



BLA 125554/S-112

## SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company  
Attention: David H. Nguyen, PharmD, MBA  
Associate Director, Global Regulatory Strategy & Policy  
P.O. Box 5326  
Princeton, NJ 08543

Dear Dr. Nguyen:

Please refer to your supplemental biologics license application (sBLA), dated and received January 13, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo (nivolumab) injection.

This Prior Approval supplemental biologics license application provides for a new indication for nivolumab, in combination with platinum-doublet chemotherapy, for neoadjuvant treatment of adult patients with resectable (tumors  $\geq$  4cm or node positive) non-small cell lung cancer.

### **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,<sup>1</sup> 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 Effectuated” (CBE) supplements.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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*.<sup>2</sup>

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 Effectuated” (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 for neoadjuvant treatment of adult patients with resectable non-small cell lung cancer.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4245-1 Conduct clinical trial CA209816 titled, “Randomized, Open-Label, Phase 3 Trial of Nivolumab plus Ipilimumab or Nivolumab plus Platinum-Doublet Chemotherapy versus Platinum-Doublet Chemotherapy in Early Stage NSCLC (CheckMate 816: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 816),” to obtain additional long-term efficacy and safety data including the interim and final analysis of overall survival (OS).

The timetable you submitted on March 4, 2022, states that you will conduct this study according to the following schedule:

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<sup>2</sup> 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>.

Interim Study Report Submission: 04/2023

Trial Completion: 01/2025

Final Report Submission: 06/2025

Submit the datasets with the interim study report and final report submissions.

- 4245-2 Conduct an integrated analysis from postmarketing data sources or ongoing/planned clinical trials enrolling a sufficient representation of 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 safety and efficacy of nivolumab in combination with platinum-doublet chemotherapy 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 reflecting of the incidence of NSCLC in each subpopulation to allow for interpretation of the results.

The timetable you submitted on March 4, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2022

Final Protocol Submission: 03/2023

Study Completion: 03/2028

Final Report Submission: 09/2028

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 125872 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.*<sup>3</sup>

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.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup>

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

## **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 Kwadwo Korsah, Pharm.D., Regulatory Health Project Manager, at (301) 796-6630.

Sincerely,

*{See appended electronic signature page}*

Harpreet Singh, M.D.  
Director  
Division of Oncology 2 (DO 2)  
Office of Oncologic Diseases (OOD)  
Center for Drug Evaluation and Research

### **ENCLOSURE(S):**

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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<sup>3</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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**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.**  
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/s/  
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