FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Afternoon Session

Thursday, September 26, 2024

1:15 p.m. to 4:29 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

William J. Gradishar, MD

Professor of Medicine/Betsy Bramsen

Professor of Breast Oncology

Chief, Hematology/Oncology

Robert H. Lurie Comprehensive Cancer Center

Feinberg School of Medicine at

Northwestern University

Chicago, Illinois

Ravi A. Madan, MD

Senior Clinician

Head, Prostate Cancer Clinical Research Section

Genitourinary Malignancies Branch

Center for Cancer Research

National Cancer Institute

National Institutes of Health (NIH)

Bethesda, Maryland

Daniel Spratt, MD

Vincent K Smith Chair, Department of

Radiation Oncology

Professor of Radiation Oncology and Urology

University Hospitals Seidman Cancer Center

Case Western Reserve University

Cleveland, Ohio

Neil Vasan, MD, PhD

Assistant Professor

Division of Hematology & Oncology

Department of Medicine

Herbert Irving Comprehensive Cancer Center

Columbia University Medical Center

New York, New York

TEMPORARY MEMBERS (Voting)

Dana Deighton

(Patient Representative; Afternoon Session Only)

Washington, District of Columbia

Lori Dodd, PhD

Mathematical Statistician

Biostatistics Research Branch

National Institute of Allergy and

Infectious Diseases

NIH

Bethesda, Maryland

Michael K. Gibson MD PhD FACP
Associate Professor of Medicine
Director of Translational Research for
Esophagogastric Cancer
Vanderbilt-Ingram Cancer Center
Vanderbilt University Medical Center
Nashville, Tennessee

Randy W. Hawkins MD
(Acting Consumer Representative)
Assistant Professor
Internal Medicine
Charles R. Drew University of Medicine & Science
Los Angeles, California

Christopher Lieu, MD
(Acting Chairperson)
Professor of Medicine
Associate Director for Clinical Research
University of Colorado
Aurora, Colorado

Heidi McKean, MD

Medical Oncologist

Avera Medical Group

GI Medical Oncology Program Director

Avera Cancer Institute

Sioux Falls, South Dakota

Jeffrey A. Meyerhardt, MD, MPH

Chief Clinical Research Officer

Dana-Farber Cancer Institute

Professor of Medicine, Harvard Medical School

Boston, Massachusetts

Hanna Sanoff, MD, MPH

Professor of Medicine

Associate Chief for Clinical Operations

Division of Oncology

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

Katherine Van Loon, MD, MPH

(via video conferencing platform)

Professor of Clinical Medicine

Gastrointestinal Oncology

University of California, San Francisco

San Francisco, California

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director

Oncology Center of Excellence (OCE), FDA

Director (Acting)

Office of Oncologic Diseases (OOD)

Office of New Drugs (OND), CDER, FDA

Paul Kluetz, MD

Deputy Center Director

OCE, FDA

Supervisory Associate Director (Acting)

OOD, OND, CDER, FDA

Steven Lemery, MD, MHS

Director

Division of Oncology 3 (DO3)

OOD, OND, CDER, FDA

Sandra Casak, MD

Clinical Team Leader (Acting) Gastrointestinal

Malignancies DO3, OOD, OND, CDER, FDA

Geetika Srivastava MD, MSPH

(Afternoon Session Only)

Clinical Reviewer

DO3, OOD, OND, CDER, FDA

Zhou Feng, PhD

(Afternoon Session Only)

Statistical Reviewer

DBV, OB, OTS, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(1:15 p.m.)

Call to Order

Introduction of Committee

DR. LIEU: Good afternoon, and welcome. I would first like to remind everyone to please mute your line when you're not speaking, and also a reminder to everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email is currently displayed.

My name is Dr. Christopher Lieu, and I'll be chairing this meeting. I will now call the afternoon session of the September 26, 2024 Oncologic Drugs Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We will start with the FDA to my left and go around the table.

DR. PAZDUR: Richard Pazdur, Director, Oncology Center of Excellence.

DR. KLUETZ: Paul Kluetz, Deputy Director, Oncology Center of Excellence.

DR. LEMERY: Steven Lemery, Director, DO3.

DR. CASAK: Sandra Casak, Division Team Leader, DO3.

DR. SRIVASTAVA: Geetika Srivastava, clinical reviewer, DO3.

DR. FENG: Zhou Feng, statistical reviewer, Division of Biometrics V.

DR. LIEU: Dr. Van Loon?

(No response.)

DR. LIEU: We can come back to Dr. Van Loon.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern University.

DR. SPRATT: Dan Spratt, UH Seidman and Case Western Reserve University.

DR. LIEU: Dr. Madan?

DR. MADAN: Ravi Madan, medical oncologist, National Cancer Institute.

DR. LIEU: Chris Lieu, GI medical oncologist, University of Colorado.

DR. FRIMPONG: Joyce Frimpong, Designated Federal Officer, FDA.

DR. VASAN: Neil Vasan, Columbia University.

DR. DODD: Lori Dodd, Clinical Trials, Research, and Statistics Branch, NIAID.

MS. DEIGHTON: Dana Deighton, patient representative.

DR. HAWKINS: Randy Hawkins, internal medicine, pulmonary medicine, Charles University, consumer rep.

DR. GIBSON: Michael Gibson, aerodigestive and GI oncology, Vanderbilt-Ingram Cancer Center.

DR. McKEAN: Heidi McKean, community medical Oncologist, Avera Cancer Institute, Sioux Falls, South Dakota.

DR. MEYERHARDT: Jeff Meyerhardt, GI medical oncologist, Dana-Farber, Boston.

DR. SANOFF: Hanna Sanoff, GI medical oncologist, University of North Carolina.

DR. LIEU: And Dr. Van Loon?

DR. VAN LOON: Hi. I'm Katherine Van Loon. I'm a gastrointestinal oncologist and Professor of

Medicine at UCSF.

DR. LIEU: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a 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 breaks. Thank you.

Dr. Frimpong will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: Thank you.

The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. 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 their 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 discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants,

CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves a discussion on the use of immune checkpoint inhibitors in patients with metastatic or unresectable esophageal squamous cell carcinoma. The current labeling for approved checkpoint inhibitors in this indication reflects broad approvals in the intent-to-treat populations agnostic of PD-L1 expression. Cumulative data have shown that PD-L1 expression appears to be a predictive biomarker of treatment efficacy in this patient population; however, clinical trials have used different approaches to assess PD-L1 expression and different thresholds to define PD-L1 positivity.

FDA would like the committee's opinion on the following: adequacy of PD-L1 expression as a predictive biomarker for patient selection in this patient population; differing risk-benefit assessments in different subpopulations defined by PD-L1 expression; and adequacy of cumulative data to restrict the approvals of immune checkpoint

inhibitors based on PD-L1 expression.

The committee will discuss the existing sBLAs, which were approved for patients with previously untreated, unresectable or metastatic esophageal squamous cell carcinoma: sBLA 125514/S-096 for Keytruda, pembrolizumab, injection, submitted by Merck Sharp & Dome, LLC, a subsidiary of Merck & Company, Incorporated; sBLAs 125554/S-105 and S-106 for Opdivo, nivolumab, injection, submitted by Bristol-Myers Squibb Company; and sBLA 125377/S-122 for Yervoy, ipilimumab, injection, submitted by Bristol-Myers Squibb Company. The committee will also discuss new BLA 761380 for tislelizumab, submitted by BeiGene USA, Incorporated, for the same proposed indication.

This is a particular matters meeting, which specific matters related to Bristol-Myers Squibb's sBLA, Merck's sBLA, and BeiGene's NDA will be discussed. Based on the agenda for 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. 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. LIEU: Thank you, Dr. Frimpong.

We will now proceed with FDA introductory remarks starting with Dr. Sandra Kazak.

FDA Introductory Remarks - Sandra Casak

DR. CASAK: Good afternoon, and welcome back. My name is Sandra Casak, and I am a team

leader in the Division of Oncology 3 at the FDA. I will provide a brief introduction to the afternoon session. Similar to this morning's session, we will discuss the predictive value of PD-L1 tumor expression and the potential for optimization of treatment using PD-1 inhibitors for patients with esophageal squamous cell carcinoma.

The first-line trials of immune checkpoint inhibitors in combination with chemotherapy that will be discussed today have demonstrated overall survival benefit for patients with metastatic or unresectable esophageal squamous cell carcinoma. The FDA approvals of pembrolizumab based on KEYNOTE-590 and nivolumab based on CHECKMATE-648, in combination with chemotherapy, or ipilimumab, at agnostic of PD-L1 expression status. Similarly, the trial of tislelizumab currently under review, RATIONALE-306, has shown a survival advantage in patients treated with tislelizumab in combination with chemotherapy.

Later today, the applicants will summarize the design of each study, and Dr. Srivastava will

highlight similarities and differences between them. For the purposes of this discussion, FDA's analysis will be centered only on the comparison of PD-1 inhibitors as add-ons to chemotherapy versus chemotherapy in patients with esophageal squamous cell carcinoma. In other words, we will not discuss the data in patients with esophageal adenocarcinoma or the results of the comparison of nivolumab in combination with ipilimumab versus chemotherapy alone.

In all three trials, overall survival results were statistically significant in all prespecified subgroup analyses of PD-L1 cutoffs. As shown in this table, the hazard ratios for the comparison of chemotherapy in combination with PD-1 monoclonal antibodies in the ITT population were 0.73, 0.74, and 0.66 in the pembrolizumab, nivolumab, and tislelizumab trials, respectively. Please note that there's an error in the slide, and the results on the bottom reflect all patients with esophageal squamous cell carcinoma. Similarly to the ITT, the overall hazard ratios for PD-1

monoclonal antibodies were 0.72, 0.73, and 0.68 in the pembrolizumab, nivolumab, and tislelizumab trials, respectively.

This table summarizes the results of the trials based on PD-L1 cutoffs. Each trial used different diagnostic test methodology to assess PD-L1 and different cutoffs for the prespecified statistical analyses, which are highlighted in colors, yellow for KEYNOTE-590, blue for CHECKMATE-648, and green for RATIONALE-306. The analysis of CHECKMATE-648 presented in this slide is based on CPS PD-L1 scoring instead of TPS, which was the original PD-L1 scoring algorithm used in the trial, as this information is now available.

Although the overall survival results were statistically significant for the anti-PD-1 containing arm in all three trials, highlighted in the red box, in subgroup analysis, the point estimates for the treatment effect appear marginally or not favorable in patients with PD-L1 less than 1 tumors and intermediate in patients with PD-L1 less than 10 tumors, as shown in the

right column. Although these results are exploratory, and uncertainty exists for each trial, the data does not appear to support the use of anti-PD-1 drugs in patients with PD-L1 less than 1 tumors, and benefit appears to be of a higher magnitude in patients with PD-L1 10 or higher expressing tumors.

FDA granted approvals for pembrolizumab and nivolumab regardless of PD-L1 status, reflecting the ITT patient populations; however, results of the prespecified cutoff, as well as exploratory analysis of additional PD-L1 cutoffs, as shown in this table, were included in FDA's product label to provide data on differential efficacy seen in patients with lower PD-L1 expression to inform treatment decision making.

Although both KEYNOTE-590 and CHECKMATE-648 were positive studies in the overall population, professional guideline recommendations for the first-line treatment for patients with unresectable or metastatic esophageal squamous cell carcinoma are generally based on subgroup analysis of the

PD-L1 cutoff of each individual study. As you can see in the slide, the guidelines and recommendations may result in inconsistent approach regarding who undergoes testing and which drug might be used at a given PD-L1 cutoff.

The ASCO and NCCN guidelines and recommendations were based on PD-L1 scoring algorithm and statistical designs using the individual studies, and as can be seen in the right-upper corner, ASCO recommendations for nivolumab is also accommodating to the use of a different scoring algorithm that one used in the clinical study supporting that particular recommendation. None of these recommendations specifically describe or require the use of individual PD-L1 tests used in each one of these trials.

As I have previously mentioned, FDA labels do not restrict indication for pembrolizumab or nivolumab and currently include information on the efficacy of both drugs for PD-L1 status in the product label. So why discuss PD-L1 in the

esophageal squamous cell carcinoma population now? Although subgroup analysis in single trials can be misleading, we now have results across three trials, suggesting lack of efficacy in PD-L1 negative or less than 1 patients.

To summarize, improvement in survival with the addition of a checkpoint inhibitor was greatest in patients with higher PD-L1 expression, 10 or more, in all three trials. Although sample sizes were limited, the point estimates for treatment effect -- 1 for pembrolizumab, 0.93 for nivolumab, and 1.34 for tislelizumab -- did not appear consistent with a beneficial effect of immune checkpoint inhibitors in patients with tumors that were PD-L1 less than 1.

Based on exploratory analysis of each trial pointing to the lack of clinically meaningful benefit in patients with PD-L1 low, the issue whether PD-L1 testing is needed to select patients for immune checkpoint inhibitor therapy for treatment of esophageal or gastroesophageal cancers have been extensively debated. In a published

meta-analysis by Dr. Yoon and colleagues of randomized clinical trials, including gastric and esophageal carcinomas, that was conducted to evaluate overall survival benefit from immune checkpoint inhibitors based on high versus absent or low PD-L1 expression, 5,067 patients with esophageal squamous cell carcinoma were included.

The meta-analysis was based on published trial-level data and further report that among patients with esophageal squamous cell carcinoma across all lines, PD-L1 tumor proportion score, or TPS, was the strongest predictor of immune checkpoint inhibitors' benefit, and TPS high was defined as TPS of 1 or greater, except in one trial that used a 10 cutoff.

In the TPS high subgroup, the overall survival hazard ratio was 0.60, while in the TPS non-high subgroup, the hazard ratio was 0.84. The second strongest predictor of benefit of treatment with immune checkpoint inhibitors was CPS high, defined as CPS of 10 or higher in all trials, except one trial which used a 1 cutoff. In the CPS

high subgroup, the overall survival hazard ratio was 0.62, while in the CPS non-high, the survival hazard ratio was 0.82. While FDA did not independently review this study, results are consistent with PD-L1 status being predictive of benefit in our patient-level evaluation of three pivotal trials.

