NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project Orbis. FDA collaborated with Health Canada (HC), Israel's Ministry of Health (IMoH), Switzerland's Swissmedic (SMC) and Australia's Therapeutic Goods Administration (TGA). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies. In this document, the sections labeled as "data" and "the applicant's position" are completed by the applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities"

Application Type	Efficacy Supplements (SE1)
Application Number(s)	BLA 125554 – S-121
Priority or Standard	Standard
Submit Date(s)	December 13, 2022
Received Date(s)	December 13, 2022
PDUFA Goal Date	October 13, 2023
Division/Office	Division of Oncology 3
Review Completion Date	Refer to electronic stamp.
Established Name	Nivolumab
(Proposed) Trade Name	Opdivo
Pharmacologic Class	Immune checkpoint inhibitor
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.
Dosing Regimen	As a single agent for adult and pediatric patients weighing ≥40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks As a single agent for pediatric patients weighing <40 kg: 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks

	In combination: nivolumab 1 mg/kg IV every 3 weeks with ipilimumab 3 mg/kg intravenously for a maximum of 4 doses
Applicant Proposed Indication(s)/Population(s)	(b) (4) treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB and IIC melanoma, (b) (4) .
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB and Stage IIC melanoma.

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Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

Regulatory Project Manager	Amy Sessums, PharmD
Pharmacology/Toxicology Reviewer(s)	Not applicable
Pharmacology/Toxicology Team Leader(s)	Not applicable
Office of Clinical Pharmacology Reviewer(s)	Lauren Price, PharmD
Office of Clinical Pharmacology Team Leader(s)	Jason Moore, PharmD
Clinical Reviewer	Jamie Brewer, MD
Clinical Team Leader	Jamie Brewer, MD
Safety Analyst (if applicable)	Not applicable
Statistical Reviewer	Yiming Zhang, PhD
Statistical Team Leader	Joyce Cheng, PhD
Associate Director for Labeling (ADL)	Doris Auth, PharmD
Cross-Disciplinary Team Leader	Jamie Brewer, MD
Division Director (DHOT)	Not applicable
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Shenghui Tang, PhD
Division Director (OOD) / Signatory	'Lola Fashoyin-Aje, MD, MPH
Office Director (or designated signatory authority)	Not applicable.

Additional Reviewers of Application

OPQ	Lei Zhang, PhD
OPDP	Andrew Nguyen
OSI	Lee Pai-Scherf
OSE/DMEPA	Sali Mahmoud, PharmD

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AE	adverse event
AJCC	American Joint Committee on Cancer
API	application programming interface
AUC	area under the curve
BLA	biologics license application
BMS	Bristol Myers Squibb
CAR	carboplatin
Cavgss	time-averaged steady-state concentration
CFR	Code of Federal Regulations
CI	confidence interval
Cmaxss	maximum serum concentration at steady state
Cminss	minimum serum concentration at steady state
COVID-19	coronavirus disease 2019
CPH	Cox Proportional Hazards
CRF	case report form
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-cell lymphocyte antigen-4
DBL	database lock
DC	discontinuation
DMC	Data Monitoring Committee
DMFS	distant metastasis free survival
DSUR	Development Safety Update Report
DTIC	dacarbazine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer quality of life questionnaire core 30
E-R	exposure-response
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FA	final analysis
GBDS	Global Biometrics and Data Sciences
HCC	hepatocellular carcinoma
HR	hazard ratio
HSV-1	herpes simplex virus 1
IA	interim analysis
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

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IL-2	interleukin-2
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IND	investigational new drug
Ipi	ipilimumab
IRB	Institutional Review Board
IRT	Interactive Response Technology
IT	information technology
ITT	Intention-to-Treat
IV	intravenous
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mel	melanoma
mono	monotherapy
NA,N.A., N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
Nivo	nivolumab
NSCLC	non-small cell lung cancer
OCE	Oncology Center of Excellence
OESI	other events of special interest
ORR	objective response rate
OS	overall survival
PAC	paclitaxel
PBO	placebo
PD-1	programmed death receptor 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PFS2	progression-free survival after the next line of subsequent therapy
PK	pharmacokinetics
PPK	population pharmacokinetics
PRO	patient reported outcome
PS	performance score
QxW	every x weeks
RCC	renal cell carcinoma
REM	racial and ethnic minority
RFS	recurrence-free survival
RTOR	Real-Time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
SASUSAR	semi-annual suspected unexpected serious adverse reaction
sBLA	supplemental biologics license application
SCP	Summary of Clinical Pharmacology
SDV	source data verification
SIP	shared investigator platform

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SMP	site monitoring plan
s/p	status post
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reaction
TEP	positron emission tomography
US, U.S.	United States
USPI	United States Prescribing Information
vs	versus
WT	wild type

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1 Executive Summary

1.1. Product Introduction

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

Nivolumab received accelerated approval on December 22, 2014, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Nivolumab is approved for the treatment of several cancers, including for the following indications in patients with melanoma:

- adult and pediatric (12 years and older) patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting based on data from CHECKMATE-238
- adult and pediatric (12 years and older) patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab based on data from CHECKMATE-037, CHECKMATE-066 and CHECKMATE-067.

The Applicant is seeking approval of the following proposed indication:

Nivolumab (b) (4) treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB and IIC melanoma, (b) (4).

The Applicant's proposed dosing regimen by age group is as follows:

- opdivo 240 mg intravenously (IV) every 2 weeks or 480 mg IV every 4 weeks in adult patients and pediatric patients age 12 years and older and weighing 40 kg or more and,
- opdivo 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks in pediatric patients age 12 years and older and weighing less than 40 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from one adequate and well controlled trial, CA20976K, to support claims of safety and effectiveness for the proposed indication. Study CA20976K is a randomized, double-blind, multicenter trial which evaluated adjuvant nivolumab compared to placebo in 790 adult patients after complete resection of Stage IIB or IIC melanoma. There were no pediatric patients enrolled to this study. Patients were randomized to receive nivolumab 480 mg intravenously (IV) every 4 weeks (Q4W) or placebo IV Q4W for up to 12 months or until disease recurrence or unacceptable toxicity. The primary objective was to demonstrate the recurrence free survival (RFS) superiority of nivolumab versus placebo. The key secondary objective was to demonstrate the overall survival (OS) superiority of nivolumab versus placebo.

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The Application contains substantial evidence that nivolumab administered at 480 mg IV Q4W is safe and effective in the indicated population. CA20976K demonstrated a statistically significant and clinically meaningful improvement in RFS in patients randomized to the nivolumab arm compared to those who were randomized to the placebo arm (HR: 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001). The effectiveness of nivolumab in the pediatric population is based on extrapolation of data from studies of nivolumab IV in adult patient populations and safety and pharmacokinetic data submitted from Study CA209070, a multicenter, open-label, single-arm, dose confirmation and dose expansion study of nivolumab IV as a single agent and in combination with ipilimumab IV in pediatric patients aged 1 to 27 years with relapsed or refractory solid tumors (neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma/peripheral primitive neuroectodermal tumors (PNET), and other stolid tumors not otherwise specified (NOS)) and lymphoma (non-Hodgkin and Hodgkin lymphoma).

The safety profile of nivolumab has been well-characterized in clinical trials of nivolumab and in the post-market setting. No new safety signals were observed in CA20976K. Treatment with nivolumab is associated with the risk of severe and potentially prolonged immune-mediated adverse events (IMAEs). In Study CA20976K 32% of patients in the nivolumab arm experienced IMAEs with 50% of patients having ongoing symptoms at the time of the database lock. However, the overall observed adverse event profile was consistent with that expected in patients receiving anti-PD-1 therapy. As there were no pediatric patients enrolled in Study CA20976K, the safety of nivolumab IV in the pediatric population is based on extrapolation from studies of nivolumab IV in adult patients, the known similarities between adolescent melanoma and adult melanoma; comparable exposure profiles of nivolumab IV in pediatric and adult patients with solid tumors and hematological malignancies; and the relatively flat exposure-response curve for efficacy for nivolumab IV and review of safety data submitted from Study CA209070. In Study CA209070, the duration of study treatment was short (median duration of treatment among all patients treated with single agent nivolumab IV was 0.84 months); however, the types of adverse events observed in the pediatric population were generally consistent with the known safety profile of nivolumab IV.

The review team concludes that the magnitude of improvement in the observed RFS provides a benefit that outweighs the risks associated with systemic therapy in this patient population. Conclusions regarding the safety and efficacy of nivolumab IV for the treatment of pediatric patients with completely resected Stage IIB and IIC melanoma is based on extrapolation of data from adult studies and the review of safety and pharmacokinetic data submitted from Study CA209070 in Supplements 117, 118, and 119. Therefore, the review team recommends granting approval of the sBLA for the indication: nivolumab for the adjuvant treatment of adult and pediatric (12 years and older) patients with completely resected Stage IIB or IIC melanoma.

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1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

An estimated 97,610 cases of melanoma will be diagnosed in the U.S. in 2023. In 2023, melanoma is expected to represent 5% of all new cancer cases in the US and 1.3% of all cancer deaths. The 5-year relative survival of patients diagnosed with melanoma is 93.5% (SEER 2023). The 5-year melanoma specific survival (MSS) rates for patients with Stage IIB or IIC melanoma are 87% and 82%, respectively. This is comparable to the 5-year MSS rates for patients with Stage IIIA melanoma (93%) and Stage IIIB melanoma (83%) (Keung 2018). The reported 5-year recurrence free survival (RFS) rates were 54.7% (95% CI: 41.4 – 72.3) for patients with Stage IIB melanoma and 26.5% (95% CI: 12.8 – 55.1) for patients with Stage IIC melanoma. Reported 5-year RFS for Stage IIIA melanoma was 56% (95% CI: 37.0 – 84.7), Stage IIIB (42.9% [95% CI: 29.1 – 63.2]), State IIIC (13.7% [95% CI: 6.7 – 28.1]) and Stage IIID (23.8% [95% CI: 8.2 – 69.1]) (Bajaj 2020).

The Applicant submitted data from Study CA20976K (CHECKMATE76K) to support approval of nivolumab IV for the adjuvant treatment of adult and pediatric (12 years and older) patients with completely resected Stage IIB or IIC melanoma. Study CA20976k is a randomized, double-blind study evaluating nivolumab IV compared to placebo in patients with completely resected Stage IIB or IIC melanoma. Adult and pediatric patients aged 12 and older were allowed to enroll in the study, however no pediatric patients were enrolled. Substantial evidence of effectiveness has been established for the nivolumab 480 mg IV Q4W regimen in this patient population based on a demonstration of a statistically significant and clinically meaningful improvement in RFS in patients who were randomized to the nivolumab arm compared to those who were randomized to the placebo arm (HR: 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001). At the time of the RFS analysis, (b) (4) ; however based on this limited information, the descriptive OS results do not indicate that there is a detriment to survival. The study remains blinded.

The data submitted to support the safety review of nivolumab is adequate to characterize toxicity in patients with completely resected Stage IIB or IIC melanoma. The safety profile observed in patients in Study CA20976K who received nivolumab is generally consistent with what has been observed in other trials of single agent nivolumab and in what would be expected in a population with early-stage melanoma.

The review team recommends that nivolumab be approved for the adjuvant treatment of adult and pediatric (12 years and older) patients with completely resected Stage IIB or IIC melanoma. Immune-mediated adverse events can be a severe and potentially life-threatening risk associated with anti-PD-1 therapy. In CA20976K, 32% of patients in the nivolumab IV arm experienced IMAEs. In CHECKMATE-238, which evaluated adjuvant nivolumab IV in patients with completely resected Stage IIIB, IIC or Stage IV melanoma, 27% of patients experienced IMAEs.

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The type and severity of IMAEs observed in CA20976K appears comparable to what has been observed in other studies of nivolumab IV. It is noted that patients in CA20976K had a median duration of treatment of 11.04 months which is numerically longer than that reported in other studies of single agent nivolumab in patients with unresectable or metastatic melanoma (range: 2.8 to 6.5 months), but comparable to what was observed in patients with completely resected Stage IIIB, IIIC and Stage IV melanoma (median duration 11.5 months). This longer duration of drug exposure should be considered when evaluating the adverse event profile. Although nivolumab is associated with a risk of IMAEs, these risks are considered acceptable in the context of the observed clinical efficacy of nivolumab in the intended population and should be discussed between patients and their healthcare providers as part of the informed consent process. Risk minimization strategies have been instituted through management guidelines included in the product labeling and the Medical Guide.

The review team recommends approval for the adjuvant treatment of adult and pediatric (12 years and older) patients with completely resected Stage IIB or IIC melanoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Melanoma accounts for 5% of all cancers and 1.3% of all cancer deaths. • It is estimated that there will be 97,610 cases of melanoma diagnosed and 7,990 people will die of this disease in the US in 2023 (SEER 2023).	Melanoma is a serious and life-threatening condition. Despite surgery, patients with Stage IIB and IIC melanoma remain at risk for relapse and death.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The 5-year recurrence free survival (RFS) rates for patients with Stage IIB melanoma is 54.7% [95% CI: 41.4 – 72.3] and for Stage IIC melanoma is 26.5% [95% CI: 12.8 – 55.1]. • Among patients with cutaneous melanoma, 0.3% of new cases of melanoma and 0.1% of deaths occur in patients who are less than 20 years old.	
Current Treatment Options	• Patients with Stage II melanoma receive curative intent treatment with wide local excision. • After surgical excision, recommended treatment includes participation in a clinical trial, observation, or adjuvant therapy with pembrolizumab (e.g., per NCCN guidelines). • Pembrolizumab was approved in December 2021 for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB or IIC melanoma after complete resection based on = RFS superiority when compared to placebo (HR=0.65 995% CI: 0.46, 0.92], p < 0.00658). • IFN-α is also an approved therapy for the treatment of melanoma in the adjuvant setting, however it is associated with significant toxicity.	Recommended adjuvant management of Stage IIB or IIC melanoma includes clinical trial participation, observation or pembrolizumab. There exists a need for additional therapies that can further improve long-term outcomes.
Benefit	• In Study CA20976K, nivolumab demonstrated a statistically significant improvement in RFS compared to placebo (HR: 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001). • Median RFS for nivolumab was not reached at the time of the data cut-off. • (b) (4) at the time of the RFS analysis.	The study met its primary objective with nivolumab demonstrating RFS superiority over placebo per investigator assessment. RFS has been used as a regulatory endpoint in the adjuvant treatment of melanoma. The observed hazard ratio of RFS in the absence of evidence of an OS detriment is considered

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		clinically meaningful.
Risk and Risk Management	• The overall safety profile of nivolumab as adjuvant treatment for patients with Stage IIB or IIC melanoma in Study CA20976K was consistent with the safety profile previously observed in melanoma studies and no new safety signals were observed. • The incidence of IMAEs were noted to be numerically higher in patients in CA20976K compared to what is reported in the USPI, however a formal analysis of IMAEs based on duration of exposure to nivolumab was not conducted. Patients in CA20976K had a longer duration of exposure (11.04 months compared to a range of 2.8 to 6.5 months) to nivolumab IV in the adjuvant setting compared to patients in other studies of nivolumab in the advanced or metastatic setting, which may be a contributing factor. • The AE management guidelines were consistent with those used in other nivolumab studies and as described in the current USPI. • The descriptive OS summary for nivolumab compared to placebo did not show a detrimental effect on survival; however, the analysis was immature.	The safety of nivolumab has been well-characterized and the risks are considered acceptable in the context of the clinical efficacy in the adjuvant setting. Routine pharmacovigilance for late toxicities is warranted.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Section 8.1.2.14
		X	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that was not submitted in the application, but was considered in this review.			

