



BLA 125554/S-097

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT**

Bristol-Myers Squibb Company
Attention: David 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 March 3, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo (nivolumab) injection.

This Prior Approval supplemental biologics application provides for the following new indication:

Adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

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,¹ that is identical to the enclosed labeling (text for the Prescribing Information,

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

and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effectuated” (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 Effectuated” (CBE) supplements, for which the 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 125554 supplement 024 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement BLA 125554 S-097 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 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 studies requirement for this application because necessary studies are impossible or highly impracticable to conduct in the pediatric population since the indication rarely if ever exists in children and an adequate study population does not exist.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated March 3, 2021, containing the final report for the following post-marketing requirement listed in the February 2, 2017, approval letter for BLA 125554/S-024.

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>.

- 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.

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all of your post-marketing requirement and post-marketing commitments acknowledged in our February 2, 2017, supplement approval letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your post-marketing commitments:

- 4125-1 Submit the second interim and final overall survival analysis and datasets from clinical trial CheckMate 274 titled, “A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab Versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma” to provide additional efficacy data for nivolumab as adjuvant therapy in patients with high-risk urothelial carcinoma that may inform product labeling.

The timetable you submitted on August 5, 2021, states that you will conduct this study according to the following schedule:

Interim Report Submission:	01/2024
Trial Completion:	05/2026
Final Report Submission:	11/2026

- 4125-2 Submit annual interim and final reports including meeting minutes and the charter from the Data Monitoring Committee analyzing the overall survival results of the upper tract urothelial carcinoma subgroup from clinical trial CheckMate 274 titled, “A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab Versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma”.

The timetable you submitted on August 13, 2021, states that you will conduct this study according to the following schedule:

Interim Report Submission #1:	12/2022
Interim Report Submission #2:	12/2023
Interim Report Submission #3:	12/2025
Final Report Submission:	11/2026

Submit clinical protocols to your IND 123867 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all post-marketing 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 post-marketing 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 post-marketing commitments should be prominently labeled “**Post-marketing Commitment Protocol**,” “**Post-marketing Commitment Final Report**,” or “**Post-marketing 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*.

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.³ Information and Instructions for completing the form can be found at FDA.gov.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).

³ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

If you have any questions, contact Jessica Kim, Regulatory Project Manager, at 240-402-0883 or Jessica.Kim1@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy 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/

AMNA IBRAHIM
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