FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Morning Session

Thursday, September 26, 2024

8:00 a.m. to 1:15 p.m.

Meeting Roster

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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

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. LIEU: Good morning, and welcome. I would first like to remind everybody to please mute your line or microphone when you're not speaking. 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 e-mail is currently displayed.

My name is Dr. Christopher Lieu, and I'll be chairing this meeting. I will now call the morning 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'll start with the FDA to my left and go around the table.

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

DR. LEMERY: Steven Lemery, Director of the

Division of Oncology 3.

DR. CASAK: Sandra Casak, team leader, Division of Oncology 3.

DR. KUMAR: Vaibhav Kumar, clinical reviewer, Division of Oncology 3.

DR. ZHANG: Yiming Zhang, statistical reviewer, Division of Biometrics V.

DR. LIEU: Dr. Van Loon?

DR. VAN LOON: Katherine Van Loon, gastrointestinal oncologist, Professor of Medicine at UCSF.

DR. GRADISHAR: Bill Gradishar, Professor of Medicine, breast oncologist, Northwestern.

DR. SPRATT: Dan Spratt, Professor and Chair of Radiation Oncology at UH Seidman and Case Western Reserve University.

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

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

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

DR. VASAN: Neil Vasan, breast oncologist at Columbia University.

DR. DODD: Lori Dodd, Chief of the Clinical Trials Research and Statistics Branch at the National Institute of Allergy and Infectious Diseases.

DR. HILLARD: James Randolph Hillard, patient representative, survivor of metastatic stomach cancer due to trastuzumab.

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

DR. GIBSON: Michael Gibson, aerodigestive and upper GI medical oncologist at the Vanderbilt-Ingram Cancer Center.

DR. McKEAN: Heidi McKean, community oncologist at Avera Cancer Institute, Sioux Falls, South Dakota.

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

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

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're looking 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 or lunch. 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 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 of the use of immune checkpoint inhibitors in patients with unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma. The current labeling for approved checkpoint inhibitors in this indication reflects broad approvals in the intent-to-treat populations agnostic of programmed death cell ligand-1, 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 the cumulative data to restrict the approvals of immune checkpoint inhibitors based on PD-L1 expression.

The committee will discuss the existing supplemental biologics applications, sBLA, which were approved for patients with previously untreated HER2-negative unresectable or metastatic gastric or gastroesophageal adenocarcinoma: sBLA 125554/S-091 for Opdivo, nivolumab, injection, submitted by Bristol-Myers Squibb Company; and sBLA 125514/S-143 for Keytruda, pembrolizumab, injection submitted by Merck Sharp & Dome, LLC, a subsidiary of Merck & Company, Incorporated. The committee will also discuss BLA 761417 for tislelizumab injection submitted by BeiGene USA, Incorporated, for the same proposed indication.

This is a particular matters meeting during 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 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. Steven Lemery.

FDA Introductory Remarks - Steven Lemery

DR. LEMERY: Good morning. My name is Steven Lemery. I'm a medical oncologist and Director of the Division of Oncology 3. I'm here today to set the stage for what will be an important discussion regarding the optimization of

treatment using PD-L1 inhibitors for the treatment of patients with gastric or gastroesophageal junction adenocarcinoma. I would like to acknowledge the herculean efforts by the FDA review teams involved in both of today's meetings. We wanted to look at the data with fresh eyes when we embarked on the need for these advisory committees with the intent of making the most scientifically and appropriate decisions for patients.

We're holding this meeting today in an attempt to bring order to a confusing situation. PD-L1 expression by IHC in gastric cancer is not a perfect biomarker; however, we would like to optimize the risk-benefit for patients and foster consistency in the treatment of gastric cancer, as well as the developmental landscape of new drugs studied for patients with gastric cancer.

PD-L1 appears to have utility in identifying which patients are more likely to benefit; however, because different studies have used different tests and different cutoffs, it can be difficult to assign a clinical effect to different PD-L1 levels,

particularly as PD-L1 expression increases above 1. Nevertheless, patients who are PD-L1 intermediate, between 1 and 10 using CPS or TAP, appear to benefit to a lesser extent, and there's uncertainty regarding these treatment effects.

At the conclusion of this meeting, we will ask the committee to consider whether class labeling at a PD-L1 level of less than 1 would be appropriate. We acknowledge, however, that arguments can be made for the selection using different cutoffs, and we're open to hearing the committee's opinions on this matter.

FDA has approved two PD-L1 inhibitors, pembrolizumab and nivolumab, in combination with chemotherapy for the first-line treatment of patients with gastric cancer. An application has also been submitted for a third drug, tislelizumab, for a similar indication. Although FDA has granted approvals to PD-L1 inhibitors in patients with previously-treated gastric cancer, we will focus the discussion today on the first-line setting, which is most relevant to current practice.

All three drugs demonstrated improvements in overall survival in the first-line setting, both in the intent-to-treat patient populations, highlighted by the red box, as well as in prespecified subgroups of patients based on PD-L1 expression, highlighted by the purple boxes.

Although FDA granted approvals in the intent-to-treat populations for nivolumab and pembrolizumab, data in the PD-L1 low groups, shown in the more heavily shaded columns, were included in product labeling to facilitate decision making. The data appeared to show a smaller treatment effect when compared to patients with higher PD-L1 expression, which is shown in the lighter shaded columns. Although not approved, the data for tislelizumab are also provided.

Although FDA granted the gastric cancer approvals in the ITT patient populations, professional society guidelines have recommended using PD-L1 to select patients for treatment with pembrolizumab and nivolumab. Likewise, international regulators have also taken such an

approach. Of note, the ASCO and NCCN Category 1 recommendations were based on the tests and statistical designs used in each of the individual studies; nevertheless, the guidelines do not specifically describe or require the use of the individual test kits that were used in the clinical trials.

To illustrate how we got here from the agency's perspective, I will highlight the challenge of the subgroup analyses with the original approval of nivolumab in 2021. Although clearly the largest treatment effect was in patients with CPS PD-L1 in the 5 or greater, which is circled in red, the CPS low data were less clear-cut, with a questionable intermediate effect in patients with CPS less than 1 as compared to the CPS less than 5 group, which is highlighted by the purple box. Additionally, the CPS low groups were not powered to demonstrate a treatment effect, leading to more uncertainty in these groups of patients.

About 16 years ago, the FDA held an advisory

committee meeting to discuss the use of subgroup analyses to support decision making. At the time, accumulating data across at least seven trials in patients with KRAS-mutant colorectal cancer appeared to show no benefit for EGFR inhibitors panitumumab or cetuximab.

During that advisory committee meeting, when considering retrospective subgroup analyses, members found that replication of results across multiple trials strengthened inferences. Furthermore, sample ascertainment was deemed important to ensure analyses represented the populations enrolled in the trials. Biological plausibility was another factor when considering these subgroup analyses. Study design considerations could include stratification and prespecification.

In each of the three trials of anti-PD-1 inhibitors under discussion today, there was prespecification of certain PD-L1 high subgroups, but not prespecification of the converse PD-L1 low groups. Although one could argue that the subgroup

effects in each of the clinical studies were underpowered, now we have the results of at least three trials with generally consistent effects. Results in PD-L1 subgroups from the three applications in the first-line, HER2-negative metastatic setting consistently showed that the largest treatment effect appears to be in patients with CPS or TAP PD-L1 greater than 10. These results will be shown in subsequent presentations.

Conversely, there's less convincing evidence of a treatment effect in patients with PD-L1 CPS or TAP less than 1, which is highlighted by the red box. Modest or more inconsistent effects have been observed in patients with PD-L1 intermediate disease.

In addition to the three trials to be discussed today, an external trial-level meta-analysis of the literature has been published by Harry Yoon, et al., that included 10 gastro or esophageal adenocarcinoma studies, including studies in both the first- and second-line settings, negative trials, and trials conducted

solely in Asia. In this analysis, CPS high was based on the different levels prespecified in each trial with trial-specific PD-L1 testing, and PD-L1 appeared to designate patients as more likely to benefit.

Of note, I'm also highlighting MSI high on this slide. Like our own analyses, patients with MSI high tumors appear to have a very high likelihood of benefit following treatment with checkpoint inhibitors. For the purposes of this ODAC, we will be limiting the discussion to patients with microsatellite stable disease, as we would not propose to modify the indication for patients with MSI high tumors irrespective of PD-L1 status.

When we talk about lack of benefit, it's important not to forget about safety. If a drug is not effective, patients may be exposed to life-altering toxicity. The table on the left is a summary of the incidence of select immune-related adverse events, or IMARs, across four clinical trials that assessed pembrolizumab or nivolumab.

In general, grade 3 or greater IMARs occurred at a rate of 3 to 11 percent, depending on the clinical trial.

Although many IMARs are treatable, IMRs can become chronic, particularly for endocrine, lung, neurologic, cardiac, or arthritis. These adverse events, or even steroids used to treat IMARs of less severity, can greatly compromise the patient's quality of life, which is important to patients with end-stage gastric cancer.

I would like to transition to how we move forward if the right thing to do is to limit the indication at a specific PD-L1 cutoff. One approach to take would be to limit the indications based on PD-L1 positive cutoffs used in each clinical trial. Although this may be a reasonable approach statistically, it's not necessarily biologically based. In other words, what would be the optimal cutoff to maximize benefit and reduce risk? Such an approach may also unnecessarily exclude patients from treatment if we selected a cutpoint that was too high. We now have data from

multiple clinical trials that can be considered to assess whether a class-wide approach would be more appropriate.

In practice, oncologists do not necessarily use the specific CPS or TAP diagnostic tests that were developed for each individual monoclonal antibody, so populations in the clinic may differ as compared to clinical trials. Perhaps more importantly, companies wanting to study dual checkpoint inhibitors, other add-on drugs, or drugs intended to target other biomarkers may have to link their clinical trial to PD-L1 levels related to a checkpoint inhibitor rather than a biological principle, which doesn't seem to be the most rational approach.

One more important consideration, however, is that all three studies used different diagnostic tests to assess PD-L1 status. As a purely hypothetical example, if a cutoff of either 5 or 10 were selected, any of the tests theoretically could be used; however, the number of eligible patients would greatly be affected depending on the test.

Importantly, irrespective of the test used, patients who were PD-L1 negative or less than 1 were less likely to benefit.

Designating a patient as PD-L1 negative may be less variable from test to test as compared with the challenges of designating the specific score; for example, PD-L1 4, 8, or 10. Of note, only a minority of patients are PD-L1 negative regardless of the assay used. If a cutoff of 1 were recommended, depending on the test, 80 to 90 percent of patients with gastric cancer would still be eligible to receive a checkpoint inhibitor.

I will summarize by providing a snapshot of the data in the PD-L1 less than 1 in 10 subgroups. Dr. Kumar will provide a much more complete review of the data, including data above and below different PD-L1 cutoff levels. Dr. Kumar will also provide FDA exploratory pooled analyses limited to patients with microsatellite stable disease to provide additional context regarding each clinical trial.

It is not shown here, but the data in patients with CPS or TAP PD-L1 greater than 10 show clear benefit. In patients with PD-L1 of less than 10 or between 1 and 10, there are more inconsistent effects; however, there may be a hint of a plateau in two of the Kaplan-Meier curves as shown by the purple arrows, and the upper bound of the 95 percent confidence intervals in the purple ovals are below 1 or close to 1. Nevertheless, this should not be considered as definitive evidence of either benefit or lack of benefit.

When one views either the median overall survival, hazard ratio, or Kaplan-Meier curves at the PD-L1 less than 1 cutoff in the red boxes, there appears to be less convincing evidence for benefit, and not even a hint of a possible plateau in the Kaplan-Meier curves when compared to the control arms. Dr. Kumar's presentation will show a stark contrast of these Kaplan-Meier curves compared to those in patients with PD-L1 tumors greater than 10 for each drug. It is important to remember that although a minority of patients will

develop severe or life-threatening toxicity, for those who do, the quality of their lives can be greatly altered.

I would like to point out the available results for KEYNOTE-811 to further support the biological plausibility with respect to PD-L1 in gastric cancer. KEYNOTE-811 is a first-line study in patients with HER2-positive gastric cancer, where pembrolizumab was administered in combination with trastuzumab in chemotherapy. Please note that I'm only providing this information for context for the committee.

Pembrolizumab received accelerated approval for this indication based on the prespecified interim analysis and response rate that demonstrated statistical significance. In a subsequent prespecified interim analysis, however, there appeared to be a potential for detriment in survival in patients with PD-L1 CPS tumors less than 1, and current labeling limits pembrolizumab to patients who are PD-L1 greater than 1.

Based on the data that I've shown so far,

there does appear to be a general replication of results across clinical trials, which is consistent with a retrospective approach used for EGFR inhibitors based on RAS mutations in colorectal cancer. This replication was seen both in the first-line gastric cancer trials in combination with chemotherapy, as well as additional trials in the Harry Yoon meta-analysis. Sample ascertainment for CPS or TAP was high in each of the three trials to be discussed today, with the results available from the vast majority of patients.

With respect to biological plausibility, although PD-L1 had variable utility as a biomarker in different tumor types, it does appear useful in select disease settings. Finally, all studies designated specific PD-L1 high populations at different thresholds; however, none of the studies were specifically designed to test for the PD-L1 negative groups. Again, all three studies used different PD-L1 testing methodology.

I would like to summarize my interpretation of the available data. Clearly, there's an

important benefit of checkpoint inhibitors in patients with gastric cancer, and their tumor is a PD-L1 score of 10 or greater, and in patients who are microsatellite instability high. Again, we're excluding MSI high from our assessment of risk and benefit. In patients with PD-L1 intermediate gastric cancer, for example 1 to 10, there may be a modest benefit; however, it's difficult to convincingly demonstrate or exclude such an effect. An additional consideration regarding uncertainty in this group may involve the accuracy of classification of PD-L1, for example, differentiating 9 from 10.

In patients with PD-L1 negative disease, although there may be some uncertainty based on a smaller number of patients, irrespective of the assay used there, there does not appear evidence of benefit, and patients may be at risk for harm. Additionally, uncertainties regarding testing may be mitigated, as PD-L1 staining will either be present and positive, absent or negative. Again, selection of PD-L1 cutoff of 1 would result in

80 to 90 percent of patients being eligible for checkpoint inhibitors and would allow consistent approach to treatment in the clinic and in clinical trials going forward.

Following all the presentations, we will ask the committee to discuss the use of PD-L1 as a predictive biomarker for the selection of patients with gastric and gastroesophageal adenocarcinoma. We welcome the viewpoints of the committee on this challenging topic. Following the discussions, we'll ask the committee to vote on whether the risk-benefit assessment is favorable in patients with gastric cancer who have PD-L1 expression less than 1.

Please note that the FDA review staff has had extensive internal discussions following the review of the totality of data prior to finalizing this question. FDA reviewers considered not just the data, but the landscape of testing and the landscape of treatment of gastric cancer. Although we are specifically asking about the cutoff of 1, we invite you to express your opinion if you

believe a different cutoff would be more appropriate. Thank you.

DR. LIEU: Thank you, Dr. Lemery.

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 Bristol-Myers Squibb.

Applicant Presentation - Ian Waxman

DR. WAXMAN: Good morning. My name is Ian Waxman, and I'm part of the Late Development Oncology organization at Bristol-Myers Squibb. I'd first like to thank the advisory committee members and the FDA staff for this opportunity to discuss the data for Opdivo in combination with chemotherapy in first-line gastric cancer.

These data come from the CHECKMATE-649 study and resulted in FDA approval for this indication in April of 2021. This marked the first approval of a new treatment for first-line HER2-negative gastric cancer since chemotherapy became the standard of care. By way of background, Opdivo was first approved in the U.S. in 2014 for the treatment of melanoma and is now approved in 11 cancer types as shown here.

Here is the indication for Opdivo in combination with chemotherapy for first-line patients with gastric cancer, GE junction cancer, or esophageal adenocarcinoma, and it's important to highlight two things: first, the approval was granted regardless of PD-L1 status; and second, since the initial approval, our interpretation of the study results has not changed with longer follow-up.

Although the indication 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 approval, results from additional gastric cancer studies have been reported with different sponsors incorporating different methods for measurement of PD-L1, as well as different cutoffs to determine positivity. NCCN has managed the situation by giving a Category 1 recommendation

for patients with higher PD-L1 expression while also getting a Category 2B recommendation for patients with lower PD-L1 expression. ASCO and ESMO guidelines have taken a similar approach.

For nivolumab, NCCN guidelines are consistent with the current FDA label with no restriction on treatment but with information provided to highlight the importance of PD-L1 expression level in determining likelihood of clinical benefit.

Given the current USPI and NCCN recommendation, it's important to understand what physicians are doing about testing in the real world. When we look at testing patterns in the U.S. based on Flatiron data, we see that physicians have indeed received the message around the importance and impact of PD-L1 expression in this disease. What we see on the left is that approximately 60 percent of all patients treated with any regimen in the first-line setting are already being tested for PD-L1 expression even without a requirement to do so; and when we look at

the middle pie chart, over 70 percent of those treated with nivolumab are being tested.

Regarding treatment patterns, also based on Flatiron data, we see that the PD-L1 test result is influencing treatment decisions in the real world today. Among patients known to be PD-L1 positive on the left, about 50 percent receive an IO regimen. In contrast, among the much smaller proportion of patients known to be PD-L1 negative, in the middle pie chart, fewer than one-third 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 see that many patients are not tested or have an unknown test result and about one-third of these patients are treated with an IO regimen. This high percentage of patients without a test result is not surprising when we consider testing rates for HER2, which is another established biomarker in gastric cancer. Approximately one-third of first-line patients are

still not tested for HER2 in clinical practice despite the long standing availability of HER2-directed therapy.

Given the high prevalence of PD-L1 positivity, most patients without a test result would be considered positive if tested. We believe these patients should remain eligible for an IO-containing regimen in the absence of a comorbidity precluding its use.

With this information in hand, we're here to discuss whether any label changes for Opdivo in gastric cancer are needed. Our goal is to ensure that each first-line gastric cancer 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 CHECKMATE-649 and a summary of challenges associated with interpretation of a PD-L1 test result are important topics to discuss when considering this goal.

Once we have covered these additional areas, I'll turn to a summary of potential options for

labeling, also briefly described here. One option is to modify the indication to only include patients with any level of PD-L1 positivity. 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 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. Additional considerations for each of these approaches are shown here and will be discussed in more detail in the next parts of this presentation.

Here's 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-649; then Dr. Robert Anders, an expert pathologist from the Johns Hopkins University, will discuss the realities of PD-L1 testing in clinical

practice; and then finally, I'll return to review the proposed 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. I'll be presenting efficacy and safety data that will highlight the benefit-risk profile of nivolumab plus chemotherapy in the CHECKMATE-649 study across PD-L1 subgroups.