Although, typically, drugs approved by the FDA are indicated for use in the total patient population studied, when there are consistent treatment effects across important study subgroups, consideration should be given towards indication to better inform use of a drug. As Dr. Lemery previously presented, when considering subgroup analysis, replication of results across multiple trials, sample ascertainment, biological plausibility, and study design considerations, including stratification and prespecification of analysis, are all factors important to the strength of the evidence.

In each of the three trials of anti-PD-1 inhibitors, there was no prespecification for the

PD-L1 low subgroups. Although for each PD-L1 cutoff subgroup, the analysis of the studies were underpowered, we now have the results of three studies with generally consistent effects, in addition to the data provided in Dr. Yoon and colleagues' meta-analysis.

When talking about lack of effect or uncertainty regarding treatment efficacy, safety should also be carefully considered. Exposure to treatment may potentially result in life-altering toxicity, which may be a risk patients are willing to take when a benefit is expected. The table at the left is a summary of the incidence of select immune-mediated adverse events across four trials with single-agent pembrolizumab and nivolumab. Although many of these events are treatable, immune-mediated adverse events can become chronic.

These adverse events, or even the steroids used to treat them, may compromise the patient's quality of life, which is fundamental to patients. In addition, although infrequent, there are deaths related to immune reactions associated with the use

of immune checkpoint inhibitors. In short, PD-1 monoclonal antibody treatments have toxicity, and benefit to patient relies on efficacy and outweighing that risk. In PD-L1 low populations, efficacy has come into question, and with it whether a favorable risk-benefit is remaining for those patients with tumors that are PD-L1 less than 1.

The table on the left is a snapshot of data for each trial. Results in the esophageal squamous cell carcinoma patients are displayed in the second column, and the PD-L1 less than 1 and less than 10 subgroups are displayed in the third and fourth columns. Later today, Dr. Srivastava will present an extensive review, including FDA's exploratory pooled analysis data, to provide additional context regarding the results of each trial.

Kaplan-Meier curves, median overall survivals, and hazard ratios in the PD-L1 low population, highlighted in the red boxes, appear to show marginal benefit across the class or even potential detriment. One cannot ascertain whether

any minor differences are related to sample size, testing methodology, or chance. Again, it is important to consider that although a minority of patients will develop severe or life-threatening toxicity, benefit to patients relies on efficacy outweighing that risk. In PD-L1 low populations, efficacy has come into question, and with it, whether a favorable risk-benefit remains for those patients with tumors that are PD-L1 less than 1.

Going back to subgroup analysis considerations, based on the data just presented, it appears the differential efficacy based on PD-L1 status is replicated across independent clinical trials. This repetition was in both the first-line esophageal squamous cell carcinoma trials in combination with chemotherapy, as well as in additional trials when assessed head to head against either chemotherapy or placebo, as described by Dr. Yoon and colleagues.

Sample ascertainment for PD-L1 expression was above 90 percent in the pembrolizumab and nivolumab trials and 84 percent in the tislelizumab

trials, with results available from the vast majority of patients. With respect to biological plausibility, although PD-L1 has variable utility as a biomarker in different tumor types, it does appear to be useful in select disease settings. Finally, a limitation of these findings is that all three studies used different PD-L1 testing methodology. PD-L1 high subpopulations were selected at two different thresholds, and none of the studies were specifically designed to test for PD-L1 negative or low subgroups.

In summary, the current U.S. FDA approvals of immune checkpoint inhibitors, in combination with chemotherapy for the first-line treatment of esophageal squamous cell carcinoma, are agnostic of PD-L1 expression status; however, three independent trials and FDA exploratory patient-level pooled analysis, as well as the published trial-level meta-analysis, support a predictive role of PD-L1 expression for treatment efficacy.

Patients with tumors with PD-L1 10 or higher appear to have the greatest magnitude of benefit.

Patients with tumors with intermediate PD-L1 expression between 1 and 10 have lesser magnitude of benefit. Patients with PD-L1 negative disease, although there may be some residual uncertainty based on small numbers of patients irrespective of the assay used, appear to have no evidence of benefit, and patients may actually be at risk for harm. Selection of the PD-L1 cutoff of 1 would result in approximately 90 percent of patients being ineligible for checkpoint inhibitors and would allow a consistent approach to treatment in the clinic.

Following all the presentations, we would like the committee to discuss the risk and benefit of the use of anti-PD-1 antibodies for the first-line treatment of patients with metastatic or unresectable esophageal squamous cell carcinoma, with PD-L1 status less than 1. Following the discussion, we would like the committee to vote on the risk-benefit assessment for the use of anti-PD-1 antibodies in first-line unresectable or metastatic esophageal squamous cell carcinoma with

a PD-L1 expression less than 1. Thank you.

DR. LIEU: Thank you, Dr. Casak.

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have 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 our first presentation from Merck.

Applicant Presentation - Catherine Pietanza

DR. PIETANZA: Good afternoon. I am Cathy Pietanza, Vice President of Clinical Research in Late Stage Oncology. I'm a medical oncologist, and prior to joining Merck, I was an attending physician at Memorial Sloan Kettering Cancer Center. We will share evidence supporting the positive benefit-risk of Keytruda in patients with esophageal cancer, which comprise both esophageal squamous cell carcinoma and adenocarcinoma. These may be referred to as esophageal cancer in this presentation.

This morning, we presented the biological rationale for combining pembrolizumab and chemotherapy, as well as the methodology for testing and validating PD-L1 CPS cutpoints used in Merck's pivotal trials. These pertain to our esophageal trials as well. I will describe

Keytruda's meaningful place in the treatment of esophageal cancer; Dr. Pooja Bhagia will then share data from KEYNOTE-590; and finally, Dr. Peter Enzinger will provide his clinical perspective.

Metastatic esophageal cancer is a rare disease, with patients having a poor prognosis, only 5 percent surviving 5 years. Before immunotherapy, the only treatment for first-line metastatic disease was chemotherapy. This malignancy has no biomarkers or targetable molecular aberrations, and as such, we face a dearth of therapeutic options.

Rigorous study design and conduct gives confidence in the positive results of KEYNOTE-590, which met success criteria for all primary and key secondary endpoints in the intention-to-treat population. The Keytruda label includes information about PD-L1 subgroups, empowering physicians to work with patients to make the best choice for therapy. The indication for Keytruda and esophageal cancer should be retained based on the safety and efficacy data in this patient

population.

KEYNOTE-590 was the first global phase 3 study to assess PD-1 inhibitors in combination with chemotherapy in advanced esophageal squamous cell carcinoma and esophageal adenocarcinoma, based on the best evidence at the time. Multiple interactions occurred with the FDA, where key design elements were jointly agreed upon. KEYNOTE-590 was approved in March 2021 and set a new standard of care for patients with locally advanced and metastatic esophageal cancer.

As you heard this morning, Merck determines the PD-L1 CPS cutpoints used in its randomized trial through the process outlined here. Pathologists were trained to use these prespecified cutpoints during patient screening for KEYNOTE-590, the validation set for assessing PD-L1 expression in the study. All PD-L1 evaluation was performed in a central laboratory. High-quality PD-L1 data informed meaningful efficacy subgroup analyses and support the allcomers indication for KEYNOTE-590.

While higher PD-L1 expression enriches for

pembrolizumab monotherapy efficacy in esophageal cancer, we cannot predict who will benefit, especially when chemotherapy is added to pembrolizumab. Finally, acknowledging that PD-L1 testing outside of clinical trials is variable, we stand by the meticulous process and data in KEYNOTE-590.

Merck phase 3 trials are designed with strict statistical methods, and these methods should be followed for labeling. Post hoc subgroup analyses without type 1 error control may lead to chance findings that could potentially be misleading, and thus should be interpreted with caution. As discussed this morning, the FDA pooled analysis has inherent limitations. Post hoc subgroup and pooled analyses should not supersede patient-specific data of a phase 3 trial with a diagnostic specifically developed for use with pembrolizumab.

Since the approval of KEYNOTE-590 in 2021, there have not been any new efficacy or safety data that change the benefit-risk profile for

pembrolizumab in this patient population. The PD-L1 assay is specific to pembrolizumab. There are key differences in determining a restriction of this indication by PD-L1 cutpoint compared to those for cetuximab or panitumumab and olaparib. Molecular alterations such as KRAS and BRCA mutations strongly predict response, whereas PD-L1 expression is a continuum, can be modulated by other therapies like chemotherapy, and is not always predictive of immunotherapy response. NCCN, ASCO, and ESMO guidelines provide detailed recommendations based on different PD-L1 cutpoints. Physicians use these guidelines, the label, and patient-specific characteristics to choose the right treatment.

Now, Dr. Pooja Bhagia will share data from the pivotal phase 3 study.

Applicant Presentation - Pooja Bhagia

DR. BHAGIA: Thank you, Dr. Pietanza.

My name is Pooja Bhagia. I am the Upper GI Cancer Clinical Lead at Merck, and I will present efficacy and safety data from KEYNOTE-590.

KEYNOTE-590 supported the approval of Keytruda for the first-line treatment of adults with metastatic esophageal cancer. In KEYNOTE-590, patients had metastatic or locally advanced unresectable esophageal cancer. The stratification factors in this study were region, histology, and ECOG status. This study had dual primary endpoints of OS and PFS and secondary endpoint of ORR. Alpha for statistical testing was initially allocated to the overall survival and progression-free survival dual primary endpoints, and then passed to the key secondary endpoint of objective response rate.

KEYNOTE-590 was initiated based on earlier studies, showing that pembrolizumab alone could trigger anti-tumor responses in esophageal cancer. Chemotherapy forms an essential backbone for treatment of esophageal cancer, and combining it with pembrolizumab may benefit patients with a wide range of PD-L1 expression as seen in other cancers. This led to the combination being used in this trial.

The study was originally designed to test

hypothesis in both the ITT group and biomarker-positive patients. After KEYNOTE-590 began, results from the phase 2 KEYNOTE-180 trial showed that patients with CPS greater than equal to 10 responded better to pembrolizumab. This led to CPS greater than equal to 10 being selected as a subgroup for analysis in KEYNOTE-590. The statistical plan was then adjusted to test hypotheses in both the CPS greater than equal to 10 group and the ITT population.

Baseline characteristics were well balanced between the two arms. Approximately 73 percent of patients enrolled had squamous cell carcinoma. PD-L1 CPS greater than or equal to 10 comprised approximately 50 percent of the population and PD-L1 CPS greater than or equal to 1 included about 85 percent of the population.

Although CPS greater than or equal to 1 was not a prespecified cutpoint in KEYNOTE-590, Merck has confidence in the accuracy of these data for two reasons. First, this cutpoint has been used in previous esophageal studies and continues to be

utilized in our ongoing esophageal studies. Second, pathologists at our testing labs were trained and certified at this cutpoint, and the testing lab had validated this cutpoint, establishing reproducibility and repeatability.

KEYNOTE-590 met success criteria for all endpoints in the intent-to-treat population, which was all patients regardless of PD-L1 status and histology. The overall survival curve favored pembrolizumab with a 27 percent reduction in the risk of death. Progression-free survival curve also favors pembrolizumab, reducing the risk of progression or death by 35 percent. At 2 years, 28 percent of patients receiving pembrolizumab plus chemotherapy remain alive versus 16 percent of those who received chemotherapy. Notice the tail of the curve, which is characteristic of pembrolizumab.

The safety profile of the investigational arm is consistent with the established safety profiles of pembrolizumab and chemotherapy. The addition of pembrolizumab adds immune-mediated AEs

and infusion reaction, which were mostly low grade and manageable. It is known that some immune-mediated AEs such as endocrinopathies will require long-term hormone replacement. These data highlight the favorable benefit-risk profile of pembrolizumab plus chemotherapy for all patients.

To address FDA's questions, we will now look at different PD-L1 cutpoints. Although a higher magnitude of benefit is seen with increasing PD-L1 expression, all subgroups are directionally consistent with the ITT population, with point estimates of the hazard ratio being less than 1. In the CPS greater than equal to 1 subgroup, the point estimate of the hazard ratio for OS and PFS is 0.7 and 0.63, respectively, demonstrating a clinically meaningful benefit.

The CPS greater than equal to 10 subgroup also shows a clinically meaningful benefit. The CPS less than 1 subgroup was not prespecified with formal statistical testing. Given the small number of patients, the OS hazard ratio confidence intervals are very wide and overlap with ITT. What

this forest plot does not show is that there were 4 patients that had a complete response in the chemotherapy plus pembrolizumab arm versus none in the chemotherapy alone arm. Of the 4 patients, 3 patients were still alive at 5 years.

In patients with CPS between 1 and less than 10, we see a benefit with an OS hazard ratio of 0.84 and confidence intervals that overlap with the ITT, indicating that the benefit is not driven by CPS greater than 10. At A 5-year follow-up assessment, the benefit of pembrolizumab is consistent with the primary analysis with an improvement in the hazard ratio, underscoring a tenet of immunotherapy.

There is no biological rationale to suggest that the safety profile of pembrolizumab would change based on PD-L1 expression. The safety profile is, in general, similar across CPS cutpoints, even when CPS less than 1 is compared with other CPS cutpoints. Of note, any death due to AEs is already accounted for in the KM curves, and the hazard ratio for the CPS less than 1

subgroup, as we see here, is less than 1.

For the ESCC patients in KEYNOTE-590, the results were similar to the ITT population with statistically significant and clinically meaningful effect regardless of PD-L1 status. At a 5-year follow-up assessment, the benefit of pembrolizumab in the ESCC is consistent with the primary analysis and maintained, suggesting long-term efficacy for this patient population.

As requested by the FDA, overall survival and progression-free survival data by additional PD-L1 CPS cutpoints are shown here. About 90 percent of patients with ESCC have tumors expressing CPS at a score of 1 or more, and this subgroup demonstrates meaningful benefit. The ESCC population with CPS less than 1 represents a subgroup of a subgroup, and therefore, meaningful conclusions cannot be made. Overall, the results in the ESCC population are consistent with the ITT population.

In summary, there is a high unmet need in first-line metastatic esophageal cancer.