X

Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Melanoma accounts for less than 5% of all skin cancers; however, it causes the greatest number of skin cancer-related deaths worldwide.[1] Because earlier stage disease has a higher incidence rate than later stage disease, most deaths from melanoma occur in individuals who are initially diagnosed with localized melanoma and not with advanced-stage disease, emphasizing the importance of intervention in the early adjuvant setting.[2 3]

Patients with Stage IIB/C resected melanoma are at high risk of melanoma recurrence (approximately one third of Stage IIB and one half of Stage IIC patients will recur within 5 years). Melanoma-specific survival of Stage IIB and IIC patients is similar to melanoma-specific survival of Stage IIIA and IIIB patients, respectively. 5-year and 10-year melanoma-specific survival is estimated to be 83%-87% and 72%-82%, respectively, for Stage IIB patients and 70%-82% and 58%-75%, respectively, for Stage IIC patients.[4,2]

Unlike other solid tumors, melanoma can affect young and middle-aged individuals (median age at diagnosis, 57 years).[5] Based on data from 2012 to 2016 in the US, the incidence rate of melanoma was highest in the non-Hispanic White race/ethnicity (28.0 per 100,000), followed by the American Indian/Alaska Native race/ethnicity (5.6 per 100,000) and the Hispanic race/ethnicity (4.6 per 100,000). The incidence rate among the Asian/Pacific Islander race/ethnicity was 1.3 per 100,000. The lowest incidence rate was among the Black race/ethnicity (1.0 per 100,000).[6]

Pediatric melanoma, a rare cancer, is usually defined as melanoma occurring in patients younger than 20 years, representing approximately 1% to 4% of all melanomas.[7],[8] Since melanoma is rare in the pediatric population, it is difficult to enroll patients in clinical studies; therefore, research on this population remains limited. Currently, the management of pediatric and adolescent melanoma is based primarily on well-established practice guidelines used for adult patients.[7]

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of Stage IIB and IIC melanoma. Despite undergoing a complete surgical resection, patients with Stage IIB or IIC melanoma may still be at increased risk of recurrent disease which includes the risk of distant metastases at the time of recurrence. Long-term prognosis can be comparable to patients with higher stage disease.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Standard of care for patients with clinical Stage II melanoma of all substages consists of wide surgical excision of the primary melanoma with the option to perform a sentinel lymph node

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biopsy. For Stage IIB/C melanomas (tumor thickness > 2.0 mm), the evaluation of the sentinel lymph node for disease involvement and a wide excision of the primary melanoma with 2-cm margins is recommended. Patients who have a positive sentinel lymph node are upstaged to Stage III and can undergo either surveillance of the nodal basin with ultrasound or complete lymph node dissection. Per current guidelines, patients with node positive disease may be offered nivolumab, pembrolizumab, dabrafenib/trametinib (for patients with a BRAF V600 activating mutation), or observation in the adjuvant setting. Current treatment recommendations for patients with a negative sentinel lymph node or for patients in whom a sentinel lymph node biopsy was not conducted for any reason is observation with periodic surveillance to detect disease recurrence. In addition to observation for patients with Stage IIB or IIC melanoma, adjuvant pembrolizumab is also a recommended treatment option in the NCCN guidelines after a clinician has a detailed discussion with a patient taking into consideration treatment benefits and risks.[9,10]

Currently, only 1 approved treatment option, Pembrolizumab, exists for Stage IIB/C resected melanoma patients, resulting in a high unmet need. In Dec-2021, pembrolizumab (Keytruda, Merck) was approved for the adjuvant treatment of adult and pediatric (≥ 12 years of age) patients with Stage IIB or IIC melanoma following complete resection and is the only approved treatment option available for these patients.

The FDA's Assessment:
FDA agrees with the Applicant's description of current treatment options for Stage IIB and IIC melanoma. The poor tolerability and inconsistently demonstrated overall survival advantage of interferon-alpha have limited its use.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Nivolumab (Opdivo®; BMS-936558, MDX-1106, ONO-4538) monotherapy was first approved by the US FDA for the treatment of unresectable or metastatic melanoma on 22-Dec-2014 and is currently approved for many additional tumor types, including treatment of urothelial carcinoma, NSCLC, RCC, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, and adjuvant treatment of Stage III/IV resected melanoma, resected esophageal cancer or gastroesophageal junction cancer, esophageal squamous cell carcinoma, and microsatellite instability-high/ mismatch repair deficient colorectal cancer.

Nivolumab was also approved in combination with:

- Ipilimumab for the treatment of unresectable or metastatic melanoma, RCC, microsatellite instability-high/mismatch repair deficient colorectal cancer, HCC, NSCLC, malignant pleural mesothelioma, and esophageal squamous cell carcinoma.
- Ipilimumab and 2 cycles of platinum-doublet chemotherapy for metastatic or recurrent NSCLC.

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- Cabozantinib for RCC.
- Chemotherapy for gastric cancer, gastroesophageal junction, esophageal adenocarcinoma, neoadjuvant treatment of resectable NSCLC, and esophageal squamous cell carcinoma.
- Relatlimab in a fixed dose combination (Opdualag) for unresectable or metastatic melanoma.

The FDA's Assessment:
The FDA agrees with the Applicant's summary of the marketing history of nivolumab.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 1: Applicant - Key Regulatory Milestones for Study CA20976K

Date	Regulatory Milestone
13-Jun-2012	Administrative split of the nivolumab parent IND (100,052) and a new IND (115,195) was filed for the indication of Melanoma.
06-Jun-2019	Initial submission of CA20976K protocol.
09-Jul-2019	FDA advice letter received for Protocol CA20976K regarding collection of assessment results and statistical analysis plan.
20-Dec-2019	Submission of BMS response to FDA 09-Jul-2019 advice letter.
14-Sep-2022	Submission of CA20976K topline efficacy and safety data to support an sBLA and request for participation in RTOR and Orbis.
15-Sep-2022	Submission of Type B pre-sBLA Meeting Request to discuss adequacy of clinical data to support an sBLA submission.
19-Sep-2022	FDA Meeting Granted Received for a Type B pre-sBLA meeting on 14-Nov-2022.
28-Oct-2022	FDA Preliminary Meeting Comments Received.
02-Nov-2022	BMS requested to cancel pre-sBLA meeting. FDA issued Meeting Request Cancelled Letter with the Preliminary Comments serving as final responses.

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment of regulatory interactions in reference to this sBLA. In addition to the Applicant's summary description, this reviewer adds that FDA requested that the Applicant conduct sensitivity analyses of Study CA20976K to assess whether potential unblinding of investigators and patients to treatment assignment may have led to bias in the primary efficacy analysis of RFS.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 3 consulted OSI to discuss an audit of overall trial conduct. Three

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clinical investigators were selected for audit, Dr. Michele Del Vecchio (site # 37), Dr. Jacek Mackiewicz (site # 103), and Drs. Jeffrey Sosman/Sunandana Chandra (site # 132). The FDA review team reviewed study site characteristics and chose these sites based on the number of patients enrolled, performance of patients enrolled at these sites compared to the overall study population, frequencies of protocol deviations, and prior inspection history (either no history of prior inspection or remote history of prior inspection).

During the inspection of Site # 37 no discrepancies were identified between source documents and data line listings for patient enrollment. All patients enrolled at the site met eligibility criteria. A subset of records were reviewed for protocol deviations and SAEs and no unreported protocol deviations or AEs were noted. The imaging assessment dates at the site were compared to the dates of the imaging studies in the data listings, and no discrepancies concerning the dates and findings from radiographic exams and reports were identified.

During the inspection of Site # 103 it was noted that adverse events were not reported in four patients and concomitant medications were not reported in three patients. Laboratory results were also missing in two patients. OSI concluded that the unreported adverse events, concomitant medications and laboratory tests do not appear to be clinically significant and that based on the nature of the protocol deviations, it is unlikely these findings significantly affect overall reliability of the safety or efficacy data generated from the site (the adverse events were grade 1-2 and either known and included in the PI, or unrelated, and the unreported concomitant medications were not prohibited). There was no evidence of patient harm related to the described findings. The missing data entries were attributed to human error. Dr. Mackiewicz acknowledged the inspection findings and subsequently proposed a Corrective and Preventive Action Plan. This was reviewed and appears to be adequate. Source records to determine the primary efficacy measure of disease recurrence and survival were reviewed and compared with the data submitted to the BLA. No discrepancies were identified. Notwithstanding the above protocol deviations, the data generated by the site appear acceptable in support of the proposed indication.

During the inspection of Site # 132 FDA determined that all reviewed patients met protocol specified inclusion and exclusion criteria and that patients signed informed consent prior to study activities. No underreporting of AEs or significant protocol deviations were identified. No discrepancies were observed between source records and data submitted to the BLA for the primary efficacy endpoint. Five concomitant medications were unreported in one patient. There was no evidence of patient harm related to these unreported concomitant medications. Despite the unreported concomitant medications in one patient, the data generated from the site appear reliable.

Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in

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support of this BLA.]

4.2. Product Quality

The submission did not contain new product information.

4.3. Clinical Microbiology

The submission did not contain new Clinical Microbiology information.

4.4. Devices and Companion Diagnostic Issues

The submission did not require a device or companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody that is currently approved for multiple indications for the treatment of various solid and hematologic malignancies. BLA 125554/S-121 is an efficacy supplement intended to support approval of nivolumab for the adjuvant treatment of adult and pediatric patients 12 years and older with Stage IIB or IIC melanoma following complete resection. The new indication would revise an existing indication for the adjuvant treatment of patients with melanoma as follows:

- Previous indication: adjuvant treatment of adult and pediatric patients 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
- New proposed indication: adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB or IIC

The request for approval of the new proposed indication is based on the results of Study CA20976K, a Phase 3, randomized (2:1), double-blind study of adjuvant nivolumab IV (n=526) versus placebo (n=264) after complete resection of Stage IIB/C melanoma. Adolescents (≥12 years) were eligible to enroll but none entered the study. Patients received nivolumab (or placebo) 480 mg intravenously (IV) every 4 weeks (Q4W) for up to 12 months. The primary endpoint was recurrence-free survival (RFS). As of the data cut-off date for the planned interim analysis (June 28, 2022), nivolumab demonstrated a statistically significant improvement in RFS vs placebo (HR: 0.42 [95% CI: 0.30, 0.59]).

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In addition to Study CA20976K, the supplement includes a brief overview of clinical pharmacology information from Study CA20976K and cross-reference to previously submitted information including nivolumab pharmacokinetics (PK) in pediatric patients (Studies CA209070, CA209744, CA209908, and CA209915) and the rationale for extrapolation of efficacy to include adolescent patients.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in BLA 125554/S-121. This BLA supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized in Table 2.

Table 2: Key FDA Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal evidence of effectiveness	The primary evidence of effectiveness is the RFS hazard ratio of 0.42 (95% CI: 0.30, 0.59) showing a benefit for nivolumab compared to placebo in Study CA20976K (see **Section 8.1.2.8**). Efficacy in adolescent patients (≥12 years) is supported by an extrapolation approach including nivolumab PK and exposure-response (E-R) relationships.
General dosing instructions	The recommended nivolumab dosing regimens for the adjuvant treatment of patients with Stage IIB/C melanoma who have undergone complete resection are as follows: • Adults (any body weight) and adolescents with body weight ≥40 kg: nivolumab 240 mg IV Q2W or 480 mg IV Q4W • Adolescents with body weight <40 kg: nivolumab 3 mg/kg IV Q2W or 6 mg/kg IV Q4W Patients should be treated for up to one year until disease recurrence or unacceptable toxicity.
Immunogenicity	Among 378 evaluable patients treated with nivolumab IV in Study CA20976K, 2.6% (n=10) developed anti-nivolumab antibodies (ADAs). Among patients who developed ADAs, 2 of 10 developed neutralizing antibodies (NAb) against nivolumab IV. The observed incidence of anti-nivolumab antibodies and NAb were within the ranges previously observed for patients treated with nivolumab IV monotherapy (1.4% to 23.7% ADA+ and 0% to 2.8% NAb+. Immunogenicity information in the labeling was moved to Section 12.6 for consistency with updated guidance.
Labeling	The proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.

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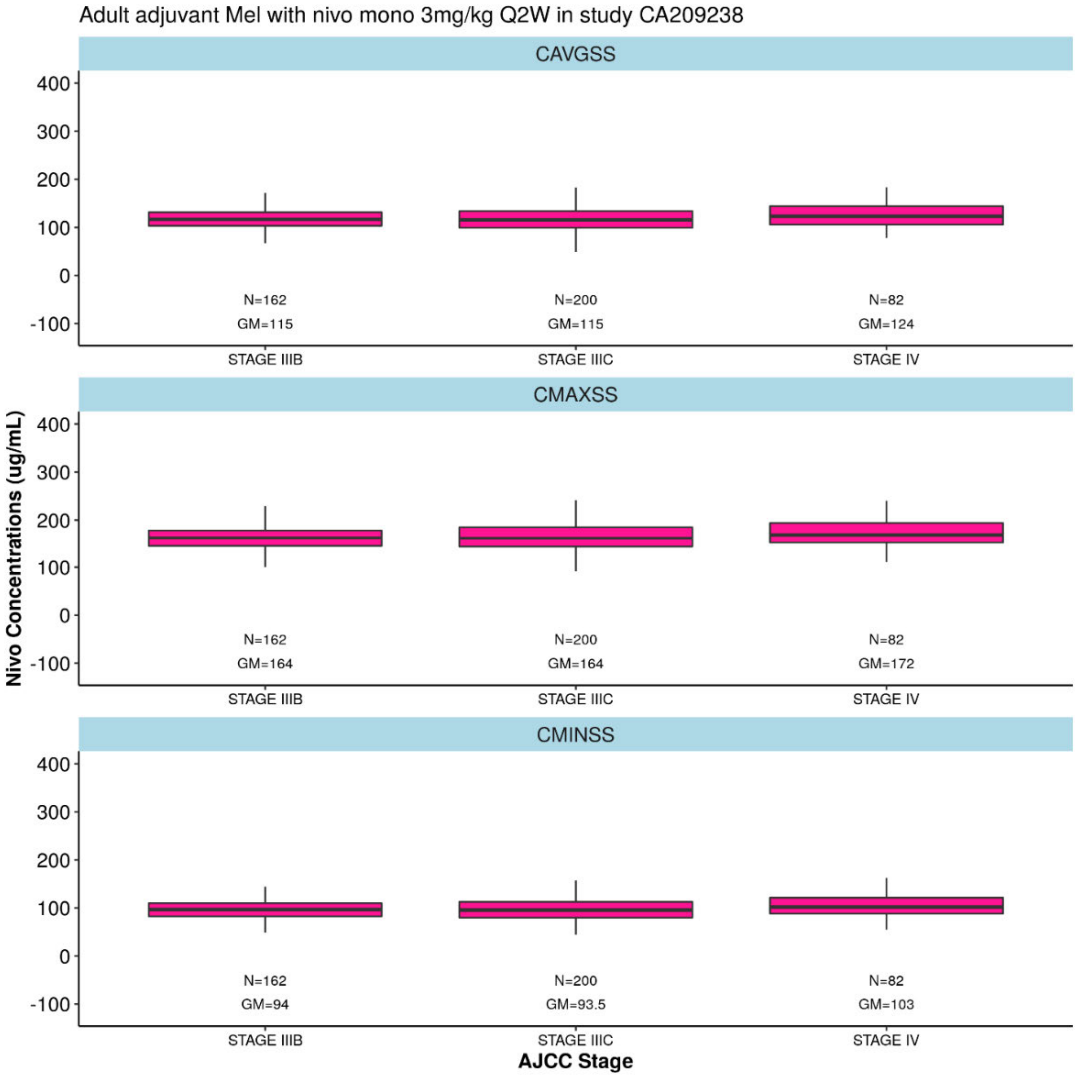
6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Figure 1: Applicant - Nivolumab Exposures (Cavgss, Cmaxss, Cminss) from Study CA209238 for 3 mg/kg Q2W Dosing in the Adjuvant Treatment of Stage III/IV Resected Melanoma by AJCC Staging



