable safety profile with outcomes that align with expectations for other PD-1 inhibitors in HPV-driven malignancies. These data are particularly meaningful because they come from a registrational program.

Importantly, patients urgently need this treatment to be approved by the FDA since access to off-label therapy is limited. PD-1 inhibitors are well-established, particularly in HPV-driven squamous cancers, and retifanlimab closely aligns with our expectations. Retifanlimab accelerated approval affords us an opportunity to make a PD-1 inhibitor accessible to patients in need who cannot afford to wait until 2025.

I appreciate the panel's deliberation today in consideration of retifanlimab. As someone who

treats these patients, I consider the data promising and meaningful, and hope to be able to prescribe retifanlimab to my patients in the future. Thank you. I will now return the presentation to Dr. Cornfeld.

Applicant Presentation – Mark Cornfeld

DR. CORNFELD: Thank you, Dr. Fakih.

I'd like to close with a brief summary of how the data from POD1UM-202 demonstrate a favorable benefit-risk for retifanlimab in platinum-treated anal cancer.

Anal cancer is rare, and patients whose cancer has progressed, despite optimal treatment, have a very poor prognosis with no approved therapies. The accelerated approval pathway is critically important to these patients since they do not have the option of waiting for phase 3 trial results.

As shown in POD1UM-202, the efficacy of retifanlimab in this advanced patient population is in line with expectations and is clinically meaningful since the NCCN guidelines already

recommend the use of pembrolizumab and nivolumab in this setting, based on pilot data.

The response rate, durability of response, and overall survival in POD1UM-202 are all consistent with previous PD-1 inhibitor studies in HPV-driven cancers, where survival benefit has subsequently been confirmed, and the efficacy of retifanlimab continues to evolve favorably with ongoing study follow-up.

The safety profile is consistent with the PD-1 inhibitor class and favorable compared to chemotherapy, and this contributes to the overall assessment of a positive risk-benefit.

It is notable that the overall response rate does not fully account for the benefits of PD-1 inhibitor therapy in HPV-driven cancers. Here, you see that modest response rates in the low to mid-teens have consistently predicted for important survival benefit in cervical and head and neck cancer, which are biologically very similar to anal carcinoma. In fact, all of the cervical and head and neck studies have now confirmed the survival

benefit with the recent disclosure of additional phase 3 study results.

The higher disease control rate seen in POD1UM-202 may be a more accurate predictor of outcome since prolonged stabilization of disease was also associated with longer survival in our study. These comparisons give us confidence that the efficacy seen to date with retifanlimab is reasonably likely to predict for definitive clinical benefit in POD1UM-303 when it reads it in 2025.

As noted, pembrolizumab and nivolumab are frequently prescribed off-label in anal cancer after progression on platinum, but these options are only routinely available to those who are fortunate enough to have comprehensive health insurance or access to a major cancer center. In fact, a wide-ranging assessment of actual PD-1 inhibitor use in the United States consistently shows that at least half of the patients who could be receiving these effective therapies for refractory anal cancer, unfortunately, are not.

Because the majority of cancer patients are treated in the community setting, we commissioned a community-focused practice survey to better understand why oncologists are not routinely prescribing PD-1 inhibitors for this patient population.

From these respondents, it is clear that insurance delays or outright denials of service are the main barrier to PD-1 inhibitor treatment in advanced anal cancer, since these impact physician's prescribing patterns and leave many patients without access.

From the insurer's perspective, this reflects the fact that no PD-1 inhibitor has been FDA-approved for this indication. The retifanlimab submission is, therefore, and opportunity to remove an important barrier that prevents a large number of Americans from receiving optimal cancer care.

Based on FDA's published guidance, retifanlimab meets all requirements for accelerated approval in this rare and understudied disease. Patients with previously treated anal cancer have

an urgent, unmet medical need, with poor survival and no FDA-approved treatments. The results of POD1UM-202 showed favorable benefit-risk in this population and are reasonably likely to predict for definitive benefit in the confirmatory POD1UM-303 study, which is already underway.

If approved for use under the accelerated mechanism, retifanlimab will provide a highly-needed treatment for patients who cannot afford to wait any longer for an effective, approved option.

This concludes our presentation. Thank you for your attention.

DR. HOFFMAN: Alright. Thank you. We will now proceed with the FDA presentation.

FDA Presentation – May Tun Saung

DR. SAUNG: Good morning. My name is May Tun Saung, and I'm a medical oncologist and clinical reviewer for this biologics license application for retifanlimab. This application was submitted on November 25, 2020 by Incyte Corporation, who I will refer to as the applicant

for the rest of the presentation.

This slide lists the members of the multidisciplinary FDA review team for this application. My presentation reflects their collective input.

I will begin with the introduction, where I will provide a brief overview of the review issues that serve as the basis for referring this application to the advisory committee. I will then briefly summarize the results from POD1UM-202 clinical trial. This will be followed by a discussion of the review issues. Finally, I will provide a summary of the FDA presentation, followed by the discussion and voting question for the committee.

I will now provide a brief overview of the review issues that serve as the basis for referring this application to the advisory committee.

It is not clear that the current results of POD1UM-202 are reasonably likely to predict clinical benefit based on the following reasons. The response rate was low in this trial, at

14 percent, with a 95 percent confidence interval of 8 percent to 22 percent. One clinical trial was submitted to support this application, POD1UM-202, and a limited total number of patients responded, 13 patients. There were also a small number of target lesions per responding patient.

Only 7 patients had responses lasting 6 months or greater. Because of the small sample size of the trial, few patients with HIV-positive status or patients who are members of racial or ethnic minority groups were enrolled in POD1UM-202, increasing the uncertainty of the true treatment effect across the U.S. population in which retifanlimab will be indicated. Furthermore, even though the safety profile of anti-PD-1 and anti-PD-L1 antibodies are well characterized, this class of drugs is still associated with uncommon but serious and sometimes irreversible or fatal toxicity.

Finally, with anti-PD-L1 or anti-PD-1 antibodies, there has been an inconsistent relationship between the low overall response rates observed in single-arm trials and the long-term

clinical benefit observed in confirmatory randomized controlled trials. Anti-PD-1 or anti-PD-L1 antibodies have received 35 accelerated approvals, and for 10 of them, their confirmatory trials did not demonstrate long-term clinical benefit.

Some of the indications had multiple confirmatory trials that did not demonstrate long-term clinical benefit. This has led to the FDA's reassessment of accelerated approvals based on low overall response rates in single-arm trials for anti-PD-1 or anti-PD-L1 antibodies, and the FDA held a three-day advisory committee meeting in April of this year to discuss this issue.

Dr. Casak reviewed the definition of accelerated approvals, in that it takes into account the availability or lack of alternative treatment. Available therapy is defined as therapy that is approved or licensed in the U.S. for the same indication being considered for the new drug, and is relevant to current U.S. standard of care for the indication.

In evaluating the current standard of care, FDA may consider recommendations by authoritative scientific bodies or guidelines based on clinical evidence and other reliable information that reflects current clinical practice.

There are no FDA-approved treatment options for squamous cell carcinoma of the anal canal. There are published reports of three single-arm trials that investigated two different anti-PD-1 antibodies, nivolumab and pembrolizumab, with overall response rate as the primary endpoint.

The overall response rate per the published report was 24 percent for nivolumab with a 95 percent confidence interval as shown, and the overall response rates were at 12 percent and 17 percent for pembrolizumab with a 95 percent confidence interval as shown.

Neither nivolumab nor pembrolizumab are FDA-approved for the treatment of squamous cell carcinoma of the anal canal. However, both are in the NCCN guidelines as second-line options with published data available as early as 2017. While

pembrolizumab or nivolumab may not be considered available therapy for strictly regulatory purposes, they are available for use and are being used in clinical practice.

During the advisory committee meeting held in April, we discussed 10 accelerated approvals granted for anti-PD-1 or anti-PD-L1 antibodies, based on results from single-arm trials. For nine of these indications, the accelerated approvals were granted based on overall response rate as the primary endpoint.

The indications in these nine accelerated approvals were urothelial cancer; small cell lung cancer; hepatocellular carcinoma; gastric cancer; and gastroesophageal junction cancer. The overall response rates ranged from 12 percent to 29 percent.

The indications for 4 of the 9 accelerated approvals were voluntarily withdrawn from the market by the companies. These four accelerated approvals are listed here. Five of the 9 accelerated approvals were discussed in detail

during the three-day advisory committee meeting held in April.

After three days of lengthy discussion and the withdrawal of four indications from the market, shown in the previous slide, it appears that low response rates, even when some of these responses are durable, do not always translate into clinical benefit when larger numbers of patients are studied in clinical trials.

Although FDA cannot discuss the follow-up with respect to the advisory committee meetings held in April, an important lesson is that when voting to maintain an indication, members of the advisory committee considered if alternative confirmatory trials were being conducted and the timing of when these trial results are expected. Thus, FDA would like to highlight that in today's meeting, we will discuss an application with a single confirmatory trial that has enrolled only 28 patients as of May 25, 2021, which is only 9 percent of the planned trial population.

In the next two slides, I'll provide a brief

overview of the trial design and the results of POD1UM-202. The applicant submitted the results of POD1UM-202 as the primary evidence to support the safety and efficacy of retifanlimab.

POD1UM-202 is an ongoing, open label, multicenter, single-arm trial. Eligible patients must have squamous cell carcinoma of the anal canal that progressed on or after platinum-based therapy unless they were ineligible for or intolerant of platinum.

Patients must have received no more than two prior lines of systemic therapy for metastatic disease, have measurable disease by RECIST 1.1, and an ECOG performance status of 0 to 1. Patients with HIV were eligible to enroll as long as their HIV was well controlled, with CD4 count greater than or equal to 300 cells per microliter and an undetectable viral load. Patients with HIV must be taking anti-retroviral therapy to be eligible. In total, 94 patients were enrolled and treated with retifanlimab.

This slide summarizes the baseline

demographics of the trial population. Sixty-five percent of the patients were women and the median age was 64 years. Only one known black patient and four known Hispanic or Latino patients were enrolled in the trial. In addition, the race of 22 percent of the patient population was reported as other or unknown.

As we note, infection for the human papilloma virus, also known as HPV, is a risk factor with the strongest association with anal cancer. Although the rate of HPV positivity among the patients tested for HPV in POD1UM-202 was consistent with the rate of HPV positivity in the general population of patients with squamous carcinoma of the anal canal, the HPV status was reported in only 62 percent of the patients in POD1UM-202.

Infection with HIV is another risk factor that is associated with anal cancer, where HIV infection is associated with a 15- to 35-fold increase in anal cancer. POD1UM-202 enrolled 9 patients who were HIV-positive with relatively

preserved immunological function, which represented 10 percent of the trial population, which is reflective of approximately 8 percent HIV-positivity among the general population of patients with anal cancer.

However, 9 patients is likely an inadequate number of patients to reasonably characterize the safety and efficacy of retifanlimab in this subgroup of patients with HIV and squamous cell carcinoma of the anal canal. Furthermore, the trial may not be representative of the effect of the drug in the broader group of patients with HIV-positive status and compromised immune function.

The primary endpoint was overall response rate. Thirteen patients had a response per independent central review, leading to an overall response rate of 14 percent with a 95 percent confidence interval of 8 percent to 22 percent. The median duration of response was 9.5 months and the 95 percent confidence interval as shown. Among the responding patients, 7 patients had a response that lasted 6 months or longer and 3 patients had a

response that lasted 12 months or longer.

As previously shown in the baseline demographics slide, 73 percent of the patients had known mismatch repair status in POD1UM-202. Among the 13 responding patients, 5 patients mismatch repair status were unknown, as it is possible that some of these patients had deficient mismatch repair status, and we know that tumors with deficient mismatch repair status have a very high likelihood of responding to anti-PD-1 or anti-PD-L1 antibodies, regardless of histology.

This lack of data regarding the patients' mismatch repair status in POD1UM-202 further increases the uncertainty of the efficacy of retifanlimab for the treatment of squamous cell carcinoma of the anal canal.