Pembrolizumab added to chemotherapy significantly improved overall survival, progression-free survival, and response rates in the ITT population with greater benefits at higher PD-L1 levels. Patients with lower CPS scores also benefited, showing that CPS alone cannot predict who will respond to pembrolizumab and chemotherapy. Health-related quality of life remains stable during treatment, was similar between arms, and consistent across CPS subgroups.

The manageable safety profile reflects the known safety profiles of the components and is generally similar across CPS subgroups. The totality of evidence supports that pembrolizumab should be available to all patients with esophageal cancer as a treatment option consistent with the approved label. Thank you, and I will now invite Dr. Enzinger to the podium.

Applicant Presentation - Peter Enzinger

DR. ENZINGER: Good afternoon. My name is Peter Enzinger. I am a GI oncologist at the Dana-Farber Cancer Institute and an associate

professor at Harvard Medical School. I'm happy to discuss my clinical perspective on the data shared today. Here are my disclosures.

Unfortunately, esophageal cancer remains understudied and underserved, leaving patients with limited options for treatment. Most patients are diagnosed at stage 4, and as we can see on the right, they have a dismal prognosis. Before approval of immunotherapy, the only option was chemotherapy. This is a difficult to treat disease, and most patients do not live to get second line. Current treatments are largely palliative, which emphasizes the urgent need for new treatment options to improve patient outcomes and quality of life.

For more than three decades, treatment has been a combination of platinum and fluorouracil. Only by borrowing the FDA indication from gastric adenocarcinoma have we been able to introduce trastuzumab and ramuciruumab for some of our adenocarcinoma patients. Pembrolizumab plus chemotherapy is practice changing for first-line

metastatic esophageal cancer and a valuable treatment option that should remain a choice. Physicians should consider urgency of treatment, timing of biomarker testing, adverse event profile, and prospect of long-term survival. Patient PD-L1 expression level can assist with individual patient management decisions.

Although PD-L1 testing aids in understanding who may have increased benefit from immunotherapy, it presents some challenges in clinical practice. Some of the reasons are as follows. There can be different assays and antibody clones used by various organizations that are not FDA approved, which may result in staining variability; and unlike a clinical trial, in the real world, patients may not have a sample of sufficient quality for PD-L1 testing. And finally, there is significant inconsistency in pathologist training in cutpoint interpretation.

To investigate PD-L1 testing and treatment patterns among advanced or metastatic esophageal cancer patients, a retrospective observational

study was conducted using the Flatiron database of adult patients who received first-line systemic treatment. Of the 670 patients treated in the first-line setting, 66 percent were evaluated for PD-L1. In this group, 41 percent were treated with chemotherapy plus immunotherapy and 58 percent received chemotherapy alone. These data suggest that physicians and patients carefully weigh the risks and benefits of available treatment options. Importantly, if the indication is restricted to patients with CPS greater than equal to 1, this will deprive approximately 11 percent of patients of potentially effective therapy.

I would like to highlight a patient treated on KEYNOTE-590. This is a western patient in her 40s with esophageal squamous cell carcinoma with lung metastases. She had a CPS score of less than 1. She was randomized to the treatment arm, and after 15 cycles of chemotherapy and pembrolizumab, imaging showed a complete response. I want to acknowledge that such responses may be seen with chemotherapy alone; however, what is

remarkable is the durability of response which lasted for about 50 months. Further, this patient was alive at 5 years.

This patient illustrates that despite a CPS score of less than 1, durable responses and long-term survival is possible, which is not typical of chemotherapy. Of note, this may not be such an unusual result. The final results of KEYNOTE-590 showed 5-year survival in approximately 11 percent of all randomized patients treated with pembrolizumab and chemotherapy compared to only 3 percent with chemotherapy alone.

In conclusion, treatment options are severely limited for this disease. Checkpoint inhibitors have revolutionized the care of patients with esophageal cancer, improving survival and maintaining quality of life. The choice to add a checkpoint inhibitor must be individualized and depends on many factors. Their ability in real-world PD-L1 biomarker testing may hinder treatment decisions. Further, the scientific community informs decision making through clinical

guidelines. The allcomer indication allows patients to have immunotherapy as a first-line treatment option at the discretion of their treating physician.

Thank you, and Dr. Pietanza will now make closing remarks.

Applicant Presentation - Catherine Pietanza

DR. PIETANZA: Thank you, Dr. Enzinger.

In summary, KEYNOTE-590 established pembrolizumab and chemotherapy as a standard of care in esophageal carcinoma. It met all its primary and key secondary endpoints in the intention-to-treat population. The label reflects the study outcome.

Metastatic esophageal cancer is a fatal disease, where survival is measured in months. Pembrolizumab combined with chemotherapy is one of the only treatment options for these patients. Data show that efficacy can occur across a range of PD-L1 expression, including in those with low or no expression. As we heard from Dr. Enzinger, restricting the indication would leave these

patients no choice but chemotherapy. The current indication allows physicians to make the best possible choice for patients with esophageal cancer. Thank you for your attention.

DR. LIEU: Thank you.

We will take a quick 10-minute break to allow for the next presentation to set up. Panel members, please remember that there will be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 2:10 p.m. Eastern Time.

(Whereupon, at 2:01 p.m., a recess was taken, and meeting resumed at 2:10 p.m.)

DR. LIEU: Welcome back, everybody. We will now proceed with our second presentation from Bristol-Myers Squibb.

Applicant Presentation - Ian Waxman

DR. WAXMAN: Good afternoon. My name is Ian Waxman, and I'm part of the late development oncology organization at Bristol-Myers Squibb. I'd once again like to thank the advisory committee

members and the FDA staff for this opportunity to discuss the data for Opdivo, this time in combination with chemotherapy, or ipilimumab, in first-line esophageal squamous cell carcinoma, also known as ESCC. These data come from the CHECKMATE-648 study and resulted in FDA approval for this indication in May of 2022.

The indication statement for this approval is shown on this slide, and it's important to highlight two things here. First, the approval was granted regardless of PD-L1 status; and second, since the initial approval, our interpretation of the study result has not changed with longer follow-up. Although the indication statement is not limited to a PD-L1 positive population, clinical data by PD-L1 expression level are included in Section 14 of the USPI. These data are included to ensure that treating physicians have sufficient information regarding the impact of PD-L1 positivity when discussing treatment options with their patients.

Since the time of this approval, results

from additional esophageal cancer studies have been reported. As was the case for gastric cancer, different sponsors incorporated different methods for measurement of PD-L1 and selected different cutoffs to determine positivity in these studies. For esophageal squamous cell carcinoma, NCCN recommendations for the Opdivo combinations are not based on PD-L1 expression level, a decision influenced by the overall high rate of PD-L1 positivity in CHECKMATE-648.

Since information regarding the impact of PD-L1 expression on outcomes is readily available, including in the USPI, it's helpful to understand how often physicians are testing their patients and whether or not their treatment decisions are influenced by those test results. What we see, based on U.S. Flatiron data, is that about 60 percent of advanced ESCC patients who receive first-line treatment are tested for PD-L1 expression, even without a requirement to do so, demonstrating that many physicians see value in PD-L1 testing today; and when we move from testing

patterns to treatment patterns, we see that physicians are oftentimes incorporating the test results into their treatment decisions, with the presence of a positive test result leading to greater likelihood of treatment with an IO regimen.

On the left-hand side of the slide, we see that among patients who test positive for PD-L1 expression, three-quarters are receiving IO plus chemotherapy, in blue, and about 8 percent receive nivo plus ipilimumab, in red. In the middle, you can see that among the small subset of patients who tested negative for PD-L1, only about one-quarter receive an IO regimen. Another way to think about this is that among all treated patients, less than 5 percent are treated with IO and known to be PD-L1 negative.

On the far right-hand side, we're reminded that some treatment decisions continue to be made in the absence of a test result. We consider use of IO to be appropriate in this patient segment since an untested patient is more likely to be positive than negative, with approximately

90 percent of ESCC patients considered PD-L1 positive when using the CPS 1 cutoff. With this in mind, we're here to discuss whether any label changes for Opdivo in first-line ESCC are needed, also using this as an opportunity to consider harmonization of product labels based on PD-L1 expression. Our goal is to ensure that each first-line ESCC patient has every appropriate therapy available to them, along with clear guidance to inform choice of treatment.

A review of subgroup analyses by PD-L1 expression level from the CHECKMATE-648 and the unique clinical considerations for this patient population are also critical parts of the discussion, and we will turn to these topics next. Once we've considered these additional points, I'll return to summarize potential options for labeling, also briefly described here.

One option is to modify the indication to only include patients testing PD-L1 positive using any FDA approved test. This would limit treatment to patients more likely to benefit based on the

clinical trial data but could leave some patients without a potentially important treatment choice. The proposal to use any approved test would minimize the impact on each institution's current testing practices since CPS is used much more widely than TPS today.

The second option is to leave the indication as is so that physicians can continue to make treatment decisions informed by the data as currently described in the USPI and consistent with NCCN guidelines. Given that ESCC is a rare disease with very high prevalence of PD-L1 expression, we consider this to be the preferred option. Additional considerations for each of these approaches are shown here and will be discussed in more detail in the next parts of the presentation.

Here is the agenda for the remainder of our time. First, Dr. Dana Walker from the drug development organization at BMS will review the relevant efficacy and safety data from CHECKMATE-648; then Dr. Ronan Kelly from Baylor University will provide his clinical perspective on

the value of PD-L1 testing for patients with ESCC; and finally, I'll return to review options for labeling. Thank you, and I'll now turn it over to Dr. Walker.

Applicant Presentation - Dana Walker

DR. WALKER: Thank you. My name is Dana Walker, and I'm the Global Program Lead for Opdivo and Yervoy for GI and GU cancers at BMS. Today, I will present data from the CHECKMATE-648 study, demonstrating the benefit-risk profile across PD-L1 subgroups in esophageal cancer.

CHECKMATE-648 is a randomized, open-label, phase 3 study that enrolled previously untreated patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma regardless of PD-L1 expression. A total of 970 patients were randomized to receive nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy alone. Stratification factors included tumor cell PD-L1. The primary endpoints of the study were overall survival and progression-free survival per BICR for patients

with tumor cell PD-L1 of 1 percent or higher, referred to as the PD-L1 positive population.

CHECKMATE-648 demonstrated both a statistically significant and clinically meaningful improvement in the primary endpoint of overall survival in the PD-L1 positive population, with a hazard ratio of 0.54 and a 6.3-month improvement in median overall survival compared with chemotherapy alone. The secondary endpoint of overall survival in the all-randomized population was also met, with a hazard ratio of 0.74.

Shown here is overall survival by TPS subgroups. The data in the blue boxes highlight the prespecified primary and secondary analysis populations. The other TPS subgroup analyses were exploratory. The overall survival benefit was observed across all PD-L1 positive subgroups, and there was a higher likelihood of overall survival benefit observed in patients whose tumors expressed PD-L1. In patients with TPS less than 1, the overall survival hazard ratio was 0.98, suggesting there is no overall survival benefit.

During the study, data began to emerge, suggesting the potential predictive value of CPS in upper GI tumors; therefore, we conducted exploratory overall survival analyses in PD-L1 CPS subgroups. Similar to the TPS less than 1 percent subgroup, the hazard ratio in the CPS less than 1 subgroup was 0.98. Please note, approximately 90 percent of patients in the trial with known PD-L1 status were CPS greater than or equal to 1; therefore, the CPS less than 1 analyses should be interpreted with caution.

Additionally, and similar to the TPS subgroups, patients were more likely to derive an overall survival benefit at any level of PD-L1 positivity as measured by CPS. In contrast to what we saw in gastric cancer, there is no evidence of increased benefit at higher CPS scores.

Here, we present the exploratory subgroup data for the nivolumab plus ipilimumab versus chemotherapy comparison. Looking at overall survival across CPS subgroups, a similar trend was observed in the nivo plus chemo versus chemo

comparison, with a higher likelihood of overall survival benefit with nivo plus ipi in all CPS positive patients. Results of long-term overall survival follow-up across PD-L1 subgroups were generally consistent with those reported at the primary analysis for both the nivo plus chemo and nivo plus ipi regimens and is discussed in more detail in our briefing document.

The safety profile of nivo plus chemo and nivo plus ipi observed in CHECKMATE-648 was consistent with the known safety profile of the individual drug components. As expected, the addition of nivolumab to standard chemotherapy was associated with added toxicity. Grade 3-4 treatment-related adverse events and those leading to discontinuation of any treatment component were numerically higher in patients receiving nivo plus chemo. Of note, in both nivo-containing arms, the majority of immune-mediated events were low grade, manageable with established treatment algorithms, and reversible. Importantly, the safety profile of both nivo-containing regimens did not differ based

on PD-L1 expression and was consistent across all PD-L1 subgroups evaluated.

In summary, CHECKMATE-648 demonstrated statistically significant and clinically meaningful overall survival benefit in the TPS greater than or equal to 1 percent in all randomized populations. Exploratory analyses suggest similar overall survival benefit across all PD-L1 positivity, and long-term overall survival follow-up data are consistent with the data available at the time of the approval. The safety profile of nivo plus chemo and nivo plus ipi was consistent with the known safety profile of the individual drug components and did not differ based on PD-L1 status. Overall, there's a positive benefit-risk profile in all PD-L1 positive subgroups.

Thank you. I will now turn it over to Dr. Kelly for his clinical perspective.

Applicant Presentation - Ronan Kelly

DR. KELLY: Thank you very much, Dr. Walker.

It's a real pleasure to be here. My name is Dr. Ronan Kelly. I'm the Director of the

Charles A. Sammons Cancer Center at Baylor University Medical Center in Dallas, Texas, and I'm the Chief of Oncology for the Baylor Scott and White Health system, which is the largest not-for-profit health system in Texas. I am a paid consultant for BMS.

The Baylor Scott and White Health system has 51 hospitals throughout the state of Texas and 13 dedicated cancer centers, which represents one of the largest Commission on Cancer network of cancer hospitals in the United States. As such, I have exposure to treatment patterns both in academic and in a community setting and in both urban and rural areas alike; therefore, I can see the challenges that exist for both medical oncologists and pathologists with regards to PD-L1 testing and PD-L1 interpretation for esophagogastric cancers in real-world treatment settings.