CHECKMATE-649 is a randomized, phase 3 study that included patients with previously untreated, unresectable, advanced or metastatic, gastric or esophageal adenocarcinoma, regardless of PD-L1 expression. Randomization was stratified according to tumor cell PD-L1 expression. This study had dual primary endpoints of overall survival and progression-free survival in CPS 5 or higher.

1,581 patients were concurrently randomized to the nivolumab plus chemotherapy versus

chemotherapy arms, of which 60 percent had PD-L1 CPS of 5 or higher. With a minimum of 12.1 months of follow-up, CHECKMATE-649 demonstrated both a statistically significant and clinically meaningful overall survival benefit in the primary and secondary analysis populations. The primary endpoint was in patients whose tumors expressed PD-L1 CPS of 5 or higher, which demonstrated a hazard ratio of 0.71 and a 3.3 month improvement in median overall survival versus chemotherapy. Of note, there was an early and sustained separation of the overall survival curves. A similar overall survival benefit was observed with nivo plus chemo in the CPS 1 or higher and the all randomized populations.

Shown here is the overall survival data in PD-L1 subgroups that was available at the time of the initial approval. The data in the purple boxes highlight the prespecified primary and secondary analysis populations. The other CPS subgroup analyses were exploratory. There was an increased overall survival benefit observed with nivo plus

chemo at higher PD-L1 cutoffs. Patients with CPS less than 1 did not derive an overall survival benefit; however, in the subgroup with CPS greater than or equal to 1, the hazard ratio was 0.76 with a 95 percent confidence interval of 0.67 to 0.87.

Now, let's take a look at 4-year follow-up data, which are presented in our briefing document. Shown here are all of the subgroups requested by FDA. Keeping in mind that these are exploratory subgroup analyses and should be interpreted with caution, these data are consistent, if not continuing to improve across subgroups relative to the initial clinical trial data.

In particular, I would like to point out that the subgroup with CPS greater than or equal to 1 to less than 10 has a hazard ratio 0.88, improved from a hazard ratio 0.95 at the initial database lock. Of note, the FDA meta-analysis does not include these updated data.

The safety profile of nivolumab plus chemotherapy was consistent with the known safety profile of the individual drug components, with no

new safety signals identified. As expected, the addition of nivolumab to standard chemotherapy was associated with ototoxicity. Grade 3-4 treatment-related adverse events and those leading to discontinuation of any treatment component were numerically higher in patients receiving nivolumab plus chemotherapy. Of note, in the nivo plus chemo arm, the majority of immune-mediated events were low grade, manageable with established treatment algorithms, and reversible. Importantly, the safety profile of nivo plus chemo did not differ based on PD-L1 expression and was consistent across all PD-L1 subgroups evaluated.

In summary, based on the data from CHECKMATE-649, nivo plus chemo demonstrated both a statistically significant and clinically meaningful overall survival benefit in the CPS greater than or equal to 5, CPS greater than or equal to 1, in all randomized populations. Exploratory analyses showed a higher likelihood of overall survival benefit in all PD-L1 positive subgroups, and the long-term follow-up data are consistent with the

data available at the time of approval and provide a clearer picture of the overall survival benefit in the CPS greater than or equal to 1 population.

The safety profile was consistent with the known safety profile of the individual drug components and similar regardless of PD-L1 status. Overall, nivo plus chemo demonstrated a positive benefit-risk profile in all PD-L1 positive subgroups. Thank you. I will now turn it over to Dr. Anders.

Applicant Presentation - Robert Anders

DR. ANDERS: Thank you, Dr. Walker.

My name is Robert Anders. I'm a Professor of Pathology at Johns Hopkins University and a paid consultant for BMS. Today, I'll be sharing with you my 17 years of experience with the technical aspects of PD-L1 testing. As you heard, about 60 percent of patients with gastric cancer are tested for PD-L1 expression, and at my institution, most patients with gastric cancer are tested. It's worth noting that most gastric cancer patients with a test are PD-L1 positive as defined by a CPS of

greater than or equal to 1.

The graph on the left shows data from CHECKMATE-649, where 82 percent of patients were PD-L1 positive. Multiple variables can affect the results of PD-L1 scoring, such as the type of tumor tissue, spatial heterogeneity, and temporal changes in PD-L1 expression. Shown here is PD-L1 staining of a full thickness gastric cancer resection from my practice. PD-L1 positive areas are stained brown and are circled with solid black lines, while PD-L1 negative areas are circled with dashed lines, and you can clearly see there's heterogeneity of PD-L1 expression.

On top of that, I've superimposed an H&E stained mucosal biopsy to give you an idea of the depth of a typical endoscopic biopsy. These are the most common types of tissue samples I see. They're more amenable to PD-L1 scoring because they have fewer cells to count, but they may underrepresent the tumor and may lead to false negatives. A surgical resection better represents the entire tumor but presents a challenge because

the heart of CPS is counting cells, both immune and tumor cells, and frankly, resections have too many cells to count. We also know that PD-L1 expression varies as a function of time, and both biopsies and resections are one moment in time.

Let's move to analytical consideration. There are three approved antibodies that recognize PD-L1. What you see here from a recent publication are serial sections of the same tumor stained with the three antibodies. The staining is similar but not identical. As a result, pathologists may count fewer or more positive cells depending on which antibody is used.

This is relevant at the patient level because differences of a few cells changes the CPS, and this could be a change across a critical threshold. So minute differences could mean the difference between a patient receiving first-line IO therapy or not, and it's worth noting that registrational trials each use different antibodies, which has implications for harmonization.

As a result of these variables I just described, CPS is a highly subjective test with high interobserver variability. I recently published a paper with Marie Robert from Yale on the level of agreement between 12 expert pathologists from around the globe. Shown here are the CPS scores for 100 gastric cancer biopsies using 22C3.

The score from each of the pathologists is represented by a different color dashed line. We report an interclass correlation coefficient, a measure of statistical observer agreement, of about 0.5, which is fair to poor agreement. For reference, the ICC for HER2 testing in breast cancer ranges from 0.8 to 1.

Here, we've taken a closer look at the individual scores from 30 of those gastric cancer biopsies. Scores are indicated by a dot for each pathologist, and we've marked the CPS cutoffs at 1, 5, and 10 as horizontal dashed lines. It's easy to see not only high variation in scores, but tremendous variation across the cutpoints,

oftentimes with just as many dots above the line as below. The implications are significant because even these world-class experts would disagree on whether a patient should receive therapy. Simultaneously, Dr. Rimm from Yale did an identical study with US-based pathologists and came to identical conclusion that CPS is a highly subjective test.

Our conclusion from these studies is that PD-L1 CPS may be a useful biomarker at the population level, but it's an imperfect biomarker at the individual patient level. In conclusion, in my experience, PD-L1 expression by CPS is complicated by spatial heterogeneity of expression, endoscopic biopsies that have the potential for false negatives.

We also have different antibodies with different assays and unacceptably high interobserver variability. I believe pathologists can reliably determine if there is PD-L1 expression or not; however, it's much more difficult to precisely quantify PD-L1 expression, which results

in the high variability we see in CPS scores.

Thank you, and I'll turn it back now to Dr. Waxman.

Applicant Presentation - Ian Waxman

DR. WAXMAN: Thank you, Dr. Anders.

As I summarize the data just presented, I'd first like to acknowledge that this is an important issue without one clear-cut solution. The FDA has asked you to consider whether the data support the use of PD-L1 expression as a predictive biomarker. The clinical trial data show that there is an overall survival benefit in patients who express PD-L1, including at the level of CPS of greater than or equal to 1.

Further enrichment for OS improvement at cutoffs higher than CPS 1 is also likely, but we must consider some practical challenges when choosing to restrict the indication to a specific higher PD-L1 cutoff. As you heard from Dr. Anders, PD-L1 is a dynamic biomarker that exhibits significant temporal and spatial heterogeneity, and PD-L1 scoring is challenging for pathologists and

subject to a high degree of variability.

The quality and availability of tissue can also be a barrier to testing. We do support testing for PD-L1 whenever possible since this result is important in informing benefit-risk, and we're reassured that such testing is already occurring in the majority of patients today, but we recognize there's a downside to requiring a test result given the numerous testing challenges just described. Therefore, we still support a broad indication; however, if the label were to be restricted, a cutoff based on CPS 1 is the most reasonable choice based on the totality of clinical data and testing considerations.

To summarize, the first option is to modify the indication and require CPS 1. A higher cutoff would not be optimal given the challenges with precise quantification of CPS in individual patients; however, this option would leave some patients with potential to benefit untreated.

The second option is to keep the existing indication given that details regarding the impact

of PD-L1 expression are already captured in the label. This approach accounts for the uncertainties associated with PD-L1 testing and leaves informed decision making in the hands of the treating physician where it lies today. This approach also provides greater opportunity for patients without a test result to benefit from immunotherapy. Although both proposals are reasonable, we consider the option that provides flexibility for patients regardless of their PD-L1 test result to be most appropriate, and thank you once again for your time and attention.

DR. LIEU: Thank you so much.

We'll take a very brief 5-minute break to allow for the next presentation to set up. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 8:50 a.m.

(Whereupon, at 8:45 a.m., a recess was taken, and meeting resumed at 8:50 a.m.)

DR. LIEU: Welcome back. We will now

proceed with our second presentation from Merck Sharp & Dohme, Incorporated.

Applicant Presentation - Catherine Pietanza

DR. PIETANZA: Good morning. 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. Thank you for the opportunity to share evidence supporting the positive benefit-risk profile of Keytruda in patients with HER2-negative gastric and gastroesophageal junction cancer, which we will refer to as gastric cancer. After my introductory comments, Dr. Pooja Bhagia will share data from KEYNOTE-859 and Dr. Yelena Janjigian will share her clinical perspective.

Keytruda helped fulfill a critical need for the treatment of patients with metastatic gastric cancer who have a poor prognosis, with only 7 percent surviving 5 years. Before immunotherapy, the only treatment for first-line metastatic disease was chemotherapy. With few biomarkers or

targetable molecular aberrations, we face a dearth of therapeutic options.

Rigorous study design and conduct gives confidence in the positive results of KEYNOTE-859, 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 in HER2-negative gastric cancer should be retained based on the efficacy and safety data for pembrolizumab. The mechanism of action of pembrolizumab is well known. Increased expression of PD-L1 enriches for response with pembrolizumab when given as monotherapy in many tumor types. PD-L1 expression is tumor type specific and interpretation is dependent on the assay and scoring method used.

We know that chemotherapy has pleiotropic immunomodulatory effects, both promoting and impairing the anti-tumor response. Adding an

anti-PD-1 inhibitor to chemotherapy can enhance the positive and reduce the negative immune effects. The complementary effects of the combination of pembrolizumab and chemotherapy can benefit patients with tumors across a broad range of PD-L1 expression, as observed in numerous indications.

I will now describe the comprehensive training and validation methodology used for PD-L1 testing in KEYNOTE-859. Clinical samples are processed using the PD-L1 IHC 22C3 pharmDx assay and interpreted using combined positive score known as CPS, which captures PD-L1 expression on tumor cells, lymphocytes, and macrophages. This is clinically important in gastric cancer, as it has a significant immune infiltration.

Merck clinical studies are used as training sets to determine cutpoints for each tumor type. Once these cutpoints are identified, we collaborate with our diagnostic partner and testing laboratory to validate these cutpoints. Pathologists were trained to use the prespecified cutpoints during patient screening for KEYNOTE-859, the validation

test set for assessing PD-L1 expression in the study. All PD-L1 expression was performed in a central laboratory. This rigor allows for informative prespecified PD-L1 subgroup analyses.

Importantly, while higher PD-L1 cutpoints can enrich for pembrolizumab's monotherapy efficacy in gastric cancer, we cannot predict who will benefit, especially when chemotherapy is added to pembrolizumab. Robust PD-L1 evaluation in KEYNOTE-859 supports the indication under discussion.

We acknowledge that PD-L1 testing outside of clinical trials is variable. The biology of the disease, the treatment mechanism of action, and the possible impact of combination established the foundation of Merck's phase 3 trials. Even when we anticipate benefit across a broad range of PD-L1 expression, we design our studies with the potential for biomarker enrichment to increase the likelihood of successful outcomes. Insights from Merck clinical trials and emerging knowledge from external sources further inform the design of

registrational studies. Of course, labeling reflects the results, as well as the statistical rigor and methodologies of phase 3 studies. When considering labeling changes, the same statistical principles apply.

Post hoc subgroup analyses at cutpoints that are neither carefully assessed nor prespecified with type 1 error control may lead to spurious findings. Additionally, evaluating numerous subgroups may demonstrate randomly high or low treatment effect estimates.

The FDA's pooled analysis also has inherent limitations. It assumes that the different immune checkpoint inhibitors have an identical treatment effect. It ignores differences between the therapies, trials, PD-L1 assays, and defined cutpoints. Most important, patient selection reflects three different tests whose interchangeability has not been established. Using the same numeric value across different tests does not mean that the values are equivalent. Combining potentially different populations treated by

different drugs estimates a quantity that does not represent any actual drug in combination with any test. Such an analysis does not meet FDA's standards for labeling.

Post hoc subgroup and pooled analyses should not supersede the findings of the phase 3 randomized trial with a diagnostic specifically developed for use with pembrolizumab. Since the approval of KEYNOTE-859, there have not been any new efficacy or safety data that changed the benefit-risk profile for pembrolizumab in gastric cancer.

The PD-L1 IHC 22C3 pharmDx assay is specifically studied for pembrolizumab in the approved indication. There are key differences in considering 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. It can be modulated by other therapies like chemotherapy and is not always predictive of

immunotherapy response.

For cetuximab, panitumumab, and olaparib, the outcome of each study was individually evaluated as opposed to a pooled analysis across three different studies. NCCN, ASCO, and ESMO guidelines specify granularity around the strength of efficacy at various cutpoints. Physicians use these clinical guidelines, the label, and importantly the individual patient's characteristics to determine appropriate treatment.

Dr. Pooja Bhagia will now share data from the phase 3 study in HER2-negative gastric cancer that led to the approved indication.

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 safety and efficacy data from KEYNOTE-859. KEYNOTE-859 supported the full approval of Keytruda for the first-line treatment of adults with HER2-negative gastric cancer. In KEYNOTE-859, patients had HER2-negative metastatic or locally

advanced unresectable gastric cancer regardless of PD-L1 status. PD-L1 CPS less than 1 versus greater than or equal to 1 was one of the stratification factors.

KEYNOTE-859 was designed based on pembrolizumab monotherapy studies, which demonstrated activity across all levels of PD-L1 expression with potential for increased efficacy in the CPS greater than equal to 1 population. The statistical plan was designed to test both the ITT and the CPS greater than equal to 1 populations. Seventy-eight percent of the population was CPS greater than equal to 1.

Following initiation of KEYNOTE-859, results from another phase 3 study in first-line gastric cancer indicated a potential for further enrichment at CPS greater than equal to 10. We adjusted the statistical plan to formally test endpoints in this population as well. Thirty-five percent of the population was CPS greater than equal to 10.

Now, let's review the data supporting full approval in the intention-to-treat population.

KEYNOTE-859 met statistical success criteria for all its endpoints: overall survival, progression-free survival, and objective response rate. The overall survival curve favors pembrolizumab with a 22 percent reduction in the risk of death. Progression-free survival curve also favors pembrolizumab, reducing the risk of progression or death by 24 percent. At 2 years, 28 percent of patients in the pembrolizumab plus chemotherapy arm remained alive versus 19 percent in the chemotherapy arm. 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 reactions, 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 the FDA's questions, we will now look at different PD-L1 cutpoints. In all PD-L1 subgroups, patients experienced a benefit with hazard ratios below 1 for both OS and PFS. A higher magnitude of benefit is seen with increasing PD-L1 expression. The CPS greater than equal to 1 subgroup was formally tested with alpha control. The point estimate of hazard ratio for OS and PFS is 0.73 and 0.72, respectively, with a statistically significant and clinically meaningful benefit in this group.

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. The magnitude of benefit is less in the CPS less than 1 subgroup, with the point estimate of the OS hazard ratio being directionally consistent with the ITT. Importantly, the median PFS was approximately 1.5 months longer with increased ORR and longer duration of response, suggesting that some patients do derive benefit in this subgroup.

In patients with CPS between 1 and less than 10, we see benefit with an OS hazard ratio of 0.83 with narrow confidence intervals overlapped with the ITT and the upper bound is less than 1. This indicates that the benefit is not driven by CPS greater than 10.

At a three-year follow-up, the benefit of pembrolizumab remained consistent with the primary analyses, underscoring a tenet of immunotherapy. The safety profile is, in general, similar across CPS cutpoints, and there is no biological rationale to suggest that the safety profile of pembrolizumab would change based on PD-L1 expression.

In conclusion, there is a high unmet need in first-line metastatic gastric cancer. Pembrolizumab added to chemotherapy provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in all patients, and the magnitude of benefit increases with higher PD-L1 expression. Some patients with lower CPS scores also experienced benefit, highlighting that CPS expression alone cannot predict which patients

will benefit from the combination of 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. Moreover, the label includes information on efficacy by PD-L1 cutpoints and supports a benefit-risk discussion between physicians and patients.

Thank you, and I will now invite Dr. Janjigian to the podium.

Applicant Presentation - Yelena Janjigian

DR. JANJIGIAN: Good morning. Thanks, Pooja, and it's such an honor to address this audience. I'm a medical oncologist, and I'm here on behalf of clinicians treating this disease, certainly our patients, and caregivers. These are my disclosures.

I'm an expert in the field. Yesterday in clinic, I saw 30 patients with this disease, and my

research practice is focused on this. Most patients in the United States are treated outside of tertiary cancer centers, so we need to really be there in the clinic with our practitioners to understand what they're facing. Most patients present with stage 4 disease. It's an orphan illness in the United States, so an oncologist sees maybe, at best, 5 gastric cancer patients a year, so they need to act fast.

We know that there's a narrow window of improvement of their quality of life. Also, the likelihood that these patients will respond to therapy will predict the likelihood they will get done second line, third line, and so forth, so we're in it now for the long game, so the response is important.

These patients tend to come in from centers that they're not getting the initial diagnosis in, so they may or may not bring unstained slides, and the therapeutic options are really driven by the clinician. As you saw by ASCO/NCCN guidelines, there is some restriction, but often we start

treatment before these biomarker testing results come back.

Immune checkpoint blockade has its downsides, and some of these adverse events can be long term, but we need to remember that most of the side effects actually come from the 5-FU oxaliplatin-based therapy, and the clinicians really know how to use immunotherapy because, as I said, most clinicians treat also lung cancer, breast cancer, renal cell cancer, so they know these agents well.

