BLA 125514/S-089
BLA 125514/S-114

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENT

Merck Sharp & Dohme Corp.
Attention: David Evans, MBA
Director, Global Regulatory Affairs
1 Merck Drive, P.O. Box 100
Whitehouse Station, NJ 08889-0100

Dear Mr. Evans:

Please refer to your supplemental biologics license applications (sBLAs), dated May 29, 2020 (S-089) and June 29, 2021 (S-114), received May 29, 2020 and June 29, 2021, respectively, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) Injection, for intravenous use.

We acknowledge receipt of your amendment dated June 29, 2021, which constituted a complete response to our March 26, 2021, action letter for S-089.

Prior Approval supplemental biologics application (S-089) provides for a new indication for the treatment of patients with high-risk, early-stage triple negative breast cancer, in combination with chemotherapy as neoadjuvant treatment, then as a single agent as adjuvant treatment after surgery.

Prior Approval supplemental biologics application (S-114) provides for the use of pembrolizumab in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic triple negative breast cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test. This indication originally received Accelerated Approval on November 13, 2020, under S-088.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are 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).

SUBPART E FULFILLED

We approved BLA 125514/S-088 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of supplement BLA 125514/S-114 fulfills your commitments made under 21 CFR 601.41.

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

[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.

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 as triple negative breast cancer does not occur in pediatrics.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated May 29, 2020, reporting on the following postmarketing requirement listed in the November 13, 2020, supplement approval letter for BLA 125514/S-088.

3956-1 Submit the final overall survival (OS) analysis and datasets with the final report from clinical study KEYNOTE-355 titled; A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer, to confirm the clinical benefit of pembrolizumab plus chemotherapy in this setting. Or alternatively, submit the final report, including datasets, based on a prespecified analysis from a randomized trial with an endpoint of disease free or event free survival in patients with triple-negative breast cancer to verify and further characterize the clinical benefit of pembrolizumab.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our November 13, 2020, supplement approval letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments under BLA 125514/S089:

4118-1 Submit the final overall survival (OS) analysis and datasets with the final report from the ongoing clinical trial, KEYNOTE-522, titled “A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab Plus Chemotherapy vs. Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs. Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC).”

The timetable you submitted on July 20, 2021, states that you will conduct this study according to the following schedule:

Trial Completion: 12/2025
Final Report Submission: 06/2026

4118-2 Submit the final overall survival (OS) analysis and datasets with the final report from the ongoing clinical trial, KEYNOTE-355, titled "A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer."

The timetable you submitted on July 20, 2021, states that you will conduct this study according to the following schedule:

Trial Completion: 08/2021
Final Report Submission: 12/2021

Submit clinical protocols to your IND #124442 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. 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

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]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://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

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 Kim J. Robertson, Senior Regulatory Health Project Manager, at (301 796-1441, or kim.robertson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Director
Division of Oncology 1
Office of Oncologic Diseases
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/

LALEH AMIRI KORDESTANI
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