Analysis-Directory: /global/pkms/data/CA/209/adjmel-early-stage/prd/ppk/final/
Program Source: Analysis-Directory/R/scripts/2-model-app.Rmd
Source: Analysis-Directory/R/plots/expo-adult-sto-mel-mono-3mg.png

Figure 2: Applicant - Nivolumab Exposures (Cavgss, Cmaxss, Cminss) from Study CA209915 for 480 mg Q4W Dosing in the Adjuvant Treatment of Stage III/IV Resected Melanoma by AJCC Staging

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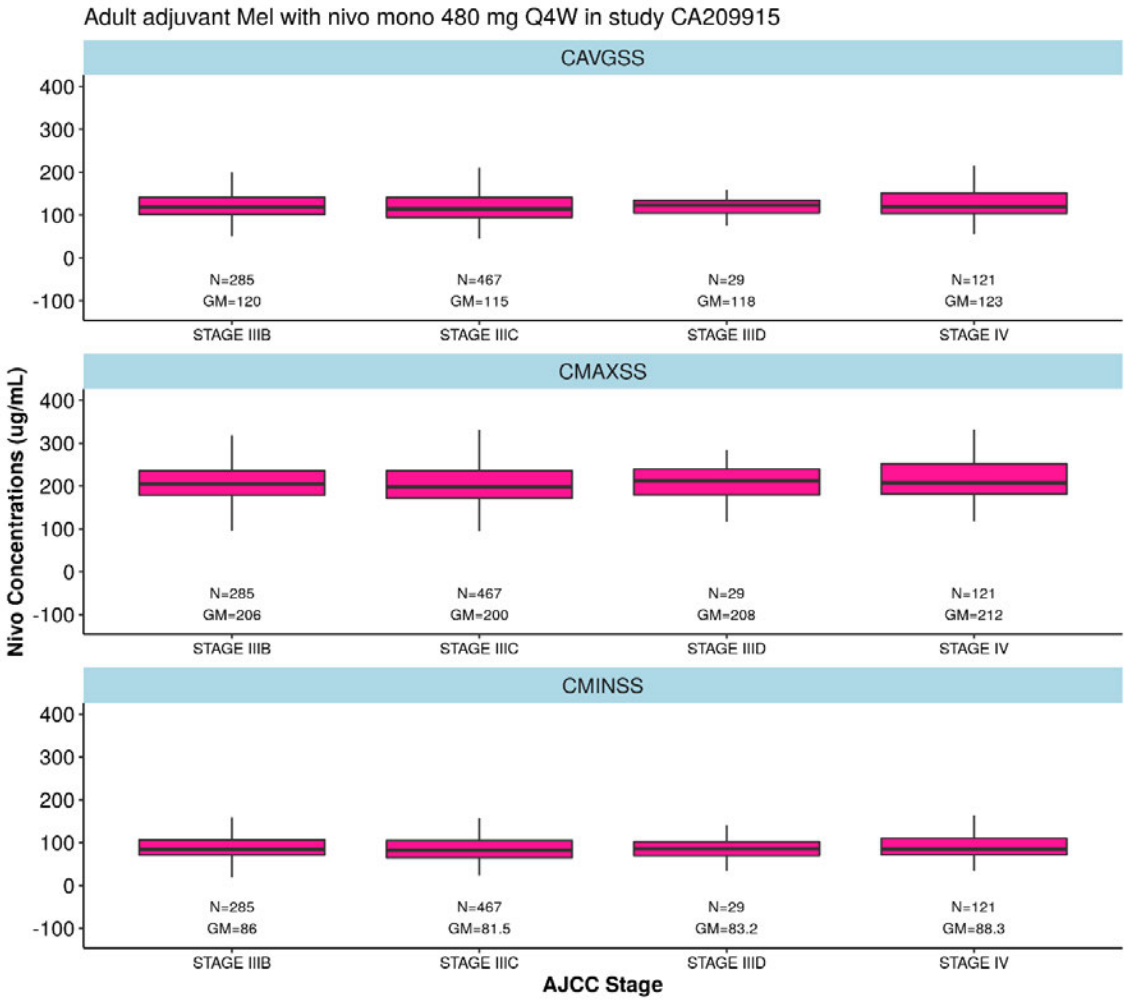

Analysis-Directory: /global/pkms/data/CA/209/adjmel-early-stage/prd/ppk/final/
Program Source: Analysis-Directory/R/scripts/2-model-app.Rmd
Source: Analysis-Directory/R/plots/expo-adult-sto-mel-mono-480.png

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Table 3: Applicant - Approved and Proposed Nivolumab Dosing Regimens for the Treatment of Melanoma in the Advanced and Adjuvant Setting for Adults and Adolescents

Indication	Approved Adult Dosing Regimens	Proposed Adult Dosing Regimens	Proposed Adolescent Dosing Regimens
Advanced Melanoma	240 mg Q2W or 480 mg Q4W	NA	**≥ 40 kg**: Nivo 240 mg Q2W or 480 mg Q4W **< 40 kg**: Nivo 3 mg/kg Q2W or 6 mg/kg Q4W
Adjuvant Treatment Resected Stage III/IV Melanoma	240 mg Q2W or 480 mg Q4W	NA	**≥ 40 kg**: Nivo 240 mg Q2W or 480 mg Q4W **< 40 kg**: Nivo 3 mg/kg Q2W or 6 mg/kg Q4W
Adjuvant Treatment Resected Stage IIB/C	NA	240 mg Q2W or 480 mg Q4W	**≥ 40 kg**: Nivo 240 mg Q2W or 480 mg Q4W **< 40 kg**: Nivo 3 mg/kg Q2W or 6 mg/kg Q4W

The Applicant's Position:

Clinical Pharmacology

Based on FDA's agreement to waive the submission of PPK/E-R reports and SCP in future new nivolumab submissions included in the waiver request, (FDA Preliminary Comments to Type C Meeting, IND 142795 dated 23-Aug-2022), BMS does not plan to submit a clinical pharmacology summary for CA20976K.

Nivolumab doses of 240 mg Q2W or 480 mg Q4W are currently approved in adults in the US, EU, and several other countries for multiple indications, including for advanced melanoma and for the adjuvant treatment of resected Stage III/IV melanoma. The approved dosing regimens for melanoma were based on robust PPK and E-R safety and efficacy analyses.[11,12,13,14,15,16,17] In addition, extensive PK and E-R safety analyses across pediatric and adult studies were conducted to recommend an adolescent (≥ 12 to < 18 years) dosing regimen in advanced and resected Stage III/IV melanoma based on pediatric extrapolation principles.[18]

Approved and Proposed Nivolumab Dosing Regimens

Nivolumab dosing regimens for the treatment of melanoma include: 1) currently approved adult dosing regimens, 2) proposed dosing regimens for a parallel submission being reviewed in adolescents for advanced melanoma and Stage III/IV resected melanoma, and 3) proposed dosing regimens for the current submission in adults and adolescents with Stage IIB/C resected melanoma (Table 3).

Clinical Pharmacokinetics and Exposure-Response

Nivolumab PK and E-R relationships in Stage IIB/C resected melanoma from Study CA20976K are expected to be similar to the PK and E-R relationships in later Stage III/IV resected melanoma. This is supported by similar nivolumab exposures across subjects with Stage III/IV

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resected melanoma and similar RFS across Stage III/IV for the 3 mg/kg Q2W dosing regimen from Study CA209238[19] and for the 480 mg Q4W dosing regimen from Study CA209915[20] (Figure 1 and

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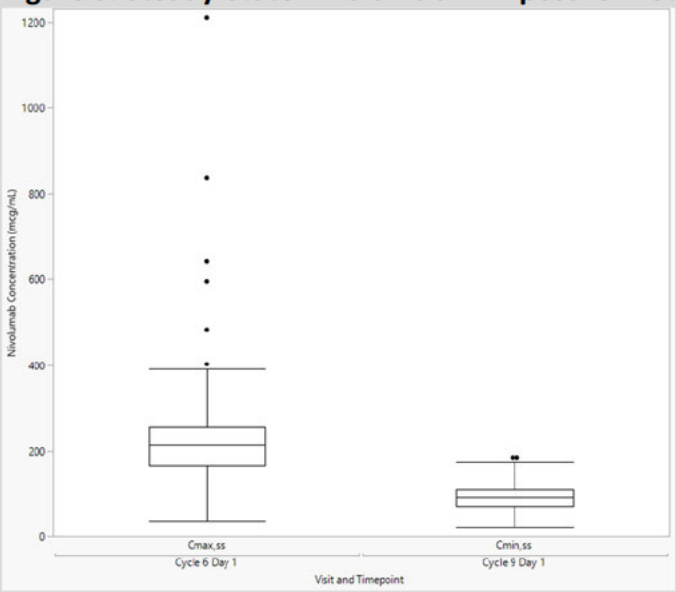
Figure 2).

The FDA's Assessment:

FDA agrees with the Applicant's position with the following clarifications or additions:

- Supplements 117, 118, and 119 were approved on February 15, 2023, during the review of the current supplement. These supplements supported extending existing indications for the treatment of unresectable or metastatic melanoma and for the adjuvant treatment of completely resected Stage III/IV melanoma to include adolescent patients (≥12 years). The approved recommended dosages of nivolumab in adolescent patients ≥12 years for these indications are:
  - Adolescent patients with body weight ≥40 kg: nivolumab 240 mg IV Q2W or 480 mg IV Q4W
  - Adolescent patients with body weight <40 kg: nivolumab 3 mg/kg IV Q2W or 6 mg/kg IV Q4W
- Figure 1 and Figure 2 display nivolumab exposure in other previously reviewed studies (CA209238 and CA209915). Observed steady-state nivolumab IV C_{max} and C_{min} in Study CA20976K are shown in Figure 3 and are consistent with the observed exposure in the aforementioned studies in Figure 1 and Figure 2.

Figure 3: Steady-State Nivolumab IV Exposure in Study CA20976K



Source: Reviewer's Analysis

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6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Rationale for Dosing Regimen Selection (Nivolumab 480 mg Q4W or 240 mg Q2W) for Pivotal Phase 3 Study CA20976K

A nivolumab dose of 480 mg administered as a 30-minute IV infusion Q4W was selected for this study based on available PK, safety, and efficacy data. An alternative nivolumab dosing option of 240 mg Q2W is also proposed in order to provide patients and clinicians with dosing flexibility and is consistent with the current approved dosing regimens of 240 mg Q2W or 480 mg Q4W in advanced melanoma and the adjuvant treatment of resected Stage III/IV melanoma (Table 3).

Given the prior extensive characterization of nivolumab E-R relationships for efficacy and safety that supported clinical equivalence of 240 mg Q2W or 480 mg Q4W in both advanced and adjuvant treatment of resected Stage III/IV melanoma, the same dosing regimens are proposed for Stage IIB/C resected melanoma patients.[12,13,14]

Adolescent subjects (≥ 12 to < 18 years) were eligible for enrollment in Study CA20976K; however, no adolescent subjects were enrolled in the study. Three sBLAs for adolescents, nivolumab monotherapy in advanced melanoma, nivolumab in combination with ipilimumab in advanced melanoma, and nivolumab monotherapy for the adjuvant treatment of resected Stage III/IV melanoma, are currently under review for approval (BLA 125554/S-117, S-118 and S-119, submitted 11-Aug-2022, Seq. Nos.1141, 1142, 1143). The same proposed dosing regimens for adolescents for the indications mentioned above (Table 2)are proposed for treatment of adolescent patients with resected Stage IIB/C melanoma. Selection of the dosing regimens for adolescents was based on an understanding of pediatric PK (1 to < 18 years), E-R safety relationships in adults and adolescents, and efficacy extrapolation principles.

Confirmation of the selected Doses and Regimens (Nivolumab 480 mg Q4W or 240 mg Q2W)

The dosing regimen in Study CA20976K (nivolumab 480 mg Q4W) and 240 mg Q2W are recommended based on the totality of clinical data from Study CA20976K, as well as the collective clinical experience of nivolumab monotherapy in melanoma.

- Clinical efficacy and safety data from pivotal Study CA20976K confirmed the favorable benefit-risk of nivolumab 480 mg Q4W as adjuvant treatment in subjects with completely resected Stage IIB/C melanoma.
- Adjuvant treatment with nivolumab 480 mg Q4W demonstrated statistically significant improvement over placebo in investigator-assessed RFS in all randomized subjects (see Section 8.1.2.8), supported by an acceptable safety profile (see Section 8.2), in subjects with completely resected Stage IIB/C melanoma.
- The stage of resected melanoma prior to treatment is not expected to impact nivolumab PK given similarity of PK across different stages of III/IV from CA209238 for 3 mg/kg Q2W dosing and from CM915 for 480 mg Q4W dosing (Figure 1 and Figure 2). Therefore,

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nivolumab PK is expected to be similar in resected stage IIB/C to that of resected stage III/IV.

- Previous PPK and E-R safety and efficacy analyses confirmed a favorable benefit-risk profile for adults in the adjuvant treatment of resected Stage III/IV melanoma[11,12] and advanced melanoma[13,14] for the 240 mg Q2W or 480 mg Q4W dosing regimens.
- Previous PPK and E-R safety analyses, as previously submitted and currently under review, show a favorable benefit-risk profile for adolescents in adjuvant treatment of melanoma Stage III/IV across adult and adolescent studies for the 240 mg Q2W or 480 mg Q4W dosing regimens for adolescents ≥40 kg and 3 mg/kg Q2W or 6 mg/kg Q4W for adolescents < 40 kg.
- Exposure differences between 240 mg Q2W and 480 mg Q4W have been extensively evaluated in advanced and adjuvant settings. Clinical equivalence of these posologies is supported by modeling and simulation with the same benefit-risk expected to apply across resected Stage IIB/C and III/IV melanoma.
- An alternative nivolumab dosing option of 240 mg Q2W provides patients and clinicians with flexibility and is consistent with the current approved regimens of 240 mg Q2W or 480 mg Q4W in advanced melanoma and the adjuvant treatment of resected Stage III/IV melanoma.
- No dose modifications are needed for any patient subgroups.