So how do we advance practice for this disease? We do biomarker testing. HER2 is seen in 20 percent, MSI is a rare but important subset, and most of the patients do have some tumor overexpression of PD-L1. So in patients, we see 80 percent plus for CPS testing if the testing is done, but is the testing done? What are the practical implications? Having the unstained slides, choosing the right assay, and also the pathology interpretation you heard is excellent earlier in the talk.

We do have difficulty obtaining slides, so the subset of patients I'm particularly worried about are the people who are not getting tested for various reasons because of the sample quality or availability. There is a huge variability in which assay is used depending on the center, and there's a learning curve. Gastric epithelium is tricky. Some of these biopsies are quite superficial, so you don't have the full tumor content. And if you're used to looking at lung cancer and grading TPS, CPS may be a challenge and there's a steep learning curve.

How are the real-world practices doing? Well, it turns out, with all of the research that we're doing in our gastric cancer world, it's not translating directly into all of our patients. A quarter of our patients never even get the PD-L1 testing or any biomarker testing, and only about 50 percent get immunotherapy, suggesting there's really no overuse of these agents in the practice. And there is a variability. For example, MSK doesn't even use any of these; we use our own

lab-developed tests, and there is a huge learning curve for CPS scoring, so TAP and different CPS cutoffs are not interchangeable.

The stakes are high here because we've changed. We've bent the curve, the survival curve, for these immunotherapies, and it's amazing to be able to sit in the clinic and tell a patient you have about a quarter chance of living long term with this disease, even if it's metastatic disease. But we only have that chance if we use the drugs in first-line setting. In the United States, we don't have approval of immune checkpoint blockade in later lines, unlike Asia where gastric cancer is very common and you still use immunotherapy in later lines.

In conclusion, we really need to push the envelope, improve long-term survival, and choice of first-line therapy really matters for our patients, so clinicians need to have these tools in the clinic. ASCO and CCN guidelines do provide really good guidelines as to which agents to use. I'm worried about the patients with unavailable testing

or testing that never gets done because, statistically speaking, 80 percent of patients would benefit from getting immune checkpoint blockade if we end up restricting.

So I think it's important to let physicians take care of the patients and to make decisions individually and not just on a population level basis. That would be my two cents on this, but I'm happy to take any questions. Thanks for your attention.

Applicant Presentation - Catherine Pietanza

DR. PIETANZA: Thank you, Dr. Janjigian.

In summary, KEYNOTE-859 met success criteria for all its primary and key secondary endpoints in the intention-to-treat population. The label reflects the study outcome. Metastatic gastric 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. While higher PD-L1 expression enriches for benefit, data show that efficacy can occur across a range of expression, including in

those with no or low expression.

As we heard, restricting the indication to PD-L1 CPS greater than or equal to 1 will leave approximately 25 percent of these patients with no other option besides chemotherapy. The current indication allows physicians to make the best possible choice for patients with gastric cancer. Thank you, and we look forward to a productive discussion.

DR. LIEU: Thank you so much.

We will take a brief 10-minute break to allow for the next presentation to set up. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 9:20 Eastern Time.

(Whereupon, at 9:10 a.m., a recess was taken, and meeting resumed at 9:20 a.m.)

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

Applicant Presentation - Mark Lanasa

DR. LANASA: Good morning. My name is Mark

Lanasa, and I'm the Chief Medical Officer for Solid Tumors at BeiGene. BeiGene is a mid-size pharmaceutical company developing innovative medicines for patients with cancer around the globe. BeiGene was founded 14 years ago and has grown into a fully integrated global company with offices around the world. We have a broad portfolio of cancer therapies with two internally discovered globally approved medicines, including tislelizumab, which is the focus of today's presentation.

Additionally, we have over 2,000 employees in the United States and recently opened a state-of-the-art manufacturing facility in Hopewell, New Jersey. I want to thank the FDA, the chair, and the members of the committee for the opportunity to share our results with tislelizumab, and to provide our interpretation for this important discussion.

During this morning's session, I will briefly provide background information about tislelizumab, and will then spend the bulk of my

time reviewing the results from our pivotal study, RATIONALE-305, along with efficacy analyses across PD-L1 expression subgroups. I will then turn it over to Dr. Uboha to provide background on gastric adenocarcinoma and her perspective on the use of tislelizumab in patients with gastric or gastroesophageal junction adenocarcinoma, which we will refer to as gastric cancer or GEJ. We also have additional functional area experts with us today to help to address your questions.

Tislelizumab is a unique anti-PD-1 designed for potent PD-1 binding in robust CD8-positive T-cell activation. Tislelizumab is an Fc engineered humanized IgG4 antibody. Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity. It binds PD-1 at a unique epitope that competitively blocks the binding of both PD-L1 and PDL-2. Tislelizumab does not bind to Fc gamma receptors, and therefore does not induce antibody-dependent cellular cytotoxicity or complement dependent cytotoxicity. These differentiating features enhance the functional

activity of T cells in in vitro cell-based assays.

Our pivotal global phase 3 RATIONALE-305 study, evaluating the efficacy and safety of tislelizumab, combined with standard chemotherapy versus placebo plus chemotherapy, in the first-line setting in patients with locally advanced, unresectable or metastatic gastric and GEJ cancers, was initiated in 2018, and the BLA was submitted to the FDA on December 28, 2023 and is currently under review.

Please note that the primary endpoint of overall survival was tested hierarchically with the primary analysis of the PD-L1 positive group occurring at an interim analysis in October of 2021 and a final analysis of the ITT population in February of 2023. Overall, results from our pivotal study show that first-line treatment with tislelizumab in combination with chemotherapy improved overall survival in patients with locally advanced unresectable or metastatic GEJ adenocarcinoma, and therefore can offer an important treatment option for these patients.

The benefit-risk of tislelizumab in first-line treatment for locally advanced unresectable or metastatic gastric cancer is favorable and is overall consistent with that of currently approved PD-1 inhibitors. We do find that PD-L1 is a predictive biomarker in gastric cancer. Based upon our primary endpoint, the benefit-risk is most reliably established in the subgroup with PD-L1 expression greater than or equal to 5 percent; however, we also observe modest but consistent benefit in patients with expression between 1 and 10 percent. Tislelizumab plus chemotherapy has a tolerable and acceptable safety profile, which is similar to other approved PD-1 inhibitors.

First, I will share with you the design and key efficacy results from Study 305. RATIONALE-305 is a randomized, double-blind, placebo-controlled phase 3 study in 997 patients with histologically confirmed gastric cancer. Overall, the design of the study parallel those of the other approved products in this indication. The study excluded

patients with either HER2-postive tumors or with prior therapy for unresectable, locally advanced or metastatic gastric cancer.

Stratification factors included geographic region of enrollment, PD-L1 expression above or below 5 percent, the presence of peritoneal metastasis, and the investigator's choice of chemotherapy. All patients were required to have at least one evaluable lesion according to RECIST version 1.1, ECOG performance status score of 0 or 1, an adequate organ function and nutritional status.

Patients were randomized 1 to 1 to receive either tislelizumab 200 milligrams or matching placebo administered by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Both treatment arms were administered in combination with physician's choice of standard chemotherapy, either oxaliplatin and capecitabine, or cisplatin and 5-FU.

The primary endpoint was overall survival hierarchically tested first in the PD-L1 greater

than or equal to 5 percent group, followed by testing in the ITT population. Multiple secondary endpoints, including progression-free survival, objective response rate, duration of response, and safety, were also evaluated. Because the primary endpoint was sequentially tested first in the greater than or equal to 5 percent group followed by the ITT population, I will share the data that informed our decision to use 5 percent to define the PD-L1 positive subgroup.

This cutoff was derived from a post hoc analysis of an early-phase, single-arm study of tislelizumab monotherapy administered as second line or later treatment to patients with advanced gastric or esophageal adenocarcinoma. An initial analysis of 46 patients led to the selection of 5 percent in the study protocol. Subsequently, a receiver operating characteristic analysis, based upon objective response rate, confirmed the potential predictive value of 5 percent. In this analysis of 77 patients, which included the initial 46 patients, a PD-L1 value of 5 percent maximize

sensitivity and specificity for ORR.

Next, I'd like to briefly explain the assay used for PD-L1 determination in RATIONALE-305. PD-L1 status for all analyses was assessed using the SP263 assay and scored following the tumor area of positivity or TAP algorithm. Both the TAP and the combined positive score are designed to measure the same biology. The TAP score was developed by Roche Tissue Diagnostics, our companion diagnostic partner.

Key differences between TAP and CPS are that TAP includes tumor-associated immune cells, and the TAP is visually estimated rather than based on cell counting. As a result, TAP can be performed more quickly by the pathologist while retaining interobserver concordance of 95 percent at the proposed cutoff value of 5 percent.

Importantly, although we have confidence in the technical operating characteristics of this validated assay at 5 percent, we also acknowledge the practical challenge that prescribers face due to various assays being utilized by different PD-1

inhibitors, as well as different assays being used at different clinical sites. For this reason, we fully support efforts towards assay harmonization within the class.

Transitioning back to RATIONALE-305 study overview, I will now share the patient demographics and disease characteristics. Baseline demographics were overall well balanced and representative of the target patient population. The median age was 60 years and the majority of enrolled patients were male. Seventy-five percent of the patients were from East Asia, consistent with the global epidemiology of gastric cancer. The remaining 25 percent of patients were enrolled in Europe and the United States.

Our intent was to enroll a larger proportion of patients in the United States, but enrollment in the U.S. became infeasible once the top-line results from the nivolumab study presented in this session became available. Similarly, baseline disease characteristics were balanced and are consistent with the patient population here in the

United States.

The median time from initial diagnosis was less than 2 months. Almost all patients had metastatic disease and approximately 27 percent of patients had prior gastrectomy. Most patients had an ECOG score of 1. Approximately half of all patients had tumors with a PD-L1 score greater than or equal to 5 percent based on the SP263 TAP score. The disease characteristics of this group, while not shown here, were consistent with the ITT analysis set.

Now, let's move on to the primary endpoint analysis. The primary endpoint of overall survival was met in both the PD-L1 greater than or equal to 5 percent population at the interim analysis and subsequently in the ITT population at the final analysis. This is the Kaplan-Meier for the PD-L1 positive population at the interim analysis. The investigational and control arm show increasing benefit over time during the period of survival follow-up.

In the PD-1 greater than or equal to

5 percent population, tislelizumab plus chemotherapy demonstrated a statistically significant and clinically meaningful 26 percent reduction in the risk of death over chemotherapy alone, with a median improvement in overall survival of 4.6 months. In the ITT population, tislelizumab plus chemotherapy demonstrated a statistically significant 20 percent reduction in the risk of death over chemotherapy alone, with a median improvement in OS of 2.1 months.

Importantly, the overall survival with tislelizumab plus chemotherapy in the PD-L1 positive population is supported by improvements in the secondary endpoints. Compared to chemotherapy alone, patients treated with tislelizumab plus chemotherapy had statistically significant prolonged progression-free survival with a 33 percent reduction in the risk of progression or death; a higher objective response rate with an absolute improvement in response rate of approximately 7 percent; and a 1.9-month improvement in median duration of response.

Next, and at the FDA's request to better understand the potential association of PD-L1 expression with survival, we conducted a number of exploratory analyses evaluating subgroups across a range of PD-L1 expression. Here we are showing a forest plot of overall survival across various PD-L1 subgroups using the final analysis cutoff date.

Recall that the analysis of patients with PD-L1 greater than or equal to 5 percent was a prespecified alpha-controlled analysis, so I am showing that subgroup first. The 5 percent cutoff did predict efficacy with an approximate 3-fold increase in overall survival effect among patients with a PD-L1 score greater than or equal to 5 percent when compared to patients with a score of less than 5 percent.

The additional subgroups presented provide additional support for an association between PD-L1 score and magnitude of overall survival benefit as measured by the Cox proportional hazards model. While we propose a PD-L1 score of greater than or

equal to 5 percent based on the treatment effect observed in the prespecified primary endpoint analysis, we also believe that the clinical data across the studies presented today are quite similar, and therefore consistency of labeling within the PD-L1 class is appropriate.

Finally, because TAP and CPS are designed to describe the same biology, we conducted an exploratory analysis to evaluate the agreement between TAP and CPS for overall survival. In this analysis, the same tumor section slides that were stained with the SP263 antibody were scored using TAP and then rescored using CPS. We observed a high level of agreement between TAP and CPS, particularly among lower PD-L1 scores, which are the expression levels most relevant to today's discussion.

Last, I'll briefly review the safety results. Overall, the adverse event profile for tislelizumab plus chemotherapy is consistent with the known safety profile of tislelizumab and other approved checkpoint inhibitors when administered in

combination with chemotherapy for advanced or metastatic gastric cancer. The frequency of treatment-emergent adverse events of any grade, as well as grade 3 and greater, was similar. As expected, a higher rate of immune-mediated AEs was observed in the tislelizumab arm, and the majority of these events were skin or thyroid function AEs. Though not shown here, there was not an association between PD-L1 score and the frequency or severity of IM AEs.

AEs leading to treatment modification were similar between the groups, which indicate these treatment modifications were largely driven by the chemotherapy component. SAEs and AEs leading to treatment discontinuation were more common in the tislelizumab plus chemotherapy group. At this tornado plot, we are showing the most frequent treatment-emergent adverse events of any grade in both the ITT and PD-L1 positive subgroup. The majority of adverse events are commonly observed in this disease and with the chemotherapy component. There is no clear trend of increase of individual

AEs or of AE severity with the addition of tislelizumab.

In conclusion, RATIONALE-305 met the primary endpoint of OS in both the PD-L1 positive and ITT populations. Evaluation of our data suggests that the benefit-risk profile is most reliably established in the PD-L1 greater than or equal to 5 percent group, which was assessed using a prespecified analysis and a validated assay. Multiple secondary endpoints support clinically meaningful improvement within this subgroup.

Additionally, we observed modest but consistent benefit in patients with PD-L1 expression between 1 and 10 percent. BeiGene supports consistency in labeling and in harmonization of PD-L1 testing across the class of PD-1 agents, as it would help provide clarity among prescribers and better support treatment decisions in clinical practice. Overall, the totality of data supports tislelizumab in combination with chemotherapy as an effective first-line treatment option for patients with locally advanced or

unresectable metastatic gastric cancer.

Thank you, and I would like to ask Dr. Uboha to provide her comments regarding gastric cancer and the potential use of tislelizumab in this indication.

Applicant Presentation - Nataliya Uboha

DR. UBOHA: Thank you, Dr. Lanasa, and good morning. I'm Nataliya Uboha, Associate Professor of Medical Oncology at the University of Wisconsin School of Medicine. My expertise is in upper GI cancer, specifically gastric and esophageal. I am also a member of NCCN for gastric and esophageal cancers and Co-Chair of the NCI Esophagogastric Task Force. I'm here today to provide some background on these cancers, the challenge in treating these patients, and my clinical views on the questions posed before you. I have been compensated for my travel but not for my time preparing for today's meeting.

Gastric cancer is an aggressive solid tumor cancer and carries a poor prognosis. Because it is asymptomatic in its early stages, initial diagnosis

commonly occurs when the tumor is already advanced. In the U.S. alone, there are approximately 26,000 new cases of gastric cancer each year and 10,000 deaths. Overall, the 5-year relative survival is only 7 percent for patients with advanced metastatic disease, and, unfortunately, we are seeing an increase in the incidence of gastric and G-junction cancers in young adults, similar to the trends observed in colorectal cancer. Effective frontline treatment is critical to improve the outcomes of patients with gastric and G-junction cancers, and many patients are not able to receive subsequent therapies because of rapid clinical decline from symptoms related to their disease progression.

Anti-PD-1 antibodies are now part of standard treatment for patients with advanced gastric and G-junction cancers, and additional PD-1 inhibitors to chemotherapy in the first-line setting prolongs overall survival in HER2-negative gastric cancer patients and results in more frequent and more durable tumor responses. This

was confirmed in the RATIONALE-305 study, as well as supported by the data from the other sponsors you have seen today. Collectively, data demonstrates that addition of immunotherapy to chemotherapy results in significant improvement in overall survival.

Today, you're being asked whether we can use immunotherapy plus chemotherapy for all patients, or whether we should limit immunotherapy use to those with certain PD-L1 cutoffs. As a clinician who treats these patients every day, hear my thoughts. In RATIONALE-305, there was a clear benefit from adding tislelizumab to chemotherapy. This was greater in patients whose tumors have higher PD-L1 score, but the benefit was also observed in the intent-to-treat population.

In addition, in the subgroup of patients with PD-L1 of 1 percent or greater tumors, we also saw improvement of overall survival, with a hazard ratio of 0.78 in this trial. At the same time, across several studies, we see a consistent lack of benefit from the addition of immunotherapy in

patients with tumors who have PD-L1 less than 1 score.

In clinics, we frequently face the question of how we should approach patients whose tumors have a low PD-L1 score. For example, should patients with PD-L1 CPS 4 be treated differently than those who have a CPS score of 6? For me, in a patient population facing high mortality, this is too fine of a line to draw.

I, along with my colleagues, want to be able to offer immunotherapy to any patient who can potentially benefit. Importantly, from a practicing perspective, a PD-L1 cutoff of 1 or greater should be unified across PD-1 inhibitors, including their use in HER2-positive upper GI tumors. This approach would allow appropriate access to therapy and will preclude offering suboptimal treatments to other patients. Thank you for your attention.

DR. LIEU: Thank you.

We will now proceed with FDA's presentation, starting with Dr. Vaibhav Kumar.

FDA Presentation - Vaibhav Kumar

DR. KUMAR: Good morning. My name is Vaibhav Kumar. I'm a medical oncologist and clinical reviewer at FDA. The purpose of my talk this morning is to consolidate FDA's perspectives on the use of PD-L1 expression as a predictive biomarker when using immune checkpoint inhibitors in patients with HER2-negative gastric or gastroesophageal junction adenocarcinoma. The members of the FDA review team are listed on this slide.

My presentation is structured to outline the data from the three pivotal trials that support the use of PD-L1 expression as a predictive biomarker when deciding to use PD-1 inhibitors in first-line, HER2-negative gastric adenocarcinoma. Importantly for the discussion and consistent across all three trials, despite the use of different biomarker assays and cutoffs, is that there is uncertainty with regards to efficacy in patients who are biomarker negative, especially at a PD-L1 expression of less than 1. We know that all

patients are exposed to the added risk and toxicity from the addition of a PD-1 inhibitor; hence, the need for a contemporary risk-benefit discussion that we're having today.