FDA does acknowledge that the vast majority of squamous cell carcinoma of the anal canal have proficient mismatch repair status. Thus, FDA conducted a subgroup analysis of the 67 patients with known proficient mismatch repair status. Among these 67 patients, there were 8 responses,

which is an overall response rate of 12 percent and a 95 percent confidence interval of 5 percent to 22 percent.

I will now summarize the main safety findings in POD1UM-202. There were no safety findings that would be considered unexpected for an anti-PD-1 antibody, and the adverse events in POD1UM-202 were consistent with the known anti-PD-1 antibody safety profile.

FDA defined immune-mediated adverse events as those adverse events described by the applicant as immune-related events, infusion reactions, adverse events that required use of any formulation of corticosteroids or other immunosuppressive medication, or required hormonal replacement. Therefore, based on this definition of immune-mediated adverse events, FDA's analysis of the incidence of immune-mediated adverse events considered more events than the applicant.

In this analysis of potential immune-mediated adverse events, 15 percent of the patients experienced grade 3 or higher immune-

mediated adverse events. Three patients possibly died from an immune-mediated adverse event, which included a fatal event of pneumonitis and 2 deaths that although attributed to pancreatic carcinoma and lymphangiosis carcinomatosa, may have been confounded or caused by immune-mediated hepatitis and interstitial lung disease, respectively.

Patients with HIV appeared to have a similar level of tolerance to the overall trial population, but this observation is limited by the small sample size of nine. It is also important to note that these safety findings are limited because the data is from 94 patients in a single-arm trial without the benefit of a control arm to help with attribution of adverse events.

In summary, the safety profile of retifanlimab is consistent with other anti-PD-1 and anti-PD-L1 antibodies, including rare but potentially fatal immune-mediated adverse events.

To confirm the clinical benefit of retifanlimab in patients with squamous cell carcinoma of the anal canal, the applicant is

conducting one randomized, placebo-controlled clinical trial, POD1UM-303, in approximately 300 patients with inoperable, locally recurrent or metastatic squamous cell carcinoma of the anal canal, who have not received prior systemic therapy for their disease, other than radio-sensitizing chemotherapy.

Patients who have well-controlled HIV are eligible to enroll. Patients are randomized 1 to 1 to receive carboplatin and paclitaxel and retifanlimab or carboplatin and paclitaxel and placebo. Patients who progress while on the placebo-containing arm may crossover to the retifanlimab-containing arm if the progression is verified by blinded independent central review.

The primary endpoint is progression-free survival based on RECIST 1.1 as assessed by blinded independent central review. Overall survival is a key secondary endpoint. The trial is estimated to be completed in the fourth quarter of 2024, and a submission of the trial report is planned for the second half of 2025. The trial is open in

77 sites, including 13 sites in the U.S., and it has enrolled 28 patients as of May 25, 2021.

Recall, the published data regarding anti-PD-1 antibody therapy in squamous cell carcinoma of the anal canal has been available as early as 2017.

I will now discuss FDA's review issues with this application. FDA is uncertain that the observed overall response rate in POD1UM-202 is reasonably likely to predict a clinical benefit and reflect a true treatment effect across the U.S. population in which retifanlimab will be indicated for the following reasons.

POD1UM-202 had a low overall response rate, a small number of target lesions in the responding patients in few patients with sustained responses lasting longer than 6 months. Furthermore, POD1UM-202 had a small number of patients with HIV or patients from ethnic or racial minorities. Finally, in trials with anti-PD-1 and anti-PD-L1 antibodies, that were approved based on similarly low response rate, long-term clinical benefit could

not be consistently confirmed in subsequent randomized trials.

The overall response rate in POD1UM-202 was 14 percent. The lower bound of the 95 percent confidence interval was only 8 percent, and the upper bound of the 95 percent confidence interval was 22 percent. The response was durable in a small proportion of the trial population. Among the responding patients, 7 patients had response that lasted 6 months or longer at the time of data cutoff, and only 3 patients had a response that lasted 12 months or longer at the time of data cutoff.

This is a swimmers plot of the 13 responding patients in POD1UM-202. Among these responding patients, only 5 patients had ongoing response at the time of data cutoff, and 1 of these 5 patients had already experienced clinical progression prior to data cutoff but hadn't had imaging prior to data cutoff.

Applicants stated that the overall response rate of 14 percent achieved from retifanlimab in

POD1UM-202 was comparable to what is demonstrated in the other trials investigating anti-PD-1 or anti-PD-L1 antibodies for the treatment of other squamous cell carcinomas.

In these trials, the overall response rate ranged from 10 percent to 20 percent, and the long-term clinical benefit was demonstrated. However, FDA does not agree that the results from other clinical trials in squamous cell carcinoma tumors support the likelihood that the overall response rate of the drugs in POD1UM-202 would predict clinical benefit.

The trials the applicant presented were randomized-controlled trials, where survival, and not overall response rate, was the primary efficacy endpoint. Just because these trials demonstrated effect on survival, one cannot necessarily conclude that one can use these low overall respond rates to predict an effect on survival, as they may simply represent epiphenomena.

More importantly, although the trials have been conducted in cancer with squamous cell

carcinoma histology, these are different cancers from the proposed indication and with different risk factors. Aside from cervical cancer, the other cancers listed here have primary risk factors that are different from those of squamous cell carcinoma of the anal canal.

Finally, the applicant is asking for an indication for the treatment of squamous cell carcinoma of the anal canal. Survival benefit and low overall response rate in these different squamous cell carcinoma cannot be used to infer the potential clinical benefit of retifanlimab in squamous cell carcinoma of the anal canal.

A trial that is submitted to support a marketing approval should stand on its own. The median duration of response was estimated in the 13 responding patients, however, the low number of responding patients contributes to the uncertainty, in our estimation, of duration of response.

In the briefing document, the applicant stated that responding patients experience notable reduction in tumor burden, including hard-to-treat

liver metastases. However, each responder had, on average, only two target lesions.

Adding to the uncertainty of clinical benefit of the efficacy results in this trial, the overall response rate of 14 percent is based on measurements in only 25 target lesions in 13 patients. Among these 25 target lesions in the responding patients, 8 of the responding target lesions were lymph nodes which were all non-bulky, with the longest perpendicular dimensions ranging from 1.6 to 3.1 centimeters. Four responding patients had only lymph nodes as target lesions.

The applicant stated that among the 33 patients with target liver lesions, measurable shrinkage of target liver lesions was recorded in 8 patients, which represents 24 percent of the patients with target liver lesions. However, FDA would like to highlight that only 5 patients had reduction in target liver lesions based on RECIST 1.1, as assessed by independent central review, which represents only 15 percent of the patients with target liver lesions in POD1UM-202.

I will now summarize FDA's review issues and position for this application. There is uncertainty that the observed overall response rate is reasonably likely to predict a clinical benefit for the following reasons.

The overall response rate was low at 14 percent, and the lower bound of the 95 percent confidence interval was 8 percent. POD1UM-202 had 13 responding patients who, on average, had two target lesions per responding patient. Only 7 of the 13 responding patients had a response lasting 6 months or more.

Given the small sample size of POD1UM-202, a small number of patients with HIV were enrolled. The racial and ethnic distribution in POD1UM-202 does not reflect the U.S. population, which is also likely partly due to the small sample size of the trial. Among the patients for whom race or ethnicity was reported only one was black and 4 patients were Hispanic or Latino. No patient was reported to be Asian.

Although mostly well tolerated, some

patients experienced significant toxicity while participating in POD1UM-202, including fatal events. The low overall response rate must be considered in the context of rare but potentially fatal immune-mediated adverse events.

In addition, the safety data is limited by the fact that this is a single-arm trial. Without a randomized control trial, no conclusive determinations can be made regarding the incidence or severity of the observed safety events.

This uncertainty of clinical benefit requires a postmarketing requirement to verify clinical benefit, but in the single trial that is ongoing to verify clinical benefit, POD1UM-303, only 9 percent of the planned trial population has been enrolled as of May 25, 2021.

To support accelerated approval based on an intermediate endpoint, the magnitude of effect on the endpoint should be reasonably likely to predict clinical benefit. The clinical benefit of low response rates with anti-PD-1 and anti-PD-L1 antibodies is not clear in the context of an

inconsistent relationship between low response rates in single-arm trials and the confirmatory randomized trials that failed to confirm long-term clinical benefit.

As Dr. Casak stated, there's a role in oncology for single-arm trials. Single-arm trials have played an important role in advancing cancer drugs that have substantial and durable response rates. However, we must question whether we have come to the point of overreliance on them, specifically for drugs with low response rate, severe toxicity, or when used in combination regimens.

Lower response rates, even if durable, increases the uncertainty of a drug's ability to demonstrate long-term clinical benefit, as discussed in the recent three-day advisory committee in April.

In addition, in settings where overall response rate is appropriate to support regulatory decision, a key and mitigating uncertainty regarding risk and benefit is having postmarketing

requirement trials underway and completed in a timely fashion; and this is an additional concern given that in the applicant's proposed postmarketing requirement trial, as of May 25, 2021, only 28 patients have been enrolled in the currently ongoing randomized-controlled trial, POD1UM-303, which is only 9 percent of the planned 300 patients, and the applicant plans to complete this trial in three years.

It is also the only ongoing confirmatory trial for retifanlimab for the treatment of squamous cell carcinoma of the anal canal. in a competitive environment, with other randomized controlled trials of anti-PD-1 or anti-PD-L1 antibodies ongoing.

Given the modest response rate observed in POD1UM-202, we believe that patients would have been better served if the randomized trial was initiated earlier. Again, single-arm data for anti-PD-1 antibody therapy has been available in squamous cell carcinoma of the anal canal since 2017.

The FDA will now present the discussion and voting question for the advisory committee. First, FDA would like the advisory committee to discuss whether the demonstrated magnitude of effect of overall survival, of overall response rate, and duration of response, are clinically meaningful and reasonably likely to predict clinical benefit in patients with recurrent advanced or metastatic squamous cell carcinoma of the anal canal.

The voting question is, should a regulatory decision on retifanlimab for the treatment of advanced or metastatic squamous cell carcinoma of the anal canal be deferred until further data are available from clinical trial POD1UM-303?

This concludes FDA's presentation. Thank you for your attention.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you.

We will now take clarifying questions for the presenters, both Incyte Corporation and the FDA. Please use the raised-hand icon to indicate that you have a question and remember to clear the

icon after you have asked your question.

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

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

Dr. Garcia?

DR. GARCIA: Thank you, Dr. Hoffman.

I have a question for Dr. Saung from the FDA and also a question for Incyte. The first one is, there were multiple references today as to the ODAC meeting from April reassessing, as you stated, how the FDA is thinking of response rate with immune checkpoint inhibitors in diseases, call them orphan or when there is an clinical unmet need, if you will.

Could you be more specific? The plan that you guys have now in the agency, is it to restructure and redefine that drug registration process, based upon your comments? That would be one.

The second question is for Incyte. When you look at the question posted, or the discussion point posted, by the FDA to the ODAC committee members, there is no doubt that the simple answer to the discussion is no.

None of us can predict if response will likely lead to survival improvement in a subsequent trial, and I think the historical precedent is clear. If you look at, actually, 9 out of 31 trials, out of all the trials that have been approved for CBIs, very few have subsequent survival data.

But the question for Incyte really is, if you look at your data and compare your response rate with historical small trials with pembro and nivo, as you stated, you talk a lot about disease response rate; disease stability, if you will. But

if you look at your presentation and the plot figure, half of your stable disease by RECIST, whether you follow IRC or not, is really patients that have tumor burden increase, which would imply, then, the only thing that we're doing is seeing the natural history of those patients evolve in front of our face while they're getting an ineffective minimally toxic agent.

Thank you, Dr. Hoffman.

DR. SAUNG: Hi. This is Dr. Saung from the FDA. What we are reassessing are single-arm trials where the ORR is low. Because these intermediate endpoints for accelerated approval would have to have the ability to predict clinical benefit, in these low ORRs in single-arm trials, it's hard to assess if these will truly predict clinical benefit.