The FDA's Assessment:

FDA agrees with the Applicant's position with the following exceptions or clarifications:

- Supplements 117, 118, and 119 were approved on February 15, 2023, during the review of the current supplement. Refer to the Multidisciplinary Review for S-117/118/119 for detailed review of nivolumab IV PK and E-R relationships in pediatric patients and the rationale for extrapolation of nivolumab IV efficacy to include adolescent patients with melanoma.
- Weight-based dosing of nivolumab (3 mg/kg IV Q2W or 6 mg/kg IV Q4W) is recommended for adolescent patients with body weight <40 kg, consistent with the regimens approved in S-117/118/119.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No intrinsic or extrinsic factors were found to have a clinically relevant impact on nivolumab exposure. Therefore, no therapeutic individualization of nivolumab is recommended.

The FDA's Assessment:

Weight-based dosing of nivolumab IV is recommended for adolescent patients with body weight <40 kg. FDA agrees that other intrinsic or extrinsic factors do not have a clinically significant effect on nivolumab IV exposure and therefore do not require therapeutic individualization.

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6.2.2.3. Outstanding Issues

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees that there are no outstanding clinical pharmacology issues for the current supplement.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

No new information is provided in the current submission.

The FDA's Assessment:
The general pharmacology and pharmacokinetic characteristics of nivolumab IV have been reviewed previously. New information in the current supplement includes sparse PK and immunogenicity data from patients treated with nivolumab IV in Study CA20976K (Table 4). Nivolumab IV exposure and incidence of anti-drug antibody (ADA) and NAb formation in patients with Stage IIB/C melanoma were consistent with prior experience in other indications.

Table 4: Nivolumab IV Exposure and Immunogenicity Incidence in Study CA20976K

Parameter	Nivolumab IV-Treated Patients
Steady-state nivolumab C_{max} (µg/mL)	201 (47%)
Steady-state nivolumab C_{min} (µg/mL)	87.2 (35%)
ADA incidence	10/378 (2.6%)
NAb incidence	2/10 (20%)

Abbreviations: ADA = anti-drug antibody; NAb = neutralizing antibody
Notes: C_{max} and C_{min} reported as geometric mean (coefficient of variation [CV] %); NAb incidence reported out of total patients who developed ADAs.
Source: Reviewer's Analysis

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
Yes, the clinical pharmacology program provides evidence that the studied dosing regimen of nivolumab 480 mg administered Q4W as monotherapy in the adjuvant setting results in a favorable benefit-risk profile in subjects with completely resected Stage IIB/C melanoma.

The proposed alternative dosing regimen of nivolumab 240 mg Q2W is used in other approved nivolumab indications. It is expected to provide dosing schedule flexibility while offering a similar favorable benefit-risk profile for resected Stage IIB/C melanoma based on the totality of

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clinical data as well as previous extensive pharmacometric analyses (PPK and E-R) as described in Section 6.2.2.1.

The FDA's Assessment:

Yes. The primary evidence of effectiveness is the RFS hazard ratio of 0.42 (95% CI: 0.30, 0.59) showing a benefit for nivolumab IV compared to placebo in Study CA20976K (see **Section 8.1.2.8**). While Study CA20976K was open to adolescents (≥12 years), no adolescent patients enrolled. Extrapolation of results from adult patients enrolled in CA20976K to adolescent patients ≥12 years is supported based on: 1) nivolumab IV exposure in adolescent patients within the range observed in adult patients and below the maximum clinically tolerated dosage based on population PK modeling approaches including data from pediatric patients treated with nivolumab IV (with or without ipilimumab) in Studies CA209070, CA209744, CA209908, and CA209915, 2) similar and relatively flat E-R relationships in patients receiving nivolumab IV for adjuvant treatment of melanoma or treatment of advanced melanoma, and 3) lower predicted rates of Grade 2+ immune-mediated adverse events in adolescent patients (≥12 years) compared to adult patients based on exposure-response analyses for safety. Refer to the Multidisciplinary Review of S-117/118/119 for details.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes, the proposed dosing regimens of nivolumab 240 mg Q2W or 480 mg Q4W for adults and adolescents weighing ≥ 40 kg, and 3 mg/kg Q2W or 6 mg/kg Q4W for adolescents weighing < 40 kg, are appropriate for the indication being sought in this submission. These dosing regimens were selected based on the totality of clinical data from the nivolumab program as well as previous extensive pharmacometric analyses results (PPK and E-R) described above.

The FDA's Assessment:

FDA agrees with the Applicant's position. Population PK analyses for nivolumab IV including pediatric patients were previously reviewed. Adolescent patients (≥12 years) with advanced solid tumors have lower nivolumab IV clearance and volume of distribution compared to adults with melanoma after accounting for the effect of body weight. Higher nivolumab IV exposure in adolescent patients is expected only in the lowest body weight band (40-60 kg) and supports body weight-based dosing regimens for adolescent patients weighing <40 kg. Refer to the Multidisciplinary Review for S-117/118/119 for details.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

Dosing individualization is not recommended as described in Section 6.2.2.2.

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The FDA's Assessment:

Weight-based dosing of nivolumab IV is recommended for adolescent patients with body weight <40 kg (see **Section 6.3.2.2**). FDA agrees that other intrinsic or extrinsic factors including age, sex, race, baseline lactate dehydrogenase, PD-L1 expression, solid tumor type, tumor size, mild to severe renal impairment, and mild to moderate hepatic impairment) do not appear to have a clinically significant effect on nivolumab IV exposure and therefore do not require therapeutic individualization.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

There are no clinically relevant food-drug or drug-drug interactions with nivolumab in the adjuvant setting in melanoma subjects.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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Lauren Price, PharmD
Primary Reviewer

Jason Moore, PharmD
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

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Table 5: Applicant - Overview of Nivolumab Phase 3 Clinical Studies in Melanoma

Study #/Type	Study Design	Study Population	Treatment	Number of Subjects	Primary Efficacy Endpoint
			NIVOLUMAB MONOTHERAPY		
CA209037 Efficacy, Safety	Phase 3, randomized (2:1) open-label study of nivo vs investigator's choice (DTIC or PAC/CAR)	Advanced melanoma s/p anti-CTLA-4 therapy, and if BRAF mutation + s/p BRAF inhibitor	Nivo group: 3 mg/kg IV Q2W Investigator's choice: DTIC 1000 mg/m^2 IV Q3W or CAR (AUC 6) IV and PAC 175 mg/m^2 Q3W	N = 370 Treated (268 nivo and 102 IC) First 120 nivo-treated subjects with 6 months follow-up for ORR analysis	ORR and OS
CA209066 Efficacy, Safety	Phase 3, randomized (1:1) double blind study of nivo vs DTIC	Previously untreated, BRAF WT unresectable or metastatic melanoma	Nivo group: 3 mg/kg IV Q2W DTIC: 1000 mg/m^2 Q3W	N = 411 Treated (206 nivo)	OS
CA209067 Efficacy, Safety	Phase 3, randomized (1:1:1), double-blind study of nivo or nivo+ipi vs ipi	Previously untreated, unresectable or metastatic melanoma	Nivo group: nivo 3 mg/kg IV Q2W Nivo+Ipi group: nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses followed by nivo 3 mg/kg Q2W Ipi group: ipi 3 mg/kg Q3W for 4 doses	N = 937 Treated Nivo group: 313 Nivo+ipi group: 313 Ipi group: 311	PFS and OS
CA209238 Efficacy, Safety	Phase 3, randomized (1:1), double-blind study of nivo vs ipi	Completely resected Stage IIIb/c or Stage IV melanoma in adults and adolescents ≥15 years of age	Nivo group: nivo 3 mg/kg IV Q2W Ipi group: ipi 10 mg/kg Q3W for 4 doses then Q12W starting at Week 24	N = 905 Treated (452 nivo and 453 ipi)	RFS
CA209915 Efficacy, Safety	Phase 3, randomized (1:1), double-blind study of nivo+ipi vs nivo	Completely resected Stage IIIb/c/d or Stage IV melanoma in adults and adolescents ≥12 years of age	Nivo+Ipi group: nivo 240 mg Q2W + ipi 1 mg/kg Q6W Nivo group: nivo 480 mg Q4W	N = 1833 Treated Nivo+Ipi group: 916 Nivo group: 917	RFS
CA20976K Efficacy, Safety	Phase 3, randomized (2:1) double-blind study of nivo vs placebo	Completely resected Stage IIB/C melanoma in adults and adolescents ≥12 years of age	Nivo 480 mg Q4W for 12 months	N = 788 Treated Nivo group: 524 Placebo group: 264	RFS

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The Applicant's Position:
The current application for the adjuvant treatment of subjects with completely resected Stage IIB/C melanoma with nivolumab is based on the data from Study CA20976K. It is also supported by data from Study CA209238, which was the basis for approval of adjuvant nivolumab in completely resected Stage III and IV melanoma.

The FDA's Assessment:
FDA agrees with the Applicant's description of Study CA20976K and Study CA209238 which serve as the basis for this supplemental BLA application. Data to support the inclusion of pediatric patients aged 12 years and older in the proposed indication is based on extrapolation of data from studies of adult patients treated with nivolumab and safety and pharmacokinetic data from Study CA209070.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CA20976K

Trial Design

The Applicant's Description:
CA20976K is a Phase 3, randomized, double-blind study designed to evaluate the use of adjuvant immunotherapy with nivolumab IV vs placebo after complete resection of Stage IIB/C melanoma in adults and pediatric subjects ≥ 12 years old (Figure 4 and Table 6).

Subjects with resected Stage IIB/C melanoma and no evidence of disease were randomized to treatment with either nivolumab IV or placebo for a duration of 12 months. In the event of disease recurrence, subjects had the option to receive on-study open-label nivolumab IV treatment or receive treatment per local standard of care. Subjects randomized to placebo who experienced disease recurrence within 3 years after the last dose of placebo, and nivolumab-treated subjects who experienced recurrence greater than 6 months and within 3 years after completing treatment, were eligible to receive on-study open-label nivolumab IV treatment. Subjects with recurrent resectable disease were offered nivolumab IV for a maximum duration of 12 months, whereas subjects with recurrent unresectable or metastatic disease were offered nivolumab for a maximum of 24 months.

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Figure 4: Applicant - CA20976K Study Design Schematic

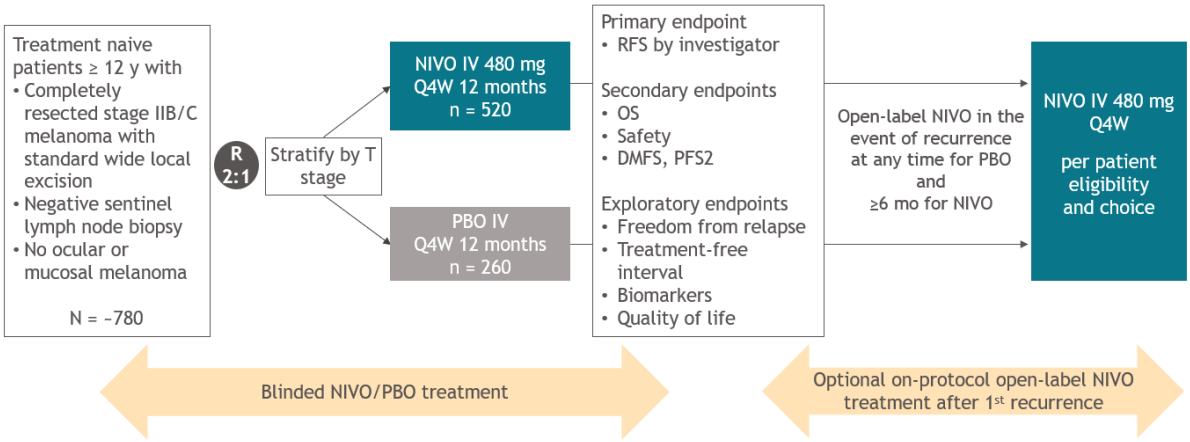

Table 6: Applicant - CA20976K Study Design Details

Design Aspect	Description
Trial Locations	986 subjects were enrolled at 129 sites in 20 countries (Australia, Austria, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Romania, Spain, Sweden, Switzerland, United Kingdom, and United States). After reviewing baseline demographics and clinical characteristics of the trial population and comparing to the overall melanoma population in the United States, the trial participants adequately represent the overall United States melanoma population.
Choice of Control Group	Placebo was chosen for the control arm, as the standard of care for Stage IIB/C melanoma after complete resection has been periodic surveillance only to detect disease recurrence.
Key Inclusion/Exclusion Criteria	**Key Inclusion Criteria** • Male and female adult and pediatric subjects (≥ 12 years) with completely resected Stage IIB/C melanoma (per AJCC Staging, 8th edition) who underwent standard wide local excision and had a negative sentinel lymph node biopsy. Subjects in whom a sentinel lymph node biopsy procedure could not be performed or a sentinel lymph node was not detected were not eligible. • Disease-free status documented by a complete physical examination (within 14 days) and imaging studies within 4 weeks (28 days) prior to randomization. • ECOG PS of 0 or 1 at the time of enrollment. **Key Exclusion Criteria** • History of ocular or mucosal melanoma. • Active, known, or suspected autoimmune disease or a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.

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Table 6: Applicant - CA20976K Study Design Details

Design Aspect	Description
	Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or agents that target IL-2 pathway or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway.
Dose Selection	Refer to Section 6.2.2.
Enrollment/Assignment to Treatment	Once enrolled using the IRT system, subjects who had met all eligibility criteria were randomized 2:1 to nivolumab (2) or placebo (1) through IRT and stratified by AJCC T category (T3b vs T4a vs T4b) at study entry. **Nivolumab (Nivolumab Arm)** Nivolumab 480 mg IV Q4W **Placebo (Placebo Arm)** Nivolumab-matched placebo (0.9% Sodium Chloride for Injection/5% Dextrose for Injection) IV Q4W
Blinding	CA20976K was a randomized, double-blind study. For the optional open-label nivolumab portion, each subject was assigned to the specific arm (Arm 1 [resectable disease] or Arm 2 [unresectable disease]) using an IRT. Access to treatment codes was restricted from all subjects and site and BMS personnel prior to DBL, with the exception as specified below. Designated staff of BMS Research & Development may be unblinded (obtained the randomization codes) prior to DBL to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) would be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.
Dose Modification/ Discontinuation	Dose escalations or reductions of nivolumab IV were not allowed. Doses of nivolumab may have been interrupted, delayed, or discontinued according to protocol guidelines.
Administrative Structure	A DMC was established to provide oversight of safety and efficacy considerations and to provide advice to the Sponsor regarding actions the committee deemed necessary for the continuing protection of subjects enrolled in the study. A SSC, consisting of Investigators and personnel members representing the Sponsor of the study, was also established to obtain scientific guidance and advice for the protocol and conduct of the study.
Procedures and Schedule	Assessments for eligibility, safety, efficacy, biomarkers, PK, and PROs were performed during screening, on treatment, and in follow-up based on the Schedule of Activities in the protocol. Radiologic tumor imaging for the blinded portion of the study was to occur within 4 weeks (28 days) prior to randomization, every 26 weeks for Years 1-3 including the treatment phase of 12 months, and then every 52 weeks for Years 4 and 5 of follow-up.
Concomitant Medications	Per study design, subjects were not to be previously treated for melanoma beyond complete surgical resection of the melanoma lesion. Subjects receiving open-label treatment after recurrence must have not received any

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Table 6: Applicant - CA20976K Study Design Details

Design Aspect	Description
	other systemic anticancer therapy (including investigational anticancer therapy) or loco-regional anticancer therapy (other than surgery for complete resection of the recurrence and radiation therapy administered with a palliative intent) between the last dose of blinded study treatment and the first dose of open-label study treatment.
Treatment Compliance	Treatment compliance was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF. Drug accountability was reviewed by the site study staff at each visit to confirm treatment compliance.
Treatment Duration	Until completion of 12 months of treatment (from first dose of study treatment), unacceptable toxicity, withdrawal of consent, disease recurrence, or the study ends, whichever occurred first.