Throughout today's discussion, the term "PD-L1 expression" or "PD-L1 status" has been repeated on several occasions. This slide does provide a broad overview of the methodologies used for assessing PD-L1 expression by immunohistochemistry across the three studies being discussed. All three methodologies consider cell membrane staining at any intensity as positive for scoring purposes.

Tumor proportion score, or TPS for short, is calculated by taking the number of PD-L1 positive tumor cells divided by the number of viable tumor cells, multiplied by 100. Combined positive score, or CPS, is calculated by taking the number of PD-L1 positive cells, which includes tumor cells, lymphocytes, and macrophages, dividing by the number of viable tumor cells, multiplied by 100. And tumor area positivity, or TAP, is based on

visual estimation of the tumor area, which consists of tumor and any desmoplastic stroma occupied by the PD-L1 positive tumor and immune cells, divided by the tumor area and multiplied by 100.

When we discuss PD-L1 expression as a biomarker, it is important to put into context the timeline for the three studies that are subject of today's ODAC. Using data from clinicaltrials.gov to provide the trial start date, CHECKMATE-649 was the first of these studies to be initiated nearly eight years ago in October 2016 and the initial approval of nivolumab for this indication was in April 2021; KEYNOTE-859 and RATIONALE-305 were initiated in 2018; and the subsequent approval for pembrolizumab and the sBLA submission for tislelizumab occurring last year.

As the data from these and other studies have matured, US-based societies and global regulatory agencies now make recommendation for patient selection based on PD-L1 status. There is heterogeneity in PD-L1-based approaches between FDA and US-based guidelines, which not only poses

difficulties for patients and providers, but also for future drug development in this disease area.

The current FDA label and approved indications for nivolumab and pembrolizumab is agnostic of PD-L1 status. That is to say the approval was based on broader intent-to-treat populations enrolled in the respective studies, CHECKMATE-649 for the nivolumab approval and KEYNOTE-859 for the pembrolizumab approval. Details on efficacy on biomarker defined subpopulations according to PD-L1 expression were made available to healthcare providers in Section 14 of the respective labels.

BeiGene has submitted their supplementary BLA for the use of tislelizumab in combination with chemotherapy for this indication. The verbiage reflects the draft label that was submitted as part of the sBLA. This application is currently under review and the supportive data here are from the pivotal study, RATIONALE-305.

In 2023, the American Society of Clinical Oncology has provided recommendations based on

histology and anatomic location. For patients with HER2-negative gastric adenocarcinoma and PD-L1 combined positive score of 0, ASCO recommendations are for the use of chemotherapy only, without the addition of nivolumab. They recommend that nivolumab be added to chemotherapy with a CPS value of 5 or greater, and for patients who are in between, i.e., CPS greater than or equal to 1 and less than 5, the recommendations for the addition of nivolumab to chemotherapy is to be made on a case-by-case basis; just a note that these guidelines were published prior to the approval of pembrolizumab based on KEYNOTE-859.

The NCCN guidelines do not specifically advocate for the use of chemotherapy alone in patients with a CPS of 0; however, they do provide a Category 1 recommendation for addition of nivolumab to chemotherapy in patients with CPS greater than or equal to 5 and a Category 2B recommendation for patients with a CPS less than 5. For pembrolizumab, the recommendations are that it be added to chemotherapy for patients with a CPS

greater than or equal to 1, with a Category 1 recommendation for a CPS greater than or equal to 10, and a Category 2B recommendation for patients with CPS values between 1 and 10. Another important point to note is that the guidance for patients with mismatch repair deficient and microsatellite instability high tumors are independent of PD-L1 status.

The study designs have already been outlined today and the schema is presented within the FDA briefing document. All of these global randomized-controlled studies share many common elements. I do want to outline some of the key differences between the studies that are relevant to today's discussion.

CHECKMATE-649 was the only study to include patients with esophageal adenocarcinoma and did allow patients with undetermined HER2 status to be enrolled. All three studies included patients irrespective of PD-L1 cutoff, and all three determined PD-L1 expressions and assay centrally, but the assay and algorithm differed for each

study. All three studies stratified randomized patients by PD-L1 status; however, the algorithms TPS, CPS, and TAP, and cutpoints did differ. CHECKMATE-649 and KEYNOTE-859 used a cutpoint at 1, whereas RATIONALE-305 used a cutoff of 5 for stratification.

OS was the primary endpoint in all; however, the hierarchical testing strategy and the primary efficacy populations did differ. CHECKMATE-649 initially compared overall survival in patients with CPS greater than or equal to 5, then 1, and then ITT. KEYNOTE-859 evaluated OS in patients with CPS greater than or equal to 10 and ITT in parallel, then in CPS greater than or equal to 1 and ITT sequentially. RATIONALE-305 prespecified evaluation of OS in patients with TAP greater than or equal to 5 and subsequently ITT.

Before I delve into the study populations of the three studies, I want to point out that further details that include differences in race, ethnicity, and region of enrollment have been outlined in the FDA briefing document. Here, I'll

focus on key proportions that are important to note, especially when we discuss patients, including the pooled analyses that will be presented later.

Approximately 14 percent of patients in CHECKMATE-649 had esophageal adenocarcinoma. The HER2 stages were unknown or not reported in approximately 40 percent of patients in CHECKMATE-649. As mentioned on the previous slide, the prespecified PD-L1 defined patient populations differed in the three studies. For CHECKMATE-649, approximately 60 percent of patients had a CPS greater than or equal to 5. For KEYNOTE-859, 35 percent had a CPS value greater than or equal to 10, and RATIONALE-305, approximately 55 percent had PD-L1 expression levels greater than or equal to a TAP of 5.

Approximately 3 to 5 percent of patients across these studies were known to have microsatellite instability high or mismatch repair deficient tumors. Over the course of the conduct of these studies, we do know that immune checkpoint

inhibitors are highly efficacious in this patient population, and just to reiterate, the discussion from today's ODAC on PD-L1 expression would be focused on patients with microsatellite stable disease, which is the predominant population evaluated across the three studies. The MSI status was undetermined anywhere from 7 to 15 percent of patients across the three studies.

This FDA analysis outlines a different composition of the intent-to-treat populations according to various PD-L1 strata. For this analysis, the raw CPS or TAP score was used to provide patient classification if a particular cutoff was not prespecified in that study, which has analytic limitations.

Patients were all in mutually exclusive strata. Focusing on the dark blue at the bottom, one notes that CHECKMATE-649 enrolled the greatest proportion of patients with PD-L1 expression level greater than or equal to 10, which comprised 49 percent of the intent-to-treat population, whereas focusing on the light gray at the top, KEYNOTE-859

enrolled the greatest proportion of the intent-to-treat population, where the CPS was less than 1, at 22 percent, and RATIONALE-305 had the greatest proportion of patients at the intermediate TAP values between 1 and 10.

Now that we have a sense of similarities and differences in study design and populations across the studies, I'll provide details of efficacy and overall survival in each study, clearly delineating the efficacy findings that were prespecified populations and the exploratory subgroups defined by PD-L1 status.

All three studies demonstrated an improvement in overall survival in the intent-to-treat population with the corresponding hazard ratios for overall survival ranging between 0.78 and 0.8 across the three studies. Now, if you focus on what was the prespecified analysis in the PD-L1 high subpopulations at a cutoff of CPS 5 and TAP 5 for CHECKMATE-649 and RATIONALE-305, CPS 10 for KEYNOTE-859, one can note that it is this population that appeared to derive the greatest

overall survival benefit; and to note also that the prespecified analyses at the lower CPS threshold of 1 in CHECKMATE-649 and KEYNOTE-859 also demonstrated a statistically significant overall survival benefit. This benefit was attenuated when compared to the PD-L1 high analyses specified in that particular study.

The next series of slides will focus on overall survival benefit in PD-L1 defined subpopulations, starting with CHECKMATE-649. Just focusing on patients who would be biomarker positive at a particular PD-L1 threshold, the population with a CPS value greater than or equal to 10 appear to derive the greatest benefit from the addition of immune checkpoint inhibitor with a corresponding hazard ratio of 0.65. This benefit in overall survival appears to attenuate at lower PD-L1 thresholds as we go from 5, then 1, and then ITT population.

Now, if we look at subpopulations who would be biomarker negative at a particular threshold, there is neither convincing evidence of benefit,

nor detriment, in these patient populations, with the point estimates for the hazard ratios being over 0.9. Now, these observations in patients with biomarker negative are similar to the findings in the populations with CPS between 1 and 10; again, the point estimates for the hazard ratios being between 0.9 and 1 with broad confidence intervals.

Visually, the Kaplan-Meier curves demonstrate nicely the observations from the forest plots in the biomarker positive outlined in the top row and the biomarker negative populations in the bottom row. We see the separation in curves in the intent-to-treat population on the left; however, the separation is most marked in patients who have a CPS 10 or greater as seen in the top right, with less pronounced separation of the curves as we work down from our CPS thresholds of 5, then 1. When looking at the biomarker negative population, there is, again, no convincing evidence of either benefit or harm in these patient populations.

Now, focusing on subpopulations in KEYNOTE-859, I want to reiterate that a CPS

threshold of 5 was not prespecified in this study and this population was identified using raw CPS values, which does have analytic limitations. Focusing on the population who would be biomarker positive, consistent with CHECKMATE-649, the greatest benefit appears to be in patients with PD-L1 CPS value of 10 or higher with a corresponding hazard ratio of 0.64. Also consistent is that the benefit appears to attenuate as we go to the lower biomarker positive thresholds and the ITT population.

In terms of the biomarker negative subgroups, patients with a CPS less than 1 have a hazard ratio of 0.92 with broad confidence intervals, once again not providing a strong argument for either efficacy or detriment. The observations for patients with CPS values less than 5 and less than 10 is a little more uncertain, where the observation is of modest benefit, where the hazard ratio is 0.85 and 0.86, respectively, with narrow confidence intervals given the larger sample sizes. The subpopulations in the

intermediate subgroups for KEYNOTE-859, focusing on the 1 to 10 row at the bottom, similar to the biomarker negative populations at less than 5 and less than 10, there is a stronger case for modest overall survival benefit in this patient population.

As one would anticipate, the Kaplan-Meier curves once again demonstrate that the greatest separation in curves are in those patients with CPS 10 or higher on the top-right of the screen, and the separation attenuates as you move left across cutoffs towards the intent-to-treat population. There does not appear to be any separation of the curves in patients with CPS less than 1, whereas that's not the case when we look at patients with CPS less than 5 and less than 10, where there is some separation, especially at the tail.

Now, focusing on RATIONALE-305, consistent with the other two studies is that patients with a TAP value of 10 or greater appear to derive the greatest benefit with a corresponding hazard ratio

of 0.57, and this benefit attenuates if we look at patients with lower TAP values. Focusing attention on the biomarker negative subgroups, at each of the TAP 10, 5, and 1 thresholds, there is no convincing argument, once more, for either efficacy or detriment in these subpopulations, similar to the findings that I discussed for CHECKMATE-649. In patients with intermediate PD-L1 expression between 1 to 10, there is, again, no clear evidence of benefit or detriment in these exploratory subgroups.

The Kaplan-Meier plots graphically demonstrate the consistent theme that I presented with the other two studies, where in the top row we see the greatest separation of the curves in patients with TAP 10 or greater and with less pronounced separation as we get to the ITT population on the left; and in the bottom row in the biomarker negative population, there really does not appear to be any true separation of the curves, especially for patients with TAP values of less than 1.

In order to anchor this risk-benefit discussion, all patients are exposed to the risks of added toxicity from the PD-1 inhibitor, and the safety of the addition of the immune checkpoint inhibitors is not known to differ across PD-L1 strata. Across the three studies, what we note is that the addition of a PD-L1 inhibitor to chemotherapy will add anywhere from 3 to 11 percent increase in the proportion of patients who experience a grade 3 or 4 treatment-emergent adverse event.

The incidence of immune-mediated adverse events was approximately 30 percent, and we know that the majority of these are low grade and endocrine; however, we know that up to 10 percent of patients will experience grade 3 or 4 immune-mediated adverse events, and these are predominantly non-endocrine events of dermatitis, pneumonitis, colitis and hepatitis. Unfortunately, there were also fatal immune-mediated adverse events, and although the incidence is thankfully low, we would not want to expose patients to these

notable risks if they're not expected to have the benefit gains from an immune checkpoint inhibitor.

Also, to help facilitate the global risk-benefit discussion across PD-L1 strata, we conducted a pooled patient-level efficacy analysis in patients with known microsatellite stable gastric or GEJ adenocarcinoma, excluding patients with MSI high disease and those with esophageal adenocarcinoma. This analysis was stratified by study.

Now, before I go over the findings, I would want to acknowledge the notable caveats of a pooled analysis such as this. Firstly, the acceptability of combining data from patients defined using different assays and the interoperability of this approach has not been determined. Similarly, the studies use different PD-L1 cutoffs, so the analytic validity of presenting these uniform PD-L1 strata has also not been determined. Additionally, the data is limited to the pooled populations that FDA has access to and excludes global studies that are being conducted, which risks the introduction

of bias.

With those caveats in mind, our pooled population excluded 211 patients from CHECKMATE-649 that had esophageal adenocarcinoma; 8 patients who were HER2 positive, including one patient from RATIONALE-305; 155 patients with known MSI high or mismatch repair deficient tumors; and 435 patients with unknown MSI status were excluded. Ultimately, this gives us 3,348 patients that were pooled, approximately 35 percent from CHECKMATE-649, 38 percent from KEYNOTE-859, and 27 percent from RATIONALE-305.

This is the forest plot of the PD-L1 subpopulations from the pooled analyses. Consistent with a theme when presenting the study results individually, we note that patients with PD-L1 expression of 10 or greater derived the greatest benefit with a hazard ratio of 0.64, and that this estimate of benefit attenuates at the lower thresholds of 5, 1 in the overall population.

When we discuss efficacy findings in the biomarker negative populations, I do want to point

out that 17 percent of patients would be classified as biomarker negative at a PD-L1 expression of 1, 45 percent at a PD-L1 expression of 5, and 62 percent at a PD-1 cutoff of 10 in this pooled data. In terms of estimates of benefit, the hazard ratio for PD-L1 less than 1 is 0.91, similar to the observations of PD-L1 less than 5 and 10, where the confidence intervals are narrower given the larger patient populations.

When we discuss patient population with PD-L1 expressions between 1 and 10, comprising 44 percent of the pooled patients, the estimates for efficacy in this patient population are similar to that of the biomarker negative subgroups, with the point estimates for the hazard ratio for the 1 to 10 subgroup being 0.93.

In my presentation, I provided an overview of FDA perspectives and analyses of three pivotal first-line studies submitted to FDA that argue for PD-L1 expression being a predictive biomarker when deciding to utilize an immune checkpoint inhibitor in patients with HER2-negative advanced gastric

adenocarcinoma. I've outlined concerns at the agency of modest estimates of efficacy, especially in patients who have PD-L1 expression of less than 1. These patients are, of course, exposed to the added toxicity of PD-1 inhibitors, and it is this patient population that is of predominant focus of our risk-benefit discussion.

FDA would like the committee to discuss whether in patients with HER2-negative microsatellite stable gastric/GEJ adenocarcinoma, does the cumulative data support the use of PD-L1 expression as a predictive biomarker when selecting patients for treatment with PD-1 inhibitor? And for the voting question, is a risk-benefit assessment favorable for the use of PD-1 inhibitors in patients with advanced HER2-negative microsatellite stable gastric/GEJ adenocarcinoma in patients with PD-L1 expression less than 1?

Now, although we're specifically asking about the cutoff of 1, we invite you to express your opinions if you believe another cutoff would be more important. Thank you.

DR. LIEU: Thank you.

We will 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 10:15 Eastern Time.

(Whereupon, at 10:02 a.m., a recess was taken, and meeting resumed at 10:15 a.m.)

Clarifying Questions

DR. LIEU: 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. Just some notes for those in the room, if you have a question, please turn your name placard sideways so that we can see that; and also, because we have three applicants in the room, please direct your specific question to a specific applicant. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your

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

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

Are there any clarifying questions for the presenters?

Dr. Hawkins?

DR. HAWKINS: Thank you very much. I have two questions at this time. The first one has to do with better testing for PD-L expression, and this is directed to Dr. Anders and Dr. Janjigian.

It's a bit concerning about the variability in testing, so my question to Dr. Anders, or both of you, is whether we can be optimistic about better testing. Is there an ability to think about artificial intelligence helping us in some way, given the the statistics you showed us about the

pathologist? Then, I noticed when you talked about different testing, Dr. Janjigian talked about how they create their own PD-L assay question. Thank you.

DR. ANDERS: Thank you. Robert Anders, Johns Hopkins pathology. Thank you for your question.

Can I have slide 1, please? My understanding is you're asking is there hope in the future for better methodologies? Well, those methodologies are trained by a gold standard, and the gold standard is the pathologist read, so it's a little bit of a back and forth where we're only as good as how we can train. As you can see from the graph there, a patient's eligibility at one of those cutoffs at 5 and 10 may be determined by which pathologist looks at it.

DR. HAWKINS: Does that mean that we should not be optimistic?

(Laughter.)

DR. ANDERS: We need a better gold standard; response.

DR. HAWKINS: Any studies on artificial intelligence helping us?

DR. ANDERS: They're trying, and there's a huge push on it. We're working on it.

DR. HAWKINS: Thank you.

DR. JANJIGIAN: Hi. Yelena Janjigian. Thanks for that question. I guess we can bring up slide 22, CG-22. I'm glad you picked up on this. Yes, lab-developed tests means that a clear approved laboratory can validate in a small cohort of samples another antibody to use, and as long as they prove a certain level of concordance, most institutions are allowed to decide what IT tests they will use. Some of these -- for example, 22C3, Dako technologies -- are considered relatively outdated, I guess, and the readers and the standards, most institutions won't invest in buying these older machines; at least that's what the pathologists tell me, and we have a pathologist here to comment on that.

There is a learning curve, and even at an institution like ours, we use our own lab-developed

tests, and I can tell you, we expect, for example, to have a certain rate of PD-L1 CPS score of 5 or greater, or 10 or greater, and 1 or greater. There was a steep learning curve in our testing. When I did the analysis review of our clinical samples initially when the testing first began, the rate of positivity was significantly lower than we would have expected from several phase 3 studies. Some of the studies you saw here, but also other studies coming out, such as with other agents, PD-1. Each company has a PD-1 inhibitor. But that's my big concern, is that there is variability in testing.

In terms of your question about AI, AI is excellent in certain things. These type of samples are quite heterogeneous, and I honestly don't think in my lifetime as an oncologist, we will be able to replace experts and pathologists with machines because they're able to tell us how good the quality of the sample is and where to look.