Esophageal squamous cell carcinoma is truly an orphan disease in the United States. If you look at the SEER data, approximately 14,000

patients were diagnosed with ESCC in the U.S. over an 11-year period, so just over a thousand patients per year, which translates into very few patients being seen by doctors across the country. Unfortunately, the majority of these patients are diagnosed with advanced disease.

Historically, the breakdown between esophageal adenocarcinoma and esophageal squamous cell carcinoma was 70 percent and 30 percent, respectively, but recent epidemiological data indicates that ESCC is decreasing in the United States because of falling smoking rates throughout this country. Treatment recommendations, therefore, in my opinion, should be kept as simple as possible for this orphan disease, and I agree with the NCCN guidelines that continue to recommend treatment for this disease regardless of PD-L1 expression.

Unfortunately, very few patients with this disease go beyond first-line treatment. The data shows that approximately 70 percent of ESCC patients receive first-line treatment but less than

a quarter of our patients, only 23 percent, make it to the second-line setting. That's an enormous drop-off, and it indicates we should not be waiting to give our best treatment options in the second-line setting or third-line setting. In fact, less than 8 percent of these patients make it to the third-line setting.

If you look at the clinical trial data from CHECKMATE-648, which includes patients who historically would have a better performance status than real-world patients, less than 50 percent of those make it to the second-line setting. It is my opinion that a PD-1 inhibitor plus chemotherapy, or the combination of nivolumab plus ipilimumab for patients who may decline chemotherapy or who may be considered by their oncologist to be too frail for chemotherapy, represents breakthrough treatment options for patients with ESCC.

It's very important for the panel to understand that ESCC is biologically different from the disease we spoke about this morning. This is not gastric cancer and it's not gastroesophageal

junction adenocarcinoma. These are two very different diseases. Notably, ESCC is also regarded as more immunogenic than the adenocarcinoma histology. You can see the cancer genome data on the right there showing that ESCC, which is highlighted in red, is genomically similar to squamous cell head and neck cancers, and the location, as you can see by the figure, also indicates this tumor occurs much more proximally in the esophagus, which leads to significant more dysphagia and significant problems for our patients.

Recent data from other large phase 3 trials, which we won't discuss today, around the world continue to demonstrate the efficacy of IO regimens in ESCC, even in patients with low PD-L1 expression. PD-L1 in esophageal squamous cell carcinoma is likely not the only factor influencing response here. ESCC develops in a chronically inflamed tumor microenvironment dominated by exhausted T cells and suppressive cell populations.

Another challenge that's different here than

what we talked about this morning is, in these patients, to relieve their discomfort, to improve their calorific intake, we often often give them palliative radiation to improve their ability to eat. Many of these patients struggle to even swallow their own saliva. When we offer them radiation, what we do is we upregulate PD-L1.

We talked this morning about the dynamic nature of this biomarker. So when we offer palliative radiation, we are changing the PD-L1 status of that patient; therefore, spatial and temporal heterogeneity may be even more problematic in this disease where radiation is the norm, and it's also not safe to continue to repeat endoscopic biopsies post-radiation, so the ability to do longitudinal biopsies as discussed this morning is not feasible in this situation.

In terms of PD-L1 testing, we know the majority of patients are tested, about 60 percent, and the vast majority of centers are utilizing CPS with less than 5 percent of centers utilizing TPS alone in this setting. We heard this morning,

again, the reality, PD-L1 is imperfect, and I'm not going to get into that again. All those reasons were discussed previously. Furthermore, ESCC has very high PD-L1 expression at baseline with about 90 percent of tumors expressing measurable PD-L1 by CPS.

So in conclusion, it's my opinion that maintaining the current indication in this disease setting is appropriate. The biology of the disease is different from gastric and gastroesophageal junction adenocarcinomas. PD-L1 may be not as important in this disease setting, which is dominated by other immunosuppressive phenotypes. Unfortunately, only about 25 percent of our patients even make it to the second-line treatment setting, so it's important to give our best treatment options upfront, and this would include nivolumab with chemotherapy or a chemo-free option with nivolumab plus ipilimumab.

At the present time, we do not require testing for ESCC as per the NCCN guidelines for many of the reasons that I've explained and the

high prevalence of PD-L1 expression in this disease setting. If a restriction is required, then PD-L1 positivity by any FDA-approved measure makes the most sense in clinical practice. Thank you very much, and I'll now turn it back to Dr. Waxman to conclude.

Applicant Presentation - Ian Waxman

DR. WAXMAN: Thank you, Dr. Kelly.

As I turn to review our proposed options for labeling, I'd first like to reiterate that this is an important issue with more than one potential solution. The FDA has asked you to consider whether the benefit-risk assessment is favorable in the ESCC patients with PD-L1 of less than 1. Regardless of how you answer that question, there are still two important options to consider.

The first option is to modify the indication based on PD-L1 positivity by any approved test, reserving treatment for those more likely to benefit and allowing for potential harmonization across the class. The second option is to keep the current indication with details regarding the

impact of PD-L1 expression remaining in Section 14 of the label. This provides clarity regarding the impact of PD-L1 on outcomes while providing an opportunity for all patients to receive immunotherapy, especially important given that most ESCC patients will be PD-L1 positive.

We believe that both of the proposed options are reasonable, although leaving the indication as it's written today provides the most flexibility for patients. Thank you once again for your time and attention.

DR. LIEU: Thank you.

We'll take another 10-minute break to allow for the next presentation to set up. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any other member of the audience. We will return a 2:40 p.m.

(Whereupon, at 2:30 p.m., a recess was taken, and meeting resumed at 2:40 p.m.)

DR. LIEU: Welcome back, everybody. We will now proceed with our third presentation from

BeiGene.

Applicant Presentation - Mark Lanasa

DR. LANASA: Good afternoon, everyone. My name is Mark Lanasa, and I'm the Chief Medical Officer for Solid Tumors at BeiGene. I again want to thank the FDA, the chair, and the members of the committee for the opportunity to share our tislelizumab results in this important discussion of squamous cell esophageal cancer.

This afternoon, I will review the results from our pivotal study, RATIONALE-306, in squamous histology esophageal cancer and share additional subgroup analyses to explore a potential relationship between PD-L1 expression and survival. I will then ask Dr. Uboha to provide her clinical perspective on the use of PD-1 inhibitors in patients with the ESCC. We also have additional experts with us today to help to address your questions.

In 2018, we initiated the global, pivotal phase 3 RATIONALE-306 study evaluating the efficacy and safety of tislelizumab combined with

chemotherapy versus placebo and chemotherapy as first-line treatment for patients with locally advanced unresectable or metastatic squamous histology esophageal cancer, which I will refer to as ESCC. Study 306 met the primary endpoint of overall survival in the ITT population at a prespecified interim analysis in February of 2022. Our BLA for this indication was submitted on July 18, 2023 and is currently under review.

On March 14, 2024, tislelizumab was approved by the FDA to treat patients with unresectable or metastatic ESCC after prior systemic therapy that did not include a PD-1 inhibitor, based on the results of the global phase 3 RATIONALE-302 study. In this study, tislelizumab prolonged overall survival as monotherapy when compared to investigator choice of available chemotherapies.

Overall, results from our pivotal study show that first-line treatment with tislelizumab in combination with chemotherapy offers substantial benefit in overall survival. Tislelizumab in combination with chemotherapy produced

statistically significant and clinically meaningful improvement in OS, as well as improvements in progression-free survival, objective response rate, and duration of response in the overall population. Tislelizumab also showed an acceptable safety profile across a broad population of patients with unresectable advanced or metastatic esophageal squamous cell carcinoma. Finally, analyses across PD-L1 expression levels show that the benefit of tislelizumab plus chemotherapy in patients with locally advanced or metastatic ESCC is most favorable among patients with a PD-L1 score greater than or equal to 1 percent.

Now, I would like to review our study design and key results. RATIONALE-306 is a global, randomized , double-blind, placebo-controlled study in 649 patients with a histologically confirmed diagnosis of esophageal squamous cell carcinoma with either metastatic or locally advanced disease that was not amenable to curative intent surgery or chemo radiation. Patients with adenocarcinoma were not eligible for the study. Stratification factors

included geographic region, whether the patient received prior curative intent therapy, and the investigators choice of chemotherapy. All patients were required to have at least one evaluable lesion per RECIST version 1.1, an ECOG performance status of 0 or 1, as well as adequate organ function and nutritional status.

Patients were randomized 1 to 1 to receive tislelizumab 200 milligrams administered intravenously every 3 weeks, or matching placebo, until disease progression or unacceptable toxicity. Both treatment arms were administered in combination with the investigator's choice of standard chemotherapy, including a platinum agent combined with either fluoropyrimidine or paclitaxel.

The primary endpoint of RATIONALE-306 was overall survival in the ITT analysis set. Additional secondary endpoints such as progression-free survival, objective response rate, duration of response, and safety were also evaluated. Overall survival was tested

hierarchically in the PD-L1 greater than or equal to 10 percent subgroup, defined as a PD-L1 score as assessed using the SP263 assay following the TAP scoring algorithm. Note that OS testing in the PD-L1 positive subgroup was a secondary endpoint and was tested after ITT analyses of both PFS and ORR. Because the requirement for PD-L1 testing was added via a protocol amendment and because central testing was retrospective, a small proportion of patients do not have an available PD-L1 score.

Next, I will share baseline demographics and disease characteristics. Overall, baseline demographics were generally balanced between treatment arms. The median age was 64 years, and 87 percent of the participants were male, consistent with the epidemiology of ESCC. The majority of patients were enrolled in East Asia, which is also consistent with the global epidemiology of ESCC, with the remaining 25 percent of patients enrolled in Europe, Australia, and the United States. As was the case with our study in gastric cancer that I presented this morning,

enrollment in the United States became infeasible after top-line results from the pembrolizumab study presented today became available.

Similarly, baseline disease characteristics were also generally balanced and representative of the target patient population. The median time from initial diagnosis was approximately 2 months. Most patients had metastatic disease at study entry and 44 percent of patients had prior curative intent therapy. Approximately two-thirds of patients had an ECOG performance status of 1. In total, 34 percent of patients had a baseline PD-L1 score greater than or equal to 10 percent, 49 percent of patients had a PD-L1 score less than 10 percent, and approximately 16 percent had an unknown PD-L1 status.

RATIONALE-306 met the primary endpoint of overall survival in the ITT population. Tislelizumab plus chemotherapy was superior to placebo plus chemotherapy with a statistically significant 34 percent reduction in the risk of death and a clinically meaningful improvement in

median OS of 6.6 months. Upon visual inspection, you can observe that the Kaplan-Meier curves separated early and maintained separation throughout the period of follow-up.

The benefit observed in overall survival is supported by the secondary endpoints. Patients treated with tislelizumab and chemotherapy had longer PFS with a statistically significant and clinically relevant 38 percent reduction in the risk of progression or death. Median PFS was extended by 1.7 months. Objective response rate also showed a statistically significant and clinically relevant benefit favoring tislelizumab. The absolute difference in response rate was 20.2 percent with an odds ratio of 2.31. The duration of response was also extended in the tislelizumab plus chemotherapy arm.

To further assess the clinical benefit in patients with PD-L1 low expression, we conducted several additional subgroup analyses across the range of PD-L1 expression levels. Here, we show a forest plot of overall survival across various

PD-L1 subgroups at the interim primary analysis data cutoff date. Although a PD-L1 score of 10 percent was the prespecified cutoff for efficacy analysis, in ESCC, we do not observe meaningful differentiation and treatment effect on overall survival above or below 10 percent; therefore, we next evaluated additional lower cutoff scores for predictive treatment effect. At a cutoff of 5 percent, a differential effect is observed, but this apparent effect is potentially driven by the underperformance in the PD-L1 less than 1 percent group.

To further explore the potential relationship between PD-L1 score and overall survival, we are now showing a forest plot of the overall survival hazard ratio within the specific PD-L1 subgroups. Please note again that the PD-L1 score is unknown in 16 percent of the ITT population and that some of the subgroups presented are quite small.

First, we observe a particularly strong treatment effect in the 5 to 10 percent group,

which further supports our position that above or below 10 percent is not an appropriate cutoff for patient selection. While we acknowledge that the hazard ratio is greater than 1 in the PD-L1 less than 1 percent group, the control arm in this subgroup is very small, only 25 patients. I will show in a subsequent slide that median overall survival in this subgroup is 16.1 months, and this result appears to be random high bias. That said, we acknowledge that a favorable benefit-risk is not established in the subgroup.

Turning to the 1 to 5 percent group, this group comprises approximately 20 percent of the total population, and therefore merits careful consideration. At the time of the primary analysis, the hazard ratio in this subgroup was 0.93. Here, we are showing the same forest plot with more mature data. These data are from the 3-year follow-up and have a data cutoff date approximately 20 months after the interim analysis. We believe that these longer term data provide a more robust assessment of effect sizes in small

subgroups given the greater data maturity.

The hazard ratio in the ITT population increased slightly from 0.66 to 0.70, but the trends are essentially identical and the median improvement in overall survival of 6.6 months is maintained with longer follow-up. With additional follow-up, we observed that the median overall survival in the 1 to 5 percent group improved to 0.86. At the 3-year follow-up in this subgroup, we observed immediate improvement in overall survival of 3.4 months supported by favorable trends in progression-free survival and objective response rate. We believe outcomes in the 1 to less than 5 percent group to be clinically meaningful and thus propose that a cutoff value of 1 percent is most appropriate for patient selection in this indication.

Next, I would like to review median overall survival across all of the subgroups presented with 3 years of follow-up. At the proposed cutoff of greater than or equal to 1 percent, the median benefit in overall survival conveyed by the

addition of tislelizumab to standard of care chemotherapy is 7.2 months.

Now, I will briefly review safety. Overall, the AE profiles observed for tislelizumab plus chemotherapy in the first-line setting were similar to the known safety profile of chemotherapy and of tislelizumab in the expected symptoms of ESCC. The overall trends in the safety data set are consistent in the overall safety data set and in the PD-L1 greater than or equal to 1 percent group.

