

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
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.

Table of Contents

1. Executive Summary	2
1.1 Recommendation	3
1.2 Post-Marketing Requirements and Commitments	3
2. Clinical Pharmacology Questions.....	3
Is the proposed 480 mg Q4W flat dose supported by clinical pharmacology findings?.....	3
3. Appendix.....	6
3.1 Population Pharmacokinetic Analyses.....	6
3.2 Exposure-Response Analyses.....	8

1. Executive Summary

Opdivo (nivolumab; Bristol-Myers Squibb) is a human immunoglobulin subtype G4 (IgG4) monoclonal antibody that blocks the PD-1 pathway-mediated inhibition of the anti-tumor immune response by binding to the PD-1 receptor on T cells and blocking the interaction with its ligands PD-L1 and PD-L2. Opdivo is currently approved for multiple oncology indications. The original approved nivolumab dosage regimen is 3 mg/kg every 2 weeks (Q2W) based on clinical studies. Later, this dosage regimen was converted to the flat dosing regimen of 240 mg Q2W based on modeling and simulation and some clinical experience.

On March 5, 2018, the FDA added a new dosage regimen of 480 mg IV every 4 weeks (Q4W) for the majority of the approved nivolumab indications: metastatic melanoma, post-surgical resection of melanoma, metastatic non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), urothelial carcinoma (UC), classical Hodgkin's lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN) and hepatocellular carcinoma (HCC). The approval of the new dosage regimen was supported by the population PK simulations, flat dose/exposure response relationships for efficacy and safety in the patient populations with approved indications, and available clinical safety data with the 480 mg Q4W dosage regimen.

In the current submission, the applicant seeks approval of 480 mg once every 4 weeks (Q4W) in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer following the similar rationale in the previous applications for other approved indications. Overall, the steady-state C_{avg} and C_{min} with 480 mg Q4W were predicted to be comparable to 3 mg/kg Q2W in patients with MSI-H/dMMR mCRC (within 20%: 6.0% higher and 14.3% lower, respectively) based on Population Pharmacokinetic (popPK) simulation. Exposure-efficacy profiles based on C_{avg} and C_{min} for ORR suggest efficacy

profile with 480 mg Q4W will not be compromised compared to the efficacy profile of approved dosing regimen 3 mg/kg Q2W. No safety liability is expected with 480 mg Q4W as the predicted C_{max} were well below the median of C_{max} achieved with 10 mg/kg Q2W, which was tested to be tolerable in patients with solid tumors.

1.1 Recommendation

The Division of Clinical Pharmacology V and Division of Pharmacometrics in the Office of Clinical Pharmacology have reviewed the clinical pharmacology information in the current application and conclude that this supplemental NDA is acceptable to support the approval of nivolumab 480 mg Q4W for the treatment of patients with MSI-H/dMMR mCRC.

1.2 Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments are required.

2. Clinical Pharmacology Questions

Is the proposed 480 mg Q4W flat dose supported by clinical pharmacology findings?

Yes. The proposed 480 mg Q4W flat dose is supported by the population PK simulations and flat exposure-response relationships for efficacy and safety in the patients with MSI-H/dMMR mCRC.

Based on popPK simulations the steady-state exposure achieved with 480 mg Q4W were in general comparable to the exposure achieved with 3 mg/kg Q2W (Table 1). In 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 compared to same exposure metrics at 3 mg/kg Q2W. Results are similar when comparing exposure achieved with 480 mg Q4W and 240 mg Q2W.

No safety concerns were expected with the proposed 480 mg Q4W. No trend of exposure-response relationship for drug-related skin adverse event, gastrointestinal adverse event and diarrhea/colitis was observed for early nivolumab exposure (Figure 1). In addition, it was demonstrated in the previous review (Reference ID: 4229532) that the predicted C_{max} achieved with 480 mg Q4W was well below the median C_{max} achieved with 10 mg/kg Q2W, which was tested to be tolerable in patients with solid tumor.