So that is what we are reassessing. I can pass it on to other FDA members for further elaboration.

DR. LEMERY: Sure. This is Steven Lemery. I can start, and then perhaps the OCE would like to

chime in as well.

Clearly, we are still going to consider accelerated approval. We are not going to change our position on that. Again, as Dr. Saung mentioned, what we have seen across many of these applications -- and not just with PD-1 inhibitors but perhaps with other classes of drugs -- is that when we have these low response rates, they are particularly not translating into an effect on overall survival or other clinical benefit, and therefore, we are reassessing these.

If this is not too low -- what is too low? Here we have a response rate with a confidence interval going as low as 8 percent, so it does seem like this is an epiphenomenon in this case. I think, clearly, we're not going to get to a situation where a company just does a trial, gets whatever the results are, and given that you've seen benefit in other trials, would say that should be approved. We're not going to go down that road.

So we do have to critically reappraise when we've seen so many negative trials. Granted, some

of the trials have been positive as well, so it's not like they've all been negative, but we have to consider is this effect reasonably likely to predict standard.

Again, it's not a whole change of the accelerated approval pathway. We are still going to approve it. For example, we recently approved -- even in a randomized trial, for example, in gastric cancer, HER2-positive gastric cancer, it was a randomized trial where we looked at response rate and the difference between the arms. Because that study was a randomized trial, that final analysis of that trial will be assessable in a reasonable amount of time.

So I think that is a good situation where response rate can be used as well in a randomized setting. I think the problem with single-arm trials is you don't get a great risk-benefit assessment because you don't have that control arm. So I think we have to carefully think about when single-arm trials should be used and perhaps when they shouldn't.

Can I pass to the OCE to see if they have any additional comments?

DR. PAZDUR: Yes. This is Rick Pazdur. Can you hear me?

DR. LEMERY: Yes.

DR. PAZDUR: We have profound concerns about continuing this practice. There's an old adage, "Those that don't learn from history are destined to repeat it." I think we had a very painful discourse over the past ODAC with many trials that had relatively low response rates not demonstrating clinical benefit. We really have to reassess this, and that's why we're bringing this to this ODAC meeting, and we'd like some discussion on this.

There is no reason why people cannot do randomized studies to get their drugs approved, and the single-arm trial is not the only way that a drug can be approved. We've advocated this multiple times to companies. As the reviewer from the FDA pointed out, this data was known many years ago of the activity of this drug, and a randomized trial could have been initiated earlier, perhaps

even in an earlier disease setting in anal canal cancer.

So there are profound concerns here of whether continuing this practice for this class of drugs -- and I want to make it quite clear -- is a reasonable registration strategy.

Here again, as Steve pointed out, there are areas where there may be areas where single-arm trials make sense. These may include where there are very high response rates for some of the targeted therapies, and we've given actually full approval on the basis of response rates here. But there's no reason why we only have to do single-arm trials for many of these diseases and then look at randomized trials.

One of the options that we would have had here is to do a randomized trial and take a look at interim analysis for response rates, and have a continuation of the trial to demonstrate clinical benefit, and we would actually have had a randomized trial going on here.

I'd also like to point out for the

committee, since many of you may not be familiar, when we take a look at single-arm trials, we are only taking a look at response rates. We cannot make any inferences regarding stable disease because this may reflect the natural history of the patients that were enrolled in the studies, nor can we make any claims regarding time to progression or overall survival.

So although that was presented in the sponsor's presentation, from a regulatory point of view, we would not be taking a look at these endpoints of disease stabilization or time to progression, or overall survival. These need to be demonstrated in the randomized setting.

DR. HOFFMAN: I think you also had a question for the --

DR. CORNFELD: Excuse me. This is Mark Cornfeld on behalf of Incyte. I think we were asked to comment also.

DR. HOFFMAN: Yes.

DR. CORNFELD: Okay. So if I may, we actually agree with FDA that not all trials will be

confirmed and should not be considered that way, but it's the biology that's the key here.

If you take a look at the list of the trials where there have been concerns -- and Incyte did not participate in the April ODAC, but we certainly followed it with interest, and we've seen the results and the news reports -- all of these trials were indications other than a squamous tumor and, specifically, none of them were in HPV-driven disease.

If you look at the trial specifically in HPV-driven malignancy, which is a very unique biology -- and remember, biology is key here -- the results are consistently predictive of survival.

Now, I'm not seeing our slides, and I'm wondering if there are technical issues that someone can possibly drive them on the part of the FDA. I'd like slide EF-49, if possible.

These are the data. If we limit our discussion to the HPV-driven cancer biology, which is unique and which is what we're talking about here today, because all of anal cancer is an

HPV-driven cancer, these very low response rates have consistently predicted for a survival benefit, and we can say that with confidence now that the KEYNOTE A-26 results have been disclosed publicly this week. And look at the overall response rates that contribute to this.

For context, the lower bound of the response rate in pembrolizumab trial was only 6 percent, so clearly that did not preclude a survival benefit from being confirmed in the randomized trial, and our results are very consistent with these, and we think should be equally predictive.

In addition, the disease control rate here is meaningful. I didn't hear an answer to my question about whether we're technically impaired at the moment, but I'd like to show, in response to your question of how are these patients with stable disease during the follow-up -- swim-lane plots -- FDA has also raised this concern in their presentation, and we do have additional data.

If you can project for me slide number -- I apologize. I don't have the slide number. But if

we looked at follow-up data for our patients, and now we're talking -- no, not this slide. It's the swim-lane plot that accompanies this, either immediately before or after.

We have an additional nine months of data. The patients have been followed continuously during that time. And what's notable is that it's not just the patients with response who have this prolonged trajectory. There are at least 15 or 20 patients with stable disease who have now been followed actively on trials for more than a year, which is clearly exceptional given what's known about the disease.

I'll just ask Dr. Fakih to comment while we're looking for this, whether this is something you'd expect to see in this disease where patients all have very advanced disease.

DR. FAKIH: Thank you, Mark.

I think what's interesting, looking at the data, is the waterfall plot as well. If you look at the patients with stable disease, it's not the fact that they just maintain stable disease for a

period of time, but you actually do have regression in their target lesions, and that's not something that is expected in the natural history of the disease.

Moreover, at least by looking at some of the data from other studies, looking at the natural history of patients who have received therapy that has not been associated with significant toxicity or significant activity, such as the listeria phase 2 trial following progression on platinum-based therapy in patients with advanced cancers at the 6-month mark, less than 15 percent of patients still had stable disease.

So to me, I do think there is a signal here, which is consistent with what we see with other PD-1 inhibitors, and I do think that's meaningful to all the patients. Thank you.

DR. HOFFMAN: Okay. Dr. Weekes is next.

DR. WEEKES: Thank you. This is Colin Weekes. My understanding is that the primary endpoint to the study was overall response of 25 percent, so please correct me if I'm wrong.

With that, with a response rate of 14 percent and the confidence interval is between 8 and 22 percent, do you think your original estimate of the overall response rate was incorrect such that we should then move forward with the 14 percent response rate and ignore the original primary endpoint? Thank you.

DR. CORNFELD: So our sample size calculations were based on the pilot data for nivolumab, since that's all that was available to us at the time the study was designed, and nivolumab response rate of 24 percent is clearly an outlier now that additional studies have been completed, including two that are much larger.

There are several credible explanations for this. There was no independent review in the nivo study and patients were not required to have received platinum as a condition for study enrollment as for two examples. But while the response assumptions that went into the design of POD1UM-202 were an overestimation, the actual sample size of 94 is still large enough to allow a

meaningful assessment of risk-benefit, particularly given that this is a rare disease.

Just for context, our study is actually slightly larger than the groundbreaking InterAACT trial, and InterAACT was conducted in a platinum-naïve population, which is easier to recruit.

We can also confidently predict that placebo responses will not occur in this refractory cancer. And as we've pointed out, the confidence intervals that we're showing overlap those for other successful PD-1 experiences in HPV-driven malignancy, notably the 6 percent lower confidence bound for pembrolizumab in cervical cancer.

DR. HOFFMAN: Alright.

Dr. Nieva?

DR. NIEVA: Thank you. This is Jorge Nieva, and my question is for Mark Cornfeld from Incyte.

The question here really relates to how well does a single-arm experience reflect the population demographics of the cancer?

As you know, Friends of Cancer has made

recommendations with ASCO to try to limit exclusion criteria, and I see that you've done a few things here to make your single-arm population healthier than average, such as making requirements for CD4 counts, for example.

So my questions are, were there any other areas where you exceeded the ASCO Friends of Cancer guidance in order to try to make your single-arm population healthier, overall, such as requiring a creatinine clearance greater than 30?

Then could you talk a little bit about the breakdown of patients who were progressed on platinum therapy versus intolerant of platinum therapy, and how the results varied in those two subgroups? Thank you.

DR. CORNFELD: Yes. So to the latter question -- that's easy to answer -- there were only 3 patients enrolled who were platinum intolerant. And again, these were well-defined protocol exclusions which were reviewed by FDA as well. But they did not contribute to the overall response history, so there's no basis for doing a

controlled comparison.

In terms of the study entry criteria, we actually had a fairly liberal exclusion criteria. Because there's been so much experience with PD-1 inhibitors in multiple populations, we were able to benefit from that experience. But since it's early in the development of retifanlimab and we didn't have that much experience of our own, we did enroll all patients regardless of any comorbidity.

So there were some restrictions based on laboratory. They're pretty modest. You asked specifically about creatinine clearance. In this study, patients with creatinine clearance lower than 30 ccs per minute were excluded.

DR. HOFFMAN: Okay. Dr. Cruz-Correa?

DR. CRUZ-CORREA: Hi. Good afternoon. Dr. Hoffman, thank you.

I have a question for the Incyte investigators; two questions actually. The first one, I would like to have your feedback again on the concept and the question that was raised by the FDA with regards to the tumor size and the number

of target lesions.

I think I remember the investigator from Incyte discussed the fact that RECIST provided or increased the limitations for the evaluation of the tumor burden, and I want to contrast that information with what was then discussed as a limitation by the FDA group.

Then the second question is with regards to the fatality. I also heard that there were some cases of fatalities, one or more, but if you could comment on this particular case. Thank you.

DR. CORNFELD: To your first question about the tumor burden -- and if I could have that slide, I think it's helpful -- this is a nuance of RECIST. And remember, RECIST exists to provide reliable, reproducible, serial measurements of tumors so that objective response rate can be calculated.

It is not designed to measure tumor burden, and, in fact, there are several nuances to RECIST 1.1, which is what we used in this study, that actually bias against assessing all of the cancer burden or, in particular, the more complex

lesions that are difficult to measure.

This picture here is actually from the primary RECIST publication, and what you're seeing in red here is the large gastric mass is actually not counted, and it's recommended that you count the much smaller lymph node because it's clearer to measure on a serial basis.

Also, there's a nuance about the lymph nodes themselves. You're supposed to actually report the smaller bidimensional measurement, not the larger one, so that's a bias. Then this other main stipulation, that if you have multiple lesions, you don't count them all; you limit it to two per organ system. So by its very nature, RECIST is an underestimate of the total tumor burden.

Now having said that, this population is still quite advanced, and I think Dr. Fakih can comment on whether they're representative of the patients that he sees in practice and whether they're the patients who are truly in need.

DR. FAKIH: Thank you, Mark.

I think what you are discussing right now is

typically what we see to these RECIST lesions. I mean, most commonly these patients present with pelvic disease. A lot of times they have recurrence in the anal canal because it's post-chemoradiation.

It's not that the tumor is not enlarging, but it is within an area of fibrosis related to prior chemoradiation, and it's very hard for the radiologist sometimes to define where it starts and where it ends very conclusively. Therefore, you do end up selecting predominantly the tumors that could be smaller but are much more defined than lymph nodes are usually defined.

In addition, when we have clustering of lymph nodes together, what we call matted lymph nodes, that's another time where also the radiologists particularly don't use that full matted lymph node structure for measurements, but actually elect to choose another lymph node that is separate, where they follow it more accurately.