As expected, immune-mediated adverse events are more frequent in patients receiving tislelizumab than in those receiving chemotherapy alone. Grade 3 or greater AEs and AEs leading to dose modification were similar between groups. Similar to the data presented this morning for gastric cancer, there is an increase of the rate of AEs leading to discontinuation and SAEs in the tislelizumab-containing arm.

In this tornado plot, we are showing the treatment-emergent adverse events of any grade in PD-L1 greater than or equal to 1 percent subgroup

occurring in 20 percent or greater of patients. The majority of adverse events are commonly observed in this disease with the chemotherapy component. As was the case with gastric cancer, there is no clear trend of increase of individual AEs or AE severity with the addition of tislelizumab .

To summarize, the primary analysis of RATIONALE-306 showed that the addition of tislelizumab to chemotherapy provided substantial improvement in overall survival with a hazard ratio of 0.66 and 6.6 months of incremental OS benefit at the median. This benefit was observed across all PD-L1 subgroups, with the exception of the less than 1 percent group. Secondary endpoints also showed clinically meaningful benefit. The safety profile was manageable and generally consistent across the range of PD-L1 expression. Based on the overall data set, benefit-risk is most favorable in the PD-L1 greater than or equal to 1 percent group.

Overall, we conclude the totality of data supports tislelizumab for the frontline treatment

of patients with unresectable advanced or metastatic ESCC. Thank you, and I'd now like to invite Dr. Uboha to provide her clinical perspective.

Applicant Presentation -- Nataliya Uboha

DR. UBOHA: Thank you.

Good afternoon, and thank you for the opportunity to address the panel again. I've been compensated for my travel but not for my time in preparing for today's meeting.

Let me start with a brief background on esophageal cancer. Patients diagnosed with advanced esophageal squamous cell carcinoma have poor prognosis and limited treatment options. In the U.S., this is a rare tumor with declining incidence and comprising roughly less than 1 percent of all cancers. Patients with advanced esophageal squamous cell carcinoma have a 5-year survival rate of only 6 percent, which is one of the lowest rates among all cancer types. These patients are generally older and have other comorbidities. Additionally, many patients have

extensive disease-related symptoms. They have trouble eating, struggle with weight loss, and have significant pain.

Over the last few years, we've seen that treatment with anti-PD-1 antibodies in combination with chemotherapy can significantly prolong overall survival for these patients. In my practice, which is not different for most other experts, PD-L1 testing is done for all patients with advanced gastroesophageal cancers regardless of histology unless tissue is unavailable. About 90 percent of patients with esophageal squamous cell carcinoma have PD-L1 positive tumor.

As a clinician who treats these patients, here's my interpretation of the results. Tislelizumab improved overall survival in the RATIONALE-306 study across the intent-to-treat population with a hazard ratio of 0.66, which was maintained at 3 years. There were very few patients who had tumors with PD-L1 TAP score of less than 1, only about 9 percent of the population enrolled in the 306 trial. The outcomes of these

patients are based on the post hoc exploratory analysis in this study and the numbers are too small to be statistically reliable. Nevertheless, in the pooled analysis shared by the FDA, the hazard ratio in this subgroup across studies is 1.1.

In my clinical practice, I offer treatment with anti-PD-1 agents in combination with chemotherapy to patients whose tumors have PD-L1 score of 1 or greater. I feel this is a clinically relevant PD-L1 expression threshold, and I would urge the committee to recommend a unified PD-L1 cutoff of 1 or greater across PD-1 inhibitors. Thank you for your time.

DR. LIEU: Thank you so much.

We will now proceed with FDA's presentations, starting with Dr. Geetika Srivastava.

FDA Presentation - Geetika Srivastava

DR. SRIVASTAVA: Thank you.

Good afternoon, everyone. My name is Geetika Srivastava. I'm a hematologist/medical

oncologist and a clinical reviewer in the Division of Oncology 3 at the FDA. The FDA is convening this ODAC meeting to discuss the risk-benefit of the use of immune checkpoint inhibitors for the first-line treatment of patients with unresectable or metastatic esophageal squamous cell carcinoma at different levels of PD-L1 expression. The members of the FDA team are listed on this slide.

As discussed in the presentation by Dr. Casak, the current label of immune checkpoint inhibitors approved in first-line ESCC are agnostic of PD-L1 testing results. These were based on the intention-to-treat population enrolled in the pivotal studies. At the time of approval of pembrolizumab in 2021 and nivolumab in 2022, less was known about PD-L1 as a predictive biomarker in ESCC, and given the exploratory nature and small sample sizes of the subgroups, FDA did not restrict labeling based on PD-L1 status, based on the results of each individual trial. Results are now available across multiple trials that make inferences based on these subgroups more reliable

and provide a framework to discuss the adequacy of PD-L1 expression as a predictive biomarker for patient selection.

I will review the data from the individual studies that led to the approval of pembrolizumab and nivolumab in this setting; the data submitted to support potential approval of tislelizumab for the same indication; and the FDA patient-level pooled analysis from these studies in ESCC.

There now appears to be a consistent pattern across three available trial data sets that the overall efficacy of immune checkpoint inhibitors in this setting is driven predominantly by PD-L1 high subgroups with a concern for lack of benefit in tumors with low PD-L1 expression, particularly those with PD-L1 less than 1. FDA believes a contemporary risk-benefit discussion evaluating the available data is required to further define the indication of anti-PD-1 antibodies based on PD-L1 expression in patients with ESCC.

The three individual study designs have already been outlined today and the schema

presented within the FDA briefing document. Before we review the efficacy results from each individual study, this table provides the key features of the three pivotal studies, KEYNOTE-590 for pembrolizumab, CHECKMATE-648 for nivolumab, and RATIONALE-306 for tislelizumab.

KEYNOTE-590 enrolled patients with esophageal and GE-junction carcinoma irrespective of histology. Overall, 73 percent of the enrolled patients in KEYNOTE-590 had esophageal squamous cell carcinoma. Both CHECKMATE and RATIONALE only enrolled patients with squamous cell histology ESCC. All three trials allowed for patients to enroll regardless of the tumor PD-L1 expression.

The tests used for determining PD-L1 expression were different for each trial. KEYNOTE-590 used combined positive scores CPS, CHECKMATE used TPS with a preplanned retrospective analysis for CPS, and RATIONALE-306 used a visually estimated CPS, also known as tumor area positivity TAP. Only CHECKMATE-648 had PD-L1 expression as a prespecified stratification factor. The primary

endpoint and the prespecified PD-L1 cutoff used in each study are listed here. In summary, each trial used a different assay for the assessment of PD-L1 expression, different scoring algorithm, and different primary endpoint based on PD-L1 cutoff.

The results of the three studies were statistically significant for overall survival analyses as prespecified in the statistical plan. The hazard ratio for the ITT population across all three trials ranged from 0.66 to 0.74. In the prespecified PD-L1 positive subgroups, which was CPS 10 or greater for KEYNOTE, TPS 1 or greater for CHECKMATE, and TAP 10 or greater for RATIONALE, the magnitude of benefit was higher, with hazard ratio ranging from 0.54 to 0.62.

To study the adequacy of PD-L1 expression as a predictive biomarker for use of immune checkpoint inhibitors in this setting, FDA conducted patient-level analyses of the three randomized studies in the relevant population of ESCC. For uniformity of comparison between the three studies, the ESCC modified population consisted of only

patients with ESCC histology who received immunotherapy in combination with chemo versus chemo alone. Patients with adenocarcinoma or those on the nivo/ipi arm in CHECKMATE were excluded.

This population therefore differed from the ITT population. For KEYNOTE-590, 548 patients were identified, excluding 201 with adenocarcinoma. For CHECKMATE, there were 629 patients identified, excluding 16 with non-squamous histology and 325 on the nivo/ipi arm. For RATIONALE, there were 648 patients, and one patient was excluded for non-squamous histology. Please note, for the remainder of the FDA presentation, we will focus on this ESCC modified population.

This table summarizes the key demographic and disease characteristics of these patients. In general, the characteristics of patients across trials were comparable. Two-thirds to three-fourths of the enrolled patients were Asian. Not shown here, however, relevant to the discussion today, there was one known MSI high patient enrolled in RATIONALE and none in KEYNOTE; however,

the MSI status of tumors for most patients in these trials was unknown.

The proportion of patients at PD-L1 cutoffs across the three studies is depicted in the bar graph here. This distribution is based on CPS for KEYNOTE-590 and CHECKMATE-648, and TAP for RATIONALE-306. The proportion of tumors that were PD-L1 less than 1 was similar across studies, ranging from 8 to 10 percent.

We will now review the efficacy results of the ESCC modified population. Again, those are patients with ESCC histology who received chemotherapy in combination with immunotherapy. These are the overall survival results. The overall survival appears to be favorable across all three trials, and this appears to be generally consistent with the results of the ITT population, with hazard ratio around 0.7.

In the following slides, I will present the FDA analysis of overall survival data for each study for the ESCC modified population based on PD-L1 cutoffs. FDA acknowledges the limitations of

small sample size and exploratory nature of these subgroup analyses.

This is the forest plot for overall survival in ESCC for KEYNOTE-590. Analysis using the prespecified PD-L1 cutoff of CPS 10 or higher, same as the ITT, was performed. This represented 52 percent of the ESCC. Improvement in survival with addition of pembrolizumab to chemo appears to be of greater magnitude for CPS 10 or greater, with hazard ratio 0.57; whereas in patients with CPS less than 10, the hazard ratio is 0.95; and in patients at CPS less than 1, the hazard ratio is 1, which appears to suggest no benefit.

For CHECKMATE-648, analysis using the prespecified PD-L1 cutoff of 1 or higher, same as the ITT, was performed. This represented 87 percent of the ESCC population when using CPS. The hazard ratio for CPS 1 or greater was 0.69, while again in the subgroup of CPS less than 1, there appears to be marginal or no benefit with hazard ratio at 0.93. Not shown here, results of analysis and TPS less than 1 were concordant as

well, and the hazard ratio was 0.96.

For RATIONALE-306, analysis using the prespecified TAP cutoff of 10 or higher, same as the ITT, was performed. This represented 34 percent of the population. Improvement in survival with addition of tislelizumab to chemo appears to be of greater magnitude for TAP 10 or greater, with hazard ratio of 0.66; however, in patients with TAP less than 10, the point estimate is 0.76. As the point estimate for the subgroup of TAP 1 to 10 is favorable at 0.65, the attenuation and benefit in TAP less than 10 subgroup is likely driven by patients with TAP less than 1, where there's a potential for detriment with a hazard ratio 1.34.

FDA acknowledges the limitations of small sample size and the exploratory nature of the subgroups. In spite of the heterogeneity amongst different trials, use of different PD-L1 assays and testing algorithm, as well as different prespecified PD-L1 cutoff for overall survival, in this FDA's patient-level analysis, over three

independently conducted trials, it appears that the overall efficacy of anti-PD-1 in this setting is driven predominantly by PD-L1 high subgroup as defined by each study; and regardless of the method used to determine PD-L1 expression, there is replication of results over three trials and a consistent pattern, suggesting lack of benefit in PD-L1 less than 1 tumors.

Seen another way, the lack of benefit in PD-L1 less than 1 is further exemplified by these Kaplan-Meier survival curves. The figure on the top is for PD-L1 1 or greater, showing separation of curves; however, in the bottom figure, in PD-L1 less than 1, the curves overlap for KEYNOTE-590 and CHECKMATE-648 and, in fact, are reversed for RATIONALE-306.

In addition to looking at trials separately using the modified ESCC population, FDA conducted an exploratory pooled analyses of patients from all three studies in the ESCC population stratified by study. This pooled analysis included patient-level data, and was therefore limited to studies that

were submitted to the FDA for review. This does not include data from other pivotal studies, either positive or negative, and can thus introduce bias.

For pooling of data, PD-L1 expression was based on CPS for KEYNOTE and CHECKMATE, and TAP for RATIONALE. For uniformity of comparison in ESCC of immunotherapy plus chemo versus chemo, as shown in the Consort diagram, patients with non-squamous histology and those on nivo/ipi arm in CHECKMATE were excluded. A total of 1825 patients were pooled; 910 received immunotherapy in combination with chemo and 915 only chemo.

In spite of limitations of pooling of data, FDA believes that a pooled analysis of patient-level data may provide the advisory committee with additional context to discuss the risk-benefit of anti-PD-1 antibodies in relationship with PD-L1 expression in this patient population.

This is the forest plot for overall survival results. There appears to be a benefit in the overall population with addition of immunotherapy

to chemo as compared to chemo alone, with hazard ratio of 0.71 indicated in the green arrow. The magnitude of benefit appears to increase with increasing PD-L1 expression, as seen by improving hazard ratios, PD-L1 of 1 or greater 0.68, PD-L1 of 10 or greater hazard ratio of 0.61. The magnitude of benefit appears to attenuate at lower PD-L1 expressions with hazard ratio for PD-L1 less than 10 at 0.82.

The hazard ratio in patients with PD-L1 between 1 and 10 is 0.77, consistent with the potential for benefit in these patients; however, again, there does not appear to be a benefit in patients with PD-L1 less than 1 with hazard ratio of 1.1. Like the independent trial results, the FDA pooled analyses shows that patients with higher PD-L1 expression benefit most, while those that are PD-L1 less than 1 appear not to be benefiting.

In summary, the current approvals of immune checkpoint inhibitors in ESCC are agnostic of PD-L1 status. As previously stated, at the time of approval of pembrolizumab in 2021 and nivolumab in

2022, less was known about PD-L1 as predictive biomarker in ESCC, and given the exploratory nature and small sample size of the subgroups, FDA did not restrict labeling based on PD-L1 status, based on the results of each individual study.

However, consistently across three applications, efficacy appears to be predicted by PD-L1 expression. Patients with tumor PD-L1 10 or greater appear to have the greatest magnitude of benefit. In patients with intermediate PD-L1 expression between 1 and 10, there may be a potential for benefit, but those with PD-L1 less than 1 do not seem to benefit.