Efficacy is unlikely to be compromised with 480 mg Q4W compared to 3 mg/kg Q2W in patients with MSI-H/dMMR mCRC. No obvious trend of significant exposure-ORR relationship was observed in 60 patients with MSI-H/dMMR mCRC (Figure 2). Extensive dose/exposure-response analyses for efficacy in other indications have been conducted in the previous review (Reference ID: 4229532) to demonstrate that a lower C_{trough} (within 20%) achieved with 480 mg Q4W compared to 3 mg/kg is unlikely to compromise the efficacy.

Overall, the comparable steady-state C_{min} between 480 mg Q4W and 3 mg/kg Q2W and lack of exposure-efficacy/safety relationship supported the use of nivolumab 480 mg Q4W in patients with MSI-H/dMMR mCRC.

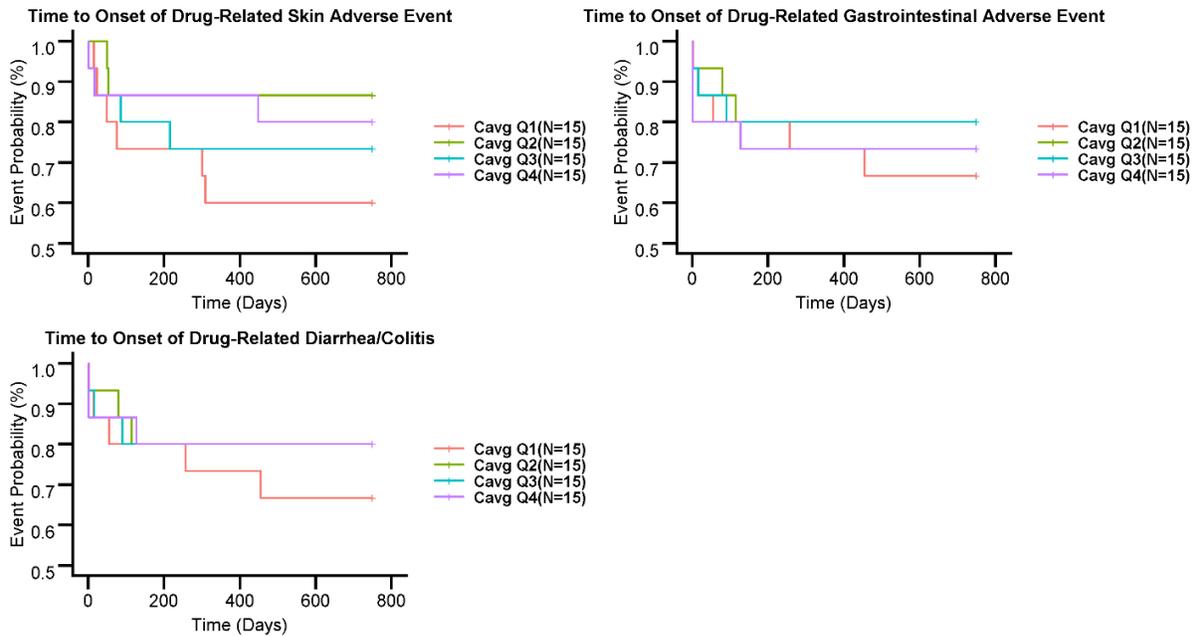
Table 1: Summary of Geometric Mean Exposure for Nivolumab 3 mg/kg Q2W, 240 mg Q2W or 480 mg Q4W in Patients with MSI-H/dMMR mCRC.