So I think that's not an uncommon scenario with this disease particularly, so I'm not

surprised.

I think the other thing I want to say is that for the non-target lesions, that there is a new lesion and that's progressive disease, and certainly we take into consideration progression of non-target lesions as a progression on the RECIST guidelines. Thank you.

DR. CORNFELD: Thank you.

Okay. As to your second question, which was about the fatalities, yes, these are the 10 fatalities that were reported as SAEs on study. Of course, many patients with advanced cancer die, and the investigator is not obligated to report all deaths that are expected. In many cases they will report, but we don't direct them in any way.

Of these, the only one that was actually interpreted by an investigator as potentially treatment-related is the lymphangiosis carcinomatosa. We reviewed this case in detail with the investigator and also with our DMC, and there are many potential confounders here.

This is a patient who had pulmonary

infiltration in the beginning but did not respond to steroids or antibiotics, and deteriorated very rapidly with no workup really being done. So the likelihood that this is treatment-related is low but, of course, can't be excluded, which is why the investigator reported it that way.

None of the other fatalities, on the face of them -- and we reviewed the SAE reporting detail and asked follow-up queries where there was uncertainty. None of them seemed to be related to anything but the underlying disease or complications of disease, and that includes this pancreatic carcinoma case, which FDA highlighted in their materials, for good reason.

But we have additional information on this case since the preliminary safety was filed, and it's very clear that this patient had immune hepatitis but completely resolved it with appropriate therapies, steroids and mycophenolate. It was only on a subsequent admission that she presented with portal obstruction as the cause of her liver failure, which was worked up. Actually,

she had an autopsy, and the finding was very clear that it was from widespread, unsuspected pancreatic carcinoma.

So we're quite confident we're not detecting new immune toxicities here that haven't been previously reported, and we fully agree with FDA's assessment that the safety is representative of the class to the extent that we've been able to show it.

DR. CRUZ-CORREA: Thank you.

DR. HOFFMAN: Dr. Lemery, you had a comment?

DR. LEMERY: Yes, I wanted just to follow up. A lot of these issues and comments that are being discussed, they're really derivative of the problems with single-arm trials.

The one thing that we brought up about target lesion size, it underscores the uncertainty based on your measurements in a relatively small number of lesions. We agree it's hard to get into how much disease burden a patient had, based on that information alone.

But again, that's the issue with a single-

arm trial and the other reason why we cannot look at a drug's effect on stable disease because it's a single-arm trial. These patients who are enrolled in trials are different than patients who are in the community. I think everyone here knows this who enroll patients.

So we have this challenge, when you have these single-arm trials, to know what's the underlying disease trajectory, not of the overall population of patients with a disease, but other patients who are enrolled on these trials. No matter what demographics you enroll, they're not the same as the overall population of patients who have the disease in the community. I think everyone here knows that.

So given that we have these uncertainties, that's why we highlight the issues about the lesion number and lesion size. It all goes to the uncertainty with providing the overall treatment effect. I think I would just stop there, and I guess we can allow the committee to ask any other questions.

DR. HOFFMAN: Let's move on, because we have other committee members who do want to ask questions, and I think we've addressed that one.

Dr. Lurain?

DR. LURAIN: Thank you, Dr. Hoffman. I have a question for Dr. Cornfeld.

A lot has been made today about the inclusion of people living with HIV in the studies, and it's very nice to see that a potential trial for registration actually included people living with HIV, the PD-1 inhibitor trial.

I think there's been a misconflation [ph] between HIV control and immune reconstitution in this population today. HIV control is measured by viral suppression, and ART is one thing, but a CD4 count cutoff of 300 in a population of patients that's undergone platinum chemotherapy and potential radiation is very unlikely to be seen in a large proportion of people living with HIV, and I'm concerned about your ability to recruit people in the subsequent POD1UM trial and wondering about your requirements for CD4 count in that trial.

Thank you.

DR. CORNFELD: Got it. Thanks. It's a very good question. It's actually something that we're already actively considering because now that we have the additional experience with retifanlimab in patients with HIV, we're a lot more comfortable about including patients who, perhaps, have lower CD4 counts since the safety was so good in the current experience.

As far as the POD1UM-303 trial is concerned, this trial is off to a really good start despite the challenges of conducting clinical research in a COVID pandemic. We're meeting all of our approval targets. We have active participation from the HIV malignancies group in France, which was a major contributor to POD1UM-202. Because of the HIV inclusion, this study is equally attractive to American physicians, and we expect recruitment to really benefit from that.

I think one of the subtexts of the questions was whether we can competently expect to complete this trial. Well, the study is well-designed. FDA

and the European Medicines Agency both gave quite a bit of input, all of which we took, as did the scientific organization that's behind it, which is the Rare Cancer Initiative that successfully conducted the last randomized trial in this disease, and all are excited about the result because of those two things. It provides both a groundbreaking, potentially practice-changing results in the first-line setting, as well as providing direct confirmatory evidence in the population we're talking about today because of the controlled crossover.

All of these factors will make it actually easier to recruit since the data that we're generating today do show clinical benefit in the patients that we treated, and that of course gives clinicians confidence and a desire to make this therapy available to their patients, since nobody is using first-line PD-1 inhibitors in this disease at the moment.

DR. HOFFMAN: Okay. Thank you.

Dr. Reidy-Lagunes?

DR. REIDY-LAGUNES: Thank you, Dr. Hoffman.

I do want to go back and ask the FDA, particularly Dr. Lemery and others that, really, I think articulated the struggles of single-arm trials. But I'm struggling because, as Incyte has shared, there's biology here, and the single-arm study is exactly where most PD-1s that we think are active fall, which is between 10 and 20 percent.

So I want to clarify does the FDA, to the first question, plan on restructuring for orphan disease and accelerated approval, that there should be a higher response rate than what we traditionally see? Because I agree, there was a painful discourse there with low response rates, but there were, not unfrequently, translation into overall survival benefits. I just want to clarify on what we think for accelerated approval. That's my first question.

The second question is, there are other studies that are obviously in registration trials now that are randomized. So if POD1UM-303 is slower to accrual, could we potentially use those

other trials to question the accelerated approval later on? I'm not sure if that's something we could do or not, meaning other trials with other PD-1s.

DR. LEMERY: I'll answer the first question, but I'm not following the second question.

DR. REIDY-LAGUNES: The second question, meaning like, for example, in gastric cancer, we change the accelerated approval for PD-1 because there are other studies that are up front with other PD-1 agents that showed efficacy, and that didn't. So meaning there could be potentially other studies that change this accelerated approval or not, based on what's coming out, if it's other PD-1s.

DR. LEMERY: Are you asking about a different drug company or a different drug?

DR. REIDY-LAGUNES: Correct. Yes. If we granted accelerate approval, could we use other data to potentially change that outcome?

DR. LEMERY: No, we couldn't use the data from another trial --

DR. REIDY-LAGUNES: Okay.

DR. LEMERY: -- if that is negative, to pull this drug off the market because this drug would be tied to its own accelerated approval requirement.

The issue, again, with these low response rates and survival benefits, again, this is just an epiphenomenon. Is it the response rate that's reasonable enough to prove benefit, or should we just throw up our hands and say approve all PD-1s in squamous cell cancers because we think that they're going to work? Is that the scenario where we're going to be?

Also, how low would you go? If you see any responses, should we just say we should approve that PD-1 for a squamous cell cancer? Again, we have a confidence interval level here that's as low as 8 percent. So I think that's one of the challenges that we have here.

Clearly, I think, if you have higher response rates that we've seen with microsatellite high cancers or targeted therapies, it's an easier call. But I think when we have these low response

rates, it's very difficult -- and again, a lot of the oncologists here will know that there have been survival improvements with drugs with even lower response rates; for example, regorafenib or TAS-102 in colon cancer, and those drugs have had response rates of less than 5 percent but demonstrated survival effect.

Again, it's really because response rate is an imperfect surrogate or intermediate endpoint for clinical benefit.

DR. HOFFMAN: Can I just remind us that we're getting off topic here? We need to focus on --

DR. LEMERY: Well, I thought I was answering the question.

DR. HOFFMAN: -- the questions today.

DR. LEMERY: I'll just ask if there's anyone else from OCE that has anything else to add?

(No response.)

DR. HOFFMAN: Alright.

Dr. Rosko?

DR. ROSKO: Hi there. My question is for

Dr. Cornfeld and the Incyte team.

You provided additional data regarding efficacy endpoints such as liver response, change from baseline, and tumor burden over time. I was wondering if the investigators could also weigh in on the patient experience. I understand you collected patient reports, quality of life assessments in this study, and could the investigators comment on that data?

DR. CORNFELD: Yes, I'd be happy to.

Can I ask the FDA that you allow us to share our slides? We're not getting automatic screen share when it's our turn to respond. And I do have two slides I'd like to share here in response to your question, which relate to the PRO exploratory endpoint. These have not been seen by FDA, so please keep that in mind.

The question, as Dr. Fakih pointed out, too, in his introductory remarks, quality of life is a major issue for these patients, so we included assessment of patient-reported outcomes as an exploratory endpoint in POD1UM-202, and we're

actually including it in POD1UM-303, which is a randomized trial.

We measured these outcomes using two well-validated scales, the EORTC QLQ-C30, which you see here, which measures several health domains. The yellow-shaded portion here corresponds to the median duration of therapy, which is where we have the most information and where you should focus your attention. At baseline, we actually had an 85 percent return on these assessments, which is quite good for this kind of work.

So what you see is that, first of all, there's no diminution in quality of life over the time interval; again, limitations being that this is an uncontrolled comparison, but also the trajectory of patients with stable disease appears to parallel that of patients with response.

If we look at the EQ-5D-3L, which is a visual analogue scale that's also assessing this kind of thing, you can see a very similar result; no diminution in quality of life, and with responders and stable disease, patients both appear

to benefit equally; again, not controlled data -- we recognize the limitations -- but certainly encouraging, and then we'll try to confer that in phase 3.

DR. HOFFMAN: Okay. We're going to take a 20-minute break now for lunch. Additional comments and questions can be discussed after the open public hearing session.

We'll take a 20-minute break. Panel members please remember that there should be no discussion of the meeting topic with anyone during the break, and let's resume at 1:05 Eastern. Thank you.

(Whereupon, at 12:47 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:07 p.m.)

Open Public Hearing

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

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 2 begin by stating your name and any organization you're representing for

the record?

DR. CHO: Hi. This is Dr. May Cho. I'm associate professor of GI oncology at University of California Irvine.

Should I start the testimony?

DR. HOFFMAN: Please.

DR. CHO: Okay. I'm honored to speak with you today. I am not being compensated for my time here today. I'm representing myself and my patients, especially anal cancer patients. In my career, I have interest in drug development, and I have been investigator in a number of clinical trials, including seven as a institution investigator for retifanlimab. It is my personal experience as an oncologist, and it is with experience with retifanlimab that I speak today.

I have been a GI oncologist for four years. In that time, I have treated a dozen of patients with squamous carcinoma of anal cancer. One of those patients I treated with retifanlimab. It's a patient in the study of HIV infection and the patient benefitted from the drug.

Generally, when my patients progress following first-line platinum doublet therapy, I have been able to give them investigator immunotherapy combination or off-label, second-line therapy based on the NCCN guidelines and on my experience.

I am unique in that I'm in an academic institution. However, in my experience from some of the [indiscernible] center, metastatic cancer patients were not able to get the immunotherapy in the second-line study.

I am encouraged by both safety and efficacy data for retifanlimab by personally treating patients including HIV patients, as well as scientific presentation of this drug. I hope that my testimony has been a helpful context to you in your consideration of the data. Thank you for giving me your time and attention.

DR. HOFFMAN: Okay. Thank you.

Will speaker number -- I think we're going to do 3 next; we'll go back to 1.

Speaker number 3, please begin by stating

your name and any organization you represent for the record.

MS. RAYMOND: Good afternoon. My name is Martha Raymond. I'm the founding executive director of the GI Cancers Alliance and founder and CEO of the Raymond Foundation. I do not have any financial disclosures.