I don't want to undermine the quality of the biomarker work that's been done by these companies, but we don't have a controlled environment with two

trained pathologists sitting in the same room looking at a tumor block that was an entry criteria. The trials mandate that tumor quality has to be a certain level for them to even enter into a clinical trial. In clinical practice, anyone with one slide that says cancer can come in and start therapy, and we do start therapy because it's urgent. So it's a different situation.

DR. HAWKINS: Thank you both.

I can circle back around. I have another question, but I don't want to hog the mic.

DR. LIEU: Thank you, Dr. Hawkins.

Dr. Spratt?

DR. SPRATT: Thank you so much. Dan Spratt, Case Western. A couple questions, and I made them very direct. To the FDA, did you perform any interaction tests given the question at hand; is this a predictive biomarker?

DR. ZHANG: Thanks. Yiming Zhang, the statistical reviewer of FDA. Yes, we did do the interaction effect test. We added one treatment by continuous interaction term to the stratified model

in the pooled analysis, and the interaction effect is statistically significant. But here I would like to acknowledge this is the unprespecified analysis, and we caution to interpret the statistical significance here and the direction of effect showing increasing treatment benefit in the PD-L1 high subgroups.

DR. SPRATT: Appreciate it. Thank you so much, and a question for BMS. This can go to Dr. Anders as well.

It's understandable why you showed your study. There's a study that just came out in June of 2024, first authors, Dr. Klempner who leads the MGH program, and the pathologist from MSKCC is on this paper. They show that across all three approved assays, there is moderate to almost perfect intra-assay kappas, as well as substantial almost perfect intra-assay agreement in gastric cancer.

So can you please explain this, especially focusing on outcome is what matters? And we are seeing the outcomes vary by PD-L1 expression level,

so clearly the pathologists can't be that wrong here given the interaction effect is statistically significant.

DR. ANDERS: Sure. Again, Robert Anders, Hopkins pathology. Thank you for the question, and, indeed, one of my slides, I showed data from the Klempner paper with the staining, so I am aware that they showed good concordance. Now, we stepped back in our study and took the people who are scoring this every day, and we consider those to be experts, and we just had poor agreement. Now, what I do think we can agree on is if there's any PD-L1 expression. When we start to move above the thresholds, that's when the agreement begins to really fall apart.

DR. SPRATT: The agreement in that study for greater than 5 or greater than 10 was around 0.75 to 0.8, just putting it out there, but I appreciate it.

DR. ANDERS: And again, there was a concomitant study done by Dr. Rimm, and we came to the same conclusions.

DR. SPRATT: Thank you so much.

The final question is going to be whoever from Merck feels it's appropriate to answer. You put in the briefing documents Q-TWiST analysis that wasn't presented here, but this basically is an analysis that's trying to weigh toxicity versus progression and benefit. You show the intention to treat, and the cutoffs are greater than 1 and greater than 10 staining; however, do you have these analyses for less than 10 or less than 1, given that most of the patients in greater than 1 in the intention to treat are enriched for the high PD-L1 expressing levels?

DR. PIETANZA: Cathy Pietanza from Merck. We have done Q-TWiST analyses in all CPS cutpoints. Slide 1 up, please. This shows the entire population in the greater than 1 and greater than 10. So for others that didn't read the background package, Q-TWiST combines efficacy, safety, and quality of life in single measure. We performed Q-TWiST analysis to evaluate the quality and the quantity of overall survival, classifying time

spent for toxicity and without toxicity before progression, as well as time after progression.

You can see here that in the ITT, the 20.9, the relative Q-TWiST shows an improvement. In the literature, a relative Q-TWiST improvement of 10 percent or greater is clinically important and a gain of at least 15 percent is clearly clinically important.

DR. SPRATT: Thank you. But, again, given almost all these are just enriched for high PD-L1 expression, do you have it for less than 10 or less than 1?

DR. PIETANZA: Yes. We have it. Slide 2 up, please. I will actually have Senaka Peter explain this a little bit further.

MS. PETER: Senaka Peter, Merck, epidemiology. I think we had a nice explanation of what Q-TWiST is. So as you can see here, based off of the clinically important cutpoints, we do see that relative Q-TWiST gain in ITT and other cutpoints that are of interest. Of course, in those that are less than 1 and less than 10,

there's a small sample size for these subgroup analyses. So while there's relative gain, they are not clinically important.

DR. SPRATT: Thank you so much. That concludes my questions.

DR. LIEU: Thank you.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan. This is another question for Dr. Anders. I wanted to pressure test this idea of the dichotomous variable versus the continuous variable here. You had said that you think the pathologists have good concordance as to whether PD-L1 is positive or not. If you could please pull up slide CG-27, again, this high in terms of variability.

Are you able to quantify what percent of pathologists, let's say, would have scored patients as greater than 1 based on your data here? And also, how does that compare to other cancer types, just as a gestalt?

DR. ANDERS: Yes. Thank you again. Robert Anders, Hopkins pathology. We have a distribution

curve of the positivity rate. I will say that a majority, about at least 50 percent of the patients, the 100 samples that we've looked at, fell within the 1 or greater, So I would estimate maybe 20 or 30 percent were below. I don't have -- but I guess we could pull that number for you -- what percentage of pathologists called something positive.

DR. VASAN: Because it seems that there's clearly a spread greater than 1 just from looking at the entire individual data points, certainly the number between zero and 1 for each individual patient I think is a smaller number.

DR. ANDERS: Yes, that's a very important observation. If there's absolutely no staining, there's no brown color, that's easy; that's zero. What happens is when there's some staining, but it might be just a little bit where it's not nearly enough to count for 1 percent, we're left in this limbo saying, "Well, we can't say it's nothing," so we sort of compromise and have that, let's call it a half, as saying, "Well, there is staining, but it

doesn't meet this 1 for 1 threshold."

DR. VASAN: Okay. Thank you.

DR. ANDERS: You're welcome.

DR. PIETANZA: I'd like to invite Dr. Janjigian, as she has another comment.

DR. JANJIGIAN: Yes. I just wanted to comment on the Klempner question. The purpose of that paper was to really look at resected surgical samples, so it's 100 surgical samples, not what we see in the clinic. And also, the purpose of it was to look at 22C3 28-8 with SP263 antibody, compare those, and also to see if CPS and TAP is comparable.

So it's very different to what we see in the clinic. Yes, you can tell if something is completely zero, but again, often when that happens, if I call the pathologist and I clarify with them how many cancer cells, or any stroma even, in that sample, often the answer is, "Well, very few cells." So we can't look at the surgical database and extrapolate that to clinical practice because most of our patients don't have surgeries.

They present with small endoscopy samples with stage 4 de novo diagnosis.

DR. LIEU: Dr. Meyerhardt, do you still have a question or is your question already answered?

DR. MEYERHARDT: Yes, it was already answered.

DR. LIEU: Okay.

Dr. Dodd?

DR. DODD: Yes. This is Lori Dodd. My question is for Dr. Anders. There's been a lot of discussion and data presented about the inter-observer variability. You also mentioned the spatial variability, spatial heterogeneity, and I didn't see any data that really speaks to the degree of spatial heterogeneity and the factors driving that heterogeneity.

Are there data that can support that, and is the heterogeneity driven, or does it result in differences in the quantitative assessment of the PD-L1 expression; or is there also heterogeneity in the evaluation of presence or lack of expression of PD-L1?

DR. ANDERS: Okay. Great. Bob Anders, Johns Hopkins pathology. Can I have slide 1?

So there was no quantification. I have not seen quantification of heterogeneity. That's part of the reason I wanted to show this particular slide. The expectation for a CPS score on that particular slide would need to count all of the cells, whether they're positive or negative. So the CPS doesn't really have any leeway for heterogeneity or a way to account for it.

Dr. Waxman?

DR. DODD: And just to clarify, though, if there were multiple samples taken, multiple biopsies taken, do we have any information about the degree of variability across multiple samples taken from the same patient?

DR. ANDERS: Right. Most of our biopsy samples are just like the pink area up there and would be endoscopic, very superficial. It's typical in my reports that I will give feedback to the endoscopist and say, "Two of the 5 endoscopic biopsies contain invasive gastric carcinoma." So

there is tremendous variability and largely undersampling in those samples.

DR. WAXMAN: Ian Waxman, BMS. If I could just add, to answer your question, Dr. Dodd, about spatial heterogeneity, we do have data for metastatic versus primary sites, and there are differences. I can call Sarah Hersey from our precision medicine group just to take you through a little bit of those data to support that.

MS. HERSEY: Sarah Hersey, Bristol-Myers Squibb, precision medicine. I'll start off first by sharing with you slide 2, which shows PD-L1 expression is dynamic. And in this publication, what you'll see is within the same patient that was sampled, they took both primary and metastatic sampling, and what they found was that the agreement was only 61 percent. That was regardless of if it was a CPS 1 or CPS 10 cutoff. In our own clinical trial, we did an exploratory ad hoc analysis of the data, and I would caution that the sample numbers were small, but we did see differences there, as well, between primary

metastatic sampling. Thank you.

DR. LIEU: Dr. Dodd, does that answer your question?

DR. DODD: Yes. Thank you.

DR. LIEU: Dr. Hawkins?

DR. HAWKINS: Thanks again. This is a question about the quality of life, and it's directed towards Drs. Bhagia and Janjigian, Merck. And I apologize; a person from BeiGene also mentioned quality of life, but I missed that name because I came back in a little late.

So my question is, folks want to live; that's why they're involved in these trials, and they want to live as long as they can. We saw information about adverse events. My question is not about adverse events. My question is about, did you do any quality-of-life objective assessments, and if you did, what tools did you use? Can you share some of that with us? That's my question.

DR. LANASA: Mark Lanasa, BeiGene. We did collect quality-of-life data in the RATIONALE-305

study, and I'll share those data. We collected a battery of general quality-of-life assessments through QLQ-C30 scores, as well as disease-specific data in QLQ-STO22 domains for gastric cancer. What I'm showing here are the C30 scores. This is the time to detriment hazard ratio. You can see that there's a slight favoring of the combination of tislelizumab with chemotherapy across these domains.

DR. PIETANZA: From Merck, we'll have Dr. Yanfen Guan actually respond to this question, followed by Dr. Janjigian.

MS. GUAN: Yanfen Guan, patient center endpoints and strategy for Merck. At Merck, for KEYNOTE-859, we also use the EORTC QLQ measures for quality-of-life assessment, and these are well-established cancer-specific, validated PRO measurements. We can show the calculated quality of life over time for the GHS/QoL.

For our study, the patients completed the questionnaire during treatment, and at baseline, the scores of the health-related quality of life

were similar to the general cancer patient population. Slide 3 up, please. During treatment, the quality-of-life scores were generally stable and similar between the treatment arms, as indicated by the overlapping confidence intervals. No decrement was observed with the addition of pembrolizumab to chemotherapy compared to chemotherapy alone. So this data supported the overall benefit-risk profile. Thank you. Slide down, please.

DR. PIETANZA: Dr. Janjigian?

DR. JANJIGIAN: Yes. We care about quality of life, and it's very important because this disease is incurable and most patients need to live lifelong with it. When you think about quality of life, obviously cancer-related symptoms is what drives it. In my experience, the patients typically respond within the first 2 to 3 cycles, so the quality of life does improve. I think most of the side effects, as I mentioned, come from the chemotherapy. The addition of immune checkpoint blockade has very minimal impact on the quality of

life, and overall, it remains adequate and perhaps more improved, although the confidence intervals overlap.

Again, , I don't want to make this too anecdotal, but when you think about quality of life, for these patients it's about mental state of continuing therapy lifelong, and to have this hope of having long-term survival with immune checkpoint blockade, immediately lightens the atmosphere in the room and gives them the strength to keep going. I think that you can't capture it on the quality-of-life questionnaire, but I think it is a factor with these patients.

DR. WAXMAN: Ian Waxman, BMS. We also collected quality-of-life data. We used a different instrument, the FACT-Ga. Can I have slide 1, please? Just to remind this audience, this is a 46-item questionnaire that covers 5 subscales, one of which is specific to gastric cancer, the other four of which are covered by the more general FACT-G.

If I can now have slide 2, please? What we

saw was that quality of life was at least maintained in every subgroup, and you can see this includes the CPS less than 1 population, albeit small numbers for that subgroup.

DR. HAWKINS: Thank you very much.

DR. LIEU: Dr. Spratt?

DR. SPRATT: This question I'll direct to Dr. Janjigian. Can you explain in that we see very clear, with every single one of these drugs, a difference in relative benefit based by the CPS or TAP score; very clear. Two of the companies actually in the presentations admitted it's predictive in their talk; statistically it's predictive, so clearly, these scores are correlating with outcomes.

So can you please explain when you state -- and I'm hearing from Dr. Anders -- there is such spatial and heterogeneous outcomes, we have poor inter-reader variability, but yet it is consistent by drug, by pathologists, by assay. Can you explain that?

DR. JANJIGIAN: Yes.

DR. SPRATT: Because it should just be random if it's that poor of correlation.

DR. JANJIGIAN: Yelena Janjigian again, medical oncology. We're making a distinction between population-based biomarker versus a clinical biomarker in the real world. I'm a researcher. I am all for biomarker testing. I think it's important to be able to translate what you discovered in the clinical trials to the clinic, and as I mentioned earlier, it's the quality of the sample and the quality of the testing.

You didn't see the data on screening failures from CHECKMATE-649 and KEYNOTE-811. I was the global PI for both of these studies, and I can tell you, many patients did not make it on to the trial because their tumor quality was insufficient, and those are the people that will never know if their PD-L1 testing was conclusive; so to understand that it's not black and white but it's a spectrum.

We're not saying that everybody should get

everything and they should get it at CVS. We're just saying let the doctors decide what patients actually would benefit. The data suggests that doctors are actually pretty good at following ASCO and NCCN guidelines, and they're not overtreating the patients. It's the patients who come in, as I mentioned, with unavailable sample or the sample quality is poor. It's a lot of barriers to getting these patients started on therapy.

DR. SPRATT: Thank you. Again, this is Dan Spratt. It didn't really address the question because you're talking about the real world, but we're talking about here. The question is, in these studies, you have the tissue; you reviewed it. Is there strong correlation, or not, between pathologists? And if there's not, why is there such strong correlation to outcomes? A separate whole question is real-world applicability.

DR. JANJIGIAN: Sure. I mean, I think we are talking about the real world because we're not in a trial --

DR. SPRATT: That's actually not the

question I'm asking.

DR. JANJIGIAN: -- but I'll let perhaps --

DR. SPRATT: And these drugs you're presenting --

DR. JANJIGIAN: -- pathologists answer that.

DR. SPRATT: -- are from clinical trials, not the real world.

DR. PIETANZA: So I'll have Dr. Chizhevsky answer that question, Dr. Spratt.

DR. CHIZHEVSKY: Thank you. Vladislav Chizhevsky, anatomical pathologist, diagnostic reference laboratory. Yes, a very good question. The idea is that in a clinical trial, the pathologists were trained specifically for the score, and the reproducibility was great in the clinical trials. It was mentioned before, patients who did not qualify under the three criteria did not make it into the trial. So in the clinical trial, it's represented very well from the score to the response, as you can see it clearly.

In the real world, as we tried to point out, there are different issues that come up. These

issues have been brought up before, and they are very specific and very important issues; however, I just wanted to point out these issues are not specific to PD-L1, they are not specific to the score of a CPS or TPS, and they are not specific to the organ; and yet, we see in numerous examples, we have HER2 in breast cancer that over time we've standardized it. We were able to show that there is a reproducible effect, and the same thing should apply here.

What we're lacking right now is a standardization of scoring. We have LDTs. We have different clones. We need a standardized scoring. We need to standardize the practice of doing it. For example, biopsies in breast are OH [indiscernible - 3:13:47] negative, followed by resection scoring. I understand it's not always possible in clinical trials, but some sort of standardization should improve the overall response from pathology to the clinical practice. Thank you.

DR. SPRATT: Much appreciated. Thank you.

DR. LIEU: Dr. Gibson?

DR. GIBSON: Michael Gibson. Thank you, Chair, for the time. I defer if my question is for a different part of the session, but I'm new to this, and just a few thoughts. It sounds like we're trying to decide, as we always do in clinical medicine, a risk-benefit ratio, and we're using data which is, number one, subjective. We have a patient advocate here who could maybe comment more on what quality of life really means in the real world.

But secondly, the main conclusion I have is that our assay is extremely flawed for many reasons but, unfortunately, we have to use what we have.

DR. LIEU: And, Dr. Gibson, we'll certainly discuss --

DR. GIBSON: Thank you; appreciate that.

DR. LIEU: -- the question.

DR. GIBSON: Sorry about that, Mr. Chair.

DR. LIEU: Do you have a specific question?

DR. GIBSON: No. I did just have a question regarding if the panel thought that as we have a

constant adverse event effect across CPS levels, and your benefit is inversely proportional to the expression, is there a concern that the risk-benefit ratio shifts as you move closer and closer to a CPS of 0, and is that something you consider in your decision?

DR. LIEU: And, Dr. Gibson, do you have a specific question for the FDA or an applicant?

DR. GIBSON: I'm sorry. I apologize.

DR. LIEU: Oh, no; otherwise, I'm sure we will definitely get there --

DR. GIBSON: Okay. Thank you very much.

DR. LIEU: -- for the panel discussion for sure.

Sure. Dr. Lemery?

DR. LEMERY: Sure, exactly. That's what we're getting at is, if there is no benefit and you have toxicity, well then, that certainly is a different situation, where you'll have toxicity -- let's take the CPS greater than 10 with its clear benefit. That trade-off is clearly you would take the drug. I don't think anyone would go

against that here, but certainly the trade-off does change as you go down, and that's what we're asking for you to consider.

DR. GIBSON: Thank you for your patience with me.

DR. LIEU: Yes. Thank you. Thank you both.

Dr. McKean?

DR. McKEAN: Heidi McKean from the community oncology setting. Looking through the data and hearing the presentations today, we can clearly see that there's a significant risk for toxicity. So if we're looking at treatment-related AEs, especially immune mediated, some of the studies would say a 30 percent chance that these patients are going to get immune-mediated side effects. But then looking at the hazard ratio for patients with CPS less than 1, it seems like the benefit for those particular patients is likely less than 10 percent.

So we heard from BMS and BeiGene about potential recommendations about looking at continuing approval for patients with CPS greater

than 1. My question is for anybody on the Merck team. How do you justify treating these patients with CPS less than 1 with immunotherapy when it seems they would have a higher risk for side effects than benefit?