Cycle	Summary Exposure	G1-Nivo 3mg/kg Q2W GM	G2-Nivo 240mg Q2W GM	G3-Nivo 480mg Q4W GM	%Diff GM G3-G1	%Diff GM G3-G2
1st Cycle	C _{avg}	26.97	28.59	42.58	57.88	48.93
1st Cycle	C _{max}	57.66	61.11	122.57	112.57	100.57
1st Cycle	C _{min}	16.81	17.81	21.23	26.29	19.2
28 days	C _{avg}	33.71	35.73	42.58	26.31	19.17
28 days	C _{max}	74.62	79.1	122.57	64.26	54.96
28 days	C _{min}	27.3	28.93	21.23	-22.23	-26.62
SS	C _{avg}	88.44	93.74	93.74	5.99	0
SS	C _{max}	128.31	136.01	185.11	44.27	36.1
SS	C _{min}	68.68	72.8	58.89	-14.25	-19.11

SS: Steady State. Unit for summary exposure: µg/mL

Source: Reviewer's analysis based on dataset "param.xpt"

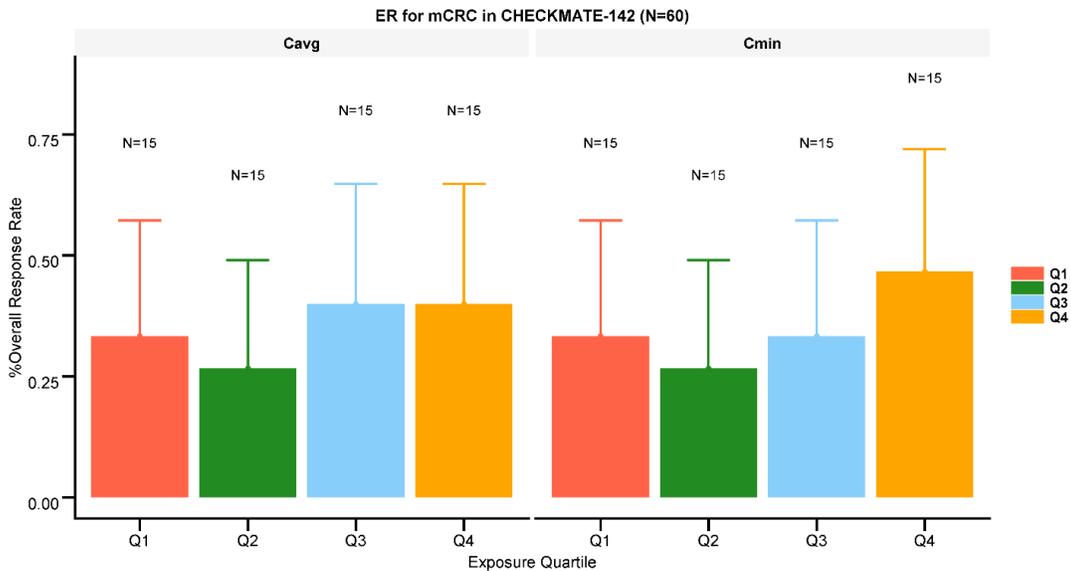
Figure 1: The Kaplan-Meier (KM) of Time to Onset of Drug-related Skin Adverse Event, Gastrointestinal Adverse Event or Diarrhea/Colitis Stratified by Exposure Quartiles in Patients with MSI-H/dMMR mCRC (N=60).



Note- Cavg: Average concentration in the first 28 days.

Source: Reviewer's analysis based on dataset "adaette.xpt"

Figure 2: Objective Response Rates (ORR) across Different Exposure Quartiles for Patients with MSI-H/dMMR mCRC (N=60).



Note- Cavg: Average concentration in the first 28 days. Cmin: Trough concentration in the first 28 days

Source: Reviewer's analysis based on dataset "adefresp.xpt"