For over three decades, I've been privileged to work with the oncology community as a patient-reported outcomes researcher, advocate, and certified oncology patient navigator. Thank you for the opportunity to speak today on behalf of the anal cancer patient community.

In preparation for my remarks and to better understand the anal cancer patient perspective and unmet needs, I convened a roundtable conversation with 25 anal cancer patients, survivors, and caregivers from across the United States. In addition, I spoke with 10 anal cancer patients individually, as they felt more comfortable in this personalized setting. Our conversations were honest, raw with emotion at times, intense, and

very meaningful.

Overarching themes from our conversations included barriers to early diagnosis and awareness, frustration and anger by the lack of new treatments, quality of life after diagnosis, including daily distress levels leading to allostatic load. Briefly, I would like to share the patient voice and perspective on these three themes.

First, lack of awareness and barriers to earlier diagnosis. Research from the National Cancer Institute indicate anal cancer rates are rising rapidly, at least 3 percent a year, with a marked increase greater than 5 percent per year in individuals 50 years and older. Anal cancer mortality rates have also increased over 3 percent per year among U.S. men and women. Lack of anal cancer awareness, embarrassment, societal stigma, and lack of knowledge including risk factors, are common barriers leading to later stage diagnosis.

Second, frustration and anger by the lack of new treatments; patients spoke at length about the

lack of new treatments, clinical trials, and treatment options. Patients refer to the current treatments, especially the grueling course of radiation, as barbaric with unbearable pain from radiation burns. Anal cancer patients feel they are forgotten and stigmatized by the oncology community and researchers as the treatment for stage 4 disease has remained essentially stagnant, basically the same since the 1970s.

Patients want and deserve cutting-edge therapies and new treatment options. Anal cancer is one of the fastest, accelerating cancers in the U.S. and patients deserve attention and research that will advance treatments far beyond the current state.

Third, quality of life; I asked each patient to report their distress level based on the National Comprehensive Cancer Network Distress Thermometer from 1 to 10, with 10 being the highest level. Seventy-five percent of patients reported a level 7 or 8, while 25 percent reported a level 9. Clearly, anal cancer patients experience very high

levels of cancer-related stress, including debilitating anxiety, depression, sexual dysfunction, pain, and lack of intimacy, social isolation and embarrassment, financial concerns, and overall feelings of helplessness.

In conclusion, the anal cancer community have many unmet needs, both physical and psychosocial. Their voices need to be heard, and their unmet needs should be taken seriously with actionable steps to meet these needs. New treatment options and research provide hope to anal cancer patients for improved outcomes as they navigate the challenging anal cancer care continuum. Thank you.

DR. HOFFMAN: Thank you.

We are trying to connect with speaker number 1, but in the meantime, we will move along with speaker number 4.

Speaker number 4, please begin by stating your name and any organization that you're representing for the record.

MS. CZUBARUK: Good afternoon. My name is

Kim Czubaruk, and I'm speaking on behalf of the Cancer Support Community. Thank you for the opportunity to address the Oncologic Drugs Advisory Committee with regard to Biologics License Application 761209, for treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal, who have regressed on or who are intolerant of platinum-based chemotherapy.

For the record, the Cancer Support Community receives funding from Incyte Corporation, however, we receive neither funding or compensation for the comments I will be sharing today.

CSC supports the development of safe and effective therapies that offer all cancer patients and their providers access to treatment options that present the opportunity to support patient goals. CSC is an international, non-profit organization that provides free support, education, and hope to those impacted by any type of cancer. As the largest provider of social and emotional support services for people impacted by cancer, and

the largest non-profit employer of psychosocial oncology professionals in the United States, CSC has a unique understanding of the cancer patient experience.

We provide $50 million in free, personalized services each year to individuals and families affected by cancer nationwide and internationally. In addition to our direct services, our Research and Training Institute and Cancer Policy Institute are industry leaders in advancing the evidenced base and promoting patient-centered public policies to ensure that the patient voice is at the center of the national dialogue.

CSC serves people with all types of cancer, including those with rare cancers like anal cancer. In 2017, there were about 8,200 new cases of anal cancer reported in the United States and an estimated 48,541 new cases diagnosed in 2018 worldwide.

While rare, the incidence of SCAC is increasing. Anal cancer has a particularly high association with human papilloma virus, with over

80 percent of SCAC being attributable to HPV. Currently, there are no FDA-approved therapies for adult patients with locally advanced or metastatic SCAC who have progressed on or who are intolerant to platinum-based chemotherapy, with the expected five-year overall survival for patients with stage 4 anal cancer to be 15.2 percent.

Given the growing incidence of anal cancer, the lack of approved treatment for patients with advanced or metastatic SCAC who have progressed beyond first-line chemotherapy, and the poor five-year overall survival rate for stage 4 anal cancer patients, having innovative, safe, and effective treatment options available would offer additional avenues of consideration for care and treatment of anal cancer, with the ultimate treatment decision always being made between the patient, caregivers, and the healthcare team, following a thorough review, which includes examination of the risk-benefit profile as it relates to the patient's particular needs.

While CSC does not endorse any specific

product, we do encourage, when appropriate, expanding opportunities that give credence to patients' options and priorities, generally, and the value patients place on both physical and psychosocial aspects of life, specifically.

As the FDA continues to strengthen its patient-focused drug development program, it's critical that through the development of safe and effective therapy options, where none existed before, we recognize and elevate it as an integral part of the PFDD program.

To the same end, we know the patient experience is much broader than patient assessment of disease symptoms, treatment side effects, and physical functioning, to also include the psychosocial impacts of a condition, therapy, and clinical investigation.

The Cancer Support Community encourages all sponsors to heighten the importance of collecting patient experience data, both pre-approval and during postmarket surveillance, by consistently identifying, collecting, measuring, and considering

the full breadth of patient experience data to better understand what is actually meaningful to patients, as well as caregivers.

This patient experience data should include such information and concerns as related to disruption to daily and family life, work, social engagement, nutrition, financial impact, and other issues that provide meaningful feedback through the patient voice in real time about issues that may not be identified through the current measures and should be.

It is important that as the ODAC is taking into consideration the risk-benefit portfolio of any treatment option, they also consider that fully-informed patient choice be a part of the right of the patient and provider.

CSC appreciates the opportunity to comment and sincerely hope that your decision will favor providing patients and providers with access to safe and effective choices that present the opportunity to support patient goals for all cancers, at all stages, including rare anal cancer

that is locally advanced or metastatic.

We also hope that future requirements on all sponsor data sets will also include patient experience metrics, which would help you assess the full spectrum of the impact of your decision and how they might touch patients and providers. Thank you.

DR. HOFFMAN: Thank you.

Will speaker number 5 begin by stating your name and any organization you're representing for the record?

MS. CADENHEAD: Thank you so much for letting me speak today. My name is Karen Cadenhead, and I'm here to tell my story as a cancer patient. Before I do that, I want to assure all of you I have no relationship, financial or otherwise, to any drug company, including Incyte.

I'm a 73-year-old artist and therapist. I live in Northern California and was diagnosed with anal cancer in September 2018. I'll always remember it because it was the week after my son's wedding.

The cancer subsequently metastasized to my lungs and liver within the next six months. I was able to get into a clinical trial, 21 months ago, using immunotherapy, and thankfully, I am thriving today, but it took a lot of effort.

I know many of my fellow patients aren't as fortunate as I've been. They, all of us, need access to more treatment options. I started my treatment with the standard protocol, chemo and radiation. I subsequently tried a second chemotherapy, but I'm here today, almost three years later, because my third try, immunotherapy, worked.

In the 20 months since I began this treatment, I've only gotten better, had minimal side effects, and even now a liver lesion, which is small, continues to shrink. I know how lucky I am to have responded to this therapy, but perhaps as importantly to have been given the opportunity to receive it. That opportunity didn't come easily.

My family and friends, a group of researchers, connectors, and physicians, moved

heaven and earth to get me to the best hospitals with doctors who had seen the most of this rare cancer and who were testing investigational therapies.

I, thankfully, have the ability to fly thousands of miles to get to and from my treatments. My husband and I did most of this during the pandemic, a time when even healthy people were staying home for safety. We both risked COVID to get access to treatment. At times, I didn't know which to fear the most, cancer or COVID.

No patient should need money, or connections, or have to risk COVID to get access to potentially lifesaving treatment. I understand that developing and getting a drug approved is and should be a data-driven process. I know it involves complicated science. I have respect for a process that values safety and demonstrated efficacy.

If you believe there is promise for this drug you are considering today, please know that

many of us with this rare cancer are running out of time and options. I've made many friends in this unique community. We are all in this together and are aware of the opportunities some have that others do not.

Three close friends who come to mind are Luisa, Phyllis, and Molly. They are here with me in spirit today. I found Luisa through the Anal Cancer Foundation. While working and raising her family in New Orleans, she flew back and forth to San Francisco for her successful treatment. She became my anal cancer coach and held my hand every step of the way.

Phyllis found me through an anal cancer chat room. While 400 miles apart, we call each other constantly when we hear of some promising new treatment. A friend connected me to Molly, who lived in Portland, Oregon. We both were artists and liked each other immediately. Molly's experience was extremely hard and ended quickly. I felt some comfort that she found out before she died that one of her paintings had been accepted

into the permanent collection of the Portland Art Museum.

I would ask the FDA to advance to my last slide. I know Molly is here with me today. I'm so glad you on this panel are people of science and medicine and data. You have difficult decisions to make weighing risk versus reward. My goal was to add human faces and their urgent hopes to these testimonies today. Included in those faces are those that continue to fight, as well as those who literally ran out of time, like Molly. We all thank you for your very important work here today.

DR. HOFFMAN: Thank you.

Will speaker number 6 begin by stating your name and any organization you're representing for the record?

Wait one moment until we reset here.

(Pause.)

DR. HOFFMAN: Okay. Please go ahead.

(Pause.)

DR. HOFFMAN: Speaker number 6, you're on.

(No response.)

DR. HOFFMAN: Maybe we're having some technical difficulty. Why don't we temporarily hold this, and can we move on to speaker number 7 then?

Begin by stating your name and any organization you're representing for the record, and we'll come back to numbers 1 and 6.

(Pause.)

MS. KREPPEL: Hello. Do you hear me?

AV TECH: Yes, I can hear you.

MS. KREPPEL: Okay. Great.

My name is Lillian Kreppel. Can you hear me?

DR. SCOUT: Yes. Hi --

MS. KREPPEL: Sorry?

DR. SCOUT: My name is Scout from the National LGBT Cancer Network.

(Crosstalk.)

DR. CHEN: I'm so sorry, everyone. There are technical issues. Please just on mute for a moment. I apologize. Just for a moment. Thank you so much.

(Pause.)

DR. HOFFMAN: Let's go back to speaker number 6. Please begin by stating your name and any organization you're representing. Thank you.

DR. ROMESSER: Hello. My name is Paul Romesser. I'm representing myself. I have no conflicts of interest in today's discussion. I was not an investigator for the retifanlimab study. I'm not being compensated for my testimony. I have no financial interest in the outcome.

While not directly pertinent to this meeting, but in the interest of full transparency, I have received research funding in the past from, and I am a consultant for a different pharmacological company, not Incyte.

Today, I wanted to testify because I'm a radiation oncologist at Memorial Sloan Kettering Cancer Center. I specialize in lower GI cancers and specifically anal cancer. I try and cure my anal cancer patients. I get to know them very well and, unfortunately, I know outcomes they face when they develop recurrent or metastatic disease after

definitive chemoradiation.

Their options are limited, and they're particularly limited in the second-line setting. The outcomes are often heartbreaking. Of course, there's exceptions to this, but these are really anecdotal. So I really want you to understand my view on three points.

First, as I mentioned and as you all know, patients in this setting have very limited options, and the options that are there are usually limited benefit. That's the reason why I'm very thankful whenever a company works in this space. Few do, given the rarity of this cancer, but we need to do more to connect research in this space to help improve these important patients with anal cancer around the United States.

