Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
September 26, 2024

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

Topic: During the morning session, the Committee discussed 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 reflect broad approvals in the intent to treat patient populations agnostic of programmed death cell ligand-1 (PD-L1) expression. Cumulative data has 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 wanted the Committee's opinion on the:

- 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 discussed the existing supplemental biologics license 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 Co. and
- sBLA 125514/S-143 for KEYTRUDA (pembrolizumab) injection, submitted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

The Committee also discussed BLA 761417 for tislelizumab injection, submitted by BeiGene USA, Inc., for the same proposed indication.

During the afternoon session, the Committee discussed the use of immune checkpoint inhibitors in patients with metastatic or unresectable esophageal squamous cell carcinoma. The current labeling for approved checkpoint inhibitors in this indication reflect broad approvals in the intent to treat patient populations agnostic of programmed death cell ligand-1 (PD-L1) expression. Cumulative data has 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:

- 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 discussed the existing sBLAs which were approved for patients with previously untreated unresectable or metastatic esophageal squamous cell carcinoma:

- sBLA 125514/S-096 for KEYTRUDA (pembrolizumab) injection, submitted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.;
- sBLAs 125554/S-105 and S-106 for OPDIVO (nivolumab) injection, submitted by Bristol Myers-Squibb Co.; and
- sBLA 125377/S-122 for YERVOY (ipilimumab) injection, submitted by Bristol Myers-Squibb Co.

The Committee also discussed the new BLA 761380 for tislelizumab, submitted by BeiGene USA, Inc., for the same proposed indication.

These summary minutes for the September 26, 2024 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on December 20, 2024.

I certify that I attended the September 26, 2024 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Frimpong, PharmD	Christopher Lieu, MD
Acting Designated Federal Officer, ODAC	Acting Chairperson, ODAC

Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
September 26, 2024

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 26, 2024, at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA, Bristol Myers-Squibb Co., Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc, and BeiGene USA, Inc. The meeting was called to order by Christopher Lieu, MD (Acting Chairperson). The conflict of interest statement was read into the record by Joyce Frimpong, PharmD (Acting Designated Federal Officer). There were approximately 1,300 people in attendance. There were 8 Open Public Hearing (OPH) speaker presentations during the morning session and 1 OPH speaker during the afternoon session.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: During the morning session, the Committee discussed 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 reflect broad approvals in the intent to treat patient populations agnostic of programmed death cell ligand-1 (PD-L1) expression. Cumulative data has 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 wanted the Committee's opinion on the:

- 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 discussed the existing supplemental biologics license 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 Co. and
- sBLA 125514/S-143 for KEYTRUDA (pembrolizumab) injection, submitted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

The Committee also discussed BLA 761417 for tislelizumab injection, submitted by BeiGene USA, Inc., for the same proposed indication.

During the afternoon session, the Committee discussed the use of immune checkpoint inhibitors in patients with metastatic or unresectable esophageal squamous cell carcinoma. The current

labeling for approved checkpoint inhibitors in this indication reflect broad approvals in the intent to treat patient populations agnostic of programmed death cell ligand-1 (PD-L1) expression. Cumulative data has 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:

- 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 discussed the existing sBLAs which were approved for patients with previously untreated unresectable or metastatic esophageal squamous cell carcinoma:

- sBLA 125514/S-096 for KEYTRUDA (pembrolizumab) injection, submitted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.;
- sBLAs 125554/S-105 and S-106 for OPDIVO (nivolumab) injection, submitted by Bristol Myers-Squibb Co.; and
- sBLA 125377/S-122 for YERVOY (ipilimumab) injection, submitted by Bristol Myers-Squibb Co.

The Committee also discussed the new BLA 761380 for tislelizumab, submitted by BeiGene USA, Inc., for the same proposed indication.

Attendance:
Oncologic Drugs Advisory Committee Members Present (Voting): William J. Gradishar, MD; Ravi A. Madan, MD; Daniel Spratt, MD; Neil Vasan, MD, PhD

Oncologic Drugs Advisory Committee Members Not Present (Voting): Toni K. Choueiri, MD; Mark R. Conaway, PhD; Pamela L. Kunz, MD

Oncologic Drugs Advisory Committee Member Not Present (Non-Voting): Tara L. Frenkl, MD, MPH (*Industry Representative*)