3. Appendix

3.1 Population Pharmacokinetic Analyses

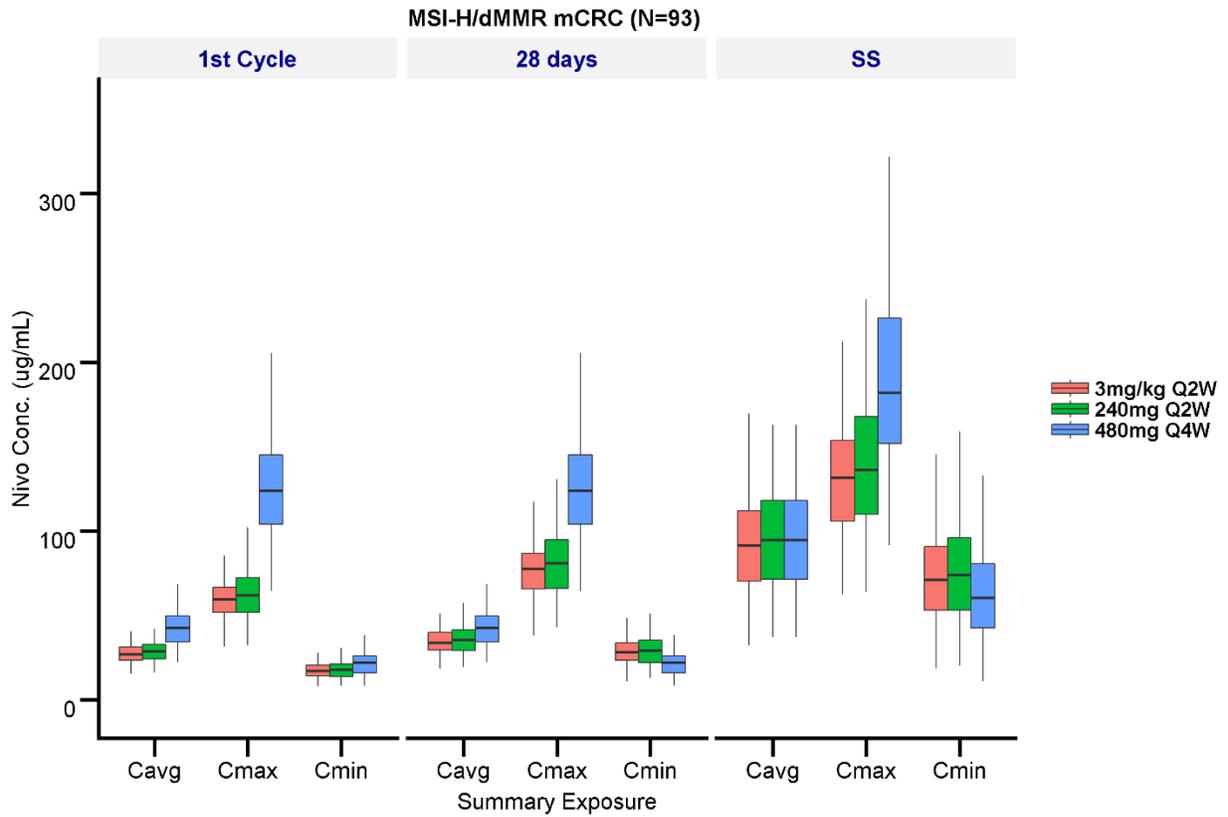
The goal of population PK analysis (popPK) was to apply established popPK model to compare summary measures of predicted nivolumab exposure produced by nivolumab doses of 480 mg Q4W relative to those produced by 3 mg/kg Q2W and 240 mg Q2W in patients with MSIH/dMMR mCRC.

The previous developed popPK model is a two-compartment, zero-order intravenous (IV) infusion model incorporating time-varying clearance (CL) described by a sigmoidal-Emax function with a proportional residual error model. It was evaluated in the previous review for use of nivolumab 240 mg Q2W in patients with MSIH/dMMR mCRC (Reference ID: 4119384). The previous popPK analysis included 1084 patients with various types of solid tumors, including NSCLC, CRC and GBM. MSI-H/dMMR mCRC patients made up 8.6% (93/1084) of the patients in the PPK dataset.

The estimates of post-hoc individual PK parameters from the 93 patients with MSI-H/dMMR mCRC were used to generate nivolumab concentration-time profiles up to a year for 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W dosage regimens. The summary exposure metrics time-averaged concentration, trough concentration, and peak concentration after 1st dose (C_{avg1st} , C_{max1st} and $C_{trough1st}$), in the first 28-day cycle (C_{avgd28} , C_{max28} and C_{mind28}) and in the steady state (C_{avgss} , C_{maxss} and $C_{troughss}$) were generated based on these profiles and provided in Table 1.