Research in this area can be productive. As we make headway in the metastatic setting, we can see this moving into the definitive setting. This is important because our chemotherapy backbone, considering our standard of care, chemoradiation, has really not changed in decades, despite having a

high rate of distant metastatic progression, approaching 40 to 50 percent of patients with locally advanced or high-risk anal cancer.

So when we think about opportunities to consider new therapies, especially in the accelerated setting, of course, the FDA will consider the risks and benefits of the treatment, alongside the need in this patient population. And I certainly think that in this patient population, given the overall limited FDA-approved therapies, there is an incredibly high need.

When I consider today's data, I'm really struck by the fact that for patients who had a response, or even stable disease, retifanlimab is really a game changer. So for responders, this agent really changes the course of their disease and has the potential to prolong their lives, allowing them more time with their patient [sic], their families, and to interact with society. This is a significant advantage, especially in the second line setting, as further chemotherapy options are highly limited and of limited efficacy.

If the FDA was to approve retifanlimab, it would also ensure uniform access for patients across the United States and would remove potential barriers to this treatment for patients all over the country. That's important. Again, in the setting of rare diseases, we have less advocates, less people speaking out on behalf of these patients who are in need.

I just want to thank everyone for the opportunity to share my thoughts today. I want to thank you all at this meeting for your time and expertise to help evaluate new therapies for patients with metastatic anal cancer.

Truly, this is a group of patients that need their voices heard and need smart people like you considering potential new therapies that can help these patients as we move the field forward for all patients with metastatic anal cancer. Thank you very much.

DR. HOFFMAN: Thank you.

We're going to hold, just very briefly before we move ahead, for technical reasons.

(Pause.)

DR. HOFFMAN: Okay.

Speaker number 7, please begin by stating your name and any organization you're representing for the record.

(Pause.)

DR. SCOUT: Hello. My name is Scout. I'm not sure what speaker number I am, because I was originally 1, but I was not connected to the meeting after caller 1 called.

So am I supposed to be 7 now?

DR. HOFFMAN: Well, number 7 is up, and if you were number 1, we're planning to come back to you.

Is speaker number 7 on the line?

MS. KREPPEL: I've been talking. Have you heard me? I've been talking.

DR. HOFFMAN: No. Just now for the first time.

MS. KREPPEL: Yes. No, I've been speaking. I guess I was not -- can I start?

DR. HOFFMAN: Please.

MS. KREPPEL: Okay.

My name is Lillian Kreppel. I represent the Anal Cancer Foundation. I don't have any financial interest in the outcome, and I am very thankful for the opportunity to speak today, and I thank for the opportunity and the very important work that you're doing. It's my first time doing anything like this.

I am a survivor of stage 2 HPV-related anal cancer, which I had when I found out in 2017. I'm almost four years out from having successfully completed my chemoradiation treatment.

Since that time, I've established the HPV Alliance to educate the medical societies and the general public on HPV and the six cancers it causes because it is not on the radar out there. And like me, I was non-diagnosed, and when I speak with patients on a daily basis, I find almost every patient that I speak to is being non-diagnosed.

Fortunately for me, I had symptoms, and I knew something was wrong, even though my gynecologist said I was fine. And I pressed on,

and I went to actually a gastroenterologist, and he caught the tumor, which was previously thought to be just a hemorrhoid from the gynecologist, and often that is the scenario.

That's not the case with many of the patients I see and talk with. Many of the cases, they want to believe their doctor, and they're dismissed with, "You may have a hemorrhoid and it's being treated," and then, unfortunately, they end up with stage 3 and 4 anal cancer.

I have become a powerful voice for patients all over the world, and my mission is to save lives. There hasn't been any new treatment or attention to anal cancer in over 30 years. It seems to be the forgotten cancer, again, starting with even being diagnosed, and nobody should die from this cancer.

Along with my organization, we're out there trying to educate and create awareness so that we can empower individuals to know and to look for signs and also the medical societies. I feel that this drug is an important breakthrough and much

needed and resolves an unmet need.

I look forward to participating in making a difference for patients, and I hope that these patients will never get to stage 3 and 4 with the help of this drug. Thank you very much for your opportunity and your very important work that you are doing.

DR. HOFFMAN: Thank you.

Speaker number 1, I think you're connected now. Please begin by stating your name and any organization you're representing for the record.

DR. SCOUT: Thank you. My name is Scout. I'm representing the National LGBT Cancer Network. I have no conflicts of interest related to this. We are funded by the Centers for Disease Control as one of eight [indiscernible] disparity networks around the country. In that capacity, we seek to spread education and connect people about cancer disparities for the LGBT population.

I appreciate the chance to speak today. I really, obviously, cannot comment on the particular merits of the drug, but I do simply want to apprise

the committee, as some of the other speakers have been saying before this, that there is an incredibly high need for new therapeutics in the anal cancer space.

I think as people may be familiar, the incidence of anal cancer has been going up in recent years, and by some measures has essentially quadrupled. A lot of that is currently attributed to HPV infection in people with HIV and the fact that we now have a cohort of people who have had that for 20 to 30 years, which is about the time that it takes for anal cancer to develop.

It's an area that, as the prior speaker said, is something that we should be able to fix. Right now, we're missing a lot of diagnostic opportunities; only one state in the country leading at standards for testing. Most providers don't even understand what an anal pap smear is, or when to test, or what populations are at particular high risk.

Then once you get to the point where, unfortunately, we have too many late-stage people

being diagnosed, then, as other speakers have said, the therapeutics are just woeful, and the quality of life after the current therapeutics, or after shall I say radiation, is awful.

So there is an incredibly high need in the population affected by this to change several issues related to this disease in our country, but adding more therapeutics to the mix is probably one of the highest needs.

I also do hope that any pharmaceutical company in this area uses the opportunity of a new drug being introduced to do more provider education, not only about what kind of screening needs to happen, but specifically which populations, particularly HIV-positive people, long-term, chronically HIV-positive people. And bi-men and transwomen are at particularly high risk and constitute a huge fault of the increasing numbers related to this disease. So there's a high need, and with that I say thank you very much.

Clarifying Questions to Presenters (continued)

DR. HOFFMAN: Thank you.

We're going to conclude the open public hearing portion. I just want to note for the record that speaker number 2, a physician from UC Irvine, forgot to state her name for the record, which is Dr. May Cho.

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

We will take some remaining clarifying questions for all the presenters thus far. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you've asked your question.

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. And it would be helpful to acknowledge the end of your question with a thank you or "That is all for my questions."

Before we broke for lunch, Mr. Berlin had his hand up, so I want to give him the first

opportunity to speak, please.

MR. BERLIN: Thank you very much. Just a question for the FDA.

Why did the FDA not include stable disease in the analysis that was presented today? Thanks.

DR. HOFFMAN: Dr. Saung, do you want to tackle that?

DR. SAUNG: Sure. This is Dr. Saung from the FDA.

In single-arm trials where we use ORR as the primary endpoint, we have not ever included stable disease because overall response rate, or ORR, is the sum of complete response and partial response.

In single-arm trials where we have only basically one arm, and not a control arm, we cannot say that the stable disease is due to the effect of the drug because it could be possibly from the natural disease progression for that patient. So without a comparative arm, we won't be able to compare this particular stable disease to a control arm. Thank you.

DR. HOFFMAN: Dr. Sanoff, I think you had a

question.

DR. SANOFF: Yes, thank you.

My question is back to the Incyte team again regarding the stable disease question. I was wondering if you could please show the slide you showed earlier with the trajectory of stable disease, because it went by a little fast to be able to see on a small computer screen. But it looked, to me, as though on the stable disease, you reported that a lot of patients had prolonged stable disease without progression, yet those yellow dots are started post-therapy.

Does that specifically mean that those patients were started on a different treatment? Because if so, I think that has direct implications for actually calling these patients having prolonged stable disease on trial. Clearly, they were switched to something for some reason.

DR. CORNFELD: Your observation is correct. We do know that none of the patients on our trial responded to post-study therapy. So the overall length of these bars, which is the period of time

where patients are presumingly doing well because the investigator doesn't feel compelled to take them off study, can be attributed entirely to retifanlimab.

The point to be made, again, since we have the slide up, is that the length of these bars exceeds one year, which to the previous comment is not a placebo response. You just do not see this with ineffective therapy or with the natural history of this disease.

If I could show the inversion analysis, which we performed --

DR. SANOFF: Well --

DR. CORNFELD: -- which is another way of -- I'm sorry, go ahead.

DR. SANOFF: -- I'm not sure that's fair to say. How can you be attributing duration of survival to a drug a patient is not on? If you go back to that slide, you have patients who come off after what looks like a month, and then live another 13.

DR. CORNFELD: Yes. The nuance here is that

the investigators are not managing according to ICR response. Actually, they're blinded to it, so they don't even know whether the ICR has called the patient stable disease or not. Only one patient received post-study immunotherapy, and with chemotherapy, you know immediately whether it's doing anything for the patient or not, and none of the patients benefitted from their salvage chemotherapy. You can see that they represent a minority of the patients who are actually on this display.

So there are, without a doubt, a large number of patients with stable disease who exceeded the natural history of this disease by quite a bit, as Dr. Fakih has already commented.

DR. SANOFF: Okay. Thank you.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: Thank you, Dr. Hoffman.

This is also for Incyte. If you can review again for the committee, slide CO-34, which is survival by response as of June 8, 2020, I do recognize survival benefit in a single-arm trial,

it has no value, but you have put a lot of weight in the statements that you just made related to response, stable disease, and the impact that dose might have in overall outcome. If you look at this, my interpretation of this, obviously, if you look at the bottom, the events are self-described here; responders to stable disease and progressive disease.

But I just wanted to try understand, how do you as a group really reflect on these Kaplan-Meier, with the imperfections of the data, and state that a stable disease will have a survival improvement?

DR. CORNFELD: Yes. Actually, in response to your question, since you noted the small number of observations here, I'd like to show the updated survival curve, which provides an additional 9 months of follow-up with the caveat that these data haven't been shared yet with FDA.

But if you see here now, the median survival has moved out another 3 months, and more importantly, we're starting to see a tail form on

this curve, which would be the hallmark of effective immunotherapy.

If you to want to see it broken down by category of response, again, we haven't shared these with FDA, but it answers your question. There is clearly a difference. We acknowledge that there are potential biases here. This is uncontrolled data, but certainly something we'd want to look at.

Patients with stable disease appear to have the prognosis that's intermediate between responders and patients with progressive disease and probably do contribute to the overall survival benefit that we think will emerge in the randomized trial.

DR. GARCIA: Thank you.

DR. HOFFMAN: Dr. Fashoyin-Aje?

DR. FASHOYIN-AJE: Yes. Good afternoon. I just wanted to make a point to expand on what I think Dr. Sanoff mentioned before. I think it's really challenging to make a regulatory decision on the basis of stable disease for many of the reasons

that we stated before.

So I just wanted to, again, emphasize that FDA regulatory action on this application would not be based upon stable disease. It will be based solely on the response rate and its durability. It's really quite challenging to attribute the stability of the disease when you don't have a comparative arm.

So while this is an important factor in clinical practice, as patients would view non-progressive disease as a favorable outcome, we don't know when, we don't have a comparative arm, whether that disease stability is due to the drug or versus due to the kinetics of the disease.

I will point out that while the applicant has made a point to say that this degree of disease stability is not consistent with the natural history of the disease, there is great variability in how patients progress. So I think it's very difficult to make those cross-trial comparisons, and that's why it's really important to have a comparative arm in these types of trials.

DR. CORNFELD: Dr. Hoffman, may I respond? This is Mark Cornfeld.

DR. HOFFMAN: Yes.

DR. CORNFELD: I tried to show this earlier. One way to address the question of whether this is just the natural history of the disease, and we got lucky and selected patients who were going to progress much more slowly and expect them -- could FDA allow us to share this slide, please?

This is something called an inversion analysis, and very simply, what we're comparing is time on whatever therapy patients got prior to entering study, which are the purple bars to the left of the zero axis, versus time on retifanlimab. It's not time to progression. It's time on study, but that's certainly a reasonable proxy for -- I'm sorry, treatment durations. It's a reasonable proxy for how patients are doing.

