Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
February 9, 2023

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed investigational new drug application (IND) 157775, for dostarlimab-gxly for injection, submitted by GlaxoSmithKline LLC. The proposed indication (use) for this product is as a single agent for the treatment of patients with locally advanced, treatment-naïve mismatch repair deficiency/microsatellite instability- high rectal cancer. FDA obtained the committee's input on the following: (1) the adequacy of the proposed trial(s) to evaluate the benefits and risks of dostarlimab for the proposed indication, including trial design, study population, clinical endpoint, and patient followup; and (2) the adequacy of the proposed data package to permit an assessment of the benefits and risks of dostarlimab for the proposed indication

These summary minutes for the February 9, 2023 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on June 13, 2023.

I certify that I attended the February 9, 2023 meeting of the Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Rhea Bhatt	Jorge A. Garcia, MD, FACP
Acting Designated Federal Officer, ODAC	Chairperson. ODAC

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
February 9, 2023

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on February 9, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and GlaskoSmithKline LLC. The meeting was called to order by Jorge A. Garcia, MD, FACP (Chairperson). The conflict of interest statement was read into the record by Rhea Bhatt (Acting Designated Federal Officer). There were approximately 759 people online. There were four Open Public Hearing (OPH) speaker presentations.

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

Agenda:
The committee discussed investigational new drug application (IND) 157775, for dostarlimab-gxly for injection, submitted by GlaxoSmithKline LLC. The proposed indication (use) for this product is as a single agent for the treatment of patients with locally advanced, treatment-naïve mismatch repair deficiency/microsatellite instability-high rectal cancer. FDA obtained the committee's input on the following: (1) the adequacy of the proposed trial(s) to evaluate the benefits and risks of dostarlimab for the proposed indication, including trial design, study population, clinical endpoint, and patient followup; and (2) the adequacy of the proposed data package to permit an assessment of the benefits and risks of dostarlimab for the proposed indication.

Attendance:
ODAC Members Present (Voting): Mark Conaway, PhD; Jorge A. Garcia, MD, FACP (Chairperson); Pamela L. Kunz, MD; Christopher H. Lieu, MD; Ravi A. Madan, MD; David E. Mitchell (Consumer Representative); Jorge J. Nieva, MD; Neil Vasan, MD, PhD

ODAC Members Not Present (Voting): Ranjana H. Advani, MD; Jaffer A. Ajani, MD; Alberto S. Pappo, MD; Ashley Rosko, MD; Anthony D. Sung, MD

ODAC Member Not Present (Non-Voting): Jonathan D. Cheng, MD (Industry Representative)

Acting Industry Representative to the Committee (Non-Voting): Albert Kraus, PhD

Temporary Members (Voting): George J. Chang, MD, MS; Kristen K. Ciombor, MD, MSCI; Evangelia Katsoulakis, MD; Paul V. Majkowski, Esq. (Patient Representative); John H. Park, MD

FDA Participants (Non-Voting): Richard Pazdur, MD; Paul Kluetz, MD; 'Lola Fashoyin-Aje, MD, MPH; Steven Lemery, MD, MHS; Sandra Casak, MD

Acting Designated Federal Officer (Non-Voting): Rhea Bhatt

Open Public Hearing Speakers: Sascha Roth; Kelly Bonito; Diana Zuckerman, PhD (National Center for Health Research); Steven J Cohen, MD

The agenda was as follows:

Call to Order	**Jorge A. Garcia, MD, FACP** Chairperson, ODAC
Introduction of Committee and Conflict of Interest Statement	**Rhea Bhatt** Acting Designated Federal Officer, ODAC
FDA Opening Remarks	**'Lola Fashoyin-Aje, MD, MPH** Deputy Director Division of Oncology Products 3 (DO3) Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**GlaxoSmithKline LLC (GSK)**
Introduction	**Ivan Diaz-Padilla, MD, PhD** Vice President, Clinical Development Head, Immuno-Oncology GSK
Standard of Care	**Andrea Cercek, MD** Head, Colorectal Cancer Section Co-Director Center for Young Onset Colorectal and GI Cancers Memorial Sloan Kettering Cancer Center (MSKCC)
Scientific Rationale Supporting cCR12	**J. Joshua Smith, MD, PhD, FACS** Surgical Oncologist and Associate Attending Surgeon MSKCC
MSKCC Study Design and Interim Results	**Andrea Cercek, MD**
GSK Design of Phase 2 Study	**Ivan Diaz-Padilla, MD, PhD**
GSK Commitment to Accelerated Approval	**Hesham Abdullah, MD, MSc** Senior Vice President, Global Head of Oncology Development, GSK
Moderator for Q&A	**Gordana Vlahovic, MD, MHS**