Importantly, we know immune checkpoint inhibitors can have added toxicity, and treating patients with PD-L1 less than 1 with immune checkpoint inhibitors may expose them to toxicity without a clear benefit. FDA has provided both prespecified and exploratory analyses of the efficacy across a range of PD-L1 expression levels and stated the notable caveats. FDA is concerned with the lack of benefit observed in patients with

ESCC and PD-L1 less than 1. In light of these findings, FDA feels that this topic warrants a contemporary discussion on the risk-benefit profile of immune checkpoint inhibitors in a biomarker-selected patient population.

FDA would like the committee to discuss the risk and benefit of the treatment with anti-PD-1 antibodies for the first-line treatment of patients with metastatic or unresectable esophageal squamous cell carcinoma for PD-L1 less than 1. Following the discussion, we would like the committee to vote, is the risk-benefit assessment favorable for the use of anti-PD-1 antibodies in the first-line unresectable or metastatic esophageal squamous cell carcinoma at PD-L1 less than 1? Thank you.

Clarifying Questions

DR. LIEU: Thank you.

We will now take clarifying questions to the presenters. 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. Again, because we have three applicants

here, please direct your question to a specific applicant, if possible. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. And 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 we can move on to the next panel member.

For our panel member joining us virtually, please use the raise-hand icon in Zoom to indicate that you have a question, and we will acknowledge you. Please remember to lower your hand by clicking the raise-hand icon again after you have asked your question.

Are there any clarifying questions for the presenters?

Dr. Meyerhardt?

DR. MEYERHARDT: Jeff Meyerhardt, Dana-Farber. This morning, we spent a fair amount of time talking about the PD-L1 assay. I'm not going to totally bring that up again. My only question is probably to any of the companies with

pathology expertise. Are there any differences how we think about the assay for squamous cell carcinoma? Thank you.

DR. WAXMAN: Ian Waxman, BMS. I'll have Dr. Anders speak to that.

DR. ANDERS: Hi. Robert Anders, Johns Hopkins pathology. I'm compensated for my travel but not my time. These are rare. There are no systematic studies of inter-observer agreement because they're rare. The caveats that I mentioned earlier would all apply here. I would just make the one comment that squamous cancers -- and I'm thinking more head and neck type squamous cancers -- are generally a little bit simpler to score. Thank you.

DR. PIETANZA: I'll also have Dr. Chizhevsky answer this question.

DR. CHIZHEVSKY: Thank you. Vladislav Chizhevsky, anatomic pathologist. I am a paid consultant to Merck. The scoring component of squamous cell carcinoma tends to be TPS more than CPS, more tumor cell sustaining, so it is simpler

to score. But the same variables apply near the cutoff as they are in gastric adenocarcinoma, but being a TPS score is a little simpler. It's more consistent in scoring. Thank you.

DR. MEYERHARDT: That's all I have. Thank you.

DR. LIEU: This is Chris Lieu from University of Colorado, and this question is to Dr. Kelly but welcome to hear from any of the other experts that have already presented. In regards to the data that BMS showed, showing that only 60 percent of patients are receiving some type of PD-L1 scoring, my question is, are the 40 percent not being scored because the approval doesn't require testing for PD-L1, or is there something fundamental about biopsying these patients, which makes it, therefore, then infeasible?

Understanding that that 40 percent that's not being tested, that number is always somewhat increased by the fact that patients are not getting tested sometimes because they're not eligible to receive therapy. But I would just like to hear

what the practicality is of the biopsy because if this indication changes, it will, therefore, then require biopsies for our patient population.

DR. KELLY: Thank you very much. Ronan Kelly from Baylor University Medical Center. That data is from the Flatiron database, which shows 40 percent across the country. Now, I think it's important for us to step back and realize the proportion of patients we're talking about. It's very hard to get exact numbers for ESCC in the United States, but I showed this year database of 14,000 over 11 years, which is about 1200. The majority of these patients are seen on the coast and very few are seen in the center of the country.

So when a patient walks into a community oncologist with this disease, they have no real prior experience of treating these patients. The patients then are incredibly sick. They have, as you know, more significant dysphasia than the distal esophageal or the gastric cancers. So the patients are walking in sick. We know only 70 percent even get first-line treatment, so the

doctor has an important decision to make. "Do I start trying to biopsy a patient to get a result or do I have to start treatment straight away?" And I think it's clear in this instance, they're choosing to go for the treatment straight away, and I think they're foregoing the biopsy.

I think that's an important thing because as we talk about the risk-benefit here for the panel, I don't want us to overlook and be so focused on biomarkers, when the reality on the ground is if we mandate testing where we've never done it before, we may actually decrease the number of patients that get treated, and I don't think that's in our interest. Thank you.

DR. LIEU: Dr. Uboha?

DR. UBOHA: Nataliya Uboha, University of Wisconsin. I would like to add to this. I absolutely agree with Dr. Kelly that these patients are very sick and that urgent indication of treatment is indicated. Most of the patients, all of the patients, we see in clinic do have biopsies. This is how the diagnosis of cancer is made. All

these patients have endoscopy or biopsy of metastatic site. I suspect that, in part, we have biomarker testing because our treatment decisions were not based on biomarkers, so there was no reason to do the testing. I think if we actually demonstrate that we need PD-L1 positivity in the testing and that treatment selection would be based on biomarkers, we will see a lot more testing done in the community.

I also think that for our community partners, both medical oncologists and pathologists, if we have unified guidelines regarding histology or regarding stage -- and this is more for reflex testing -- the way we do when we look for mismatch repair protein expression, it is rare to see it, but yet we look in all GI tumors regarding stage, and it will make it easier so that neither our clinicians nor pathologists have to think about it, look at the cutoff, and figure out which antibody to use. We need to make it simple. Another point is all these patients can be started on chemotherapy, and then when PD-L1 testing is

ongoing, either nivolumab, tislelizumab, pembrolizumab can be added with cycle 2 day 1.

DR. LIEU: Thank you.

Comment from --

DR. ENZINGER: Sure. Peter Enzinger, medical oncologist, Dana-Farber. I agree with Dr. Kelly. I think many of these patients are extremely sick. Their esophagus is basically failing them, they're unable to eat, they're losing weight, they're getting very weak. We often need to move very quickly.

I think the problem is that we often need to make a decision very quickly to start therapy because if we don't, they get weaker, and then they can't tolerate platinum 5FU therapy anymore. So I think that excluding 10 percent of patients from treatment, we're really putting 90 percent of the patients at risk for failing, and I think by removing this 10 percent group, we're actually significantly harming the other 90 percent of the patients that benefit from this immunotherapy. Thank you.

DR. LIEU: Thank you.

Dr. Sanoff?

DR. SANOFF: A question and a comment. I'll start with a comment. I'd like us all to take a step back and understand what Flatiron data tell us. We're seeing patients not getting tested, but we have to be careful not to say why they're not getting tested. And if you look at biomarker testing, for lots of diseases for really important indications, including, I think as we heard, HER2 testing in gastric cancer this morning, it's not getting done. That's a quality-of-care issue. That's not necessarily related to what oncologists are testing for based on their treatment decision making, so let's all be cautious about our interpretation of that.

To respond and ask Dr. Enzinger actually to come back about this, and Dr. Kelly, you could comment as well, both of you are incredibly experienced and expert clinical trialists and very good scientists. If you were writing a grant with the PD-L1 negative population, would you expect

your grant to be funded if it were investigating ongoing immunotherapy in that population; and because of that, should we actually be giving it to these people?

DR. LIEU: We'll start with Dr. Enzinger.

DR. ENZINGER: Peter Enzinger, medical oncologist, Dana-Farber. I think that's an interesting hypothetical question. I think we clearly need to find better therapies for these patients who have low CPS scoring, and frankly, I do think you should fund me --

(Laughter.)

DR. ENZINGER: -- if I have something that I can improve upon. I think we all realize that there are limitations to checkpoint inhibitors, and we're all now trying to improve upon the outcomes that we have seen here today. And if I have a treatment that theoretically is going to be better and specifically may address these low CPS scoring patients, I do think that this should be funded, and I think that it actually should have a priority funding because this is a significant unmet need.

Thank you.

DR. LIEU: Thank you.

Dr. Kelly?

DR. KELLY: Ronan Kelly, Baylor University Medical Center. Thank you for the comments. If you actually look at the CHECKMATE-648 data, the 4-year data is better now. The hazard ratio in the less expressors is 0.85. We always talk about the tail on the curve, and as the data matures, it seems to get better, and I think that's important for us to be aware of.

The other thing is there have been newer trials done. We're not talking about all the trials here. As you know, there's been a lot in Asia in the last couple of years, and they are showing in the low expressors, the CPS less than 1, esophageal squamous responses. There was one study, the JUPITER-06, toripalimab, less than 1 hazard ratio 0.61. So we're beginning to see this data now, and I think it's playing into the fact that we're seeing benefit in some of those patients, not everyone, but some of those in the

lower group. Thank you.

DR. LIEU: Dr. Spratt?

DR. SPRATT: Thank you. Can you pull up one of the FDA slides, number 11, 6 Kaplan-Meier curves and a table next to it? The question will be, actually, for Dr. Enzinger, if we can get the slide up.

DR. CASAK: Is it from the first presentation by Dr. Casak?

DR. SPRATT: Yes, and Dr. Kelly, you're free to respond as well.

When I look at this and I hear the anecdotes of a patient who gets the combination therapy and has this long response, I also see pretty much overlapping curves here with the chemotherapy arm here. I try to think about the comment you made about 90 percent of patients are benefiting or 10 percent that may not. But even in the ones that are benefiting, just to be clear, it's not 90 percent of patients are benefiting; there's a small percent that are benefiting over chemotherapy.

So even in the PD-L1 less than 10, when I look at 2 year, and let's say we look at 3 year, depending on which trial you look at, you're talking about a couple percentage points, so number needed to treat of 40 to 50. And when you look at the median here of, let's say, PD-L1 less than 1 in terms of the median survival as another metric, you're talking about days. The KEYNOTE study, it's identical. You look at the CHECKMATE study, and it actually appears to be worse, and the same with the last one.

I guess I'm just trying to understand what do you mean when you say that 90 percent of patients are benefiting from receiving immunotherapy?

DR. ENZINGER: I think that one of the most exciting things about KEYNOTE-590 was when we saw the long-term results of that study, where we see that about 11 percent of the patients who receive chemo and immunotherapy are alive at 5 years; whereas only 3 percent with chemotherapy alone. So I ask you as individuals, if you had esophageal

squamous cell carcinoma, would a 1 in 10 chance of being alive at 5 years be worthy of consideration?

DR. SPRATT: I completely agree; however, that's the overall trial, and when you look here, you see functionally no difference. So I guess I would say, would you rather take a more expensive agent that increases toxicity for the exact same probability of long-term survival and median survival? And I know what my answer would be.

DR. ENZINGER: Well, I just want to add that among those long-term survivors, there were patients, several patients, with squamous cell carcinoma and adenocarcinoma who had CPS scores of less than 1.

DR. LIEU: Thank you, Dr. Enzinger.

DR. SPRATT: Thank you. I appreciate it.

DR. LIEU: Thank you, Dr. Spratt.

Dr. Vasan?

DR. VASAN: Neil Vasan. This is a question for Dr. Enzinger and Dr. Kelly. Just going back to what you were saying earlier about, first of all, this being a rare disease and these patients being

quite sick and infirmed, that even getting a biopsy sometimes can be challenging, are you referring to a second biopsy after the cancer diagnosis has been established or meaning that the first biopsy was inadequate to obtain PD-L1? Can you just clarify what you mean by that?

DR. KELLY: Yes. Look, I think it's clear we can get biopsies on patients. The question is, is it the right thing to do when someone comes in that's so sick, who's failing, who's losing weight? And if we offer radiation to that patient, is it safe to try to do a biopsy post-radiation?

That wasn't part of the trial, but that's what happens in the community because the patient's so sick they come in, they have to give them something to relieve the discomfort, to open up the esophagus. It's not safe to be just biopsying post-radiation, to put another endoscope in. So there are real-world challenges to getting a biopsy in this setting, which may not have existed in gastric because it's more distal, and it's not the same presentation and the same level of morbidity

that the patients are having.

DR. VASAN: But presumably in that scenario, they would have gotten some biopsy initially to confirm diagnosis, a mucosal resection or something like that. Or are you talking about people who are just being treated based on their clinical phenotype, they're a smoker, and it's consistent with squamous -- those patients would have had an initial biopsy of some sort; is that correct?

DR. KELLY: Yes. As I said, you can get a biopsy, but then is the biopsy enough to make a diagnosis? Was it the right biopsy? All of the issues that play into real-world challenges that we see every day in clinic.

DR. VASAN: Do we have any sense -- sorry, Dr. Enzinger.

DR. ENZINGER: I just wanted to bring up, Dr. Kelly brings up the frontline patient, the patients who present with this disease. We often have locally advanced patients who, unfortunately, have recurrences. So here I am 2 years later, and the only biopsy I have is from the original

diagnosis 2 years earlier. It's an alligator clamp biopsy. Now, 2 years later, they have lung mets, so my choice is, currently, I can go to that biopsy, that alligator clamp biopsy. If it's positive, great, if it's negative, I still have approval. If you remove this approval, I basically now have to show that the current disease is actually CPS positive, and I may actually have to do a lung biopsy, and lung biopsies, as many of you know, are risky. I mean, people die from lung biopsies. So I think it's worthwhile if you want to prove recurrence or if there's an important reason, but to prove that, yes, there's CPS positivity, it may not reach that level, in my mind, for a lot of patients.

DR. KELLY: If I could, I'd like to show you a slide on radiation and what it can do in this setting. If we can pull up slide number 1, please? This is from CHECKMATE-577, which I had the privilege of being the global PI for. It's in a different disease setting, but it shows what we think radiation is doing in this setting.

What we showed here was we had matched biopsy samples pre-radiation and post-radiation, and you can see on the left the significant change in PD-L1 CPS score post-radiation. This is the only data I'm aware of in a phase 3 setting. This was a retrospective analysis, but it still is interesting to look at. You can see 51 percent of the patients, PD-L1 score changed post chemo radiation. So this is important because we talked about the dynamic nature of this, this morning, but we didn't look at the biology of what we do and does it impact.

