Office of Clinical Pharmacology Review

BLA Number	BLA 125554/ S-70_SE2 (SDN 2476)
Link to EDR	\\CDSESUB1\evsprod\BLA125554\0344&0468
Submission Date	June 18, 2018
Submission Type	Standard
Communication Type	Review Addendum
Brand Name	OPDIVO
Generic Name	Nivolumab
Dosage Form and Strength	Injection: 40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial
Route of Administration	Intravenous infusion
Proposed Indication	Include a dosing regimen of 480 mg every 4 weeks as an IV infusion over 30 minutes for Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
Applicant	BMS
OCP Review Team	Youwei Bi, Ph.D.; Jiang Liu, Ph.D.; Xiling Jiang, Ph.D.; Hong Zhao, Ph.D.

This review addendum is to concur the proposed updated dosing regimen in pediatric patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer who are 12 years and older, in addition to the primary clinical pharmacology review dated Feb-12-2019 (Reference ID: 4389041):

- ≥ 40 kg: OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks.
- < 40 kg: OPDIVO 3 mg/kg every 2 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 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.

In our previous review, we concluded that the steady-state nivolumab Cavg and Cmin with 480 mg Q4W were expected to be comparable to 3 mg/kg Q2W and 240 mg/kg Q2W in adult patients with MSI-H/dMMR mCRC (within 20%: 6.0% higher and 14.3% lower, respectively) (Reference ID: 4389041). OPDIVO flat dosage of 240 mg Q2W was original approved for adolescent patients with MSI-H or dMMR mCRC 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). The newly updated 40 kg cut-off was to be in line with 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 is expected to be more appropriate than the flat dosing regimen for safety without a substantial risk of compromising efficacy.

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/

YOUWEI N BI
04/15/2019 02:15:04 PM

JIANG LIU
04/15/2019 02:37:31 PM

XILING JIANG
04/15/2019 02:46:03 PM

BRIAN P BOOTH on behalf of HONG ZHAO
04/15/2019 03:03:07 PM