Vice President, Medicines Development Lead
GSK

GUEST SPEAKER PRESENTATION

Overview of the Management of Stage II-III Rectal Cancer	**Kimmie Ng, MD, MPH** Associate Chief, Division of Gastrointestinal Oncology Associate Professor of Medicine, Harvard Medical School Director, Young-Onset Colorectal Cancer Center Co-Director, Colon and Rectal Cancer Center Director of Translational Research in Gastrointestinal Cancer Dana-Farber Cancer Institute

FDA PRESENTATION

Dostarlimab Development in dMMR/MSI-H Locally Advanced Rectal Cancer	**Sandra Casak, MD** Clinical Team Leader Gastrointestinal Cancers Team DO3, OOD, OND, CDER, FDA

Clarifying Questions to Presenters

BREAK

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the adequacy of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment.

   Committee Discussion*: A majority of the Committee members stated that it is impractical to conduct a randomized trial due to the high response rate observed in the Memorial Sloan Kettering (MSK) trial preliminary data. The Committee discussed concerns regarding the variability of reviewing clinical complete response (cCR) and emphasized the importance of standardizing the cCR endpoint assessment (i.e., endoscopy and MRI conduct and interpretation) across clinical sites. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss the adequacy of the proposed clinical endpoints (i.e., complete clinical response rate, event free survival), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses.

   ***Committee Discussion**: The Committee discussed the limitations of evaluating event free survival and other time-to-event endpoints in single arm trials agreed that cCR rate alone was insufficient to characterize the benefit of treatment with dostarlimab. Committee members expressed uncertainty regarding whether the cCR12 rate could predict effects on long term outcomes. Committee members stated that there is a need to add additional endpoints into the clinical trials to characterize long-term benefit and assess the risks of treatment with dostarlimab in the locally advanced setting. Proposed additional endpoints included organ-preservation rate and quality of life endpoints that are critical to ensure the success of these approaches since morbidity of standard of care is known. Please see the transcript for details of the Committee's discussion.*

3. **DICUSSION:** Discuss the study population with Stage II/III LARC dMMR/MSI-H for a non-operative management approach.

   ***Committee Discussion**: Committee members agreed that the proposed non-operative management approach in the proposed study population of stage II and III LARC dMMR/MSI-H was reasonable to investigate . Committee members noted that there are no concerns regarding the inclusion of patients with Lynch syndrome, but noted that there may be surgical considerations due to the nature of the disease and the possibility of new recurrences. Due to the trial's single-arm design, Committee members agreed that stratifying enrollment of patients based on staging may be challenging. Committee members noted that stratifying based on tumor stage may be challenging based on the limitations of imaging to precisely identify tumor stage as well as the accuracy of identifying the number of pathological lymphi nodes. However, several members emphasized the importance of pre and post treatment staging since there is variability between what is seen objectively in endoscopic and imaging assessments and what is found pathologically. Please see the transcript for details of the Committee's discussion.*

4. **DISCUSSION:** Discuss the potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes.

   ***Committee Discussion**: Committee members agreed that clinical centers with less experience with non-operative management and with the interpretation of cCR assessment results should be included in the studies supporting a future marketing application and should receive appropriate training. Some members emphasized the importance of correctly identifying patients with dMMR/MSI-H and minimize the potential to expose falsely positive patients to dostarlimab. Some Committee members raised concerns about variability in biomarker testing across some community sites. Committee members agreed that it is important to see heterogeneity in study sites to further understand implications in the real world setting outside of the clinical setting (clinical trial participants, access to health care, site expertise, etc). Committee members generally agreed on the significance of educating*

and training the medical community on imaging and response assessment protocols (endoscopic evaluations, MRI, etc) and outlining the definition of a clinical complete response. Please see the transcript for details of the Committee's discussion.

5. **VOTE:** Will the data from the proposed single arm trials enrolling a total of 130 patients be sufficient to characterize the benefits and risks of dostarlimab in the curative intent setting for patients with dMMR/MSI-H LARC?

   Vote Result: Yes: 8 No: 5 Abstain: 0

   Committee Discussion*: The majority of the committee members agreed that the data from the proposed single arm trials is sufficient to characterize the benefits and risks of dostarlimab in the curative intent setting for patients with dMMR/MSI-H LARC. The committee members who voted "Yes", noted clinical complete response at 12 months was an adequate endpoint, but most members expressed concerns regarding the ability of cCR12 to predict the long term outcomes of dostarlimab treatment in patients with dMMR/MSI-H LARC. Committee members further noted the importance of quality of life and secondary and tertiary endpoints. The committee members who voted "No", noted that the existing data is insufficient to demonstrate the desired clinical outcome and also expressed concerns about the ability of the proposed endpoints to predict the long-term outcomes of dostarlimab in patients with dMMR/MSI-H LARC. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:30 p.m. Eastern Time.