Here, you can see the TPS score is not changing. We think the TPS score is driven by internal oncogenic signaling, but the CPS score is driven by cytokine release, interferon gamma from the radiation upregulating PD-L1. And if you look at slide number 3, which is a busy slide, what you'll see in this particular study, we showed that if you upregulate PD-L1, which you can see at the top -- this is CPS change -- the hazard ratio went to 0.3 for disease-free survival.

So I'm just making the point that when we introduce chemoradiation into these patients, we alter the PD-L1 score, and I'm just not sure it's the right thing to do, to be mandating everyone have a PD-L1 score for a couple of 100 patients, not minimizing the number of patients, but the delay in treatment is a bigger risk factor for me than getting a biopsy.

DR. VASAN: Yes, I understand what you're saying. I guess what I'm trying to say is there are two groups of patients. There's one group of patients that had localized disease that then recur; then there's a second group of patients that have de novo metastatic disease. The patients with de novo metastatic disease would have a biopsy to establish their diagnosis, and presumably that could be tested for PD-L1. Of course, there might be issues with that, but I think those are two different groups of people, and we don't necessarily have statistics going into that, that I'm aware of. So I guess what I'm trying to say, this question about the morbidity of a biopsy, that

issue doesn't apply to all patients. Thank you.

DR. LIEU: Dr. Meyerhardt?

DR. MEYERHARDT: Dr. Kelly, before you pull that slide up again, could you clarify what is the post-biopsy? Really, for most of these, we're talking about their metastatic disease, so is that a biopsy of their metastases? Because as you know, we've all hoped and prayed that there's abscopal effect from radiation, and we really don't see that, so I'm just trying to understand what the post-biopsy is.

DR. KELLY: Yes. Great question. CHECKMATE-577 was not a metastatic study; it was an adjuvant study, so we had the sample before chemoradiation, and then we had the surgical sample at the time of resection. So they were the two timepoints we were looking at. It's the only data that I'm aware of in a phase 3 setting showing the impact of radiation in esophageal cancer.

DR. MEYERHARDT: Thank you.

DR. LIEU: Any other questions?

(No response.)

DR. LIEU: Okay. We'll take a 15-minute break. Panel members, please remember that there will be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 3:50 p.m., 3:50 p.m. Eastern Time. Thank you.

(Whereupon, at 3:34 p.m., a recess was taken, and meeting resumed at 3:50 p.m.)

Open Public Hearing

DR. LIEU: 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 you may

have with the applicant. For example, this financial information may include applicant'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 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.

For any presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you.

Speaker number 1, please state your name and any organization you are representing for the record. You have five minutes.

MS. MORDECAI: Thank you. I'm Mindy Mintz Mordecai. I am the President, and CEO, and Founder of the Esophageal Cancer Action Network, ECAN. ECAN does receive funding from all three of the applicants. My travel and my presentation here today was not funded by any of them.

I don't envy any of you, the decisions you have to make here. You're looking at statistics and numbers, and that's your job, but I come to you today to represent patients and families who are struggling to stay alive in the land of very little hope. Esophageal cancer accounts for 1 percent of cancer diagnosis in the U.S. but 2.6 percent of the cancer deaths. Fewer than 1 out of 17 stage 4

patients will survive 5 years. That's less than 6 percent.

My husband was diagnosed with esophageal cancer when our kids were 6 and 11. He went through punishing chemoradiation and a radical esophagectomy, and then less than 3 months later, he started having pain when he was walking. PET scan showed that he had a 6-centimeter tumor in his liver, mets to his pelvis, ribs, and lungs. We tried some experimental targeted therapies, but we lost him exactly 6 months to the day of his esophagectomy. That was in 2008.

I know what it is to stay up all night searching for a study that might save the life of a person you love more than anything in the world. You're always looking for that glimmer of hope. But what I learned very quickly is that esophageal cancer patients have been woefully neglected, especially in the area of research funding and focus, and that's why I started ECAN in 2009.

That very next year, the National Cancer Institute drew up a list of 20 cancers for its

groundbreaking genome mapping project and esophageal cancer wasn't on the list. ECAN made a very strong push, and we were successful in getting esophageal cancer included in the TCGA, but the reason this was so important to us was that we believed that if esophageal cancer was not included in TCGA, it would be like every other opportunity for progress for our patients. The train would leave the station, and esophageal cancer would be left behind. And we wanted to change that dynamic, but our community had very little faith that progress was possible.

We started campaigns to increase research funding, and I had calls from people who said, "You're an idiot. This is never going to happen. Nobody cares about esophageal cancer patients, and they sure aren't going to fund any research for us." That's what happens when you're up against a cancer that's often thought of as a death sentence, and you live in an environment that provides no reason for hope.

The approval of immunotherapy for our

patients has been our best reason for optimism yet, and I have to say that today, it's demoralizing; that after waiting so long for progress and finally getting it, the powers that be are considering cutting back on access to these therapies for some of our patients.

Approval of the proposal before you will take away hope that we've fought really hard to find. We believe that the original FDA approval is the one that's appropriate. We've heard that there's no new data that shows a change in the risk-benefit equation, and then Dr. Kelly talked to us about more mature data that's actually showing much higher benefits. And given the significant questions that have been raised about testing and scoring of PD-L1 expression, it doesn't seem to me like this question is ready for prime time. I don't know why it has to be done now. I think there are a lot of reasons to wait until you have better information and until we have better tests that can actually tell us what is that PD-L1 score that we're looking at and is it reliable, because

unreliable tests should not form the basis of whether our patients have hope for the future.

So I'm asking you that when you make your decision, you think about whether it's worth giving up the opportunity for somebody to save their life, possibly even for a short enough period for that next discovery to extend their life further; that you don't vote to extinguish their hope. Thank you.

Questions to the Committee and Discussion

DR. LIEU: Thank you so much.

This concludes the open public hearing portion of the meeting, and we will no longer take any further comments from the audience.

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 comment. We will now proceed with the questions to the committee and panel discussions. 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. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed with our first question, which is a discussion question. FDA would like the committee to discuss the risks and benefits of the treatment with anti-PD-1 antibodies for the first-line treatment of patients with metastatic or unresectable esophageal squamous cell carcinoma with PD-L1 expression less than 1.

Are there any issues or questions with the wording of our discussion question?

(No response.)

DR. LIEU: Seeing none, we'll go ahead and open the question to discussion, and I'll go ahead and start again. I think that many of our comments are likely going to mirror what we heard this morning.

Certainly, what we're looking for are these durable responses, and the consistency that we see in the evidence, of course, is that in the high expressing PD-L1 tumors, we see significant

benefit. At 1 to 10, there's some modest activity, but plausible activity, and that's certainly less than 1. We had the same story of lack of overall survival benefit, and I think that we can take a little bit, I guess, of safety knowing that whatever decision that we make here regarding CPS score less than 1 is only going to impact somewhere between 8 to 10 percent of the patient population, so that makes me feel a little bit better.

The challenges we've discussed significantly before the PD-L1 scoring, but I really got a point to the fact that we're trying to assess data from a group that is CPS less than 1, or PD-L1 less than 1, that has 77 in the treatment arm and 87 patients in the control arm. This is an unbelievably small data set, and I have trouble determining whether or not patients should or should not receive therapy based off of this few patients.

But to answer the question again, what are the risks and benefits, we just don't see any overall survival benefits, so I don't think we can make any conclusive evidence that it's helping

patients. And to the open public hearing speaker, we hear you. We want to offer these therapies to as many patients as possible, but not if there's no survival benefit.

I really like Dr. Uboha's point of standardizing this testing, making it simpler for practitioners but also ensuring that the right testing gets done on the right patients. And right now, I believe that that's in patients whose PD-L1 score is greater than 1, but I really would love to hear other people's perspectives on this.

Dr. Sanoff?

DR. SANOFF: Hanna Sanoff, UNC. Chris, I think I agree with everything you said, and I really want us to think about that small number. That's my biggest concern. We've seen reproducible evidence across a couple of trials, but it starts to become a lot less certain when you're talking about such small numbers, and that makes me a little more uncomfortable about these subgroup analyses.

I think, like the prior one, I don't think

you can make much of the 1 to 10 subgroup analyses. They're sort of all over the place and not consistent or reproducible. We see no benefit at all. We see nothing to offer hope to our patients with the PD-L1 at zero from these data, but is that enough if you're talking about 120-130 people? I don't know the answer to that.

DR. LIEU: Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. I think the presentation by the FDA was appropriately cautious. There was a lot of conditional language, "exploratory analysis may." It was very clear that we're working with very small numbers here. I'd like to flip the equation on its head and say if this was a paper, a grant, or a company coming to you with a very interesting subset analysis, with 8 to 10 percent of the patients reading out in a different way, you'd say, "That's a good hypothesis. Go explore that in a subsequent trial."

So that's what I'm left with. I'm again left with I'm not seeing clear benefit, but I'm not

seeing robust enough numbers that I feel I can make an honest determined -- not honest; "honest" is not the right word. But I'm not comfortable making a determination based on 8 to 10 percent subset analysis.

DR. LIEU: Thank you.

Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman and Case Western. Yes. This is, I think, more challenging, and two points just to respond to Dr. Madan. One is, these are small sample sizes, but let's not forget the event rates. Almost everyone is having an event. So in trials that have 500 patients having 100 events, many of them are powered for things such as that. I think that's one point.

The second is, to push a bit on the FDA here -- and this isn't the first time -- these primary endpoints for at least two of the trials, these companies decided, and designed, and powered their trials based on these subsets. They wanted the CPI or these various scores to be enriched for a very specific reason, a priori. It was

shown -- and I actually commend BMS who showed -- that the label literally says the hazard ratio, I think you highlighted, was 1.0 in the low PD-L1 expression, not dissimilar to the elaborate data, not to re-bring that. But someone else brought up approval across 15 mutations when we knew, a priori, the investigators made a cohort with the biomarkers that were likely to be enriched, and there was no evidence of response later.

It seems far more practical to be giving approvals for the primary endpoint population, especially when it was known at that time when there's a large potential benefit. And to then walk back and encourage the trials to be done in these unknown populations -- because we're now in a stance that, yes, could there be some subset of some subset that benefits? But if we saw all this data initially, if this was a pooled trial of all of these, and it was a stratified analysis, and you saw in these 150 or 100 patients these Kaplan-Meier curves, these median survival curves -- I mean,

there's no evidence of any benefit in this population.

So I think the broad approvals create a very challenging time. I don't know how we'll get better data because as one of the companies said, it may be impossible to run these trials in the U.S. once these approvals were given.

DR. LIEU: Thanks, Dr. Spratt.

Does the FDA have a response?

DR. LEMERY: Sure. We hear you. When these studies were done, we had discussions with the companies about both the biomarker positive and the ITT populations. I think learning over time, we are seeing that maybe we do need to push more on the biomarker negative population to get enough patients and events in those to get better data for these studies. This is the way they were done, and these are the results we have. It's not optimal. We hear you and, optimally, we would have had a better powered study for including more of the PD-L1 low patients. We are here in the situation now, so we ultimately have to make a decision.

DR. SPRATT: Yes. This is Dan Spratt, UH Seidman. Still, though, it's the primary endpoint; it's powered for this subset, but the approval goes to the entire trial. So that's a decision that -- again, for example, the third company, BeiGene, I think it was not their primary endpoint, based on that. But I think going to the erlotinib/gefitinib history here, if the erlotinib trial was initially designed and EGFR mutant patients were powering this, and you approved it for everyone, people would be like, "What the heck are you doing?" It wasn't. So that is, I guess, at least my hindsight 20/20 advice, which is easy to give.

DR. LEMERY: I hear you. In this case, PD-L1 is a little bit more challenging than the EGFR situation, but we do hear you.

DR. LIEU: Dr. Dodd?

DR. DODD: This is a question to the FDA statisticians. Did you do an interaction test looking at the effect of the two groups less than 1 and greater than 1, and what was the p-value for

that?

DR. FENG: Zhou Feng, statistical reviewer at FDA. Yes, we did analysis of the interaction, in fact, between treatment and the PD-L1 status using Cox model. I can quickly take a look at the p-value. I think, absolutely, it's less than 0.05. We used the PD-L1 less than 1 and it indicates the p-value is 0.017. Thank you.

DR. DODD: Thank you. That answers my question.

DR. LIEU: Dr. Spratt?

DR. SPRATT: Dan Spratt. To that point, talking about sample size, a lot of times people will say, "Oh, it's underpowered." Well, if you have a significant interaction test, it's powered that these are significantly different effect sizes.

DR. LIEU: Any other comments?

Dr. Dodd?

DR. DODD: Can I just add to that, though? Just to add further strength to that, when we do interaction tests, because we know they're

historically underpowered, we sometimes allow a p-value of 0.1 for an interaction test. So 0.01 I think, to me, is pretty convincing.

DR. LIEU: Dr. Vasan?

DR. VASAN: Yes. Just to address one of Dr. Spratt's points and I think what Dr. Van Loon said in the last session as well, is that because this is just such a dynamic field, one difference between this today and, let's say, olaparib is that here we have three different drugs that have a lot of similarities in a similar patient population, and it's when we do the pooled analysis that we see these higher order effects.

I think in some of these other drugs, at least here, I think we as a field have to be prepared for the fact that if there are other drugs approved in the same setting for a specific cancer type that do show these higher order effects, where a specific biomarker cutoff does not meet the mark, I think we just have to be prepared for that; that if we have these high-quality analyses, that may change the way we treat our patients. For example,

there are other PD-1 antibodies that are approved regardless of PD-L1 status, and maybe there's going to be more data that comes out to that effect.

DR. LIEU: Ms. Deighton?

MS. DEIGHTON: Dana Deighton, patient representative. This is kind of a lay question. Before the approval is pulled back from that population that is PD-L1 less than 1, is there anything else that can be looked at in that population, like MSI status or anything like that? There usually is a subset of people that do respond differently.