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The FDA's Assessment:
FDA agrees with the Applicant's summary of the trial design. At the initiation of this study, standard of care in the adjuvant setting consisted of observation with periodic surveillance assessments for patients with Stage IIB or IIC melanoma and a comparator arm of placebo was appropriate. FDA notes a minor correction to the Applicant's position above. Although the study report states that the study was open for enrollment at 129 sites, 986 patients were enrolled at 119 sites in 20 countries according to the data set in this submission.

8.1.1.1. Eligibility Criteria

The Applicant's Description:
The study population included male and female adult and pediatric subjects (≥ 12 years) with completely resected Stage IIB/C melanoma who underwent standard wide local excision and had a negative sentinel lymph node biopsy. Refer to Table 6 for key inclusion and exclusion criteria.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study population. Patients must have had a complete resection of the primary melanoma tumor with negative margins and a negative sentinel lymph node biopsy within 12 weeks prior to randomization. The trial excluded patients with ocular/uveal or mucosal melanoma, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery.

8.1.1.2. Study Endpoints

The Applicant's Description:

Table 7: Applicant - CA20976K Key Endpoints for Nivolumab vs Placebo

Primary Endpoint	Definition
RFS per Investigator	RFS was programmatically determined based on the disease recurrence date provided by the investigator and was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma (including melanoma in situ), or death (due to any cause), whichever occurred first. For subjects who remained alive and whose disease had not recurred, RFS was censored on the date of last evaluable disease assessment. For those subjects who remained alive and had no recorded post-randomization tumor assessment, RFS was censored on the day of randomization.

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Table 7: Applicant - CA20976K Key Endpoints for Nivolumab vs Placebo

Secondary Endpoints	Definition
OS	OS was defined as the time between the date of randomization and the date of death, from any cause. For subjects who were alive, their survival time was censored at the date of last contact (or "last known alive date"). OS was censored at the date of randomization for subjects who were randomized but had no follow-up. OS will be followed continuously while subjects are on the study drug and every 12 weeks via in-person or phone contact after subjects discontinue the study drug.
Occurrence and severity of AEs as defined by NCI CTCAE version 5.0	The assessment of safety was based on the incidence of AEs, including drug-related AEs; SAEs; AEs leading to discontinuation, dose modification, or death; IMAEs; OESI; and deaths. The use of immune modulating medications were also summarized. In addition, clinical laboratory tests and immunogenicity (ie, development of anti-drug antibody) were analyzed. Toxicities were graded using the NCI CTCAE version 5.0.
DMFS per Investigator	DMFS was programmatically determined based on the first date of distant metastasis provided by the investigator and was defined as the time between the date of randomization and the date of first distant recurrence or the date of death (due to any cause), whichever occurred first.
PFS2	The definition of next line therapy is any systemic anti-cancer therapy for melanoma with a start date on or after the date of first dose of study drug (randomization date if subject was never treated). Accordingly, Progression-free survival through next-line therapy (PFS2) was defined as the time from randomization to recurrence/objective disease progression after the start of next-line of systemic anti-cancer therapy, or to the start of second next-line systemic therapy, or to death from any cause, whichever occurred first.
End of next-line treatment	In case PFS2 cannot be reliably determined, end-of-next-line-treatment was defined as the time from randomization to recurrence/objective disease progression after the start of next-line systemic anti-cancer therapy, or discontinuation of next-line therapy, or to death from any cause, whichever occurred first.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the trial endpoints. Given the primary endpoint was RFS per investigator, FDA recommended that the Applicant include and clearly describe methods in the protocol and statistical analysis plan to reduce bias in disease assessment by the investigator, and that the analysis plan be revised to include sensitivity analyses that would enable an assessment of whether there was bias associated with potential unmasking of investigators and patients to treatment assignment. FDA did not object to distant metastasis-free survival (DMFS) as a descriptive secondary endpoint. .]

8.1.1.3. Statistical Analysis Plan and Amendments

The Applicant's Description:

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The statistical analyses are documented in the SAP version 2.0 (approval date: 24-Jul-2022), which was finalized prior to clinical DBL (data cutoff date on 28-Jun-2022, DBL on 17-Aug-2022).

Sample Size and Power

The sample size of the study was based on a comparison of the RFS distribution between subjects randomized to nivolumab and subjects randomized to placebo. Simulation models incorporating aspects of immunotherapy, such as delayed separation (observed as late separation of survival curves between the experimental and placebo arms) and long-term survival benefits (observed as a long-lasting plateau towards the tail of the survival curve) were developed for sample size estimation. Sample size calculations for this study design were done using EAST (version 6.4.1).

For this comparison of RFS between nivolumab and placebo in all randomized subjects, approximately 154 RFS events were required for a two-sided experiment-wise alpha = 0.05 log-rank test to show a statistically significant difference in RFS between the treatment arms with at least 90% power when the average HR of the nivolumab arm to the placebo arm is 0.573. Given an estimated accrual rate, the accrual of 780 subjects (ie, 520 subjects in the nivolumab arm and 260 subjects in the placebo arm) would take approximately 29.6 months.

Statistical Analysis Timing

One interim analysis and one final analysis for RFS (primary endpoint) was planned for Study CA20976K. No formal OS interim analysis was planned at the time of interim analysis for RFS.

The RFS interim analysis was planned when approximately 123 RFS events (80% information fraction) were observed. The estimated timing for this interim analysis was at 53.3 months. The stopping boundaries at the interim and final analyses were derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. With an interim RFS analysis at approximately 123 RFS events, the type I error was 0.024 (two-sided), the power 62.8%, and an observed HR of 0.65 or less would result in a statistically significant improvement.

Although formal OS testing was planned at OS final analysis, descriptive statistics for OS were to be prepared at RFS interim analysis and/or RFS final analysis upon regulatory requests. If OS results (beyond the frequency of deaths per arm) including Kaplan-Meier curves were requested, an administrative alpha of 0.0001 was to be spent as alpha penalty. Were such analyses to be conducted, only a BMS restricted team would have access to OS descriptive results.

The projected number of deaths that would have occurred at the time of interim or final RFS analysis is 53 deaths (or 19% of the 277 final deaths) and 87 deaths (or 31% of the 277 final deaths), respectively. To ensure sufficient maturity of the OS data at the time formal analysis was to be performed, .one formal OS interim analysis was to be conducted when approximately 166 deaths (60% information fraction) were reached among all randomized participants, which was expected to occur after the final analysis of RFS.

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We estimated that this would occur when all participants had a minimum follow-up of approximately 63 months from the randomization of the last participant. The estimated timing for this interim analysis was at 93 months. The stopping boundaries at the interim and final analyses were to be derived based on the exact number of OS events using Lan DeMets alpha spending function with O'Brien-Fleming boundaries. With an interim OS analysis at approximately 166 deaths, the type I error would be 0.008 (two-sided), the power 30.7%, and an observed HR of 0.644 or less would result in a statistically significant improvement. The type I error to be used for final OS analysis would be 0.048 (two-sided).

COVID-19 pandemic

The COVID-19 pandemic contributed to enrollment and administrative challenges. Due to the potential for delays in study drug administration, imaging, and safety assessments, mitigation steps were taken to collect data and monitor the impact of the pandemic. The SAP was amended (version 2.0) to incorporate pre-specified COVID-19 analyses for COVID-19 related disposition events, COVID-19 related dose modifications, and COVID-19 related AEs.

Table 8: Applicant - CA20976K Statistical Analysis Plan

Endpoint	Description
Primary (RFS)	The primary RFS analysis was conducted using a stratified two-sided log-rank test. The stratification factor that was used in the analysis was AJCC T category (T3b vs T4a vs T4b) at study entry (as recorded per IRT). The two-sided stratified log-rank p-value was reported. The estimate of the RFS hazard ratio of nivolumab to placebo was calculated using a stratified CPH model, with treatment as the sole covariate, stratified by the above stratification factor. Ties were handled using the exact method. A two-sided 100x(1-adjusted α)% and 95% CI's for the hazard ratio was also presented, along with the two-sided stratified log-rank p-value. The RFS function for each treatment group was estimated using Kaplan-Meier product limit method and was displayed graphically. Median RFS along with 95% CI was constructed based on a log-log transformed CI for the survivor function. RFS rates at fixed time points (6, 12, 18, 24, 30, 36, 42, 48 months, depending on the minimum follow-up) were derived from the Kaplan-Meier estimate, and the corresponding confidence intervals were derived based on Greenwood[21] formula for variance derivation and on log-log transformation applied on the survivor function.[22]
Secondary (OS)	OS will be compared between the treatment groups at the OS interim and final analyses, using stratified two-sided log-rank test stratified by AJCC T category (T3b vs T4a vs T4b) at study entry (as recorded per IRT). The two-sided stratified log-rank p-value will be reported. The estimate of the OS hazard ratio, of nivolumab to placebo, will be calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate, stratified by the above stratification factor. Ties will be handled using the Exact method. A two-sided 100x(1-adjusted α)% and 95% CI's for the hazard ratio will also be presented. The OS function for each treatment group will be estimated using Kaplan-Meier product limit method and will be displayed graphically. Median OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at fixed

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Table 8: Applicant - CA20976K Statistical Analysis Plan

	time points (6, 12, 18, 24, 30, 36, 42, 48 months, depending on the minimum follow-up) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. Sensitivity analyses of OS will also be conducted based on the secondary definition of OS. These analyses will be the same as those specified above. No formal OS interim analysis was planned at the time of either RFS interim or final analysis due to anticipated immaturity of the OS data.
Secondary (DMFS)	DMFS analysis was performed in all randomized subjects. Analysis results are considered descriptive. DMFS was analyzed using similar analysis methods as for RFS and following the treatment policy estimand strategy. No multiplicity adjustment was applied. The estimate of the DMFS hazard ratio of nivolumab to placebo was calculated using a stratified Cox proportional hazards model with treatment as the single covariate. A two-sided 95% CI for the hazard ratio is also presented. The DMFS distribution for each treatment group was estimated using Kaplan-Meier techniques. Median DMFS along with 95% CI was constructed based on a log-log transformed CI for the survivor function. DMFS rates at fixed time points (6, 12, 18, 24, 30, 36, 42, 48, months, depending on the minimum follow-up) were derived from the Kaplan-Meier estimate and the corresponding confidence intervals were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.
Secondary (PFS2)	PFS2 was defined as the time from randomization to recurrence/objective disease progression after the start of next-line of systemic anti-cancer therapy, or to the start of second next-line systemic therapy, or to death from any cause, whichever occurred first. The hazard ratio and corresponding 95% CIs were estimated using a Cox proportional hazards model, with treatment group as a single covariate. Analysis results are considered descriptive, as the type I error rate was not controlled for this analysis.
Safety	Safety analyses were performed in all treated subjects. Descriptive statistics of safety were presented using NCI CTCAE version 5.0 by treatment group (for the nivolumab and placebo arms). All on-study AEs, treatment related AEs, SAEs, treatment-related SAEs, select AEs, IMAEs, AEs leading to death, and OESIs were tabulated using worst grade per NCI CTCAE version 5.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver functions, thyroid functions, and renal functions were summarized using worst grade NCI CTCAE version 5.0 criteria.
Other	Per statistical design, all other analyses were descriptive with no formal hypothesis testing.

The FDA's Assessment:

FDA agrees with the description of the statistical analysis plan as presented.

FDA adds that compared with the original SAP (dated 01/21/2022), the SAP version 2.0 (dated

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04/21/2022) modified the efficacy sensitivity analyses for RFS, DMFS, and OS, added definition of end of next line treatment, slightly modified the definition of PFS2, and excluded basal cell carcinoma (BCC) as part of second non-melanoma primary cancer in the RFS censoring rule.

8.1.1.4. Protocol Amendments

The Applicant's Description:

The original protocol for this study was dated 13-May-2019. As of the 17-Aug-2022 DBL, there were a total of 3 global protocol amendments, 3 site specific amendments, and 3 administrative letters (Table 9).

Table 9: Applicant - Summary of Key Changes to Protocol CA20976K

Document (Amendment)/ Date	Summary of Key Changes	Planned Sample Size	Total No. of Subjects Randomized at Time of Protocol Amendment
Protocol Amendment 01/ 16-Oct-2020	The interim analysis (IA) plan for the primary endpoint, RFS, was changed to be conducted at 80% information fraction, following feedback from Health Authorities that the RFS IA at 67% information fraction may not provide an accurate estimate of the treatment effect size due to immature data. Sample size is reduced from 1000 to 780 to allow adequate projected minimum follow-up time (expected ~24 months) at the interim analysis of primary endpoint.	780	230
Protocol Amendment 02/ 15-Oct-2021	Protocol updated to align the management of AEs in trial subjects, as well as the reporting of such AEs, per the CTCAE version 5.0. Language was inserted to provide descriptive OS data at the time of positive read out of the primary endpoint (RFS), as well as the projected number of deaths at the time of interim and final RFS analysis.	780	789
Protocol Amendment 03/ 28-Apr-2022	Added formal interim analysis for OS at 60% Information Fraction. OS events are expected to accrue over a long period of time (approximately 11 years since the first patient was treated) in stage IIB-C melanoma patients. The interim OS analysis is expected to occur approximately eight (8) years since the first patient was treated and may help provide preliminary survival data in a timely manner.	780	790

The FDA's Assessment:

FDA agrees with the Applicant's description of key protocol changes.

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8.1.2. Study Results - Study CA20976K

8.1.2.1. Compliance with Good Clinical Practices

The Applicant's Position:
The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the ICH and in accordance with the ethical principles underlying EU Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

The protocol, amendments, administrative letters, and subject informed consent form received IRB/IEC approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analyzed was monitored according to BMS standard operating procedures.

After review of the reported protocol deviations, it was determined that there was no impact on the interpretability of study results.

The FDA's Assessment:
The FDA agrees with the Applicant's position that there is no evidence that compliance with good clinical practices was violated during the conduct of Study CA20976K.

8.1.2.2. Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19.2). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA20976K clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:
The Applicant provided financial disclosure information for Study CA20976K. There were 19 investigators or sub-investigators at five sites who disclosed financial interests or arrangements with the Applicant. The financial interests and arrangements included payments to the investigators' institutions for research (n=2), payments to the investigators' institution for participation in the International Immuno-Oncology Network (II-ON) (n=15), equity holdings (n=2), and speaking and consulting services (n=2).

FDA has determined that the impact of financial bias on the outcome analyses in Study CA20976K is minimized by the following and is unlikely to have significantly biased the interpretation of study results:

- Investigators were not aware of the treatment patients were randomized to due to the double-blind study design.
- The primary study endpoint, RFS, was assessed via blinded independent central review.

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- The secondary endpoint of overall survival is unlikely to be affected by bias.
- The total number of patients randomized by investigators who reported financial disclosures was low (3.6%).

The FDA concluded that it is unlikely that the reported financial disclosures led to significant bias in the conduct of this study. Additional information is provided in Section 19.2.