In general, the C_{avg} and C_{max} were higher with 480 mg Q4W; whereas the C_{min} was lower for 480 mg Q4W. 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 compared to same exposure metrics at 3 mg/kg Q2W. The difference in all exposure metrics between 480 mg Q4W and 3 mg/kg Q2W over the first 28-days of treatment is bigger compared to steady state. Results are similar when comparing exposure achieved with 480 mg Q4W and 240 mg Q2W. The distribution of key exposure metrics in boxplots in 93 patients with mCRC was presented in Figure 3. The geometric mean (with 90% CI) nivolumab concentration-time profiles for the 480 mg Q4W and 240 mg Q2W dosing regimens over the course of the first 28 days of treatment and at steady-state are presented in Figure 4.

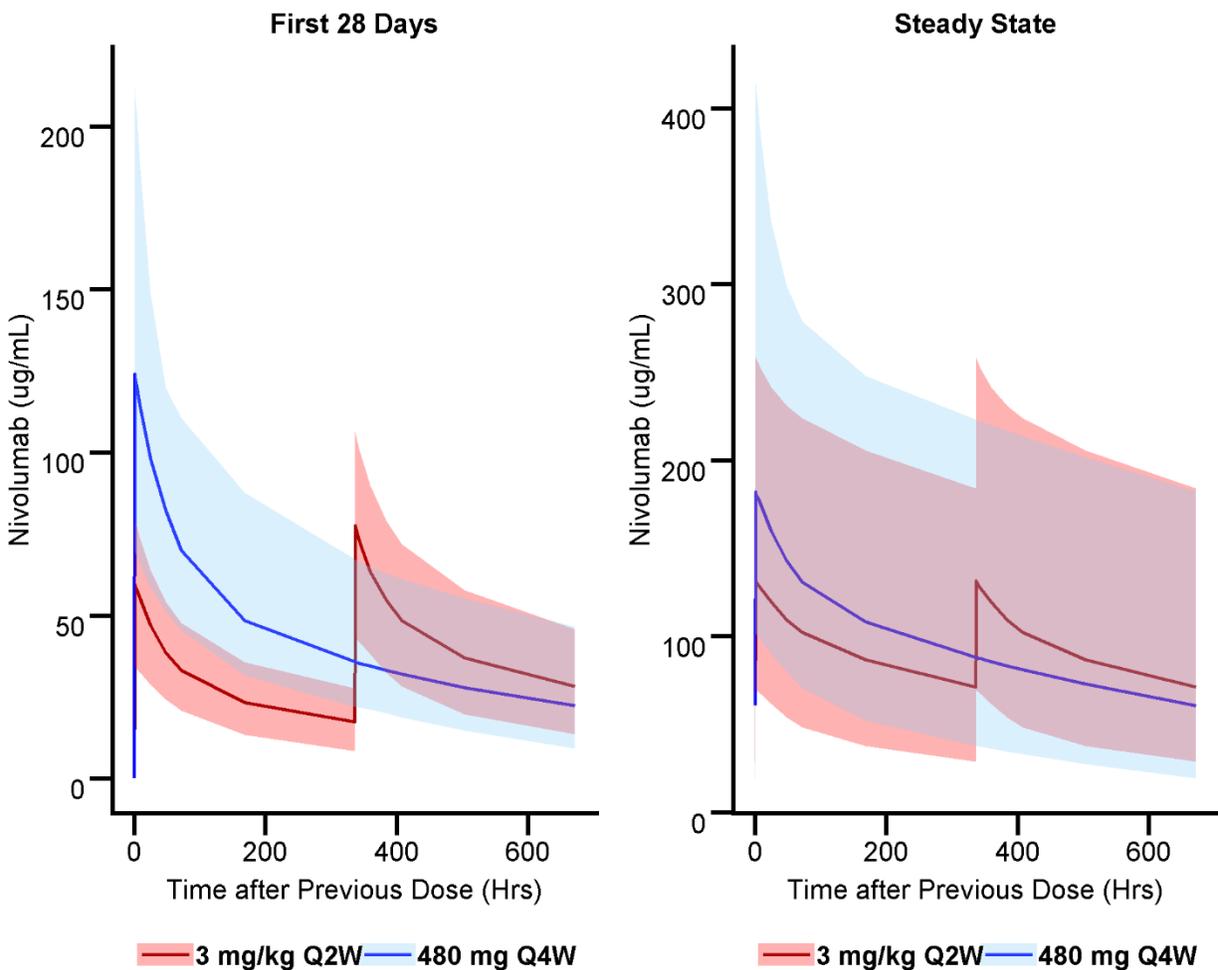
Figure 3: Boxplots of Exposure (3 mg/kg Q2W, 240mg Q2W, and 480 mg Q4W) in Patients with MSI-H/dMMR mCRC.