DR. PIETANZA: Thank you. Cathy Pietanza from Merck. We understand that this is a very important question that we're here to address today. When we look at our data, we look at the overall clinical risk-benefit for the entire treatment population, as well as subgroups, and here, we did look at PD-L1 less than 1. When we see that the hazard ratios are consistent with the intention-to-treat population, we have acknowledgement that the entire patient population is benefiting.

We recognize the magnitude of benefit may be less than CPS less than 1; however, the hazard ratio was less than 1, and PD-L1 is a continuum, and the score does not predict who will respond. There are patients with low to no expression that respond and there are patients with high PD-L1

expression that respond. We acknowledge that the safety is an issue; however, the safety of pembrolizumab across all PD-L1 subgroups was the same and maintained, as was health-related quality of life.

Merck really wants to keep the label as it is because it gives patients an option, and it gives physicians an option in clinic when faced with a patient with a fatal disease to make that decision. The label has the information, as does the NCCN, ASCO, and ESMO guidelines. Guidelines can help guide the physicians. Having a full label or having a broad label will enable the option for all patients.

DR. LIEU: Does that answer your question, Dr. McKean?

DR. McKEAN: It does. Can I ask one more question?

DR. LIEU: Sure, if it would be brief, though. We're starting to run out of time here.

DR. McKEAN: Oh, sorry.

My question is about those NCCN guidelines.

Are you, all three companies, seeing across the country that if NCCN categorizes a recommendation as Category 2B, that insurance will not cover those medications?

DR. PIETANZA: I would have to ask Dr. Janjigian because I no longer see patients in clinic.

DR. JANJIGIAN: Sorry. Can you clarify the question? The question is whether or not NCCN guidelines affect the practice?

DR. McKEAN: Correct. If the medication is categorized as Category 2B, insurance companies are starting to not cover that. Are you seeing that around the country?

DR. JANJIGIAN: A bit. I think it depends on the pair. Typically, a phone call to the insurance company, that clears that up, though. Again, it's a case-by-case basis. Most of the time if it's a negative case and we think that tumor quality is sufficient, we would not prescribe immunotherapy; so for CPS, completely negative cases. So it's a rare occurrence that we have to

deal with this.

DR. LANASA: Mark Lanasa, BeiGene. I'd like to invite Dr. Uboha to share her experience.

DR. UBOHA: Nataliya Uboha, University of Wisconsin. I would like to echo that it's very important what actually makes NCCN guidelines. The insurance companies do pay very close attention to what's on the guidelines, and we are running into more and more struggles with having limited access for the patients to medications because of how the medications are ranked on the guidelines.

DR. LANASA: Thank you.

DR. LIEU: Does that answer your question, Dr. McKean?

(No audible response.)

DR. LIEU: Thank you.

Dr. Hillard?

DR. HILLARD: Yes. This is a question for the Merck team. If you could put up the slide, which was the OS and PFS, directionally consistent across all the cutoff points.

DR. PIETANZA: Can we have the forest plot

from the key presentation? Slide one up, please.

DR. HILLARD: Yes. This is what I wanted to see if I'm interpreting correctly; that in general, with all of the studies we've seen, there is a positive overall correlation that would appear between the PD-L higher cutoff points and a better response. On the other hand, if I'm reading this correctly, even the people with the score of less than 1, still most of them did benefit. So again, if we were just looking at this as a single point, well, that's not statistically significant, but then again, neither is the space between 5 and 10.

I guess from a patient perspective, I would like to have the option of trying these based on these numbers. And also, based on the numbers, the level 3 and 4 side effects were only 3 to 11 percent greater with the immune checkpoint inhibitors. So is that a correct way to think about it?

DR. PIETANZA: Yes, that is the way Merck is thinking about it, and there are patients that do benefit, although the magnitude of benefit is less.

But there are patients that do benefit, and we want to maintain that benefit for some patients with this fatal disease.

DR. WAXMAN: Can I add to that?

DR. LIEU: If we can keep the comments short, please.

DR. WAXMAN: Yes. We've actually looked with our longer follow-up data -- we have 4-year follow-up data now -- and in that specific 1 to 10 population where there's the question, we do see improved overall survival hazard ratio now with separation of the curves that was not there at the initial time of the lock. And we have that Kaplan-Meier, and I can pull it up for you in just a second. But what it does show -- slide 1, please -- just very briefly, on the left-hand side of this slide, you'll see the Kaplan-Meier for the 1 to 10 population at the time of the initial lock, and then with the 4-year follow-up, a clear separation with significantly less censoring, hazard ratio decreased to 0.88.

DR. LIEU: Dr. Hillard, does that answer

your question?

DR. HILLARD: Yes.

DR. LIEU: Dr. Madan?

DR. MADAN: Sure. As we kind of grapple with this, I'm trying to understand this kind of binary cutoff of 1 and what it means. We focused a lot on the toxicity it brings those patients who are below 1. I think another relevant part is the missed benefit in those patients below 1 who could get treated and get benefit.

I'm not sure the best way to understand that, but is there response rate data from the patients who have the lower scoring? I don't know if you guys showed -- because we've been looking at this as largely a population, and clearly the higher expression, the population is going to do better. But do you guys have response rate data from these low expressing patients?

DR. WAXMAN: Ian Waxman, BMS. We do have response rate data in the CPS less than 1 population, and we can pull that up for you as we're getting that slide. Slide 1, please. What

we see here is improved response across all PD-L1 subgroups, including in the CPS less than 1, so about a 7 and a half percent improvement in response in that particular population with all the other cutoffs listed here as well.

DR. PIETANZA: Sorry. Cathy Pietanza with Merck. Slide 2 up, please. Here again, as Dr. Bhagia explained, patients in the less than 1 subgroup have an improved progression-free survival. The median progression-free survival improvement was about one and a half months with increased objective response rates for these patients and an improvement in median duration of response compared to chemotherapy alone. So these are also important clinical endpoints for patients.

DR. LIEU: Dr. Lanasa?

DR. LANASA: Mark Lanasa, BeiGene. Here we're showing a forest plot of objective response rate across all the groups being discussed today. You can see that the objective response rate is favorable, does favor the investigational arm across all these groups, though the confidence

interval is very, very wide in the less than 1 percent group, and the incremental increase in response rate is relatively modest between 1 and 10 percent.

DR. LIEU: Dr. Kumar, did you have a response or a question?

DR. KUMAR: I just wanted to add to Dr. Hillard's point about less than 1 populations, and BMS' response specifically with the Kaplan-Meier curve for the 1 to 10. If BMS wouldn't mind, just for Dr. Hillard's benefit, also showing the Kaplan-Meier curves for the less than 1 with the prolonged follow-up.

DR. WAXMAN: Sure. We can pull that up for you. As that's coming up, in the less than 1 population, the hazard ratio remains close to 1, in the 0.9 range, but let me get the latest version of that up for you here. Slide 1, please. While we saw that improved hazard ratio in the 1 to 10, we did not see that same improvement in the CPS less than 1. Here's the original, as well as the 4-year follow-up.

DR. KUMAR: I just wanted to clarify that because that was a specific question that Dr. Hillard had.

DR. LIEU: Thank you, Dr. Kumar.

DR. KUMAR: Thank you.

Dr. Meyerhardt?

DR. MEYERHARDT: This question is for Dr. Anders. Both during the presentation and question and answer, you indicated that you feel confident that pathologists are pretty good at less than 1. We've also heard multiple times about the concern that a lot of these patients with metastatic disease have very small biopsies or just mucosal [indiscernible - 3:27:57] biopsies. So I just want to know if that statement holds for people with a small biopsy versus a whole tissue resection.

DR. ANDERS: Yes. Robert Anders, Hopkins pathology. Thanks. The requirement for CPS is that there are 100 cancer cells to be present. That's the minimum for the score. If the tumor cells are present, I feel confident that we can

mediate whether there's positive or negative. In fact, if there are fewer cells, it might actually be a little bit easier. But my concern is that smaller samples or superficial endoscopic samples underrepresent the tumor. So we look at it, we do everything perfectly, and everybody agrees that it's zero in that sample, it's that the biology really is in the deeper invasive edge of the cancer.

Does that answer your question?

DR. MEYERHARDT: Thank you.

DR. LIEU: Dr. Lemery, did you have an additional response?

DR. LEMERY: Yes. Thanks. Steven Lemery. I wanted to just respond a little bit to response rate PFS discussion. Again, with PD-1 inhibitors, we've seen funny things with response rate with not good correlation between different effects and response rate and survival, and they go both ways. Sometimes you'll see benefits in response and no benefit in survival, and sometimes you see the opposite.

So I think we have to be careful with reading too much about these response rates, and this includes some patients that may be in there with MSI high tumors as well. I think we have to be a little bit cognizant. We're predominantly looking at survival, where we see Kaplan-Meier curves on top of each other.

I acknowledge if you're a patient, individual patient, it's better to have a response than not a response, but I think when we look at overall population data, we've seen, again, funny things with response rate. If we're looking at PFS effects with one month, what does that even mean? So I think we just want to be a little bit careful when interpreting some of that data.

Open Public Hearing

DR. LIEU: Thank you, Dr. Lemery.

Seeing no other questions, we'll conclude our clarifying questions portion of this meeting, and we'll move on to the open public hearing session. So we will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the 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 those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

MS. EIDELMAN: Hello. My name is Andrea Eidelman, and I'm the CEO of Debbie's Dream Foundation: Curing Stomach Cancer. We are the largest international patient advocacy group for stomach cancer. I have not received any compensation from any sponsors or speakers for my presentation here today. I am here because this issue goes to the heart of the mission of the Debbie's Dream Foundation.

Our founder, Debbie Zelman, founded the organization in 2009 after one year of being diagnosed with stage 4 incurable stomach cancer. Debbie was just 40 years old, mother of three young children, practicing attorney, and the wife and daughter of a prominent physician. Debbie found through her own personal journey that there had not been a new treatment for gastric cancer in over 30 years. Her life mission became to start the foundation, to fund research, and provide as many treatment options for stomach cancer patients as possible.

As CEO since 2017, I have seen patients

struggle through the same journey as Debbie, and I have personally interacted with patients who have benefited from these particular treatments that are being discussed today, and they have made an extraordinary impact. DDF's position is to maintain access to immunotherapy for patients with low or negative PD-L1 scores, and that is necessary because it allows more access to treatments. There is already a lack of treatment options for gastric cancer patients, and allowing this access, we have seen through our own patient community, which you will hear from today, that these benefits have been seen for these patients.

Patients want and need to be empowered and want to have shared decision making with their physicians. Patients in this situation, mostly 80 percent, are late stage, stage 4, and there is a sense of urgency in being able to access treatments immediately. This satisfies the patient's desire to take action and take a sense of control over their illness.

Our long-term DDF patient and mentor, Amy

Jacobs, has also submitted a written letter and shared her own survivorship personal journey with these treatments and the importance of allowing patients and physicians to decide what is best for them in their particular situation. Please don't take these choices away. Thank you for your time.

Do you have any questions for me?

DR. LIEU: Thank you, speaker number 1.

Speaker number 2, please state your name and any organization you are representing for the record.

MS. SMITH: My name is Aki Smith. I'm a caregiver, patient advocate, and the Founder and Executive Director of Hope for Stomach Cancer. While we do receive independent grant funding from a variety of sponsors, including those represented here, I am not being compensated for my time, travel, or expenses to be here. I'm here today to share my father's story and express my concerns about the potential impact of FDA cutoffs on treatment decisions and patient access to immunotherapy.

My father was diagnosed with advanced stomach cancer in late 2013 and given 6 months to live by our local hospital. A second opinion saved his life. They re-staged him to stage 3B and discovered he was HER2 positive. At the time, Herceptin had just been approved, and while it was considered experimental in his curative treatment, it gave him a fighting chance. Today, we typically don't use Herceptin in a curative setting, but the flexibility that existed back then allowed my father to benefit from a treatment that possibly cured him.

One of my main concerns is how FDA cutoffs could restrict a doctor's discretion and treatment. Once these cutoffs are in place, insurance companies will likely follow suit, refusing to pay for treatments outside of these parameters. I've seen firsthand how insurance can influence life-saving decisions. For example, my father's power port was initially denied, forcing us through a lengthy appeals process while his Herceptin was approved. These kinds of decisions can profoundly

affect the quality of life and care a patient receives.

As the founder of Hope for Stomach Cancer, we provide navigational support to patients and caregivers through our programs. I've learned many things about our healthcare system and the disparities that restrict patients from accessing novel treatments. Not all patients are tested for biomarkers. Not all patients know their biomarkers. Through our website, stomachcancerbiomarkers.org, we've developed resources, including charts and NCCN guidelines/ summaries to help patients navigate biomarker testing and treatment options. While I believe these guidelines are crucial, we must be careful not to take the flexibility that can save lives.

Stomach cancer is a deadly disease, and for many patients, treatments are measured in months, not years. In cases where doctors are weighing toxicity against potential benefits, we need to remember that many patients are facing fatal outcomes regardless of their treatment.

Restricting access to treatment based solely on biomarker cutoffs may mean that some patients lose the chance for life-extending therapies. We must balance the science with the real-world complexities of patient care, ensuring that doctors retain the ability to make decisions tailored to individual patients.

I want to thank you so much for your time and consideration. We did leave a video in the open comments that was created by patients, and I encourage all of you to watch the video. Thank you.

DR. LIEU: Thank you.

Speaker number 3, please state your name and any organization you are representing for the record.

MS. KAVCHOK: Hello. My name is Alison Kavchok, and I'm here on behalf of Merck. I'm not being compensated for my time here today; however, I did receive support for my travel from Merck, my sponsor. I'm a 42-year-old mother of two, speaking as a caregiver for my husband, Ron. I'd like to

share my experience advocating for my husband's treatment options and how he has benefited from immunotherapy despite having a low PD-L1 cutoff and poor biomarker expression.

Ron has diffused gastric cancer, which is an aggressive under-researched cancer with a pathology that tends to be chemo resistant, resulting in patients being subjected to multiple lines of treatment to keep it stable. He was 47 years old and relatively healthy when he was diagnosed via a routine endoscopy with stage 1B gastric cancer in the fall of 2020. We sought out multiple oncologists' opinions from NCI designated facilities across the U.S., all of whom echoed the benefits of immunotherapy; however, at that time, it was not approved in the first-line setting therefore, we opted for the standard of care per NCCN guidelines, which he completed.

Ron had a partial gastrectomy in March of 2021, wherein we learned he had zero chemo response and will be upstage to 3B. He had more chemo and radiation but would ultimately have a reoccurrence

in the fall of '22. It was then that we sought out immunotherapy to be included in his next line of treatment. We knew the odds were against us in getting insurance approval due to Ron's low PD-L1 and biomarker threshold, but our oncologist advocated for us to receive it, as we collectively knew that systemic chemotherapy alone would not be enough to fight his cancer.

As we have feared, we were swiftly denied multiple times by our insurance company for lack of statistical proof, but after about 2 months of back and forth, which was very timely when you have stage 4 cancer at this point, we were able to receive Keytruda via compassionate care.

The feeling of having no other option besides chemo, despite seeing the stability of immunotherapy in clinical trial settings, as well as other patients, took an emotional toll on Ron. Ron is a part of a younger population who are seeing a rise in digestive cancers and who deserve to have access to potentially life extending treatment options.

Our surgical team is part of an NCI designated research hospital, and they too feel strongly that despite Ron's treatment history and his low PD-L1 score, Keytruda, the immunotherapy utilized in his case, is doing the heavy lifting and keeping his disease stable. He is still on it 2 years later with low systemic chemotherapy as well. It has afforded him a decent quality of life and disease stability. He is tolerating it well. It has given us 8th grade graduations, vacations, and cherished memories of which I am hopeful there will be more.

If we take away these options for patients like Ron, we're not only losing an opportunity to observe immunotherapy's effects in clinical settings like his, but we're also doing a disservice to patients and their families, many of whom are young and have so much to lose. So for the sake of gastric cancer patients and medical research, please consider continuing to provide immunotherapy regardless of PD-L1 indication, for which patients like Ron may continue to receive

life extending treatment. He is your data, and he's the face of your science. Thank you.

DR. LIEU: Thank you.

Speaker number 4, please state your name and any organization you are representing for the record.

MS. WILSON: Hello. My name is Kimberly Wilson. I'm not being compensated for my time here today; however, I did receive support for my travel from Merck, one of the sponsors. May I have my first slide?

I'm a Maryland resident and a stage 4 esophageal cancer thriver, but more importantly, I'm a mother, wife, daughter, sister, aunt, and friend. In April 2022, at the age of 43, I was diagnosed with stage 4 esophageal adenocarcinoma at my GI junction. The diagnosis hit hard and continues to impact my life and those around me daily. My diagnosis came exactly 6 weeks after marrying the man of my dreams. With the support of my family, I received preoperative chemo radiation, underwent a 12 and a half hour 3-field McKeown

esophagectomy that resulted in clear margins but, unfortunately, I was faced with a reoccurrence 3 months later.

I personally would like to thank all attendees and participants who are here today. I recognize that everyone in the room is working to create greater awareness surrounding the topic of esophageal and gastric cancers. Whether it's working towards finding a cure, uncovering new treatment options, exploring the possibilities of conjunctive therapies, and more, as a patient, it brings me great joy to see that there are people here who are interested in the topic and people who work and understand scientifically what this disease encompasses.

Today, I come before you to make a request. Please do not limit my choices and options related to therapies and medications that my fellow esophageal and gastric cancer patients and I have access to. I am proof that stage 4 esophageal cancer patients can and should be provided with therapies that ensure they're able to live the

fullest life possible. While none of our stories are exactly the same, we all do wish to overcome the challenges and the trials we are faced with, and ultimately say that we survived.

Since my first day of diagnosis, I've had a care team who consists of amazing medical professionals who have been integral in my care. Thanks to them, I'm here today. Just this Monday, I received my 28th Opdivo immunotherapy infusion along with my 48th 5-FU and leucovorin infusions. I was disconnected yesterday. Today, I stand before you.

While Thursdays are generally my most challenging days of each cycle, something greater is living within me today to allow me to be here and stand before you. Despite my challenges during the journey and my low PD-L1 threshold, I excitedly share with you that my PET scans and circulating DNA tumor markers have shown no evidence of disease since spring of 2023.

You can see that I'm living a full life, a bit different than I once pictured, but full

nonetheless; full of love, full of adventure, and full of hope. Please show compassion in your vote and any future decisions that you make related to the treatment options for esophageal and gastric cancer patients. We all want the best chance of living life, and know that means a variety of options to meet all of our unique needs and circumstances. Please do not limit the indicators for eligibility or limit the options for treatments. I still have a long life to live, and to my knowledge, no one has yet written a guide for how I should explain this all to my children if my options become limited by individuals who are not my immediate medical care team. Thank you for your time.