8.1.2.3. Patient Disposition

Data:

Table 10: Applicant - End of Treatment Period Subject Status Summary - Blinded Phase - All Treated Subjects in CA20976K

Status (%)	Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
TREATED	524 (99.6)	264 (100.0)
NOT TREATED	2 (0.4)	0
REASON FOR NOT TREATED*		
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.2)	0
OTHER	1 (0.2)	0
NOT TREATED DUE TO COVID-19	0	0
ONGOING TREATMENT	64 (12.2)	39 (14.8)
COMPLETED TREATMENT	257 (49.0)	158 (59.8)
DISCONTINUED TREATMENT	203 (38.7)	67 (25.4)
REASON FOR DISCONTINUATION OF TREATMENT		
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	29 (5.5)	0
SUBJECT WITHDREW CONSENT	18 (3.4)	7 (2.7)
DEATH	6 (1.1)	2 (0.8)
LOST TO FOLLOW-UP	1 (0.2)	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.2)	0
STUDY DRUG TOXICITY	94 (17.9)	7 (2.7)
ADVERSE EVENT UNRELATED TO STUDY DRUG	11 (2.1)	1 (0.4)
MAXIMUM CLINICAL BENEFIT	1 (0.2)	2 (0.8)
DISEASE RECURRENCE	26 (5.0)	41 (15.5)
OTHER	16 (3.1)	7 (2.7)
DISCONTINUED TREATMENT DUE TO COVID-19	7 (1.3)	2 (0.8)
REASON FOR DISCONTINUATION OF TREATMENT DUE TO COVID-19		
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (0.2)	0
SUBJECT WITHDREW CONSENT	0	1 (0.4)
DEATH	1 (0.2)	1 (0.4)
STUDY DRUG TOXICITY	2 (0.4)	0
ADVERSE EVENT UNRELATED TO STUDY DRUG	3 (0.6)	0

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Table 8: Applicant - End of Treatment Period Subject Status Summary - Blinded Phase - All Treated Subjects in CA20976K

Status (%)	Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
ONGOING STUDY	501 (95.6)	255 (96.6)
DISCONTINUED STUDY	23 (4.4)	9 (3.4)
REASON FOR DISCONTINUATION OF STUDY		
DEATH	6 (1.1)	2 (0.8)
SUBJECT WITHDREW CONSENT	14 (2.7)	7 (2.7)
OTHER	3 (0.6)	0
DISCONTINUED STUDY DUE TO COVID-19 **	2 (0.4)	2 (0.8)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19		
DEATH	1 (0.2)	1 (0.4)
SUBJECT WITHDREW CONSENT	1 (0.2)	1 (0.4)

* Two subjects were found to be ineligible after randomization and therefore, were not treated. One subject was found to have suspected autoimmune disease (sarcoidosis) and the other subject was found to have elevated liver enzymes.
** These discontinuations are part of the overall reasons for treatment discontinuations above but were also assigned a secondary reason of having relationship to COVID-19.
Percentages based on subjects entering period.
Data prior to the open label first dose date is being reported.
For subjects receiving open label nivolumab, the treatment period for the original arm is considered to have stopped.

The Applicant's Position:

Data are reported based on a 28-Jun-2022 data cutoff. At the time of data cutoff, the median follow-up (date of randomization to the last known date alive or death date) for all randomized subjects was 15.84 months for the nivolumab arm and 15.93 months for the placebo arm. Minimum follow-up (defined as the time from the last subject's randomization date to cutoff date)) was 7.8 months for the nivolumab arm and 8.7 months for the placebo arm (Table 14).

986 subjects were enrolled into the study. A total of 790 subjects were randomized 2:1 in the nivolumab and placebo arms: 526 to the nivolumab arm and 264 to the placebo arm. 788 subjects were treated: 524 with nivolumab and 264 with placebo (Table 10). The most common reason for discontinuation of treatment was study drug toxicity in the nivolumab arm and disease recurrence in the placebo arm.

At the time of the data cutoff, there were 486 (92.7%) subjects in the nivolumab arm and 247 (93.6%) subjects in the placebo arm continuing in the study overall.

The FDA's Assessment:

FDA generally agrees with the results presented in this section. Ninety-nine percent of randomized patients received study treatment. More patients in the nivolumab IV arm discontinued study treatment than in the placebo arm. The main reason for treatment discontinuation in the nivolumab IV arm was due to toxicity, while the main reason for

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treatment discontinuation in the placebo arm was due to disease recurrence. There was also a numerically higher number of patients that requested to discontinue study treatment in the nivolumab IV arm. There was a small proportion of patients in both arms who withdrew consent. Overall, the observed differences between treatment arms are unlikely to have significantly impacted the interpretation of study results.

8.1.2.4. Protocol Violations/Deviations

The Applicant's Position:

Important Protocol Deviations are a subset of protocol deviations that could significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Routine monitoring of protocol deviations was conducted and where appropriate additional follow-up and training was conducted with sites and site-facing roles.

The Protocol Deviations Assessment Plan was utilized to assess the protocol deviations. A review of the 415 Important Protocol Deviations from both the blinded phase and open-label phase of Study CA20976K determined that there was no detriment to subject safety and no significant impact on the interpretability of study results.

Relevant protocol deviations are a subset of important protocol deviations that could affect the interpretability of key study results; they are programmable deviations from the clinical database and are protocol-specific. For Study CA20976K, there were no relevant protocol deviations reported.

The FDA's Assessment:

There were 156 patients (30%) in the nivolumab IV arm and 96 patients (36%) in the placebo arm with at least one important protocol deviation. The higher proportion of protocol deviations in the placebo arm are related to a slight increase in protocol deviations related to inclusion/exclusion criteria, informed consent and/or independent ethics committee and institutional review board, and safety reporting (see Table 11).

The most common protocol deviations on either study arm were related to "informed consent and/or independent ethics committee and institutional review board" and "trial procedures"). These protocol deviations are unlikely to have had a meaningful impact on interpretation of study results.

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Table 11: Summary of Important Protocol Deviations

Nivolumab
BMS-936558

CA209-76K
Response to FDA Query Dated 19-Sep-2023

Protocol: CA20976K

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Important Protocol Deviation Summary
All Enrolled Subjects
Based on RFS Interim Analysis Database Lock (17-Aug-2022, CSR)

	Not Randomized N = 196	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 986
SUBJECTS WITH AT LEAST ONE DEVIATION	2 (1.0)	156 (29.7)	96 (36.4)	254 (25.8)
INCLUSION/EXCLUSION CRITERIA	0	18 (3.4)	13 (4.9)	31 (3.1)
INFORMED CONSENT AND/OR INDEPENDENT ETHICS COMMITTEE AND INSTITUTIONAL REVIEW BOARD (IEC/IRB)	2 (1.0)	57 (10.8)	39 (14.8)	98 (9.9)
PROHIBITED CONCOMITANT MEDICATION	0	2 (0.4)	0	2 (0.2)
SAFETY REPORTING	0	6 (1.1)	8 (3.0)	14 (1.4)
STUDY INTERVENTION (I.E., STUDY TREATMENT)	0	23 (4.4)	10 (3.8)	33 (3.3)
TRIAL PROCEDURES	0	95 (18.1)	45 (17.0)	140 (14.2)

Source: Applicant response to Information Request dated 9/19/23]

8.1.2.5. Table of Demographic Characteristics

Data:

Table 12: Applicant - Baseline Demographic Characteristics - All Randomized Subjects in CA20976K

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
AGE (YEARS)			
MEAN	59.9	59.3	59.7
MEDIAN	62.0	61.0	62.0
MIN , MAX	21 , 87	19 , 92	19 , 92
Q1 , Q3	51.0 , 71.0	51.0 , 69.0	51.0 , 70.0
SD	13.9	13.6	13.8
AGE CATEGORIZATION 1 (%)			
< 65	305 (58.0)	155 (58.7)	460 (58.2)
>= 65	221 (42.0)	109 (41.3)	330 (41.8)
AGE CATEGORIZATION 2 (%)			
< 18	0	0	0
>= 18 AND < 65	305 (58.0)	155 (58.7)	460 (58.2)
>= 65 AND < 75	140 (26.6)	77 (29.2)	217 (27.5)
>= 75 AND < 85	77 (14.6)	30 (11.4)	107 (13.5)
>= 85	4 (0.8)	2 (0.8)	6 (0.8)
SEX (%)			
MALE	322 (61.2)	161 (61.0)	483 (61.1)
FEMALE	204 (38.8)	103 (39.0)	307 (38.9)
RACE (%)			
WHITE	515 (97.9)	262 (99.2)	777 (98.4)
BLACK OR AFRICAN AMERICAN	2 (0.4)	1 (0.4)	3 (0.4)
ASIAN	1 (0.2)	0	1 (0.1)
OTHER	7 (1.3)	1 (0.4)	8 (1.0)
NOT REPORTED	1 (0.2)	0	1 (0.1)

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Reference ID: 5260748

Table 12: Applicant - Baseline Demographic Characteristics - All Randomized Subjects in CA20976K

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
ETHNICITY (%)			
HISPANIC OR LATINO	11 (2.1)	6 (2.3)	17 (2.2)
NOT HISPANIC OR LATINO	317 (60.3)	140 (53.0)	457 (57.8)
NOT REPORTED	198 (37.6)	118 (44.7)	316 (40.0)
COUNTRY BY GEOGRAPHIC REGION (%)			
US AND CANADA	97 (18.4)	46 (17.4)	143 (18.1)
CANADA	11 (2.1)	7 (2.7)	18 (2.3)
UNITED STATES	86 (16.3)	39 (14.8)	125 (15.8)
WESTERN EUROPE	303 (57.6)	160 (60.6)	463 (58.6)
EASTERN EUROPE	58 (11.0)	28 (10.6)	86 (10.9)
AUSTRALIA	68 (12.9)	30 (11.4)	98 (12.4)

The Applicant's Position:

Baseline demographic characteristics in all randomized subjects were balanced between the nivolumab and placebo arms (Table 12). Among all randomized subjects, the median age was 62.0 years, 39.4% had stage II disease, and the majority of subjects were White (98.4%) and male (61.1%) (Table 12 and Table 13).

As observed in the population enrolled in CA20976K, there is a low prevalence of melanoma in racial and ethnic minority groups in the general melanoma population. This is consistent with the racial and ethnic breakdown of the crude incidence of melanoma for 2015-2019 (percentage amongst all cases), which showed 92.1% White, 0.4% Black, 0.3% American Indian/Alaska Native, 0.3% Asian/Pacific Islander, and 2.3% Hispanic.[23]

The FDA's Assessment:

FDA agrees with the demographic data presented for the ITT population and agrees that these characteristics were generally balanced across the treatment groups. The median age of patients in Study CA20976K was 62 years. The is slightly higher than the median age that has been reported for patients in the AJCC melanoma staging database with Stage I and II melanoma (Black 2013). The trial included very few patients of American Indian/Alaskan Native, Asian/Pacific Islander, or Black race, or Hispanic ethnicity. Cases per 100,000 of new cases of melanoma are lower in historically underrepresented racial and ethnic populations compared to non-Hispanic White: 8.7 American Indian/Alaskan Native, 1.3 Asian/Pacific Islander, 1.0 Black, 4.5 Hispanic (SEER 22). FDA notes a minor correction to the Applicant's position above and clarifies that, among all randomized patients, 39.4% had stage IIC disease and 60.6% had stage IIB disease.

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8.1.2.6. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 13: Applicant – Other Baseline Disease Characteristics – All Randomized Subjects in CA20976K

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
BASELINE ECOG PS			
0	495 (94.1)	245 (92.8)	740 (93.7)
1	31 (5.9)	19 (7.2)	50 (6.3)
BASELINE LDH I			
<= ULN	470 (89.4)	232 (87.9)	702 (88.9)
> ULN	50 (9.5)	25 (9.5)	75 (9.5)
NOT REPORTED	6 (1.1)	7 (2.7)	13 (1.6)

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Table 13: Applicant - Other Baseline Disease Characteristics - All Randomized Subjects in CA20976K

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
BASELINE LDH II			
<= 2*ULN	520 (98.9)	257 (97.3)	777 (98.4)
> 2*ULN	0	0	0
NOT REPORTED	6 (1.1)	7 (2.7)	13 (1.6)
WEIGHT (KG)			
N	525	264	789
MEAN	84.21	85.58	84.67
MEDIAN	82.10	83.35	82.50
MIN - MAX	43.0 - 162.7	47.1 - 187.7	43.0 - 187.7
Q1 - Q3	71.00 - 95.60	72.10 - 96.30	71.90 - 95.90
SD	18.91	19.93	19.26
TIME FROM WIDE LOCAL EXCISION SURGERY TO RANDOMIZATION (WEEKS)			
N	525	264	789
MEAN	10.35	10.20	10.30
MEDIAN	10.00	10.21	10.14
MIN - MAX	1.3 - 34.0	3.6 - 28.9	1.3 - 34.0
Q1 - Q3	8.14 - 11.86	8.00 - 11.71	8.00 - 11.86
SD	3.66	3.57	3.63
< 3	3 (0.6)	0	3 (0.4)
3 - < 6	35 (6.7)	27 (10.2)	62 (7.8)
6 - < 9	140 (26.6)	69 (26.1)	209 (26.5)
9 - < 12	235 (44.7)	114 (43.2)	349 (44.2)
12 - < 15	71 (13.5)	34 (12.9)	105 (13.3)
15 - < 18	16 (3.0)	7 (2.7)	23 (2.9)
18 - < 21	16 (3.0)	9 (3.4)	25 (3.2)
>= 21	9 (1.7)	4 (1.5)	13 (1.6)
NOT REPORTED	1 (0.2)	0	1 (0.1)
TIME FROM SENTINEL LYMPHADENECTOMY SURGERY TO RANDOMIZATION (WEEKS)			
N	526	263	789
MEAN	9.45	9.09	9.33
MEDIAN	9.71	9.14	9.57
MIN - MAX	2.9 - 18.7	0.4 - 22.0	0.4 - 22.0
Q1 - Q3	7.71 - 11.43	7.29 - 11.00	7.57 - 11.29
SD	2.35	2.51	2.41
< 3	1 (0.2)	1 (0.4)	2 (0.3)
3 - < 6	40 (7.6)	28 (10.6)	68 (8.6)
6 - < 9	171 (32.5)	94 (35.6)	265 (33.5)
9 - < 12	244 (46.4)	118 (44.7)	362 (45.8)
12 - < 15	65 (12.4)	20 (7.6)	85 (10.8)
15 - < 18	4 (0.8)	1 (0.4)	5 (0.6)
18 - < 21	1 (0.2)	0	1 (0.1)
>= 21	0	1 (0.4)	1 (0.1)
NOT REPORTED	0	1 (0.4)	1 (0.1)
DISEASE STAGE AT STUDY ENTRY (PER CRF)			
STAGE IIB	316 (60.1)	163[a] (61.7)	479 (60.6)
STAGE IIC	210 (39.9)	101 (38.3)	311 (39.4)
STAGE OTHER	0	0	0
STAGE UNKNOWN	0	0	0
T STAGE AT STUDY ENTRY (PER CRF)			
STAGE II PATIENTS	526 (100.0)	264 (100.0)	790 (100.0)
T3B	204 (38.8)	104 (39.4)	308 (39.0)
T4A	112 (21.3)	58 (22.0)	170 (21.5)
T4B	210 (39.9)	102 (38.6)	312 (39.5)

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Table 13: Applicant – Other Baseline Disease Characteristics – All Randomized Subjects in CA20976K

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
MELANOMA SUB-TYPE			
SUPERFICIAL SPREADING MELANOMA	151 (28.7)	82 (31.1)	233 (29.5)
NODULAR MELANOMA	266 (50.6)	133 (50.4)	399 (50.5)
LENTIGO MALIGNA[b]	13 (2.5)	3 (1.1)	16 (2.0)
ACRAL LENTIGINOUS MELANOMA	28 (5.3)	15 (5.7)	43 (5.4)
DESMOPLASTIC MELANOMA	21 (4.0)	8 (3.0)	29 (3.7)
OTHER	44 (8.4)	22 (8.3)	66 (8.4)
NOT REPORTED	3 (0.6)	1 (0.4)	4 (0.5)

[a]Includes a subject incorrectly categorized as Stage IIB instead of Stage IIC.