DR. LIEU: Yes. It's a wonderful point. The analyses that were presented, it did exclude the MSI high population, but as also was discussed with some of the experts that have already presented, I think that really is the call to action in this subgroup. Certainly, it's small. There are not a lot of patients that are PD-L1 negative, but at the same time there are patients that clearly have a benefit. We have no idea who those patients are, and I think that really is

incumbent upon us. And it goes to Dr. Sanoff's question about the grant that you would write to further investigate this population.

But it really does speak to the fact that we don't know everything that there is to know about biology, but we should, and I think that that's where the science will certainly lead us, to better therapies in a patient population that obviously desperately needs better therapy.

DR. DEIGHTON: Thank you.

DR. LIEU: Dr. Casak?

DR. CASAK:

DR. CASAK: Sandra Casak, FDA. Thank you. Just to clarify, the analysis actually included all patients, not only MSS, but because we have very few patients that were MSI high and we have a very high rate of unknowns, we didn't separate those. Having said so, this approval does not affect patients that are MSI high.

MS. DEIGHTON: Thanks. I appreciate that.

DR. CASAK: That will be treated anyway.

MS. DEIGHTON: Yes.

DR. LIEU: Thank you, Dr. Casak.

Dr. Van Loon?

DR. VAN LOON: I have a comment and a question. I think unlike this morning's conversation, where really the decision was to align with existing guidelines from NCCN, if you look at the existing guidelines for use of nivo and pembro for this particular indication, they are all over the map, where currently nivo doesn't have a biomarker -- nivo-ipi doesn't have a biomarker requirement and pembro does.

So I'm asking, is the goal, now that there are three drugs, to have some consensus around a biomarker indication that would unify guidelines and actually help clinicians who very rarely see this disease?

DR. LIEU: Does the FDA have a response to that?

DR. PAZDUR: Yes. Your decision should be based on the data that has been presented. There's no attempt here to unify guidelines whatsoever. That is not part of our procedure, so to speak, or

our objectives here. It's really on the data that is presented here. We do not know what went in or who made the decisions in the guidelines, so there is absolutely no attempt here to provide some unification of the guidelines with an FDA label.

DR. LEMERY: I will say, though, when we started doing some of these analyses, we knew about the 10 with one of the drugs and Category 1 recommendations. We didn't want to be set on, "Okay, that's what we have to focus on." We wanted to look at the totality of the data because, really, when you look at the pooled analysis between 1 and 10, again, it's exploratory and you need to take it with some caveats, but forest plots were clearly to the left of 1.

So we wanted to make sure that if there was going to be a limitation, we wanted it to be on as few patients as possible. If we have an effect, we want to make sure those patients get that. So we didn't want to be limited to what was in the guidelines. Thank you.

DR. LIEU: Dr. Madan?

DR. MADAN: I'm looking back through my slides here. Your interaction score -- which I'm not a statistician, so I'm trying to understand it better -- that's with all three trials pooled together; correct?

DR. FENG: Zhou Feng, statistical reviewer at FDA. Yes, we used the pooled data to do that analysis.

DR. MADAN: If I remember correctly -- Dan, what was that slide you had pulled up before, Dr. Spratt?

DR. SPRATT: It was 11 of the FDA's talk, the first one.

DR. MADAN: The intro. I'm trying to remember because it looked like not all the curves are exactly similar if we look at that. Our question here is focused on three trials. Some of them cross, some of them don't, so you could understand where the interaction score tells part of the story, but maybe not all of the story for all of the trials. That would just be my naive perspective as a non-statistician.

DR. LIEU: Dr. Spratt?

DR. SPRATT: Just to be clear, obviously, you did the analysis, but what the interaction is, is looking at the columns -- well, actually, this isn't the slide that would even have it, but it's basically the PD-L1 less than 1. And I don't know; there's probably a slide that has a PD-L1 greater than 1.

It's comparing those two hazard ratios. So it's not comparing these curves, really, that you're seeing here. So it's hazard ratios of basically 0.6-ish versus hazard ratios about 1,is there a significant difference in those relative benefits, is the interaction, treatment biomarker interaction.

DR. MADAN: Yes.

DR. SRIVASTAVA: This is Geetika Srivastava, FDA. Slide 28 from my slide deck that was presented.

(Pause.)

DR. LIEU: Can we have slide 28 from Dr. Srivastava's presentation, please?

(Pause.)

DR. SRIVASTAVA: And for RATIONALE, they were reversed.

DR. LIEU: Dr. Dodd?

DR. DODD: I think for me, slide 30 is a little more instructive. It's basically testing the rows, the PD-L less than 1 and the PD-L greater than 1; is there evidence to suggest that there's a treatment effect difference between those two groups? And according to the statistical criteria, yes, there is. So it's the 1.1 versus 0.68, roughly speaking.

Am I correct, FDA?

DR. LIEU: Dr. Feng?

DR. FENG: Yes, that's correct. Thank you.

DR. LIEU: Dr. Meyerhardt?

DR. MEYERHARDT: Jeff Meyerhardt, Dana-Farber. You may have not done this, but the interaction term that we've been talking about, how much of it's driven by the tislelizumab? Because the hazard ratio -- I know the numbers will get much smaller and you'll have much less power, and

it's only like 50 per each arm if you just take the nivo and the pembro, but the tislelizumab, given that the hazard ratio is 1.34, is probably driving some of that interaction more than others. So I don't know if you just did the two groups to see what that interaction looked like.

DR. FENG: Zhou Feng, statistical reviewer at FDA. For that analysis, we used the pooled data, including the data from three trials only, but here we observed a consistent pattern across the three studies with the PD-L1 less than 1 subgroup. Thank you.

DR. LIEU: Any additional comments, or discussion questions, or points?

(No response.)

DR. LIEU: I'll try to summarize this discussion. I think unlike the discussion that we had this morning, while I believe that there's consensus in regards to some concern about how the CPS less than 1 or PD-L1 less than 1 group is doing with the treatment, I think the entire group is really concerned about the sample sizes that were

being discussed. I think, statistically, that makes things very difficult, so we had a lot of conversation about the analyses and the interactions performed on the pooled analysis.

Having said that, I think that maybe the differences in our discussion here is that now that we have a pooled analysis, which is something that we haven't had, at least on a trial level with the individual trials, we can start to make some conclusions, but I hear a little bit of discomfort in regards to making a determination based off of the current data that we have in hand.

Any additional comments or questions to that?

(No response.)

DR. LIEU: Okay. Moving on, we will now proceed to question 2, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin to vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If

you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

For question 2, which is a voting question, is the risk-benefit assessment favorable for the use of anti-PD-1 antibodies in first-line unresectable or metastatic esophageal squamous cell carcinoma with PD-L1 expression less than 1?

Are there any questions or comments concerning the wording of the question?

(No response.)

DR. LIEU: Seeing none, we will now begin

the voting process.

(Voting.)

DR. FRIMPONG: There is 1 yes, 11 noes, and 1 abstain.

DR. LIEU: Now that the vote is complete, we'll go around the table and have everyone who voted state their name and their vote, and if you want to, you can state the reason why you voted as you did into the record, and we will start with Dr. Van Loon.

DR. VAN LOON: This is Katherine Van Loon, and my vote was no.

DR. LIEU: I think we'll go ahead and go around the table from the other side, so Dr. Sanoff?

DR. SANOFF: Hanna Sanoff. My vote was no, the reason being, though we heard a lot about how inflamed these tumors are in their microenvironment, there must be something different about the PD-L1 negative patients given the completely overlapping survival curves and even some suggestion of no benefit at all, even

potential harm. So I just did not see enough evidence to suggest -- and despite the small sample size, I think the fact that the effect of treatment is statistically modified by PD-L1 is pretty compelling, as well as the event rates.

DR. LIEU: Thank you.

Dr. Meyerhardt?

DR. MEYERHARDT: Jeff Meyerhardt, Dana-Farber. My vote was no for similar reasons. I think the consistency across the three trials, where the hazard ratio really is 1 or even higher, despite the small sample size, made me vote no.

DR. LIEU: Dr. McKean?

DR. McKEAN: Heidi McKean, Avera Cancer Institute. My vote was no. My honest answer to that question, is the risk-benefit assessment favorable? No. Despite the small numbers, I think this is the best data set we're going to get.

DR. LIEU: Dr. Gibson?

DR. GIBSON: Michael Gibson. I also answered no. I would like, just for the record, to state that the data, as I see it now is and

described and commented on by my colleagues, stands alone. But I know that I will also have to take this decision into consideration when I'm in clinic, and I appreciate the opportunity to be a part of the decision. Thank you.

DR. LIEU: Thank you.

Dr. Hawkins?

DR. HAWKINS: I voted no with some apprehension about removing something that was available but could not ignore the numbers. I suspect, as my colleague to the right made mention, some doctors will probably still attempt to offer this to patients who feel that I'm willing to take a chance given the opportunity, to continue to use the drug irrespective of their low PD-L1 number.

DR. LIEU: Thank you, Dr. Hawkins.

Ms. Deighton?

MS. DEIGHTON: Dana Deighton, patient representative. I understand the numbers and I understand the concerns. The numbers are low, but as a patient, I also had no options and had to fight for anything I could find. I do believe in

the Hail Mary passes, and sometimes things do work and you don't know why, so that's why I voted yes.

DR. LIEU: Thank you.

Dr. Dodd?

DR. DODD: This is Lori Dodd, and I voted no. The question stated does the risk-benefit profile favor the use of this in PD-L1 less than 1? There was no evidence of benefit in this group, and in particular, there was evidence of a clear treatment by PD-L1 status interaction. So in spite of that, I think there needs to be more done. I also tried to approach this as if we were presented with these data de novo today, would we approve this in this group, and there's just simply not evidence to suggest that it would provide a benefit in this subgroup. Thank you.

DR. LIEU: Thank you, Dr. Dodd.

Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia. I voted no based on the totality of the data; that despite the small numbers, this was a statistically sound analysis. I will say that I think today's

discussion, both in the morning and the afternoon, has really been quite instructive and I think also shows us the importance of while some people may accuse oncology of having so-called "me too" drugs, these multiple pooled analyses actually allow us to refine a very complex biomarker that really could help us better identify who's really responding to these drugs. Thank you.

DR. LIEU: Thank you.

DR. LIEU: This is Chris Lieu. I voted no. I agree with the statement that this is probably the best data that we're going to have. Some of this is related to how the question was asked. It really asks is the risk-benefit profile in favor of, and I'm not really sure you can look at this data and say that the answer is yes. Having said that, I do share everybody's concern that this data set is still quite small, but I am thankful that, again, this is a minority of the patients that are going to be treated.

Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer

Institute. I voted to abstain. Again, it's actually not that different than Dr. Lieu's comment; it's just, from my perspective, I don't think that I feel comfortable with 8 to 10 percent of the patients from these trials that didn't all have universal readouts in terms of the curves and things that were pooled together. I know there are unique opportunities here to look at this, but to use a legal term, I'm not sure there was enough to "convict" so to speak, so that's why I abstained. I just don't think the question could be answered in a comfortable way based on the data we saw.

DR. LIEU: Thank you, Dr. Madan.

Dr. Spratt?

DR. SPRATT: Dan Spratt, UH Seidman and Case Western. I voted no. It's really challenging, especially from some of the comments we've heard -- which, again, we're not voting for a regulatory change; that's not what the ODAC does -- does this take away hope? I think often we forget, and it's been brought up before, that pretty much every single therapy causes toxicity,

every single therapy, especially when we're talking about these agents, can cause substantial toxicity or financial toxicity, if you have it.

Even the numbers -- we'll just take when you say it's going to benefit 1 in 10, which is a phenomenal -- first, we haven't really said, these drugs are amazing drugs. These drugs have changed many patients' lives, so we're talking about a subset. Is potentially harming 9 patients, does that always justify helping 1? And in this case it might be harming 99 patients to maybe help 1.

So if you're that one that's helped, that's great, but if you potentially are harming many more, I think that's something that I'm not sure the question, this risk-benefit ratio, that we've seen evidence that there's going to even be that one that we could clearly reliably identify. So that's why I voted no. But again, I don't think any of us want to take hope away. We don't want to harm patients; we want to help them.

DR. LIEU: Thank you, Dr. Spratt.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern. Succinctly, despite the concerns about small numbers, there was no evidence of benefit, period.

DR. LIEU: And just for the record, you voted?

DR. GRADISHAR: No.

DR. LIEU: No. Okay.

To summarize the discussion, certainly I think there is fairly widespread consensus across the panel that the risk-benefit profile does not favor the use in patients that have PD-L1 score less than 1. I think there is fairly good consensus that the available data do not support its use. Having said that, I think that we've heard from the panel members that there's some discomfort with the small amount of patients that we're trying to make decisions from, understanding that the data is never always going to be perfect; and this is a very good example of that, but we have to make decisions based off of the data that we have.

I think that we heard from Ms. Deighton the desire to offer as many therapies as possible to our patients, and I think that we all feel that. At the same time, to Dr. Spratt's point, there's certainly a number needed to treat to help people, but there's also a number needed to harm, where when you treat enough patients, you are going to deliver harm from some of these therapies; and therefore, I think that's really what sums up the risk-benefit profile and the reason the vote came out the way it did.

Any other questions or comments?

(No response.)

DR. LIEU: Okay.

I know that this was an incredibly long day, and I will tell you, having three applicants in the room, the presentations from the applicants and the FDA were outstanding. The information that was provided was outstanding. So really, from the panel, to the applicants, and the FDA, thank you so much, and also for all the incredible work that has gone into all of this. To our open public hearing

speakers, thank you for sharing your stories. Please know that those impact us as well and encourage us to do even better in clinic, and for our patients, and the research that goes on in this room, and then obviously beyond.

To the FDA, do you have any final comments?

Dr. Lemery?

DR. LEMERY: Just to thank everyone, and reiterating your thanks and appreciation for everyone, their hard work, their travel and time to come out and participate in this meeting.

Adjournment

DR. LIEU: Wonderful.

And with that, we'll adjourn, and thank you guys so much. Appreciate it. Safe travels.

(Whereupon, at 4:29 p.m., the afternoon session was adjourned.)