DR. LIEU: Thank you.

Speaker number 5, please state your name and any organization you are representing for the record.

MS. MORDECAI: My name is Mindy Mintz Mordecai. I am the CEO of the Esophageal Cancer Action Network. Our organization receives funding

from all of the applicants. I am not being paid for my testimony here today or any of my travel costs.

In 2009, after losing my husband to esophageal cancer -- sorry, now I'm crying, too -- I started ECAN because I was appalled at how little research and awareness existed for esophageal cancer. The next year, 2010, the National Cancer Institute drew up a list of 20 cancers for its groundbreaking genome mapping project called the Cancer Genome Atlas or TCGA. Esophageal cancer wasn't on that list. ECAN begged the NCI to include esophageal cancer in TCGA. We even offered to orchestrate the tissue sample collection and raise a half million dollars to pay for the launch of that project, and it worked.

The esophageal cancer pilot project of TCGA began in 2011, and its findings published in 2017 showed that esophageal adenocarcinoma was genomically similar to gastric cancer. The result was that our patients were included in clinical trials focused on stomach cancer, including the

trials that led to the approval of Opdivo and Keytruda for patients with esophageal adenocarcinoma or GE junction adenocarcinoma. That approval was just three years ago, and now we're seeing more survivors of stage 4 esophageal cancer and something that we could only dream about when my husband was being treated.

So I'm here asking you, what's going to be gained by making this proposed change? Initial FDA approvals were based on sound data. They showed promise for our patients, and in some cases, that was regardless of their PD-L1 status. We know patients who are PD-L1 negative who are thriving because of their immunotherapies.

Take Jim Bennett of Mount Pleasant, South Carolina. He's a 77-year-old survivor who lost 40 pounds at the time of his stage 4 esophageal adenocarcinoma diagnosis; that was 18 months ago. Since then, he's been on Folfox and Opdivo, and not only has he gained back all of his weight and seeing his tumor and mets shrink, he's now running 5Ks, riding his motorcycle, and feeling, as he

describes it, as if he doesn't have cancer at all. If the FDA decides to restrict his access to immune checkpoint inhibitors, Jim's lifeline will be gone.

Jim is not the only PD-L1 negative patient who's experiencing these positive responses. Dr. Kumar repeatedly said, "No convincing evidence of benefit or harm for PD-L1 negative patients has been found," no convincing evidence of benefit or harm. When you're looking at possibly 17 percent of our patients, shouldn't that decision be made by the doctor and the patient, not an FDA panel, especially when we look at the issues with the kind of tissue samples that we're looking at to come up with these scores and the variability in the responses?

DR. LIEU: My apologies. If you could conclude your statement, please.

MS. MORDECAI: Yes.

This is not the time to pull the plug on this progress. I hope that when you make your decision, you will remember Jim Bennett. His chances for survival are very few. His doctors

should be able to help him make a good decision. He believes that losing access to immunotherapy will cost him his life, and that is too high of a price to pay. Thank you for the opportunity.

DR. LIEU: Thank you.

Speaker number 6, please state your name and any organization you are representing for the record.

MS. AARON: Good morning. I'm Betsy Aaron. I'm not affiliated or receiving compensation from any organization. I'm going to share my story of delays and restrictions in getting access to immunotherapy during a time of disease progression. I'm 70 years old. I was diagnosed with stage 4 gastric adenocarcinoma in July of 2022. I was told that my treatment would be palliative and that I didn't meet the minimum requirements to receive immunotherapy. I received instead 42 rounds of chemotherapy every other week for 2 years.

I was then given a chemo, quote/unquote, "holiday." After about 6 weeks, I had an endoscopy and learned that the primary tumor had returned. I

also learned from tests on the fresh tumor tissue that my PD-L score was now 20. My doctor and I discussed treatment options. The one I wanted was treatment with two immunotherapy drugs. I was told that I would need to obtain compassionate care since I did not have the approved biomarkers.

During this time of waiting for approval, my symptoms continued to increase. After waiting 5 weeks, my doctor and I agreed that I had to start treatment, so we opted for a chemotherapy plus one immunotherapy drug. This treatment option also involved getting approval since third-line treatment for anyone over 65 is currently also restricted. That approval took an additional week. After a total of 6 weeks, I received approval for the treatment I wanted.

In my view and in my experience, access to immunotherapy treatments needs to be made easier for people living with gastric cancer, and not more restrictive. Thank you for hearing my story and considering my words.

DR. LIEU: Thank you so much.

Speaker number 7, please state your name and any organization you are representing for the record.

MR. KAVCHOK: Hi. My name is Ronald Kavchok. I'm the husband of speaker number 3, Alison Kavchok. I reside in Ringoes, New Jersey and have access to a lot of doctors, but I don't have any affiliation or receive any compensation from anyone.

I want to share my story regarding my diagnosis and treatment of gastric cancer. I was diagnosed almost 4 years ago at the age of 47. I'm married with two children, ages 10 and 12 at the time. This was obviously devastating news, but I felt confident that I could fight this. I wanted to see my children graduate elementary school and hopefully on to college.

My initial diagnosis was stage 1B stomach cancer in November of 2020. I went ahead and got opinions from my oncologist and her team. I also got second opinions from many doctors across the entire United States. In all cases, in all of our

conversations, I was told that my gastric cancer is tough and chemo resistant, and that getting a clinical trial or including immunotherapy in my treatment would be the best case for my survival. Immunotherapy was not yet approved yet for my cancer, so I moved forward with the standard of care as indicated in the NCCN guidelines. I was ultimately upstaged to stage 3B 6 months after my diagnosis.

The good news is I have continued to remain disease free for 14 months until routine EGD in October of 2022 discovered a reoccurrence. The good news about that is, though, is there was no tumors and my scans are all clean. My cancer was just microscopic.

So what are my treatment options for this reoccurrence? Getting more chemotherapy for a chemo-resistant cancer is not my best route. My oncologist's opinion for my best outcome is to get me on immunotherapy, so a mini battle ensued. My oncologist fought the insurance company, but I did not meet the PD-L1 requirements and I was past

first-line treatment.

But after a short fight, I got good news in December of 2022. Almost 2 years ago now, I was able to get Keytruda off label as a second-line treatment. Since then, I've experienced very positive results. I'm not dealing with any harsh side effects of chemotherapy, I'm enjoying a better quality of life, and I'm spending a lot of time with my family.

Myself and everyone on my team all agree that the immunotherapy has been key in my current success. My oncologist was not just looking at PD-L1 scores; she used her experience with similar patients' outcomes, my resistance to chemotherapy, the fact that my disease is microscopic, and I'm in generally good health besides the cancer.

Using stories like mine, as well as countless other patients with low PD-L1 scores, should really be considered. In short, chemotherapy did not work for me, but immunotherapy is. My children have went on to graduate elementary school, and now both of them are in high

school, and I'll be seeing them graduate there soon. So thank you for your consideration.

DR. LIEU: Thank you so much.

Speaker number 8, please state your name and any organization you are representing for the record.

MS. HALL: Good morning. My name is Pamela Hall. I'm speaking today as a patient on behalf of myself and others who are struggling with gastric cancer. I've received no compensation for my appearance here today. I'm a 68-year-old retired banking executive and a devoted yoga practitioner. My husband and I have been married for 31 years. We have 3 children and 8 grandchildren.

Six years ago, in August of 2018, at the age of 62, I was diagnosed with stage 3 gastric cancer. This diagnosis has forever changed the course of my life and that of my family. The first line of treatment I was given included chemotherapy, and it was then followed by a total gastrectomy. Since then, my cancer has recurred 5 times. Needless to say, I've been subjected to every cancer treatment

Western medicine has to offer. This includes participation in two separate drug trials.

In all but this last recurrence, treatment has worked for me for a short time to eradicate my disease, only for it to return time and again. When I was initially diagnosed, immunotherapy drugs were not even considered an option for first-line treatment. No one understands why some people respond to certain therapies and others don't. Likewise, no one knows why cancer in some people persistently recurs, while others remain cancer free after only one line of treatment.

We do know, however, that cancer's smart, and it can morph and change to evade the immune system and render treatments ineffective. My case is a good example of this happening. After multiple biopsies through the past 6 years, my results came back this past May for the very first time as PD-L1 positive. Does this mean that the immunotherapy drugs that didn't work for me in the past will work for me now? I don't think anyone knows the answer to that question. What I do know

is that I want my doctor to feel free, without reservation, to try all the weapons in his or her arsenal to treat my disease.

The indications set by the FDA have an immediate and an outsized impact on what treatments insurance companies will and will not approve. Frankly, I don't have the energy to fight both this disease and my insurance company, who by the way are not doctors. I don't want to argue with them over whether or not I should have an immunotherapy drug. My ask today is that you consider, first, the patient's perspective before setting or changing your indications or guidelines for this class of drugs. Thank you for your time.

Questions to the Committee and Discussion

DR. LIEU: Thank you so much, and thank you to all of our open public hearing speakers. The portion of this meeting has now concluded, and we will no longer take comments from the audience.

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

public comments. We will now proceed with the questions to the committee and panel discussions. I'd 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. In patients with HER2-negative microsatellite stable gastric/ gastroesophageal junction adenocarcinoma, does the cumulative data support the use of PD-L1 expression as a predictive biomarker when selecting patients for treatment with PD-1 inhibitors?

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

(No response.)

DR. LIEU: Seeing none, we will now open the question to discussion. Please turn your name placards sideways if you want to make a comment regarding this discussion question, and I'll take

the opportunity to go first.

I really appreciate all the data and all the work that's gone into these presentations. I will tell you, when treating these patients, I know our patients don't want incremental benefits and overall survival. They want to see that tail of the curve and see those durable responses over a prolonged period of time. I think that there's some consistency in all the evidence that we have been presented with. I think that PD-L1 is predictive of response. I think we see significant activity at PD-L1 greater than 10. I would say we see modest -- and I use that term very seriously. I think we see some modest benefit between 1 and 10, and I see no evidence of benefit in PD-L1 scores less than 1.

I think there are also some significant challenges here. I see a biomarker that is not binary. This is measured on a gradient, and there's no standardization that has been mentioned. I think that there is reporter variability, which is concerning to me. Is a 5 the same as an 11? Is

a 12 a 4? I don't think we know the answer to that, and I think that limiting immunotherapy using a somewhat unreliable biomarker is a little bit concerning.

But to answer this particular question, I will tell you, I do believe the PD-L1 expression is a predictive biomarker in this disease. I do see significant activity at levels greater than 10. I do not see any activity in scores less than 1. And I would love to see patients have the opportunity to receive these drugs between scores of 1 and 10, but I think that that requires some discussion between the patient and their provider in terms of the risks, because we're asking our patients to undertake greater grade 3 and 4 risks for unclear benefit, particularly at lower scores.

Dr. Spratt?

DR. SPRATT: Dan Spratt, Case Western. The question is not should we impose some restriction and cutpoint? The question is, does the cumulative data support the use of PD-L1 expression as a predictive biomarker? And a predictive biomarker

at its core is simply there's a different relative effect size by biomarker status, period, end of story. There are ways to test this. It is a predictive biomarker. There are significant interaction effects by subgroup. There are different relative effect sizes.

Every trial of each of the companies, the primary endpoint, specifically, a priori, picked the CPS or TAP thresholds to be included. So it's acknowledged, I hope -- other than one of the companies, it seems to acknowledge there is very significant differences in relative benefit.

I think, as you just pointed out, that's very challenging when you get from the binary less than 1 to greater than 1. But a point that I think gets confused a lot, in some of even the amazing open public hearing comments and touching stories, is just because a patient has an amazing response to chemo and IO doesn't mean they wouldn't have an amazing response to chemo; and you have a hazard ratio of almost 1, they probably had a similar probability of having that benefit. That's all I

have to say.

DR. LIEU: Thank you.

Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. I think that, clearly, there's some degree by which all of this is telling a predictive story, but I think the clinical utility and how the data supports that, it's a read between the lines a little bit. But the context of the discussion here is -- I'm just not fully convinced that this is the data set that should be used to address this. This is hypothesis generating data that poses the question of, is this cutoff required to bring about benefit versus risk?

Again, as was raised by the FDA, is the cutoff that's proposed the right cutoff? We don't know. We never really went into these studies asking this question. So that's where I have some trouble, and that is, I'm not sure this is how we would power this data set. We're trying our best to glean what we can from existing data that was never really designed to answer this question, in

my opinion. That's kind of where my thoughts come from as a non-GI oncologist, so I welcome thoughts from the panel in that regard.

DR. LIEU: Thanks, Dr. Madan.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern. I share the sentiments that have been expressed up to this point. I think this is a predictive biomarker despite the flaws, the caveats, that have been discussed about it. Certainly for above 10 and 1 to 10, I think that gets into the realm of letting doctors be doctors, where they have an opportunity to talk to their patients and make a discussion in conjunction with their patient about whether this is worth doing, taking into account the side effect profile that these drugs have. I'm not in any way particularly impressed with any of the data that's been presented for anything less than 1, and in that group of patients, I'm not seeing any real effect.

I would also echo with Dr. Spratt just mentioned. I empathize with the compelling stories

that were described, but we've seen patients -- I'm a breast oncologist. During the era of bone marrow transplant for patients with breast cancer, there was a lot of enthusiasm for that until there wasn't, and many of those patients might have done just as well with standard therapy, and we just don't know. So that's my view.

DR. LIEU: Thank you, Dr. Gradishar.

Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia University. I agree with everything that's been said. I'm a breast oncologist and, for me, the analogy that I keep coming back to is actually not the mutational examples that have been brought up like with KRAS and olaparib, and another continuous variable, which is HER2.

The two things that I'm really thinking about are, number one, obviously the field optimized and decided thresholds of positivity in these large trials were designed to test those questions, but I think the difference is, is that in the HER2 field, small subsets were tested, and

then slightly larger, and then slightly larger, encompassing that biomarker.

I think what we had here is actually the opposite, where it got approved in the initial data based on the best available data, and we're maybe backtracking and refining that biomarker. I think taken to an extreme, I agree that these post hoc analyses can, of course, have biases, but I'm thinking about other trials like NSABP-47 and actually testing HER2 antibodies in patients who had low levels of HER2. Are we thinking about an extreme possibility like that or are we just making use of the best available data that we have at the time? Thank you.

DR. LIEU: Thank you, Dr. Vasan.

Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, Charles University. I agree with what's been stated thus far, and particularly Dr. Lieu's initial summary. PD-L1 is helpful, but it's not definitive. We've talked about the need to get more tissue to be able to better get an idea for this particular marker

and whether it exists on this patient. And does that explain why some people do better than others just because they had more tissue to get included?

It appears that we need to work harder if we're going to continue to use this marker to develop better assays or criteria for getting what is an acceptable tissue or assay for PD-L1. Of course, it means that we need to continue to search for other markers that may be more helpful than PD-L1. Thank you.

DR. LIEU: Thank you, Dr. Hawkins.

Dr. Meyerhardt?

DR. MEYERHARDT: Jeff Meyerhardt, Dana-Farber. I think to this question, to me, it's fairly straightforward. The data is clear; there are different levels of PD-L1 expression that have different levels of overall survival and progression-free survival. I think the question, obviously, is, is there a cutoff, and are we going to deny patients of the potential for a therapy if you choose some cutoff, whether it's 1 or another number?

The reality is, for good or bad, we do that all the time in oncology. We don't give gemcitabine for gastric cancer. Is there a gastric cancer patient who potentially could benefit from gemcitabine? I'm sure there is. There's probably multiple, but we still have to use some data to be able to decide who's potentially going to benefit or not; and overall, as a population, is there some benefit, and is that benefit enough to weigh the risks?

DR. LIEU: Thanks, Dr. Meyerhardt.

Dr. Spratt?

DR. SPRATT: I don't know if you want to --

DR. LIEU: Oh, sorry. Yes. Dr. Spratt does defer to Dr. Hillard.

Dr. Hillard?

DR. HILLARD: Yes. I do think that just looking at the data, there is predictive value; that if you do have higher PD-L1 expression, you're more likely to benefit. But on the other hand, most of the patients in the studies, even with the PD-L1 less than 1, on the average, had some

benefit, even though it's not statistically significant. So yes, cumulative data suggest it's a predictive biomarker, but at this point, I don't think it's clinically something that will outweigh all the other factors that might go into the clinical decision.

DR. LIEU: Thanks, Dr. Hillard.

Dr. Sanoff?

DR. SANOFF: Hanna Sanoff, UNC. I was curious to hear the panel's thoughts on the discussion about tissue inadequacy and availability of biopsy samples. This is true across oncology at this point. We use biomarker testing for every single disease. Is there something unique to the group about gastric and esophageal cancers that would preclude us from re-biopsying someone? I think we heard from Dr. Janjigian that patients respond the best in the first few cycles of treatment. I completely agree with that, but that's chemotherapy response; that's not IO response in gastroesophageal cancer, which is different than, say, melanoma.

So to me, that did not strike me as something we should use as a deciding factor here because, to me, I feel like we could biopsy as fairly readily available, but I'm curious to see if that sways other panel members at all.

DR. LIEU: Does anybody have a response to Dr. Sanoff's question?

DR. SPRATT: Speaker number 7 who spoke --

DR. LIEU: And can you state your name? Sorry.

DR. SPRATT: Oh, Dan Spratt, and I am not a GI medical oncologist. But speaker number 7 I think spoke very eloquently and was denied and received chemo first, and then later on received IO, and he's doing very well right now. So I guess to your point, it seems that the necessity of this being immediate, at least in his case -- we're talking about anecdotes right now, but I'd defer. I think someone else had their hand up.

DR. LIEU: Dr. Gibson?

DR. GIBSON: Michael Gibson. I think I'm in the appropriate session to comment. Sorry guys. I

just wanted to say that one of our speakers, it may have been Dr. Janjigian, mentioned that this is a dynamic biomarker, which means, as was pointed out by one of our speakers, it changes over time. I don't think getting another biopsy -- although I'm not the patient, I haven't had patients not agree to do that if we have justification such as retesting for a marker that may have been negative the first time. I do think this is an appropriate biomarker; it's dynamic. And the question to whether biopsying again, I think that's an important consideration that is practically possible.

DR. LIEU: Thank you, Dr. Gibson.

Dr. Van Loon, I see that you had raised your hand. I didn't know if you wanted to respond to Dr. Sanoff's question as well or had a separate comment.

