Clinical Review Memorandum

From:	Lorraine Pelosof, Medical Officer, DOP2
Through:	Martha Donoghue, GI Oncology Team Leader, DOP2
To:	Patricia Keegan, Division Director, DOP2
Subject:	BLA 125554 Supplement 70 (SDN# 2476)
Submit Date:	June 18, 2018
Receipt Date:	June 18, 2018
PDUFA Date:	April 18, 2019
Product:	Nivolumab
Applicant:	Bristol Myers Squibb, Inc.
Date:	April 17, 2019

Executive Summary:

On June 18, 2018, Bristol Myers Squibb, Inc. (BMS) submitted this Prior Approval Supplement (PAS) requesting revision of the currently approved dose regimen of nivolumab as a single agent for the treatment of adult and pediatric patients 12 years of age and older and weighing 40 kg or more with Microsatellite Instability-High (MSI-H)/Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan from 240 mg intravenously (IV) every 2 weeks (240 mg IV Q2W) to *either 240 mg IV Q2W or 480 mg IV every 4 weeks* (480 mg IV Q4W). With this PAS, BMS also proposed to include the following new dosage regimen for pediatric patients 12 years of age and older weighing less than 40 kg:

> *For pediatric patients age 12 years and older and weighing less than 40 kg, the recommended dose is 3 mg/kg every 2 weeks, administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.*

On March 21, 2019, BMS submitted an amendment to this PAS requesting revision of the approved dosage regimen for nivolumab in combination with ipilimumab for the same patient population from nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 240 mg IV Q2W to nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then *nivolumab 240 mg IV Q2W or 480 mg IV Q4W*. Additionally, BMS proposed the same weight-based dosage for nivolumab (3 mg/kg every 2 weeks) following completion of 4 doses of the combination for pediatric patients 12 years of age and older who weigh less than 40 kg.

The proposed dosage of nivolumab as a single agent for the treatment of MSI-H/dMMR mCRC is as follows:

> *The recommended dose of OPDIVO for adult patients and for pediatric patients age 12 years and older and weighing more than 40 kg is either:*
> - *240 mg every 2 weeks or*

- *480 mg every 4 weeks*

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

For pediatric patients age 12 years and older and weighing less than 40 kg, the recommended dose is 3 mg/kg every 2 weeks, administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

The proposed dosage of nivolumab with ipilimumab for the treatment of MSI-H/dMMR mCRC is as follows:

The recommended dose of OPDIVO in combination with ipilimumab for adult patients and for pediatric patients age 12 years and older and weighing 40 kg or more is 3 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for 4 doses [see Clinical Studies (14.9)]. After completing 4 doses of the combination, administer OPDIVO as a single agent, either:

- *240 mg every 2 weeks, or*
- *480 mg every 4 weeks*

as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

The recommended dose of OPDIVO in combination with ipilimumab for pediatric patients age 12 years and older and weighing less than 40 kg is 3 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for 4 doses [see Clinical Studies (14.9)]. After completing 4 doses of the combination, administer OPDIVO 3 mg/kg as a single agent every 2 weeks as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

This reviewer concurs with BMS that the population PK data submitted support the proposed labeling update.

Agreement on the final proposed label between FDA and BMS was reached on April 12, 2019. This reviewer recommends approval of this revised version.

Background:

Nivolumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to programmed death receptor-1 (PD-1) and blocks its interaction with its ligands PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

On July 31, 2017, FDA granted accelerated approval to nivolumab for the treatment of patients 12 years and older with dMMR and MSI-H metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. On July 10, 2018, FDA granted accelerated approval to nivolumab in combination with ipilimumab for the treatment of adults and pediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

On June 18, 2018, BMS submitted this PAS requesting revision of the currently approved dose regimen of nivolumab as a single agent for the treatment of MSI-H/dMMR mCRC from 240 mg intravenously (IV) every 2 weeks (240 mg IV Q2W) to *either 240 IV Q2W or 480 mg IV every 4 weeks* (480 mg IV Q4W).

On March 21, 2019, BMS submitted an amendment to this PAS requesting revision of the approved dosage regimen for nivolumab in combination with ipilimumab to include the nivolumab 480 mg IV Q4W regimen as an option following completion of four doses of the combination of nivolumab/ipilimumab.

This submission includes labeling updates, a clinical overview, a population pharmacokinetic (PK) study report, and population PK datasets. As part of this review process, FDA clinical reviewers requested that BMS provide any available data on single agent nivolumab 480 mg IV Q4W for patients with CRC to support the proposed change in dosage regimen; however, BMS stated that there currently are no BMS-sponsored clinical trials with such data, (b) (4) .

This review contains an assessment of the information presented in this Prior Approval Supplement.