What you see here -- with the exception of one patient who is actually an anomaly because this patient had a CR, but had to be taken off for toxicity after the first dose and really had a much

more favorable experience than what's depicted here -- all of our patients actually did far better on retifanlimab than on whatever prior treatment they were getting.

So that tells you that the natural history or the kinetics of the disease were entirely reversed by retifanlimab and we're not just seeing a chance occurrence that might of happened because we selected patients with a more favorable prognosis for study.

DR. HOFFMAN: Okay. Thank you.

Dr. Sanoff?

DR. SANOFF: Sorry, I forgot to follow instructions and unraise my hand.

DR. HOFFMAN: Okay.

Dr. Reiss Binder?

DR. REISS BINDER: Hi. This is Dr. Reiss Binder. My question is directed at Incyte. I appreciate the inversion analysis, but to go back to Dr. Sanoff's previous point, was such an analysis also done on the patients who had stable disease as their best response to therapy?

Thank you.

DR. CORNFELD: No, I do not have that analysis to show you, but we would assume that since we didn't know, a priori, whether patients were going to respond or not, that the type of patients we've included for study would be similar at baseline in both the responder and the stable disease cohorts.

DR. REISS BINDER: May I respond to that, Dr. Hoffman?

DR. HOFFMAN: Please.

DR. REISS BINDER: I think you could say that, but I think you're also sub-selecting, so I would assume, or you would think, that the patients who were responding actually did have ultimately a different disease biology than those who simply had stable disease or progressed. So to only show the patients who are responding in that analysis seems like a biased way to look at it to me. Thank you.

DR. HOFFMAN: Dr. Cruz-Correa?

DR. CRUZ-CORREA: Thank you, Dr. Hoffman. I want to go back to the question of the population

of HIV patients. It was mentioned before that the response rate among the HIV population was I think higher than maybe 24, 23 percent. There was also a question about the inclusion criteria for the HIV positive with regard to the CD4 count.

My question is, can you elaborate a bit more in that HIV population to see whether or not there were any factors that could help us predict this, [indiscernible], or are we seeing HIV patients that are significantly different from the HIV community that presents with advanced cancer? Thank you.

DR. CORNFELD: It was a little bit difficult to hear some of your exposition. Are there specific factors that you would want to know with regard to these patients that perhaps we could respond to?

DR. CRUZ-CORREA: Well, I mean we see this advanced disease among patients with HIV that are those that, unfortunately, have worse outcomes. I am very excited about the fact that HIV patients were included; of 8, a small number, but they were included.

The question is, do you as an investigator feel comfortable with the HIV patients that were included in this clinical trial, with regards to how well do they represent the response of the HIV population with advanced anal cancer; because maybe they were too healthy? That's what I'm trying to understand. I think it's key. Thank you.

DR. CORNFELD: I understand. It's a good question. We did not have selective criteria for HIV patients as opposed to the general population. The exclusions were the same for everyone, and if patients had active infection or were being treated for an active infection, which I guess would be the major differentiator here, they weren't allowed on study until the infection had resolved.

Here you see the HIV criteria that we used. It was patterned after the ASCO guidelines and with input from FDA on what would be an acceptable population for us to study in our first attempt at this disease.

DR. CRUZ-CORREA: Okay. Thank you.

One last question. I also noted that the

age population that were older than 75 among your group, the patients, they had a better response, too. Do you have any hypothesis why we saw that?

DR. CORNFELD: No, we don't. I actually would not expect that patients who were older would somehow do better than patients who were younger. What we see, given the limitations in the data, is that there's really no population that didn't benefit at all from retifanlimab in our study, and that's an important observation because it means you can generalize this to standard practice.

DR. CRUZ-CORREA: Thank you.

Questions to the Committee and Discussion

DR. HOFFMAN: Okay. 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. And I certainly encourage members of the committee who may be non-voting members to participate as they see fit.

The discussion question is to discuss whether the demonstrated magnitude of effect on overall response rate and duration of response is clinically meaningful and reasonably likely to predict clinical benefit in patients with recurrent advanced or metastatic squamous cell carcinoma of the anal canal.

So I'm opening up to the panel for comments about this that may not have been aired already.

Dr. Garcia?

DR. GARCIA: I can start, Dr. Hoffman. Jorge Garcia. The way that I see this is, to me, it's clear. I don't believe with existing data and with the data that the FDA group presented today, with the historical approval for checkpoint inhibitors using overall response, I do not believe response is, in fact, an ideal endpoint for registration, and I do recognize the historical perspective that we have had with checkpoint

inhibitors.

I recognize also the FDA and their interest in perhaps readdressing that issue, but I also feel guilty, to some extent, because there is no guidance yet as to what that reassessment will look like. It is clear, based upon the historical data and the lack of confirmatory studies for most of those CPIs, that we have to have a change.

I do feel using response in orphan diseases, we have created a self-inflicted wound, if you will, because we all like checkpoint inhibitors, especially PD-1 and PD-L1 inhibitors, because they're easy for patients. Most patients do not have a lot of toxicities, and we see some degree of benefit, if you will. Whether that's clinically meaningful or not, I think all of us have different opinions as to that.

There's no doubt that if you look at those who actually truly have a complete radiographic response or a solid PR, then those are the patients who do benefit from therapy the most, yet there is not a predictive biomarker that we have, for most

cancers using CPIs for that matter.

I think that the question for me, and as I struggle to make this decision, is we have historical experience for approval, pending confirmatory trials, yet, we also know that thus far, many of the approvals have failed to demonstrate subsequent benefit in confirmatory trials.

So I don't know if POD1UM-303 will be any different to other historical regimens in the past, but I am also struggling with the fact that if you look at NCCN guidelines, look at the use of nivo or pembro in that refractory patient population, we pretty much are putting those patients at the mercy of payers to define if you can use nivo or pembro. And therefore, perhaps it makes some clinical sense to me to have, finally, one approved for that patient population so we don't have those patients basically at their mercy, or physicians or patients at the mercy of payers to define who gets that checkpoint inhibitor and who does not.

I'd love to hear other comments because

that's why I'm struggling right now as I think of this data and how we can move forward with this data.

Thank you, Dr. Hoffman.

DR. HOFFMAN: I think that's a fair summary of what probably a number of us are feeling.

Dr. Sanoff, your question or comment?

DR. SANOFF: Yes, I agree very much with Dr. Garcia's comments. I think, at the end of the day, it is very clear that people who have a strong response to these drugs are having a clinically meaningful benefit. But I'm afraid right now, we have such a small proportion of this study having a demonstrable benefit, I just really do not believe that we can hang our hat on this stable disease, and we can't look at the overall survival numbers for a stable disease population where we have no idea what those people's outcomes would have been had they received the placebo, for example.

We are being asked the question about this specific drug, not how we want to deal with the U.S. healthcare's management of NCCN guidelines in

nivolumab and pembrolizumab. So I'm afraid I have to take this question at face value, and I think it's very difficult to say for sure that the results of this trial are going to result in a meaningful improvement in either quality of life, patient function, or overall survival when we have final study data.

DR. HOFFMAN: All right. Thank you.

Dr. Nieva?

DR. NIEVA: Thank you. I want to just emphasize the question I think Dr. Weekes asked, which is we had an anticipated response rate on this study of 25 percent, and our response rate at the end of the study didn't cross that boundary.

Effectively, it seems that this is scientifically a negative trial. It didn't achieve the response rate that was anticipated. I think when looking at single-arm studies, we should at least ask that they match that hypothesis that they presented.

Really, the issue here is how low should the bar be set for absence of other therapies? I think

that's the challenge here. I think the fact that it was a negative trial, I think should have some meaning for us. Thank you.

DR. HOFFMAN: Dr. Pazdur?

(Pause.)

Dr. Pazdur, are you on?

DR. PAZDUR: Hello?

DR. HOFFMAN: Now we've got you.

(Pause.)

DR. HOFFMAN: Actually not.

DR. PAZDUR: Can you hear me now?

DR. HOFFMAN: Yes.

DR. PAZDUR: Okay, good.

The point I want to make is the committee should be looking at the safety and efficacy of the drug and whether this endpoint is reasonably likely to predict clinical benefit. We do not get into the area of cost of drugs at the FDA in making a regulatory decision or reimbursement practices. This is outside of the scope of this meeting, and I just want to make that perfectly clear to the committee members.

The question at hand is safety and efficacy of the drug; and number 2, is this endpoint that we're using and the magnitude of benefit reasonably likely to predict clinical benefit, given the context of discussions that we have had at hand?

We cannot get into issues of reimbursement nor prices of drugs. This is not something that the FDA takes into consideration. So I would advise the committee not to bring that into the decision-making process here.

DR. HOFFMAN: Okay.

Dr. Reiss Binder?

DR. REISS BINDER: Thank you, Dr. Hoffman.

I wanted to really just agree with Dr. Garcia and Dr. Sanoff, and I share some of guilt that Dr. Garcia speaks about, not in terms of cost, but in terms of what we've heard as the testimonials and as I see in my own clinic, that this disease is orphan and that there are very few options for patients.

But as Dr. Pazdur just said, this is about safety and efficacy, and based on what we have seen

today, purely on what we have seen today and also reflecting on the history of other accelerated approvals and how those have gone when final data emerges, it does not seem to me that we can say with -- or I cannot say with certainty, or with a degree of certainty that I feel comfortable with, that this data suggests that this is an efficacious drug for this patient population.

I wish that was not the case because I know, even if it's 1 in 12 patients who respond, for that person, that's saving a life. And I understand that, but I don't think that this collective data, at this time, is enough for me to say that this drug is ready to be out there with an FDA approval. Thank you.

DR. HOFFMAN: Dr. Lurain, you're next.

DR. LURAIN: Thank you, Dr. Hoffman. I think a lot has been made about comparing this with the other single-arm trials that have now been reversed and where data has come out from subsequent randomized trials. I think an important distinction for me between those trials, where the

decisions for approval have been reversed and those that have not so far, has been the viral positivity of this tumor. I do think that that's an important distinction to make in looking at the biologic significance of the HPV positivity of the tumors where similar overall responses were seen and their approval still holds.

I really would also just like to say that I think the company really did itself a disservice by putting such a high standard for a CD4 count for the patient population here. There's multiple perspective clinical trials now showing safety and efficacy down to CD4 counts of 100, and that data just continues to grow.

So I would encourage them, they may, in fact, see better responses in patients where receiving a T-cell sparing immune therapy may boost the actual tumor response in the future in their ongoing clinical trial. I do think that there is clinical benefit that I'm seeing in the data presented today, although I see many of the points of the other committee members today. Thank you.

DR. HOFFMAN: I'm sorry. Dr. Lurain, can you clarify for me what you started at there at the beginning of that comment? The fact that these are typically HPV associated, how does that alter your thinking regarding the value of --

DR. LURAIN: Thank you, Dr. Hoffman.

Yes. I think a lot has been made by -- FDA had made, I think, very good points that many of these trials, where they were single-arm and overall response rate was the final efficacy point, these accelerated approvals have been overturned. But the ones that, to me, if I'm recalling the data correctly, where the approval has subsequently been removed, were not for predominantly virally-driven tumors. And those HPV-positive tumors, those approvals still stand.

The one being hepatocellular carcinoma, which was reviewed and overturned, that can be driven by HBV or HCV, but much lower, and that's a very different oncogenesis pathway. So I do think there is a distinction between those trials and the one we're looking at today, if that clarifies my

point.

DR. HOFFMAN: Yes. Thank you.

Okay. I don't see any other comments, so I think we'll move to the next question. I think to summarize what we've been hearing, I think many of the people commenting have summarized it well that this is a fairly low response rate, yet on the good, some of these responses are prolonged. There has been considerable controversy about the value of stable disease, and I can say from decades of experience that that question has been ongoing for a long time.

Perhaps there is something different about a virally-driven cancer compared to others. I think everyone is in agreement that from the safety standpoint, this drug does not appear to be any more difficult than any other immune checkpoint inhibitor, so of course that's for the good as well. But I think concern has been raised about whether we're premature in concluding that this is going to be an active drug in this setting, and some variation of opinion on that.

