# Division Director Summary Review

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| **Date** | April 18, 2019 |
| **From** | Patricia Keegan, M.D. |
| **Subject** | Division Director Summary Review |
| **BLA Supplement #** | BLA 125554/S-070 |
| **Applicant** | Bristol-Myers Squibb |
| **Date of Submission** | June 18, 2018 |
| **PDUFA Goal Date** | April 18, 2019 |
| **Proprietary Name** | OPDIVO |
| **Established or Proper Name** | nivolumab |
| **Dosage Form(s) and Strengths** | Injection; 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL solution dispensed in single dose vials |
| **Applicant Proposed Indication(s)/Population(s)** | None |
| **Action:** | *Approval* |
| **Approved/Recommended Indication(s)/Population(s)** (if applicable) | Proposed new dosage regimens<br>• OPDIVO 480 mg IV every 4 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity for adult patients and for pediatric patients age 12 years and older and weighing more than 40 kg<br>OPDIVO 3 mg/kg every 2 weeks administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity for pediatric patients weighing 40 kg or less<br>for the following approved indications:<br>• OPDIVO is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.<br>• OPDIVO is indicated, in combination with ipilimumab. for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan |

| Material Reviewed/Consulted | Names of discipline reviewers |
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| Regulatory Project Manager | Kwado Korsah |
| Medical Officer Review | Lorraine Pelosof |
| Clinical Pharmacology Reviews | Youwei N. Bi & Xiling Jiang |
| Quality Review | Lei N. Zhang |
| DMPPr | Sharon Mills |

OND=Office of New Drugs
DMPP=Division of Medical Policy Programs

# 1. Background

This supplement seeks approval of

- a new dosage regimen (480 mg intravenously every 4 weeks (480 Q4W)) in adults and pediatric patients weighing ≥ 40 kg,
- the modification of the approved dosage regimen of 240 mg intravenously every 2 weeks to limit this regimen to adults and pediatric patients ≥ 4 kg; and
- a new dosage regimen (3 mg/kg intravenously every 2 weeks) for pediatric patients less than 40 kg

for the approved indication for OPDIVO for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Bristol-Myers Squibb (BMS) submitted this application on June 18,2 018. On March 21, 2019, BMS submitted an amendment to this supplement requesting that the new dosage regimen (480 Q4W) and revisions to the approved dosage regimen also apply to indication approved on July 10, 2019 (sBLA 125554/S-63) for OPDIVO, in combination with ipilimumab, for treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This supplement relied primarily on pharmacokinetic modeling data as there were no clinical trials using the 480 mg Q4W dosage regimen.

The review team concurred that the 480 mg intravenously every 4 weeks dosage regimen would provide exposures that are comparable to that achieved in adults and pediatric patients ≥ 40 kg with the approved dosage regimen for these indications, based on the pharmacokinetic model. Thus, there is confidence that the efficacy results can be extrapolated to this new dosage regimen. The pharmacokinetic modeling data support a conclusion that the dosage regimen is reasonably safe with one exception, i.e., patients aged 12 years and older with a body mass of less than 40 kg. For patients less than 40 kg, the endotoxin exposure would exceed established limits under USP. Therefore, the 480 Q4W regimen is approved only for patients 12 years and older with a body mass of 40 kg or more.

In addition, the review team concurred with modification of the approved regimen of 240 mg intravenously every 2 weeks, to limit this dosage regimen to adults and pediatric patients ≥ 40 kg and the inclusion of the dosage regimen of nivolumab 3 mg/kg intravenously every 2 weeks for pediatric patients with a body mass of less than 40 kg.

Consistent with approval of the indication for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, the Oncology Center for Excellence Pediatric Research Committee (OCE PeRC) concurred that safety and efficacy data in adults should be extrapolated to adolescents (ages 12 to less than 18 years) for the new dosage regimen and that a waiver should be granted for patients less than 12 years of age, based on the rarity of these cancers in this subpopulation of pediatric patients.

## 2. Product Quality

The application contained no new CMC quality information and was limited to the request for a waiver (categorical exclusion from the preparation) of an environmental assessment. The quality reviewer concluded that the proposed new dosage regimen would not significantly affect the quality of the environment and met the criteria for categorical exclusion under 21 CFR 25.31 (c).

## 3. Clinical Pharmacology

The clinical pharmacology review team concluded, based on well-characterized pharmacokinetic (PK) model that included data from 1084 patients across 7 clinical studies, that the steady-state nivolumab Cavg and Cmin with 480 mg Q4W were predicted to be comparable to exposures achieved with the 3 mg/kg Q2W and 240 mg/kg Q2W dosage regimens in adult patients.

The dosage regimen of OPDIVO 240 mg as an intravenous infusion every two weeks (Q2W) was approved for adolescent patients with MSI-H or dMMR mCRC, regardless of body mass, based on evidence from adequate and well- controlled studies of OPDIVO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of nivolumab (i.e., the effect of weight on nivolumab clearance is moderate with a power coefficient estimated to be 0.584). However, Bristol-Myers Squibb's proposed limitation of the 240 mg Q2W regimen to adolescents ≥ 40 kg was considered appropriate, in light of the recently published oncology adolescent guidance (*Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry. U.S. FDA*: *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ UCM609513.pdf*).

For adolescent patients weighing less than 40 kg, the body-weight adjusted dosing regimen 3 mg/kg Q2W was determined to be acceptable as it would provide adequate exposure (thus not compromising efficacy).

## 4. Clinical

There were no clinical study data with the proposed dosage regimen of 480 Q4W. Safety and efficacy for this new regimen relied on the predicted pharmacokinetic profile based on the PK model, which indicated comparable exposure and Cmin with the proposed 480 Q4W and the dosage regimen studied in clinical trials supporting these approvals (nivolumab 3 mg/kg IV every 2 weeks). Additionally, the clinical review team relied on the PK properties of nivolumab based on the PK model, including that tumor type has no effect on nivolumab PK and relatively flat exposure-response and exposure-toxicity relationships for nivolumab in other tumor types, given the lack of exposure-response data in patients with MSI-H/dMMR metastatic colorectal cancer.

# 5. Pediatrics

Bristol-Myers Squibb's request for waiver of the full requirements for pediatric studies was reviewed by the Oncology Center for Excellence Pediatric Research Committee (OCE PeRC) on February 6, 2019. While OCE PeRC initially concurred with the request for full waiver, OCE PeRC subsequently concluded that safety and efficacy data in adults should be extrapolated to adolescents (ages 12 to less than 18 years) for the new dosage regimen and that a waiver should be granted for patients less than 12 years of age, based on the rarity of these cancers in this subpopulation of pediatric patients.

# 6. Labeling

- DOSAGE AND ADMINISTRATION section
  FDA agreed with the proposed revisions to the dosage regimen for these indications, which are:

  OPDIVO administered as a single agent:
  - ≥ 40 kg: OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks.
  - < 40 kg: OPDIVO 3 mg/kg every 2 weeks.

  OPDIVO administered in combination with ipilimumab
  - ≥ 40 kg: OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks.
  - < 40 kg: OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks.

- The proposed deletions to section 8.4 (Pediatric Use) to reflect the changes to the recommended dosage regimen for pediatric patients weighing less than 40 kg were accepted. The proposed additions were also deleted as this information is cross-referenced in this section and do not need to be re-stated.

- The clinical review team and DMPP consultant agreed with the proposed revisions to the Medication Guide.

# 7. Postmarketing

I concur with the recommendations of the review team that this application raised no new safety concerns that would require postmarketing studies under 505(o) or risk evaluation and mitigation strategies to ensure safe use.

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