U.S. FOOD & DRUG ADMINISTRATION

BLA 125514/S-139

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Janice Kim, PharmD, MS
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
RY34-B332
Rahway, NJ 07065

Dear Dr. Kim:

Please refer to your supplemental biologics license application (sBLA), dated December 16, 2022, received December 16, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) injection.

This Prior Approval sBLA provides for the following new indication:

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated

- for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at

FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.
Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for this application because necessary studies are impossible or highly impracticable.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4531-1 Complete Study KEYNOTE-671 including all final and planned interim analyses 3 and 4 of overall survival of adult patients with resectable stage II-IIIB NSCLC treated with pembrolizumab in combination with neoadjuvant platinum-containing chemotherapy followed by surgery and adjuvant pembrolizumab.

The timetable you submitted on October 9, 2023, states that you will conduct this study according to the following schedule:

Interim Report 3 Submission:	12/2024
Interim Report 4 Submission:	12/2025
Trial Completion:	12/2026
Final Report Submission:	07/2027

4531-2 Conduct an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of older adults ages 75 years and older, and United States (U.S.) racial and ethnic minority patients that is reflective of the U.S. population of patients with NSCLC, to further characterize the efficacy and safety of pembrolizumab in combination with platinum-containing chemotherapy and pembrolizumab as a single agent in these patients. In the analysis, include a sufficient number of patients enrolled in the U.S., ages 75 years and older, and a sufficient number of racial and ethnic minorities reflective of the incidence of NSCLC in each subpopulation to allow for interpretation of the results. The analyses should support comparative efficacy and safety outcome analyses between the aforementioned populations and White, and younger patients.

The timetable you submitted on October 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	10/2024
Final Protocol Submission (Analysis Plan):	04/2025
Study Completion:	12/2027
Final Report Submission:	12/2028

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 116833 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Idara Ojofeitimi, Chief, Project Management Staff, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Harpreet Singh, M.D.
Director
Division of Oncology 2
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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