Let's move on to question 2, which is our voting question, and that question is, should a regulatory decision on retifanlimab for the treatment of advanced or metastatic squamous cell carcinoma of the anal canal be deferred until further data are available from clinical trial POD1UM-303?

Dr. She-Chia Chen will provide the instructions for the voting.

DR. CHEN: Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

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

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

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

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

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

DR. CRUZ-CORREA: One question. This is Dr. Cruz-Correa.

DR. HOFFMAN: Yes?

DR. CRUZ-CORREA: Thank you, Dr. Hoffman.

As I'm reading through the question, does it mean that we need to wait until the study, POD1UM-303, is completed in full or does it incorporate intermediate analysis?

DR. HOFFMAN: I'll probably have to defer that to the FDA.

DR. PAZDUR: It could also be an interim analysis.

DR. CRUZ-CORREA: Okay. Thank you, Dr. Pazdur.

DR. HOFFMAN: So just to review then, the question is, should the regulatory decision on retifanlimab for the treatment of advanced or metastatic squamous cell carcinoma of the anal canal be deferred until further data are available from clinical trial POD1UM-303? If there are no questions or comments concerning the wording of this question, we'll now begin the voting.

Any comments or questions about the wording that we haven't covered?

(No response.)

DR. HOFFMAN: Okay. Dr. Chen.

DR. CHEN: Thank you, Dr. Hoffman.

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

(Pause.)

DR. CHEN: It is now complete. The vote results are displayed. I will read the various totals into the record, a total of 13 yeses, 4 noes, and zero abstentions. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also say the reason why you voted as you did, if you want to.

DR. HOFFMAN: Okay. Thank you.

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

Dr. Nieva.

DR. NIEVA: George Nieva. Yes.

DR. HOFFMAN: Do you want to make any comments?

DR. NIEVA: No additional comments. Thank you.

DR. HOFFMAN: Dr. Rosko?

DR. ROSKO: I voted yes that the decision should be deferred. I had concerns about the low overall response rate and the clinically meaningful endpoints. So that's my decision.

DR. HOFFMAN: Dr. Reidy-Lagunes?

DR. REIDY-LAGUNES: Thank you, Dr. Hoffman.

I voted yes. I think that Dr. Garcia said it beautifully, and I echo everything that he said. I think Dr. Pazdur, though, said it even more importantly, that I was voting based on the safety and efficacy of the data, and the data are the data in this single small study with this small overall response rate that did not meet the endpoint. I could not vote otherwise, so that was my vote.

DR. HOFFMAN: Okay. Dr. Lewis?

DR. LEWIS: This is Mark Lewis. I voted yes. This was certainly a wide-ranging discussion looking at both historical precedent, and even potentially a reevaluation of RECIST criteria. But I appreciate Dr. Pazdur refocusing us specifically on the questions of safety and efficacy in this specific agent.

While I didn't see any new concerning safety signals, I think it's dangerous to extrapolate a response rate, even if it's lower than projected, into clinical benefit for these patients. And I do think the schema and the endpoints of POD1UM-303 are such that we will get an endpoint answer, but it will take more time and more data.

DR. HOFFMAN: Dr. Lurain?

DR. LURAIN: I voted no that the decision should not be deferred based upon some clinically meaningful benefit to participants, including those living with HIV.

DR. HOFFMAN: Dr. Cristofanilli?

DR. CRISTOFANILLI: Yes. I'm Dr. Cristofanilli. I voted yes. And the reasons

were already explained from most of the speakers, the presenters.

Clearly, this is a single-arm study with no control, where the response rate is very low and certainly inferior to what was expected. And we just need a randomized study to really prove that this drug, a PD-1 inhibitor together with chemotherapy in that case, will impart a long-term outcome for these patients. We all understand that these patients need better treatment.

DR. HOFFMAN: Dr. Kunz?

DR. KUNZ: Thank you. This is Pamela Kunz. I voted yes to defer regulatory decision; agree with statements that have been previously made, and I believe strongly in trying to find better treatments for rare diseases. However, I also share the concern about the low total number of respondents of 13, and of those for the low response rate.

I also have some concerns about lack of applicability to a broader population given the lack of diversity of this particular patient group.

On the low number of HIV patients, I agree it's important. I'm very happy that they were included, but I think there's a low number of HIV-positive patients and a low number of underrepresented minorities. Thank you very much.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: Thank you, Dr. Hoffman.

I voted yes. Although I don't have any safety concerns with the agent, I agree with many of my committee members. The study failed to achieve the primary endpoint of response, and although there was a mathematical benefit, I'm not sure that that can fully translate into an overall outcome improvement.

I also do not believe -- perhaps I'm concerned as to the statistical design of the POD1UM-303 trial, as that trial allows patients who receive placebo plus carboplatin and a taxane to go on upon progression to receive the agent in question, perhaps complicating their readout if there's no advantage between the two arms.

Thank you, Dr. Hoffman.

DR. HOFFMAN: Thank you.

Mr. Berlin?

MR. BERLIN: Hi. I voted no. I certainly have heard everyone's concerns about the low rate. I personally would prefer that some sense of stable disease be taken into account, because as a stage 4 rectal cancer patient, every day that I have stable or without progression is a good day.

I would prefer to have this decision in the hands of a patient and their oncologist if there is potentially some benefit, which at least to me it appeared there was. But thank you for letting me participate, and I certainly trust all of you doctors with your decision making. Thank you.

DR. HOFFMAN: Dr. Lieu?

DR. LIEU: This is Chris Lieu and I voted yes, that I believe the decision should be deferred. I think the comments have been eloquently stated by a lot of the panel members. A response rate of 14 percent with only half of that population really showing a significantly durable response is certainly problematic and doesn't

necessarily predict clinical benefit.

I think everybody feels the pressure and the stress of wanting to improve treatment options for patients with what is essentially an orphan disease, but unfortunately the response rate is simply just, I think, too low to support an indication at this time. Thank you.

DR. HOFFMAN: Thank you.

Dr. Reiss Binder?

DR. REISS BINDER: Hi. This is Dr. Reiss Binder. I voted yes for the same reasons that many of my committee members have stated, very low response rate, and unclear that this response rate will translate ultimately in an actual benefit for patients. And certainly, I also feel the pressure to have something for my patients in this setting that's easily reachable and to be able to reach for, but I feel the data's not ready for us to say that this should be approved. Thank you.

DR. HOFFMAN: This is Dr. Hoffman. I voted no. Interestingly, I resonated with many of Dr. Garcia's comments earlier where he summarized

many of the pros and cons, and I came down to no to defer on that.

I think that it's true with checkpoint inhibitors, in general, the measurable response rates are often low, but some patients do get durable responses and there is not something else good for some of those patients.

I also found some of the public comment speakers very compelling about this. I thought that waiting four or five more years for the randomized trial was too long not to have something available to try for many of these patients.

Mr. Mitchell?

MR. MITCHELL: Thank you, Dr. Hoffman.

As always, I would prefer to advance a drug, especially when there's unmet need. Given that I have an orphan disease that is incurable, these are tough decisions. But given the uncertainties with respect to risk-benefit, confirmation of a clinical benefit with a randomized-controlled trial, or importantly, partial results from that trial needed now, when Dr. Pazdur clarified that we don't

necessarily have to wait until 2024 or 2025, that partial results could pave the way for approval, whether on an accelerated basis or not, that kind of tipped the scales for me to let's wait, get confirmation that this is going to work for patients, and then act. Thank you.

DR. HOFFMAN: Dr. Halabi?

(No audible response.)

DR. HOFFMAN: I'm sorry. We didn't hear the beginning.

DR. HALABI: Okay. Thank you, Dr. Hoffman.

In my opinion, the data are not solid. That's the main reason why I voted yes, that the regulatory decision on the drug should be deferred.

Similar to other members of the committee, I had concern on the limitation of the phase 2 trial and 13 patients out of 94 had responded, and out of those 13 only 1 patient experienced CR, and a small proportion of patients had response.

Clearly, we all recognize the need. There is a huge unmet need for patients with anal cancer, but also knowing the limitation here on the

phase 2, I believe the small response rate that has been observed would not be translated to clinically meaningful or clinical benefit to the patient.

Also, the last point has to do with the lack of generalizability to the patient population in terms of an underrepresented proportion of minorities and HIV patients that have been enrolled in this phase 2 trial. Thank you.

DR. CHEN: Excuse me to interrupt. This is DFO She-Chia. Just a friendly reminder for all the panel members, please state your name and your vote for the record. Thank you so much.

I'll hand it to you, Dr. Hoffman. Thank you.

DR. HOFFMAN: Dr. Weekes?

DR. WEEKES: Hi. This is Colin Weekes. I voted yes. My reason for voting yes is this study is essentially a negative study that did not meet its primary endpoint. I think, unfortunately, the low response rate does not really translate into clinical benefit, and I do appreciate the urgency to be able to offer our patients options, but I

think we should be offering our patients the correct options.

I do think that we need to have better evidence that there is benefit in the randomized controlled trial that will hopefully provide that evidence. I think this study also highlights the need to incorporate biomarker plans into these types of studies, or actually have them, so that we can potentially understand those patients who will benefit from these studies. Thank you.

DR. HOFFMAN: Thank you.

Dr. Sanoff?

DR. SANOFF: Yes. This is Hanna Sanoff. I voted yes for deferment. I did that, really, because in terms of the question of risk versus benefit. The likelihood of a severe adverse effect from this was almost as high as the likelihood of response. There also, on the waterfall plot, were a couple of patients who looked to have hyperprogression. I believe there was three of those, and when you put those in with the severe adverse effects, that is a real significant risk

that needs to be taken into account when there is some question of what is the real benefit.

I think, as Chris Lieu said, the durability of response was also not as convincing to me as we've seen in some other diseases. So while I'm very hopeful, based on the biology of disease, that this will actually turn out to be a staple of treatment, I really think we need to see some more information from POD1UM-303 before being able to approve this. Thank you.

DR. HOFFMAN: Thank you.

Dr. Cruz-Correa?

DR. CRUZ-CORREA: Thank you. Marcia Cruz-Correa, and I voted no. The reason behind that, it's multi-layered. The thing that impressed me the most is understanding the biology of these HPV-driven cancers. The people that we see that are affected by these type of HPV-driven malignancies that fail to respond to therapy, they really anecdotally, and on our data, the few data that is published, they do respond well to this type of therapy.

It is true and I agree with everything that was said before, that we do need to have a randomized clinical trial. I was hoping that that intermediate analysis, that hopefully will be in the next couple of years or maybe sooner than that, would allow us to have supportive data, original data, to determine the efficacy of this agent.

I was also impressed with the response rate among the group of patients that had HIV, which unfortunately is disproportionately affected by this disease and the lack of available therapies. But I appreciate the opportunity and I really enjoyed learning from the other team members' perspectives.

DR. CHEN: I'm sorry again to interrupt, Dr. Hoffman. This is DFO She-Chia again. So during the recording of the voting process, can Dr. Halabi please state your name and your vote into the record again? I think it wasn't captured. Please, thank you.

DR. HALABI: Yes, certainly. My name is Susan Halabi, and I voted yes.

DR. HOFFMAN: Okay. Did we have everyone else's recorded?

DR. CHEN: Yes. Thank you, Dr. Hoffman.

DR. HOFFMAN: Okay.

I think just to review, we have 13 votes to defer this accelerated approval, and 4 not to. I think that the majority of the votes to defer were based on the low response rate and relatively short overall benefit for patients, and the no votes related to the potential to have something available pending further studies for what I think everyone would agree is an unmet need.

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

DR. LEMERY: This is Steven Lemery. I'd just thank everyone for their time, and expertise, and comments, both from the committee, from the open public hearing, and the sponsor. All the participation is appreciated. Thank you.

Adjournment

DR. HOFFMAN: Okay. I think we'll now adjourn the meeting. Thank you, everyone, for

participation and work, and we'll see you next time.

(Whereupon, at 2:40 p.m., the meeting was adjourned.)