SS: Steady State

Source: Reviewer's analysis based on dataset "param.xpt"

Figure 4: Predicted Geometric Mean (with 90% CI) Nivolumab Concentration-Time Profiles (First 28 Days and Steady-State), by Dosing Regimen (3 mg/kg Q2W or 480 mg Q4W) in Patients with MSI-H/dMMR mCRC.



Source: Reviewer's analysis based on dataset "param.xpt"

3.2 Exposure-Response Analyses

The exposure-responses analyses were conducted independently by the reviewer using data from study CA209142 to explore the relationship between exposure of nivolumab and efficacy and safety in patients with mCRC. Efficacy endpoints included overall response rate (ORR). Logistic regression models were used to evaluate the relationship between nivolumab exposure and binary endpoint ORR.

The exposure response analyses for safety events were characterized based on drug-related skin adverse event, gastrointestinal adverse event and diarrhea/colitis as these were the most common drug-related adverse events. Time-to-event exposure-response models were developed for these safety endpoints using Cox proportional hazards (CPH) model.

Model-predicted average (Cavg28) and trough (Ctrough28) concentrations over the first 4 weeks were selected for the primary analyses of E-R. Sixty mCRC patients with evaluable nivolumab exposure were included in the ER analysis for efficacy and safety.

The crude rates of ORRs were compared among patients with mCRC in different exposure quartiles. No obvious trend of significant exposure-ORR relationship was observed (Figure 2). Logistic regression analysis also suggested no significant association between nivolumab exposure and ORR in patients with mCRC. Although the lack of ER relationship for ORR was limited by the narrow exposure range achieved within a single dosing regimen (3 mg/kg) and small sample size, extensive D-R and E-R analyses for efficacy have been conducted for other indications in the previous review (Reference ID: 4229532) to demonstrate that a lower Ctrough (difference within 20%) achieved with 480 mg Q4W compared to 3 mg/kg is unlikely to compromise the efficacy.

The effect of nivolumab exposure on drug-related AE was examined via Kaplan-Meier curves stratified by early nivolumab exposure Cavg28 (Figure 1). No trend of E-R relationship for drug-related skin adverse event, gastrointestinal adverse event and diarrhea/colitis was observed for early nivolumab exposure. Cox proportional hazards model also didn't reveal any significant association between nivolumab exposure and evaluated drug-related AE in patients with mCRC.

Signatures:

Youwei Bi, Ph.D.
Reviewer
Division of Pharmacometrics

Jiang Liu, Ph.D.
Team Leader
Division of Pharmacometrics

Xiling Jiang, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Hong Zhao, Ph.D.
Team Leader
Division of Clinical Pharmacology V

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/

XILING JIANG
02/11/2019 02:19:53 PM
No action needed.

YOUWEI N BI
02/11/2019 02:34:49 PM

JIANG LIU
02/11/2019 02:41:26 PM

HONG ZHAO
02/12/2019 09:06:23 AM
I concur.