DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-024

ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: John Huber, PhD
Associate Director, Global Regulatory, Safety and Biometrics-Oncology
PO Box 4000
Princeton, NJ 08543-4000

Dear Dr. Huber:

Please refer to your Supplemental Biologics License Application (sBLA), dated September 2, 2016, received September 2, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo® (nivolumab) Injection, for intravenous infusion, 40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial.

This Prior Approval supplemental biologics application provides for a new indication in locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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.

WAIVER OF HIGHLIGHTS SECTION

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: 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 MS Word format that includes the changes approved in this supplemental application.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trial to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If postmarketing clinical trial fails 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 January 24, 2017. This requirement, along with required completion dates, is listed below.

This clinical trial is subject to the reporting requirements of 21 CFR 601.70:

3151-1 Submit the final report with datasets for the clinical trial entitled "CA209274: A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab Versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma", examining the effect on disease-free survival.

Trial Completion:	07/2021
Final Report Submission:	02/2022

Submit clinical protocols to your IND 123867 for this product. In addition, under 21 CFR 601.70 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 trial, number of patients entered into each 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, 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 because this disease/condition does not exist in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3151-2 Conduct an updated duration of response analysis for the clinical trial CA209275 entitled, "A Phase 2 Single Arm Clinical Trial of Nivolumab in Subjects with Metastatic or Unresectable Urothelial Cancer Who Have Progressed or Recurred Following Treatment with a Platinum Agent." Present an updated median duration of response for patients with tumor PD-L1 expression ≥1% along with updated information on the range of the duration of response in all patients and in patients whose tumors have <1% and ≥PD-L1 staining. Submit the final report with datasets.

The timetable you submitted onJanuary 24, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	07/2017
Final Report Submission:	01/2018

3151-3 Submit to FDA the appropriate analytical and clinical validation study for the assay used to identify patients with urothelial cancer with PD-L1 ≥1% and <1% in clinical trial CA209275 entitled "A Phase 2 Single Arm Clinical Trial of Nivolumab in Subjects with Metastatic or Unresectable Urothelial Cancer Who Have Progressed or Recurred Following Treatment with a Platinum Agent" to inform product labeling for both the device and for nivolumab.

The timetable you submitted onJanuary 24, 2107, states that you will conduct this study according to the following schedule:

Final Report Submission:	08/2017

Submit clinical protocols to your IND 123867 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 trials, number of patients entered into each 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 PI (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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.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, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
02/02/2017