Temporary Members (Voting): Dana Deighton (*Patient Representative; Afternoon Session Only*); Lori Dodd, PhD; Michael K. Gibson, MD, PhD FACP; Randy W. Hawkins MD (*Acting Consumer Representative*); James Randolph Hillard, MD *(Patient Representative; Morning Session Only)*; Christopher Lieu, MD (*Acting Chairperson*); Heidi McKean, MD; Jeffrey A. Meyerhardt, MD, MPH; Hanna Sanoff, MD, MPH; Katherine Van Loon, MD, MPH (*via video conferencing platform*)

FDA Participants (Non-Voting): Richard Pazdur, MD; Paul Kluetz, MD; Steven Lemery, MD, MHS; Sandra Casak, MD; Vaibhav Kumar, MD, MS *(Morning Session Only);* Geetika Srivastava MD, MSPH (Afternoon Session Only); Yiming Zhang, PhD (Morning Session Only); Zhou Feng, PhD *(Afternoon Session Only)*

Acting Designated Federal Officer (Non-Voting): Joyce Frimpong, PharmD

Open Public Hearing Speakers:
Morning session: Andrea Eidelman (Debbie's Dream Foundation: Curing Stomach Cancer); Aki Agata Smith (Hope for Stomach Cancer); Alison Kavchok; Kimberly Jeanette Wilson; Mindy Mintz Mordecai (Esophageal Cancer Action Network (ECAN)); Betsy Aaron; Ronald Kavchok; Pamela Hall

Afternoon session: Mintz Mordecai (ECAN)

The agenda was as follows:

Call to Order and Introduction of Committee	**Christopher Lieu, MD** Acting Chairperson, ODAC
Conflict of Interest Statement	**Joyce Frimpong, PharmD** Acting Designated Federal Officer, ODAC
FDA Introductory Remarks	**Steven Lemery, MD, MHS** Director Division of Oncology 3 (DO3) Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Bristol-Myers Squibb Co.**
Introduction	**Ian Waxman, MD** Vice President, Late Development Oncology Bristol Myers Squibb
Benefit Risk Profile in PD-L1 Subgroups	**Dana Walker, MD, MSCE** Vice President, Global Program Lead, Opdivo/Yervoy, GI & GU Bristol Myers Squibb
PD-L1 Testing in Clinical Practice	**Robert A. Anders, MD, PhD** Division of GI and Liver Pathology The Johns Hopkins University
Conclusion	**Ian Waxman, MD**
BREAK	
APPLICANT PRESENTATIONS	**Merck Sharp & Dohme LLC,** **a subsidiary of Merck & Co., Inc.**
Overview of Pembrolizumab and PD-L1 22C3 PharmDx	**M. Catherine Pietanza, MD** Vice President, Clinical Research Global Clinical Development, Late-Stage Oncology Merck Sharp & Dohme LLC

KEYNOTE-859 Results in HER2-Negative Gastric Cancer	**Pooja Bhagia, MD** Executive Director Global Clinical Development, Late-Stage Oncology Merck Sharp & Dohme LLC
Clinical Management of Gastric Cancer	**Yelena Y. Janjigian, MD** Chief Attending Gastrointestinal Oncology Memorial Sloan Kettering Cancer Center
Concluding Remarks	**M. Catherine Pietanza, MD**

BREAK

APPLICANT PRESENTATIONS	**BeiGene USA, Inc.**
Tislelizumab Background	**Mark Lanasa, MD, PhD** Senior Vice President Chief Medical Officer Solid Tumor BeiGene
Rationale 305 Results	**Mark Lanasa, MD, PhD**
PD-L1 Subgroup Analyses	**Mark Lanasa, MD, PhD**
Clinical Perspective	**Nataliya Uboha, MD, PhD** Hematology and Medical Oncology Associate Professor University of Wisconsin School of Medicine

FDA PRESENTATIONS

PD-L1 Expression and Immune Checkpoint Inhibitors for the Treatment of Patients with HER2 Negative Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma	**Vaibhav Kumar, MD, MS** Clinical Reviewer DO3, OOD, OND, CDER, FDA