DR. VAN LOON: I think I was responding maybe to one speaker earlier. From the perspective of a gastrointestinal oncologist, I also wanted to reference the breast oncologist who had mentioned

HER2 as a biomarker and remind everybody that we use different cutpoints in different diseases for different biomarkers. We use HER2 thresholds differently in upper gastrointestinal cancers than we do in breast cancer, and I think that's a reference to the fact that we're learning as we go and, unfortunately, we're dealing with an assay that has limitations with PD-L1. But based upon the current preponderance of evidence, it certainly seems to be a predictive biomarker for this particular disease.

I think we all have to acknowledge that we are still learning about it, and there is certainly a demand to address the limitations of the biomarker testing for future decision making. But sitting with the data that we currently have is really important.

DR. LIEU: Thank you, Dr. Van Loon.

Dr. Spratt?

DR. SPRATT: Two things. And I commend the applicant for providing that Q-TWiST, which is really probably the one method of analyzing this

quality-of-life toxicity, and then freedom from progression or death, and nicely harmonized. I mean, it's imperfect, but I appreciate them putting it in. They showed nicely -- to what I think one of the panel members said -- that when you get to the scores less than 1, essentially, not that there's necessarily a uniform agreed upon clinical significance threshold -- they cite 10 from an old paper, and sometimes it might be appropriate to be less than 10 -- but it's very clearly different. There's about 4 to 5 percent versus over 30 percent for expression levels over 30.

So I think someone said, is there potential harm of these agents? If there's no potential harm of these agents, then yes, just make it available, ignoring cost in and of itself as a toxicity. If you factored financial toxicity into that Q-TWiST analysis, I think we'd find something strikingly different given that combined nivo and pembro is over $30 billion a year, I think, for 2024. So who's paying for that? Patients are paying a percentage of that out of pocket, even if it's not

the majority.

I think we just need to be thoughtful to the potential harms. The point that Dr. Janjigian brought up, which is spot on, and I think you were just trying to address, is the real-world aspect of this without tissue. I guess what I don't know -- and I'd love if someone can answer -- is what is the real-world efficacy data in this patient subset that's not enriched for these high PD-L1 scores? Because again, you can't talk about trials and the accuracy but then not talk about real-world efficacy. Are these patients going to have far poorer response rates because they are not as enriched? And I don't know if anyone knows that.

DR. LIEU: Any responses to Dr. Spratt's question?

(No response.)

DR. LIEU: This is Chris Lieu from Colorado. And yes, I'm not sure that we necessarily have that real-world evidence data, and I think that just speaks to the reality of the problem that we live

in a nonclinical trial world, and we're going to have biopsies that are not going to be able to get a score on. And that really goes back to Dr. Sanoff's point and that others have made about re-biopsy. I think that, in reality, that's what our patients may have to undergo if this decision is made to start cutting off at particular CPS scores.

Dr. Madan?

DR. MADAN: Ravi Madan, NCI. Again, I'm just stuck a little bit here. I'm bleeding into the question a little bit and the CPS score of 1.0. Why is 1.0 the cutoff? Is it 0.8? Is it 1.2? If we're going with the harms thing, maybe we're harming everybody who's 1.1. Maybe all the responders are sub 1 or 0.8 and above. This is where I struggle with saying that we have enough data, at least when it comes to the voting question to assign a cutoff.

DR. LIEU: Thank you, Dr. Madan.

Unfortunately, only if the sponsors are directly asked a question can they come up.

Any other comments from the panel in regards to this discussion question?

(No response.)

DR. LIEU: Okay. I'll do my best to summarize this discussion. Hearing everybody on the panel, I feel like there's some consistency in thinking that PD-L1 expression is a predictive biomarker for immunotherapy. I think that's really what the discussion question is asking. I think that there are significant concerns from the panel in regards to the efficacy that we're seeing in PD-L1 scores that are less than 1, and I think that there are concerns about the overall survival data that we see.

To use Dr. Vasan's point and Dr. Van Loon's point, refining the population of patients that are most likely to benefit from these therapies, as well as learning as we go, there are some practical issues here about the assay itself, about standardization, about measuring it, about the ability to do this outside of tertiary care centers and major molecular companies that do this type of

testing, and the real-life situation of having to re-biopsy patients to determine a CPS score and what cutoffs could mean.

Also, Dr. Madan had made a point that this may not be the best data set to answer some of these questions about cutoffs given that we're really starting to cut up the data into incredibly small subsets and trying to make treatment decisions based off of those small subsets in trials that weren't designed to ask the questions that we're trying to ask: less than 1, 1 to 5, 5 to 10. These aren't trials that were designed to do that, but luckily we do have a significant amount of data.

Any questions or comments in regarding question 1, the discussion question?

(No response.)

DR. LIEU: Okay. 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.

The voting question is, is a risk-benefit assessment favorable for the use of PD-1 inhibitors in first-line advanced HER2-negative microsatellite stable gastric/GEJ adenocarcinoma in patients with PD-L1 les than 1?

Are there any issues or questions in regards to the voting question?

Dr. Madan?

DR. MADAN: Ravi Madan, NCI. On our slide, it actually has the options for answers are yes or no, but is there an abstain option, traditionally?

DR. LIEU: There is an abstain option, so you can abstain.

DR. MADAN: I was asking for a friend.

(Laughter.)

DR. LIEU: Yes, you can vote to abstain.

Any other questions or comments?

(No response.)

DR. LIEU: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly after you have made your selection. The light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. FRIMPONG: There are 2 yeses, 10 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, vote, and if you want to, you can state the reason why you voted as you did into the record. I believe we'll start with Dr. Van Loon.

DR. VAN LOON: My vote was no, based upon the --

DR. LIEU: If you could state your name. Sorry.

DR. VAN LOON: Sorry. This is Katherine Van Loon, and my vote was no, based upon the preponderance of evidence at this time. I think the risk-benefit ratio is not favorable.

DR. LIEU: Thank you.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar. My vote was no, as I outlined a few moments ago for those reasons.

DR. LIEU: Thank you.

Dr. Spratt?

DR. SPRATT: Dan Spratt, Case Western. My vote was no. Again, the voting question's not for us to decide the change of the cutpoint, but the risk-benefit ratio favored use of PD-L1 in this decision-making process. I think when we look at credibility of subgroup analysis, this was part of the most primary endpoint analysis and was measured a priori, with significant interaction effects. Pretty much, it was a priori. The hypothesis and direction of effect was correct. This is a very good data set, just to disagree, and I think with hazard ratios almost approaching 1.

The other point that I want to bring up is let their doctor decide. Dr. Janjigian, who's a world expert, said the average doctor sees five of these a year, so I'm just not sure we want to let their doctor make this decision when these hazard ratios are almost 1, and there are financial and toxicity impacts for these patients.

The last point I'll make is when you look at

the tails of where they converge, there's less than a 1 percent absolute difference in this less than 1 subgroup. That's a number needed to treat over 100, if not close to 1,000. That means you're treating hundreds of these patients to benefit one. Thank you.

DR. LIEU: Thank you, Dr. Spratt.

Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. I voted to abstain. I think our quest for biomarkers has been going on since our quest to develop better therapeutics, and I think, unfortunately, most biomarkers fall short. I think PD-L1 has also fallen short in many diseases, including this one, because of issues with acquisition, characterization, variability, and sampling error.

So when it comes to that context, it's hard for me to say that this is the data set to make this decision. Again, I'm not sure that it should be higher or lower. I'm just not sure this is how I would ask the question.

DR. LIEU: Thank you, Dr. Madan.

This is Chris Lieu from University of Colorado. I voted no. As I stated before, I just don't see any overall survival benefit in this group less than 1. I would love to hear others on the panel in terms of where they believe the cutoff should be. I do think that the cutoff should be 1 because of the perceived benefit that I see in that patient population between 1 to 10, and I do think that that is the conversation, as has been mentioned before, that needs to happen between a patient and their physician. But to give them the opportunity to have that conversation, I think is really critical.

Dr. Vasan?

DR. VASAN: Neil Vasan. I voted no. I agree, based on the totality of the data, that there was not a favorable risk-benefit for this PD-L1 low population. To address Dr. Lieu's point, for me it was clear that across these data sets, a clear benefit in the greater than 10, no benefit in less than 1. And it's that intermediate range that

this is where we need clinical trials to help answer questions where we have levels of equipoise, and with any continuous variable, the important question's in the field. Thank you.

DR. LIEU: Thank you.

Dr. Dodd?

DR. DODD: Lori Dodd. I voted no because of the preponderance of evidence presented with the meta-analysis in those who were PD-L1 less than 1. The question was I think very carefully worded to say those that were less than 1 because we don't have enough data for those who we don't have a result from, as well as those who are between 1 and 10.

DR. LIEU: Thank you.

Dr. Hillard?

DR. HILLARD: Yes. James Hillard, patient. I voted yes in that it's clear that there's some variability in terms of how this is assessed in different settings; that clearly having a high PD-L1 ligand measurement is associated with greater efficacy. I don't think there's clear evidence for

the null hypothesis, that there's no chance that the less than 1 is going to be valuable.

DR. LIEU: Thank you, Dr. Hillard.

Dr. Hawkins?

DR. HAWKINS: Yes, a difficult question. I voted yes with some reservation. I think there were enough responders who are less than 1 to make me say it's possible. I felt that the side effect profile was good once you got past chemotherapy. One thing I would emphasize would be, really, the importance of educating GI specialists, GI oncologists, and those that are in private practice because they're the ones that see the patients first, I believe.

We really need to emphasize the importance of tissue size. We need enough tissue for this imperfect assay, and we need to work on this assay. We also need to look really hard for additional markers that may help us do a better job with this group of patients. Thank you.

DR. LIEU: Thank you, Dr. Hawkins.

Dr. Gibson?

DR. GIBSON: Thank you. Michael Gibson. I would start out by saying this is a bit of a wrenching question for me. I made my decision objectively on the data that I saw today and I have reviewed before; however, I might add I am also a clinician, and I do appreciate the considerations from the group.

DR. LIEU: Thank you, Dr. Gibson.

Dr. McKean?

DR. McKEAN: Heidi McKean. My vote was no based on the hazard ratios for overall survival, PD-1 or CPS PD-1 less than 1. I just want to comment, though, as a community oncologist, I too saw 30 patients a day earlier this week, but that meant 15 different cancers. So it is often overwhelming for a community oncologist to keep all of this straight, so some great effort from FDA/NCCN to put in guidance does help the community oncologist.

DR. LIEU: Thank you.

Dr. Meyerhardt?

DR. MEYERHARDT: Jeff Meyerhardt. I voted

no. In addition to the comments, I think it's telling that multiple guidelines, NCCN, ASCO, and others, have all actually chosen a cutoff despite a broad indication right now. So while the FDA should have an independent decision on this, I think multiple experts, including some that have spoken today, sit on those guidelines and the agreement that there should be some cutoff.

In terms of your question regarding should it be less than 1 or something higher, I think the one concern I have with the 1 to 10 patients is when you look at the pembrolizumab breakdown data, the 5 to 10 who actually also had a hazard ratio of 0.92 and then the 1 to 5, there's clearly some variability there. But I think the testimony where there was more confidence in less than 1 being truly negative is helpful.

DR. LIEU: Thank you.

Dr. Sanoff?

DR. SANOFF: Alright. Hanna Sanoff. I also voted no, and as the last person, probably a little bit repetitive. I think a couple pieces of

evidence are really important here. First, as Dr. Spratt explained, this is really high-quality evidence. We had a priori cutpoints. We have repeatedly demonstrated evidence here. I think one thing that's really difficult here is this question of are there people in this less than 1 subgroup who do benefit? What do we make of these responders?

I think there may be people who respond, but we're not seeing that tail of the curve. I think that's really important, the question of can we provide people hope, offering them long-term survival with advanced gastric cancer who have PD-L1 less than 1? To me, that really looks like the answer is no. Now, it may evolve over time for those patients, which may mean repeat biopsy and subsequent availability of these drugs is important, but that's not what was asked here.

The other thing is -- even though I cannot even tell you how moving it is to hear everyone come up and speak -- the folks we don't have at the microphone are the folks who have passed away from

getting PD-1 inhibitors, and everyone around this table has probably seen one of those patients. These are not just grade 3 and 4 toxicities. These are also also grade 5 fatal toxicities, and that is very moving to me when you look at these curves that do not show long-term survivors from these drugs in a PD-L1 negative population.

So I really hope we can see how this evolves and how we can get immunotherapies to be effective in this PD-L1 negative population, but until we do that, I just did not see enough evidence that we're helping people and not harming them.

DR. LIEU: Thank you, Dr. Sanoff.

So to summarize, a majority of this panel did vote no. I think those that voted no spoke to the really essentially negative data that we see in the CPS or PD-L1 less than 1 cohort, that that cutoff appeared to be at least reasonable. There are some variability in terms of where people believe that that cutoff should lie.

I think the greater than 10 is pretty obvious, and then 1 to 10 really has a decent

amount of variability in terms of overall survival benefits, so there's some concern there as well; and then to the point that the guideline committees have also instituted these cutoffs as well.

For those that voted yes or abstained, I think there's a really understandable concern about missing patients that may truly get benefit from these agents, and I think that we heard from the open public hearing speakers how meaningful it has been to them as well, as well as some concerns in regards to the data sets that we have available, and that we're trying to answer questions that those trials weren't necessarily designed to answer. But overall, there is fairly good consistency across the vote for the panel.

I do want to say thank you so much to our applicants, BMS, Merck, BeiGene, the FDA, and the incredible amount of work that's gone on to producing wonderful presentations and a wonderful summary of all the data that's available, as well as to our open public hearing speakers who, really, their stories have been truly moving, and thank you

so much for adding to our meeting.

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

Dr. Pazdur?

DR. PAZDUR: It's a rare opportunity that I get three drug companies in front of me simultaneously -- .

(Laughter.)

DR. PAZDUR: -- so question number one, when these drugs were being developed, we spent a great deal of time and having conferences, trying to coordinate with the drug companies uniform marker development, PD-1 drug development marker. Obviously, those efforts failed.

Could you address this, each one of the companies, and express your willingness as we go forward in the field of immunology, really, to harmonize efforts between companies, or amongst companies, to have standard PD-1 or whatever biomarker development?

Merck, since you have the leading drug here, what is your position on standardization as we move

forward?

DR. PIETANZA: Thank you. I will actually have Dr. Scott Pruitt respond to this question.

DR. PRUITT: Scott Pruitt, Merck translational oncology. We'd be very interested in working to try to see if we can make these assays interchangeable. It would be great if they were interchangeable, but I think the data to date suggest that they're actually not. We would have to do cutpoint mapping studies, analytical and bridging studies, which we may or may not have sufficient --

DR. PAZDUR: Yes. This boat has sailed, so to speak. Our ship has sailed, but I'm talking about as we move forward because there will be further developments in biomarker development in this area, obviously. This is not the end of the story, the PD-1 assays that we have today.

DR. PRUITT: Oh, absolutely. We would try to focus on --

DR. PAZDUR: So you're on record, you'll collaborate with anybody.

DR. PRUITT: Absolutely.

(Laughter.)

DR. PAZDUR: Let's hear from BMS on this. Are you going to collaborate with everybody, put away your own commercial concerns here and come to a kumbaya with everybody that's developing a similar type of drug?

(Laughter.)

DR. WAXMAN: We do welcome efforts for harmonization. I think our goal here is to simplify the process for patients and physicians. The process by which we do that is up for discussion, but overall --

DR. PAZDUR: Because I think we've learned from this experience. This has been not a great experience, obviously, having all of these different tests here. And here again, I want to emphasize, we did bring people together. We made a concerted effort, the FDA, in trying to harmonize these tests with several conferences and telephone calls with Friends of Cancer Research and other external organizations.

So you're on board, right? Okay.

(No audible response.)

(Laughter.)

DR. PAZDUR: Okay. BeiGene?

DR. LANASA: As I mentioned in my presentation, yes, BeiGene absolutely is supportive of harmonization.

DR. PAZDUR: Okay. So here again, this ship has sailed. I don't think we could do anything more about this, but as we move forward, and looking at new biomarkers, we really have to develop platforms across the commercial concerns of companies.

Okay. Second question. If, and I underline if, we restrict the labels to less than 1, you are concerned, Merck, that some patients who may potentially benefit will not receive this drug. Would you be willing to offer the drug on an expanded use program or a compassionate use program for those people that are less than 1, free of charge?

DR. PIETANZA: Merck understands the

financial toxicities of patients with these diseases and, yes, we do already have programs in place for patients with financial hardships, and we actually also provide drug free of charge for patients who have --

DR. PAZDUR: Because, here again, if it's not an approved indication, obviously insurance companies may not approve it. So would you have an expanded use protocol, for example, or a so-called compassionate use protocol, providing the drug free of charge for these individuals?

DR. PIETANZA: We have provided drug free of charge to eligible individuals who cannot financially pay for it.

DR. PAZDUR: So you would consider an expanded use protocol in this situation?

DR. PIETANZA: We'll have to take it back and think about it.

DR. PAZDUR: We'll be in contact with you.

How about BeiGene?

(Laughter.)

DR. PAZDUR: Very seldom do I have this

opportunity. That's why I want to make full use of it.

(Laughter.)

DR. LANASA: Sure. I guess I would say I don't exactly understand the context of the question.

DR. PAZDUR: The drug will not be reimbursed if the indication is late.

DR. LANASA: Sure, but the committee just voted the benefit-risk is not favorable.

DR. PAZDUR: I know, so you would not. But other companies have stated that there might be people because of the ambiguities of this assay.

DR. LANASA: Certainly, we have an expanded access program that's available globally, and those requests actually come to me, so certainly I'd be happy to review if a physician felt that a patient would benefit.

DR. PAZDUR: Okay. Bristol-Myers? I just want to get this on because there are other avenues for use of the drug or access to these drugs.

DR. WAXMAN: If a physician and their

patient deemed that there may be benefit, we would look for mechanisms by which we could help them achieve access.

DR. PAZDUR: So you would consider that?

DR. WAXMAN: Yes. There's a lot of steps that need to be discussed.

DR. PAZDUR: Okay, because I do want to address the concerns of patients. We realize the issues here with the biopsy, et cetera, and if we do restrict it, and if somebody wants the drug, it probably would not be paid for. So we want to make our views patient-centric here, that there might be other avenues that patients may have access to this drug. Okay. Thank you for the opportunity.

Adjournment

DR. LIEU: Thank you, Dr. Pazdur.

We will now adjourn the morning session and break for lunch. We will convene at 1:15 p.m. Eastern Time. That's 1:15 p.m. Eastern Time. Panel members, please remember that there will be no chatting or discussion of the meeting topics during the break amongst yourselves or with any

member of the audience. Additionally, for the panel, you should plan to reconvene at 1:05 p.m. Eastern Time to ensure you're seated before we reconvene at 1:15. Thank you.

(Whereupon, at 1:15 p.m., the morning session was adjourned.)