[b]Refers to lentigo maligna melanoma, a primary invasive melanoma.

The Applicant's Position:

Baseline disease characteristics in all randomized subjects were balanced between the nivolumab IV and placebo arms (Table 13). The predominant melanoma subtypes were nodular (50.5%) and superficial spreading (29.5%). Per CRF, T-stage was T3b in 39.0%, T4a in 21.5%, and T4b in 39.5% of all randomized subjects.

The FDA's Assessment:

[FDA agrees with the Applicant's position.]

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance: Nivolumab was administered IV by trained medical personnel at each site. Treatment compliance was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF.

Concomitant Medications: In the blinded phase, most treated subjects (96.2% nivolumab, 93.6% placebo) received concomitant non-study medications.

Immune-modulating medications were recommended for the treatment of certain AEs. The list of immune-modulating medications was derived from the World Health Organization Drug Dictionary and included all drugs belonging to the following categories: corticosteroids, immune-modulating agents, immunosuppressive agents, and glucocorticoids. Among all treated subjects in the blinded phase, immune-modulating concomitant medications were administered to 46.8% of subjects in the nivolumab arm and 26.1% of subjects in the placebo arm. For management of AEs, immune-modulating concomitant medications were administered to 43.7% of subjects in the nivolumab arm and 19.3% of subjects in the placebo arm.

Subsequent Cancer Therapy: Subsequent cancer therapy was defined as any systemic therapy,

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surgery, or radiotherapy for melanoma with a start date on or after the date of first dose of study drug (randomization date if subject was never treated).

Among all randomized subjects, a lower proportion of subjects received subsequent cancer therapy in the nivolumab arm than in the placebo arm (9.5% vs 23.5%), driven by fewer subjects receiving subsequent systemic therapy (5.7% vs 18.6%) and subsequent surgery (6.8% vs 14.8%).

Rescue Medication Use: Not applicable

The FDA's Assessment:
[FDA agrees with the Applicant's summary.]

8.1.2.8. Efficacy Results – Primary Endpoint

Data:

Table 14: Applicant – Primary Efficacy Endpoint of Recurrence-free Survival per Investigator – All Randomized Subjects in CA20976K

Endpoints	Nivolumab N = 526		Placebo N = 264
PRIMARY ENDPOINT			
RFS per Investigator			
Events, n/N (%)	66/526 (12.5)		69/264 (26.1)
HR[a] (95% CI) (96.7% CI)		0.42 (0.30, 0.59) (0.29, 0.61)	
log-rank p-value[b]		< 0.0001	
Median RFS[c] (95% CI), months	N/A (28.52, N/A)		N/A (21.62, N/A)
Rate at 6 months[c], % (95% CI)	95.1 (92.8, 96.6)		88.1 (83.4, 91.5)
Rate at 12 months[c], % (95% CI)	89.0 (85.6, 91.6)		79.4 (73.5, 84.1)

Data cutoff: 28-Jun-2022; Minimum follow-up: nivolumab arm 7.8 months, placebo arm 8.7 months

[a] HR is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.

[b] 2-sided log-rank test stratified by the same factor as used in the Cox proportional hazard model. Boundary for statistical significance p-value < 0.033.

[c] Based on Kaplan-Meier estimates.

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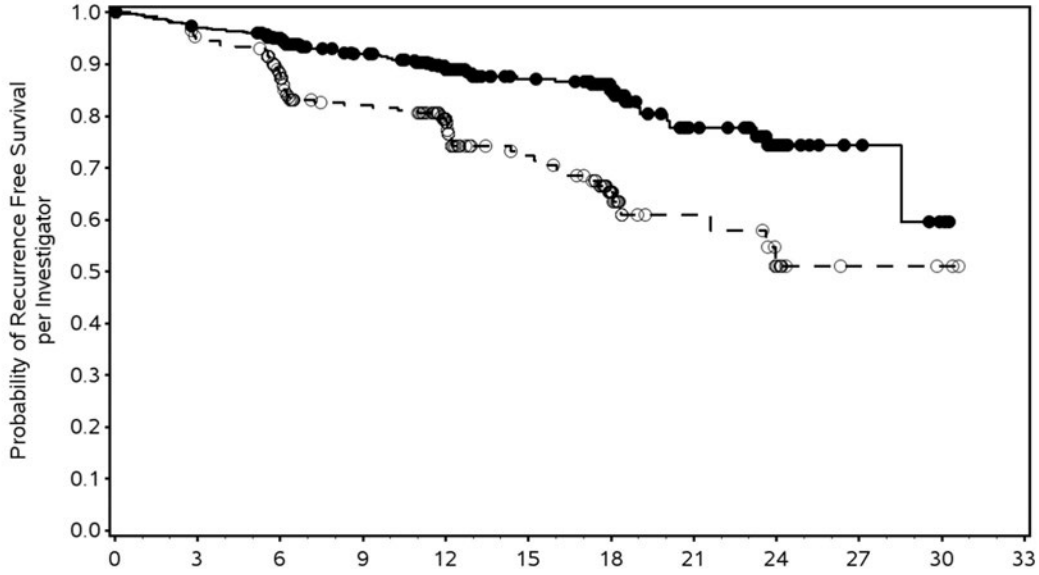
Figure 5: Applicant – Kaplan-Meier Plot of Recurrence-free Survival per Investigator – All Randomized Subjects in CA20976K



Number of Subjects at Risk

Nivolumab 480 mg Q4W	526	492	444	364	261	185	116	54	19	6	2	0
Placebo Q4W	264	243	205	161	119	77	40	20	11	3	2	0

—●— Nivolumab 480 mg Q4W (events: 66/526), median and 95% CI: N.A. (28.52, N.A.)
– ⊖ – Placebo Q4W (events: 69/264), median and 95% CI: N.A. (21.62, N.A.)
Nivolumab 480 mg Q4W vs Placebo Q4W - hazard ratio (95% CI): 0.42 (0.30, 0.59)
Nivolumab 480 mg Q4W vs Placebo Q4W - hazard ratio (96.7% CI): 0.42 (0.29, 0.61)
Stratified log-rank test p-value: <0.0001

Hazard Ratio is Nivolumab over Placebo from Cox proportional hazard model stratified by AJCC T Stage at Study Entry (T3b vs T4a vs T4b) as entered into the IRT.
P-value from 2-sided Log-rank test stratified by the same factor as used in the Cox proportional hazard model.
Symbols represent censored observations

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Table 15: Applicant – Reason for Censoring, Recurrence-Free Survival per Investigator – All Randomized Subjects

	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
NUMBER OF EVENTS (%)	66 (12.5)	69 (26.1)
TYPE OF EVENTS (%)		
RECURRENCE	56 (10.6)	66 (25.0)
DISEASE AT BASELINE	0	0
DISTANT RECURRENCE	26 (4.9)	31 (11.7)
REGIONAL NODE RECURRENCE	11 (2.1)	20 (7.6)
IN TRANSIT METASTASIS RECURRENCE	0	0
LOCAL RECURRENCE	8 (1.5)	7 (2.7)
NEW PRIMARY INVASIVE MELANOMA	4 (0.8)	3 (1.1)
MALIGNANT MELANOMA IN SITU	7 (1.3)	5 (1.9)
DEATH	10 (1.9)	3 (1.1)
NUMBER OF SUBJECTS CENSORED (%)	460 (87.5)	195 (73.9)
CENSORED ON DATE OF RANDOMIZATION	14 (2.7)	3 (1.1)
INCOMPLETE OR NO BASELINE TUMOR ASSESSMENT (1)	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT WITH EITHER NO RECURRENCE/DEATH OR RECURRENCE/DEATH WITH PRIOR SUBSEQUENT THERAPY/SECOND NON-MELANOMA PRIMARY CANCER (1)	14 (2.7)	3 (1.1)
RECURRENCE/DEATH WITH PRIOR SUBSEQUENT ANTI CANCER THERAPY	0	0
RECURRENCE/DEATH WITH PRIOR SECOND NON-MELANOMA PRIMARY CANCER	0	0
NO RECURRENCE/DEATH	14 (2.7)	3 (1.1)
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI CANCER THERAPY/ SECOND NON-MELANOMA PRIMARY CANCER*	446 (84.8)	192 (72.7)
RECEIVED SUBSEQUENT ANTI-CANCER THERAPY (2)	0	0
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	0
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0

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Table 12: Applicant – Reason for Censoring, Recurrence-Free Survival per Investigator – All Randomized Subjects

	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
SECOND NON-MELANOMA PRIMARY CANCER (2)	9 (1.7)	8 (3.0)
ON STUDY	425 (80.8)	180 (68.2)
ON-TREATMENT	61 (11.6)	39 (14.8)
IN FOLLOW-UP	364 (69.2)	141 (53.4)
OFF STUDY	12 (2.3)	4 (1.5)
LOST TO FOLLOW-UP	2 (0.4)	2 (0.8)
PARTICIPANT WITHDRAW CONSENT	7 (1.3)	2 (0.8)
OTHER	3 (0.6)	0

*Basel cell carcinomas were excluded from the censoring definition for new-non melanoma primary malignancies.
(1) Disease assessments and death if any, occurring after start of subsequent anti-cancer therapy or second non-melanoma primary cancer are not considered.
(2) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy or experienced second non-melanoma primary cancer without a prior reported RFS event. Those subjects were censored at the last evaluable disease assessment prior to/on start date of subsequent anti-cancer therapy or second non-melanoma primary cancer.
Some subjects may have been treated with more than 1 type of subsequent anti-cancer therapy.
Open-label nivolumab treatment will be considered as a new anticancer therapy.

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Figure 6: Applicant – Forest Plot of Treatment Effect on Recurrence-free Survival per Investigator in Pre-defined Subsets – All Randomized Subjects in CA20976K

		Nivolumab 480 mg Q4W			Placebo Q4W			Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
	N	N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	
Overall	790	66 (526)	N.A. (28.52, N.A.)	89.0 (85.6, 91.6)	69 (264)	N.A. (21.62, N.A.)	79.4 (73.5, 84.1)	0.43 (0.31, 0.61)
Age Category I								
< 65	460	33 (305)	N.A. (28.52, N.A.)	91.5 (87.4, 94.4)	39 (155)	N.A. (21.62, N.A.)	81.2 (73.5, 86.9)	0.40 (0.25, 0.64)
>= 65	330	33 (221)	N.A.	85.4 (79.3, 89.8)	30 (109)	23.62 (18.07, N.A.)	76.8 (66.8, 84.2)	0.48 (0.29, 0.78)
Age Category II								
< 18	0	0 (0)			0 (0)			
>= 18 and < 65	460	33 (305)	N.A. (28.52, N.A.)	91.5 (87.4, 94.4)	39 (155)	N.A. (21.62, N.A.)	81.2 (73.5, 86.9)	0.40 (0.25, 0.64)
>= 65 and < 75	217	16 (140)	N.A.	89.2 (81.9, 93.6)	18 (77)	N.A. (18.07, N.A.)	79.7 (67.9, 87.5)	0.45 (0.23, 0.88)
>= 75 and < 85	107	17 (77)	N.A.	78.2 (65.6, 86.6)	11 (30)	16.03 (10.28, N.A.)	68.4 (46.1, 83.0)	0.46 (0.21, 0.99)
>= 85	6	0 (4)	N.A.	N.A.	1 (2)	17.08 (N.A., N.A.)	100.0 (100.0, 100.0)	
Sex								
Male	483	39 (322)	N.A.	89.9 (85.6, 93.0)	51 (161)	23.62 (18.07, N.A.)	76.5 (68.6, 82.7)	0.33 (0.22, 0.51)
Female	307	27 (204)	28.52 (28.52, N.A.)	87.6 (81.6, 91.7)	18 (103)	N.A.	83.9 (74.1, 90.2)	0.71 (0.39, 1.29)
Race								
White	777	65 (515)	N.A. (28.52, N.A.)	88.7 (85.3, 91.4)	68 (262)	N.A. (21.62, N.A.)	79.7 (73.8, 84.4)	0.44 (0.31, 0.62)
Black	3	1 (2)	23.66 (N.A., N.A.)	100.0 (100.0, 100.0)	0 (1)	N.A.	N.A.	
Asian	1	0 (1)	N.A.	N.A.	0 (0)			
Other	8	0 (7)	N.A.	100.0 (100.0, 100.0)	1 (1)	1.08 (N.A., N.A.)	0.0 (N.A., N.A.)	
Not Reported	1	0 (1)	N.A.	N.A.	0 (0)			

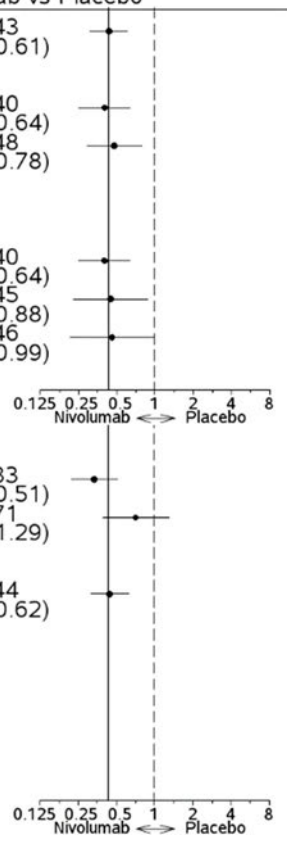

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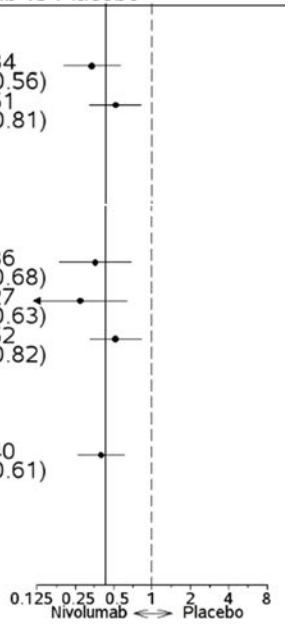
Figure 5: Applicant – Forest Plot of Treatment Effect on Recurrence-free Survival per Investigator in Pre-defined Subsets – All Randomized Subjects in CA20976K

	N	Nivolumab 480 mg Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Placebo Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Disease stage category								
Stage IIb	479	26 (316)	N.A. (28.52, N.A.)	92.6 (88.6, 95.2)	36 (163)	23.95 (18.37, N.A.)	84.1 (76.8, 89.3)	0.34 (0.20, 0.56)
Stage IIc	311	40 (210)	N.A. (23.66, N.A.)	83.8 (77.5, 88.4)	33 (101)	N.A. (16.03, N.A.)	72.0 (61.6, 80.0)	0.51 (0.32, 0.81)
Stage Other	0	0 (0)			0 (0)			
Stage Unknown	0	0 (0)			0 (0)			
T stage								
T3b	308	16 (204)	N.A.	92.6 (87.2, 95.7)	22 (104)	N.A. (18.37, N.A.)	83.4 (73.8, 89.7)	0.36 (0.19, 0.68)
T4a	170	10 (112)	28.52 (28.52, N.A.)	92.6 (85.1, 96.4)	14 (58)	23.62 (15.67, N.A.)	85.2 (70.7, 92.8)	0.27 (0.12, 0.63)
T4b	312	40 (210)	N.A. (23.66, N.A.)	83.8 (77.5, 88.4)	33 (102)	N.A. (16.03, N.A.)	72.3 (61.9, 80.2)	0.52 (0.33, 0.82)
Region								
US and Canada	143	8 (97)	N.A. (20.04, N.A.)	92.7 (84.2, 96.7)	8 (46)	N.A. (15.67, N.A.)	84.2 (67.8, 92.7)	
Western Europe	463	41 (303)	N.A. (28.52, N.A.)	89.0 (84.5, 92.3)	46 (160)	23.62 (17.91, N.A.)	78.0 (70.0, 84.0)	0.40 (0.26, 0.61)
Eastern Europe	86	8 (58)	N.A.	84.5 (71.3, 92.0)	9 (28)	23.95 (16.10, N.A.)	80.2 (58.6, 91.3)	
Australia	98	9 (68)	N.A.	87.9 (76.2, 94.1)	6 (30)	N.A.	78.8 (58.7, 89.9)	
ROW	0	0 (0)			0 (0)			



HR is not computed for subset category with less than 10 events per treatment group.
The solid vertical reference line presents overall HR value.
Note: One subject with T Stage T4b melanoma was incorrectly entered as Stage IIB instead of Stage IIC.