BREAK

Clarifying Questions

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

LUNCH

Call to Order and Introduction of Committee	**Christopher Lieu, MD** Acting Chairperson, ODAC
Conflict of Interest Statement	**Joyce Frimpong, PharmD** Acting Designated Federal Officer, ODAC
FDA Introductory Remarks	**Sandra Casak, MD** Clinical Team Leader (Acting) Gastrointestinal Malignancies DO3, OOD, OND, CDER, FDA
APPLICANT PRESENTATIONS	**Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.**
Overview of Pembrolizumab and PD-L1 22C3 PharmDx	**M. Catherine Pietanza, MD**
KEYNOTE-590 Results in Esophageal Cancer	**Pooja Bhagia, MD**
Clinical Management of Esophageal Cancer	**Peter Enzinger, MD** Gastrointestinal Oncologist Dana-Farber Cancer Institute
Concluding Remarks	**M. Catherine Pietanza, MD**
BREAK	
APPLICANT PRESENTATIONS	**Bristol-Myers Squibb Co.**
Introduction	**Ian Waxman, MD**
Benefit Risk Profile in PD-L1 Subgroups	**Dana Walker, MD, MSCE**
Clinical Perspective	**Ronan J. Kelly, MBBCh, MBA, FASCO** Charles A. Sammons Cancer Center Baylor University Medical Center
Conclusion	**Ian Waxman, MD**
BREAK	
APPLICANT PRESENTATIONS	**BeiGene USA, Inc.**
Rationale-306 Results	**Mark Lanasa, MD, PhD**
PD-L1 Subgroup Analyses	**Mark Lanasa, MD, PhD**
Clinical Perspective	**Nataliya Uboha, MD, PhD**
FDA PRESENTATIONS	

PD-L1 Expression and Immune Checkpoint Inhibitors for the First Line Treatment of Metastatic or Unresectable Esophageal Squamous Cell Carcinoma (ESCC)	**Geetika Srivastava, MD, MSPH** Clinical Reviewer DO3, OOD, OND, CDER, FDA
Clarifying Questions	
BREAK	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

Morning Session

1. **DISCUSSION**: In patients with HER2-negative microsatellite stable gastric/gastroesophageal junction (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-inhibitors?

   Committee Discussion: *Overall, Committee members agreed that PD-L1 expression is a predictive biomarker for PD-1 inhibitors; however, there were concerns from the panel regarding the optimal PD-L1 cut-point. Some Committee members commented about the practical issues with the assay, standardization, and the real-life situation of having to re-biopsy patients. Although efficacy may also be lower in patients with PD-L1 less than 5 or 10 (compared to in patients with tumors PD-L1 greater than 10), given challenges with reliably assigning a specific PD-L1 level in a patient, the committee generally recommended using PD-L1 >1 as the threshold (i.e., PD-L1 positive) to designate the group of patients with a favorable risk-benefit assessment for pembrolizumab, nivolumab, or tislelizumab.*

   Please see the transcript for details of the Committee's discussion.

2. **VOTE**: 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 expression < 1?

   Vote Result: Yes: 2 No: 10 Abstain: 1

   Committee Discussion: *The majority of the Committee agreed the risk benefit assessment is not favorable for the use of PD-1 inhibitors in first line advanced HER2 negative microsatellite stable gastric/GEJ adenocarcinoma in patients with PD-L1 expression <1.*

Those who voted "No", commented on the negative data that was seen in PDL <1 cohort and that cutoff appeared to be at least reasonable. There was variability in where Committee members believe that the cut off should lie. The one Committee member who voted to abstain stated that their reasoning for voting this way was due to the insufficiency of data presented. Please see the transcript for details of the Committee's discussion.

Afternoon session

1. **DISCUSSION:** FDA would like the committee to discuss the risk and benefits of the treatment with anti PD-1 antibodies for the first line treatment of patients with metastatic or unresectable esophageal squamous cell carcinoma with PD-L1 expression <1.

   Committee Discussion: *Although the committee generally agreed that the favorable risk-benefit of PD-1 inhibitors was limited to patients with PD-L1 greater than 1, concerns regarding the review of the data included the sample sizes of the subgroup analyses. Please see the transcript for details of the Committee's discussion.*

2. **VOTE**: Is the risk: benefit assessment favorable for the use of anti-PD-1 antibodies in first line unresectable or metastatic esophageal squamous cell carcinoma with PD-L1 expression <1?

   Vote Result: Yes: 1 No: 11 Abstain: 1

   Committee Discussion: *The majority of the panel agreed that the benefit assessment is not favorable for the use of anti-PD-1 antibodies in first line unresectable or metastatic esophageal squamous cell carcinoma with PD-L1 expression <1. Although committee members noted the small sample sizes of the PD-L1 negative subgroups, overall the committee felt that patients with tumors that were PD-L1 of 1 or greater benefited from treatment with a PD-1 inhibitor; however, the totality of data in patients with PD-L1 expression of less than one did not support a favorable risk-benefit assessment. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:30 p.m.