BLA 125514/S-065

ACCELERATED APPROVAL

Merck Sharp & Dohme Corp.,
a subsidiary of Merck & Co., Inc.
Attention: Lynn May Brown, PhD
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, RY34-B293, P.O. Box 2000
Rahway, NJ 07065

Dear Dr. Brown:

Please refer to your supplemental biologics license application (sBLA), dated June 17, 2019, received June 17, 2019, submitted under section 351(a) of the Public Health Service Act for KEYTRUDA® (pembrolizumab) for injection, for intravenous use, 50 mg and for KEYTRUDA® (pembrolizumab) injection, for intravenous use, 100 mg/4 mL.

This Prior Approval supplemental new drug application provides for the following indication: KEYTRUDA®, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

APPROVAL & LABELING

We have completed our review of this application. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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,

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

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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).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 16, 2019. This requirement, along with required completion dates, is listed below.

This postmarketing study is subject to the reporting requirements of 21 CFR 601.70:

3700-1 Submit the analyses and datasets with the final report for PFS and OS for the ongoing clinical trial E7080-G000-309/KEYNOTE-775, entitled, "A Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

[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.

Draft Protocol Submission:	09/2017
Final Protocol Submission:	03/2018
Trial Completion:	09/2022
Interim /Other (Last Patient Enrolled)	04/2020
Final Report Submission:	03/2023

Submit clinical protocols to your IND 122753 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report 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 entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(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 study requirement for this application because necessary studies are impossible or highly impracticable in children. Endometrial cancer occurs, for the most part, in the adult population. The incidence of this cancer type in pediatric patients is extremely rare and as such, clinical pediatric studies are impossible or highly impracticable.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3700-2 Submit the analyses and datasets with the final report for PFS for the ongoing clinical trial E7080-G000-313/MK-7902-001, entitled, "A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2019
Trial Completion:	09/2022
Final Report Submission:	03/2023

If PFS is negative, the CSR will not be produced until positive OS interim analysis or when final OS analysis is reached. If PFS is positive at IA2 and OS is negative, the study will continue for OS**.**

3700-3 Submit the analyses and datasets with the final report for OS for the ongoing clinical trial E7080-G000-313/MK-7902-001, entitled, “A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma” to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2019
Trial Completion:	11/2023
Final Report Submission:	05/2024

3700-4 Commitment to support the availability of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are mismatch repair proficient through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission:	09/2023

3700-5 Commitment to support the availability of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are not microsatellite instability-high through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2024

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 122753 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 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

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry.[3]

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, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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/

JULIA A BEAVER
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