Review:

No new clinical pharmacology trials were conducted to support the proposed nivolumab 480 mg IV Q4W flat dosing for the MSI-H/dMMR mCRC indication. Similar to the approach used to support the 480 mg IV Q4W dosage regimen for other indications, BMS conducted a clinical pharmacology assessment using a population PK model-based simulation for this MSI-H/dMMR mCRC application. Specifically, BMS used data from 1084 patients who received nivolumab monotherapy, and for whom nivolumab concentration values were available, across 7 different clinical studies in the NSCLC 2L+, GBM, and MSI-H/dMMR mCRC settings. These data included values from 93 patients with MSI-H/dMMR mCRC. The range of body weights in the population PK dataset for adult patients with MSI-H/dMMR mCRC was 34.9-160.0 kg. Regarding pediatric patients, BMS stated that age and body weight do not have clinically significant effects on the exposure of nivolumab in adult patients with CRC and thus concluded that the exposures for pediatric patients with CRC who are older than 12 years are expected to be similar to adult patients with CRC of the same body weight.

According to the FDA Clinical Pharmacology review of the submitted data:

- For the 93 patients with MSI-H/dMMR mCRC, the geometric means of steady state C_{avg} and C_{min} achieved with 480 mg Q4W were 6.0% higher and 14.3% lower, respectively, compared to 3 mg/kg Q2W. Similar results were obtained when the exposures achieved with 480 mg IV Q4W and 240 mg IV Q2W were compared.
- The exposure-efficacy profiles based on C_{avg} and C_{min} for objective response rate (ORR) support the conclusion that efficacy resulting from treatment using the 480 mg IV Q4W dosage regimen will not be compromised when compared to the efficacy demonstrated for nivolumab using the 3 mg/kg IV Q2W dosage regimen.
- The 480 mg IV Q4W dosage regimen is unlikely to result in increased toxicity because the predicted C_{max} for this regimen is below the median of C_{max} for the 10 mg/kg IV Q2W dose.
- PK data supports the following proposed dosage regimens for pediatric patients ≥ 12 years of age:
    - ≥ 40 kg: OPDIVO 240 mg IV every 2 weeks or 480 mg IV every 4 weeks.
    - < 40 kg: OPDIVO 3 mg/kg IV every 2 weeks.
    - ≥ 40 kg: OPDIVO 3 mg/kg IV followed by ipilimumab 1 mg/kg IV on the same day every 3 weeks for 4 doses, then OPDIVO 240 mg IV every 2 weeks or 480 IV mg every 4 weeks.
    - < 40 kg: OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg IV on the same day every 3 weeks for 4 doses, then OPDIVO 3 mg/kg IV every 2 weeks.

Please see clinical pharmacology review for additional details.

Review of Efficacy:

BMS stated that exposure-response (E-R) analyses for efficacy or safety were not assessed for MSI-H/dMMR mCRC because data from only one dose level (3 mg/kg IV Q2W) was available. However, E-R analyses for overall survival (OS) following treatment with nivolumab have previously been conducted in patients with non-small cell lung cancer (NSCLC), advanced melanoma, and renal cell carcinoma (RCC). In each of those analyses, BMS concluded that nivolumab exposure was not a significant predictor of efficacy or safety. Additionally, BMS states that because most exposure measures are predicted to be higher with the 480 mg IV Q4W dosage regimen compared to the 3 mg/kg IV Q2W dosage regimen, a negative impact on efficacy is not expected in patients with MSI-H/dMMR mCRC.

Reviewer Comment:
An E-R analysis was not performed in patients with MSI-H/dMMR mCRC because only data from the 3 mg/kg IV Q2W dose level are available. In reviews for prior nivolumab supplements supporting the 480 mg IV Q4W dosage regimen for other indications, the FDA Clinical Pharmacology review team has noted that E-R analyses conducted at a single dose level may be confounded by changes in total body clearance over time. Because the previously-conducted E-R analyses for OS in patients with NSCLC, advanced melanoma, and RCC indicate that nivolumab exposure does not appear to be a significant predictor of efficacy or safety and because most of

the exposure measures are predicted to be higher with the 480 mg IV Q4W dosage regimen compared to the 3 mg/kg IV Q2W dosage regimen, additional efficacy analyses are unlikely to significantly change the overall benefit-risk analysis for the 480 mg IV Q4W flat dosage regimen for patients with MSI-H/dMMR mCRC.

Review of Safety:

No new safety analyses were conducted for this application. BMS stated that although the population PK model predicts the 480 mg Q4W C_{max1} to be approximately 117% higher than with the 3 mg/kg Q2W dosage regimen, that difference is reduced to 48% at steady state. Additionally, BMS stated that the 480 Q4W C_{max} is less than the 10 mg/kg Q2W C_{max} (based on an analysis of 157 patients receiving 10 mg/kg Q2W nivolumab from Studies MDX1106-01, MDX1106-03, and CA209005), which has an acceptable safety profile in other tumor types.

Reviewer Comment:
No additional safety analyses were performed for this application. However, previously-conducted E-R analyses for OS in patients with NSCLC, advanced melanoma, and RCC indicate that nivolumab exposure does not appear to be a significant predictor of safety or efficacy. Additionally, based on the population PK data and comparisons between the 480 mg Q4W flat dosage regimen and the 3 mg/kg Q2W and 10 mg/kg Q2W weight-based dosage regimens, the safety profile of is not expected to be negatively impacted by the 480 mg Q4W dosage regimen.

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/s/

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