DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049/S-006

SUPPLEMENT APPROVAL

EMD Serono, Inc.
Attention: Jennifer L. Stevens, JD
Global Program Regulatory Lead, Immuno-Oncology
One Technology Place
Rockland, MA 02370

Dear Dr. Stevens:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 11, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Bavencio® (avelumab) Plus Inlyta® (axitinib), 800 mg Injection and 5 mg Oral.

This Prior Approval supplemental biologics application provides for a new indication for Bavencio® (avelumab) in combination with Inlyta® (axitinib) for first-line treatment of patients with advanced renal cell carcinoma (RCC).

APPROVAL & LABELING

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 study requirement for this application because necessary studies are impossible or highly impracticable.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3588-1 Provide the third interim analysis for overall survival analysis, datasets, and labeling with the final report from the clinical trial Javelin Renal 101 entitled; "A Phase 3, Multinational, Randomized, Open-Label, Parallel-Arm Study of Avelumab in Combination with Axitinib (INLYTA) versus Sunitinib (SUTENT) Monotherapy in the First-Line Treatment of Patients with Advanced Renal Cell Carcinoma."

The timetable you submitted on April 15, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2020

3588-2 Provide the final overall survival analysis, datasets, and labeling with the final report from clinical trial Javelin Renal 101 entitled; "A Phase 3, Multinational, Randomized, Open-Label, Parallel-Arm Study of Avelumab in Combination with Axitinib (INLYTA) versus Sunitinib (SUTENT) Monotherapy in the First-Line Treatment of Patients with Advanced Renal Cell Carcinoma."

The timetable you submitted on May 8, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2018
Trial Completion:	05/2024
Final Report Submission:	11/2024

3588-3 Reanalyze anti-drug antibodies (ADA) in the stored samples from 249 avelumab-treated patients with urothelial cancer (UC) (Study EMR100070-001) and 88 avelumab-treated patients with Merkel cell carcinoma (MCC) (Study EMR100070-003 Part A) that are evaluable for treatment-emergent ADA with the new ADA method. Using the updated treatment-emergent ADA data from the above two studies and emerging treatment-emergent ADA data from approximately 350 patients with UC in Study B9991001, conduct an assessment of the effect of treatment-emergent ADA on pharmacokinetics (PK) and key efficacy endpoints in patients with metastatic Merkel cell carcinoma or locally advanced or metastatic urothelial carcinoma. The final report should include the following analyses and datasets:

a) Individual trial analyses assessing the effects of ADA on the pharmacokinetics as geometric and arithmetic mean changes in drug clearance (CL) and C_{min} with corresponding standard deviation and statistical significance between ADA-negative and treatment-emergent ADA-positive patients.

b) The ADA rate; median time to detection of ADA; median duration of ADA positivity in months, and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.

c) Effect of "early" ADA (e.g., based on ADA at Week 5 or at another early visit with adequate justification) on efficacy outcome measures (overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR) if appropriate) in individual trials.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on May 8, 2019, states that you will conduct this study according to the following schedule:

Study Completion:	09/2020
Final Report Submission:	03/2021

3588-4 Using the emerging treatment-emergent ADA data from 116 patients with MCC in EMR100070-003 Part B, conduct an assessment of the effect of treatment-emergent ADA on PK and key efficacy endpoints in patients with metastatic Merkel cell carcinoma. The final report should include the following analyses and datasets:

a) Individual trial analyses assessing the effects of ADA on the pharmacokinetics (PK) as geometric and arithmetic mean changes in drug clearance (CL) and C_{min} with corresponding standard deviation and statistical significance between ADA-negative and treatment-emergent ADA-positive patients.

b) The ADA rate; median time to detection of ADA; median duration of ADA positivity in months, and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.

c) Effect of "early" ADA (e.g., based on ADA at Week 5 or at another early visit with adequate justification) on efficacy outcome measures (OS, PFS, ORR and DOR if appropriate) in individual trials.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on May 8, 2019, states that you will conduct this study according to the following schedule:

Study Completion:	06/2026
Final Report Submission:	12/2026

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 126065 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

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy 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

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/

AMNA IBRAHIM
05/14/2019 03:59:16 PM