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The Applicant's Position:

RFS per Investigator: As of the data cutoff for this planned interim analysis (28-Jun-2022), 135 RFS events had occurred (87.7% information fraction). Based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundaries, the adjusted alpha stopping boundary is 0.03334.

Adjuvant nivolumab 480 mg Q4W demonstrated a statistically significant and clinically meaningful improvement in RFS vs placebo in subjects with completely resected Stage IIB/C melanoma (HR: 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001; Table 14).

- Separation of the Kaplan-Meier curves favoring nivolumab over placebo occurred at ~3 months, with increased separation over time (Figure 5).
- RFS rates were higher in the nivolumab arm compared with the placebo arm: 95.1% vs 88.1% at 6 months, 89.0% vs 79.4% at 12 months.
- 12.5% of subjects receiving nivolumab and 26.1% of subjects receiving placebo experienced a recurrence event (Table 14). The reduction in recurrence events with nivolumab was primarily driven by fewer distant recurrences (4.9% with nivolumab vs 11.7% with placebo) and regional recurrences (2.1% with nivolumab vs 7.6% with placebo; Table 15).
- At data cutoff (minimum follow-up of 7.8 months and 8.7 months for the nivolumab and placebo arms, respectively), 87.5% and 73.9% of all randomized subjects in the nivolumab and placebo arms, respectively, were censored for RFS. No subjects in either arm were censored due to receiving subsequent anti-cancer therapy, and 1.7% and 3% of all randomized subjects were censored due to secondary non-melanoma primary cancer (excluding basal cell carcinoma). 425 (80.8%) in the nivolumab arm and 180 (68.2%) subjects in the placebo arm were either continuing on-treatment or in follow-up in the nivolumab and placebo arms, respectively, and continue to be at risk for RFS events.

In a pre-specified subgroup analysis for all randomized subjects, RFS HRs (95% CI) for all subgroups favored (HR < 1) nivolumab vs placebo (Figure 6). Consistent treatment effect was observed across subgroups. Although the 95% CI for the treatment effect in the female subgroup crosses 1, the overall direction of effect is consistent with the ITT, and the 95% CI includes the ITT unstratified HR of 0.43.

Results of supportive analyses were consistent with the primary RFS analysis and confirm the robustness of the primary analysis results. The supportive analyses using the Kaplan-Meier method, stratified (unless otherwise specified) Cox proportional hazards model, and stratified (unless otherwise specified) log-rank test included:

- Unstratified RFS
- Unstratified RFS with stratification factor used as a covariate
- RFS accounting for assessment on/after subsequent therapy or on/after second non-melanoma primary cancer

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  - RFS was defined similarly to the primary definition except that events (recurrence or death) and disease assessments that occurred on or after subsequent anti-cancer therapy or on or after second non-melanoma primary cancer were considered (no time point truncation).
  - Only 2 additional events in the placebo arm are added in this supportive analysis based on RFS estimand (ITT definition, irrespective of Subsequent Therapy). The HR estimation is similar to the primary RFS analysis.
- RFS accounting for missing disease assessment prior to RFS event
  - A subject is considered to have two or more missing tumor assessments if the elapsed time between the RFS event and the last assessment prior to the events is greater than the time interval of two scheduled assessments. In cases where a subject has two or more consecutively missing disease assessments, the subject was censored at the last evaluable disease assessment prior to the missing assessments prior the RFS event. The primary definitions of RFS were used in this analysis.
  - No additional events are added in the RFS analysis due to this supportive analysis.

In a multivariate analysis of RFS, the treatment effect when adjusted for age (≥ 65 years vs < 65 years), gender (male vs female), baseline ECOG performance status (PS) (1 vs 0), disease stage (Stage IIC vs Stage IIB), and time from surgical resection to randomization (≥ 6 weeks vs < 6 weeks) was consistent with the primary RFS analysis.

The FDA's Assessment:

FDA agrees with the efficacy results presented in this section. FDA conducted a proportional hazards diagnostic test to check the proportional hazards assumption of the stratified Cox model. No non-proportional hazard issue was identified. The point estimates and 95% CIs of the RFS rates at 6 and 12 months are considered exploratory since they do not represent the entire effect size of the treatment and the chosen landmark time points are arbitrary.

In addition, FDA notes that results from the subgroup analyses are considered exploratory only. While FDA agrees that consistent treatment effect was observed across most subgroups, these results do need to be interpreted with caution, particularly in smaller groups with small event numbers.

Further, FDA agrees that the primary analysis of RFS appeared to be robust across a number of supportive analyses. The results of the supportive analyses are considered exploratory only.

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8.1.2.9. Data Quality and Integrity

The Applicant's Position:

Data cleaning and quality control checks were implemented by BMS and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF and externally loaded data. Continuous data quality review was performed throughout the study to ensure data completeness, accuracy, and integrity. Any issues or findings were followed up for resolution during Data Quality Sub-team meetings and Data Review Meetings. The Vendor Data Quality Oversight Plan was used to ensure oversight of Data Management review performed by (b) (4). In addition, a further period of enhanced data review was performed by BMS GBDS and clinical teams to ensure the quality and completeness of the data prior to data cutoff. The BMS RAVE Clinical database was also audited prior to the data cutoff. The Database Lock Checklist was completed prior to database lock; this documented that the database was complete, accurate, and all prerequisites for the database lock had been achieved.

The FDA's Assessment:

In general, the data quality is acceptable. The FDA reviewer was able to reproduce the efficacy results based on the submitted AdaM dataset for Study CA20976K.

8.1.2.10. Efficacy Results – Secondary and other relevant endpoints

Data:

Table 16: Applicant – Secondary Efficacy Endpoints – All Randomized Subjects in CA20976K

Endpoints	Nivolumab N = 526		Placebo N = 264
KEY SECONDARY ENDPOINTS			
DMFS per Investigator			
Events/number of subjects, n/N (%)	42/526 (8.0)		41/264 (15.5)
Median DMFS[c] (95% CI), months	N/A (28.52, N/A)		N/A
HR[a] (95% CI)		0.47 (0.30, 0.72)	
Rate at 6 months[c], % (95% CI)	97.6 (95.9, 98.6)		93.5 (89.7, 96.0)
Rate at 12 months[c], % (95% CI)	92.3 (89.3, 94.5)		86.7 (81.4, 90.5)
PFS2 per Investigator			
Events/number of subjects, n/N (%)	23/526 (4.4)		17/264 (6.4)
Median[c] PFS2 (95% CI), months	N/A		N/A
HR[a] (95% CI)		0.68 (0.36, 1.27)	

Data cutoff: 28-Jun-2022; Minimum follow-up: nivolumab arm 7.8 months, placebo arm 8.7 months

[a]HR is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.

[b]2-sided log-rank test stratified by the same factor as used in the Cox proportional hazard model. Boundary for statistical significance p-value < 0.033.

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[c]Based on Kaplan-Meier estimates.

The Applicant's Position:

DMFS per Investigator: In all randomized subjects, adjuvant nivolumab was associated with an improvement in DMFS per Investigator compared with placebo (HR = 0.47 [95% CI: 0.30, 0.72]). DMFS results are descriptive and not part of formal statistical testing (Table 16).

PFS2 – Primary Definition: PFS2 was defined as the time from randomization to recurrence/objective disease progression after the start of the next-line of systemic anti-cancer therapy, or to the start of a second next-line systemic therapy, or death from any cause, whichever occurred first. Subjects who were alive and without progression after the next line of therapy were censored at their last known date alive.

As of the data cutoff, relatively few PFS2 events (n = 40) occurred. In all randomized subjects, 23 (4.4%) PFS2 events occurred in the nivolumab arm and 17 (6.4%) events occurred in the placebo arm. PFS2 HR favored nivolumab vs placebo: 0.68 (95% CI: 0.36, 1.27), PFS2 results are descriptive and median PFS2 was not reached in either treatment arm at the time of this interim analysis(Table 16). After clinical review of the subjects with PFS2 events, it was determined that the primary definition of PFS2 reliably captured PFS2 events, and therefore, analysis of end of next-line therapy was not required.

OS: Per protocol, no OS analysis has been conducted and BMS remains blinded to the OS data. The datasets for OS have been submitted to FDA.

The FDA's Assessment:

FDA agrees with the descriptive efficacy results for the secondary endpoints DMFS and PFS2 presented in this section.

FDA conducted a descriptive OS analysis to check if there is a detrimental effect on OS of the treatment arm. At the data cutoff of RFS interim analysis, (b) (4) The data do not indicate any harm or detriment to survival at this time.

8.1.2.11. Dose/Dose Response

The Applicant's Position:

Previous PPK and E-R analyses that support the CA20976K dosing regimens are described in Section 6.2.2.1.

The FDA's Assessment:

FDA has no additional comment. See Section 6 for FDA assessment of dose-response relationship and data to support the proposed dosing.

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8.1.2.12. Durability of Response

The Applicant's Position:
See Section 8.1.2.13 "Persistence of Effect" below.

The FDA's Assessment:
See FDA response below in Section 8.1.2.13.

8.1.2.13. Persistence of Effect

The Applicant's Position:
In CA209238 in Stage IIIB/C and IV resected melanoma, the risk of recurrence was highest in the first year, after which the event rate slowed down considerably, particularly after 2 years. The RFS HR between nivolumab IV and ipilimumab IV remained largely consistent from the first analysis at 18 months minimum follow-up (HR 0.65, 0.51-0.83) to 3 years (HR 0.68, 0.56-0.82) to 4 years (HR 0.71, 0.60-0.86).

Analysis of hazard rates from CA209238 compared with mortality rates in the general population suggested likely emergence of a plateau in the RFS after Year 3.

In Stage IIB/C, the risk of recurrence is highest in the first 12-24 months. Given the treatment effect observed in CA20976K (HR 0.42, upper bounds of 95% CI 0.59) with a median follow-up of ~16 months in each arm, and the results from CA209238, there is likely to be a similar sustained clinical benefit in this population. Analyses of DMFS and PFS2 are also supportive.

The FDA's Assessment:
PFS2 is considered an exploratory endpoint (b) (4) the Applicant's analyses for PFS2 and DMFS were not adjusted for multiplicity.

8.1.2.14. Efficacy Results – Exploratory PRO endpoints

The Applicant's Position:
Patient-reported outcomes (PROs) captured quality of life using the QLQ-C30 and EQ-5D-5L measures. Results from both measures showed that subjects who underwent treatment with nivolumab maintained their quality of life during treatment similar to those in the placebo arm.

The FDA's Assessment:

Patients were asked to complete three PRO instruments in this study, including European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the Functional Assessment of Chronic Illness Therapy (FACIT) GP5, and the EuroQoL Group's 3-level version of the EQ-5D (EQ-5D-5L). All PRO instruments were administered during on-treatment and follow-up phases. During on-treatment phase, patients were expected to report all PRO instruments on Baseline, week 5, and every 4 weeks up to Week 53. Patients were also expected to complete the PRO instruments on the nominal Day 31 Post Last Dose Date (Follow-up 1) and the nominal Day 101 Post Last Dose Date (Follow-up 2). PRO endpoints included change from baseline in EORTC QLQ-C30 scores of functional scales, symptom scales, global health status/QoL scale and single items, summary changes and frequency of responses in FACIT-GP5

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item measuring bother due to side effects of treatment, and change from baseline in scores in both the EQ-5D-5L visual analog scale and the utility index.

During the blinded phase, the completion rates (number of patients with valid questionnaire assessment / number of patients expected to have an assessment) at baseline and all on-treatment visits were above 90% in both nivolumab arm and placebo arm for all three PRO instruments. The available data rates (number of patients with valid questionnaire assessment / number of randomized patients) were generally lower in the nivolumab IV arm compared with the placebo arm. The available data rates for all three PRO instruments dropped below 80% at week 21 in the nivolumab IV arm, while in the placebo arm, the available data rates for EQ-5D-5L and FACIT-GP5 dropped below 80% at week 37 and the available data rate for EORTC QLQ-C30 dropped below 80% at week 41.

FDA reviewed the PRO results submitted by the Applicant but did not independently verify all the results. (b) (4)

.

In terms of patient-reported tolerability, patients in the placebo arm reported "not at all" side effect bother at a higher rate at all timepoints compared to nivolumab. In both arms, very few patients (less than 5% at each timepoint) reported "quite a bit" or "very much" side effect bother according to the FACT-GP5 item.

8.1.2.15. Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

8.1.3. Integrated Review of Effectiveness

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

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8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Study CA20976K is a well-designed, placebo-controlled clinical trial. The submitted data meet the statutory evidentiary standard for substantial evidence of effectiveness. The data support the proposed indication of nivolumab as adjuvant treatment of patients with completely resected Stage IIB/C melanoma with no evidence of disease.

In Study CA20976K, adjuvant nivolumab 480 mg Q4W demonstrated a statistically significant and clinically meaningful improvement in RFS vs placebo in subjects with completely resected Stage IIB/C melanoma (see Section 8.1.2.8). An improvement in DMFS was also observed with nivolumab vs placebo (see Section 8.1.2.10). Results of supportive Study CA209238 demonstrate a sustained benefit in RFS and DMFS with adjuvant nivolumab over ipilimumab in subjects with completely resected Stage IIIB/C or Stage IV melanoma (see Section 8.1.2.13).

The FDA's Assessment:

The analysis of effectiveness of nivolumab IV for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB and IIC melanoma, (b) (4) was based on data submitted by the Applicant for the 790 patients randomized in Study CA20976K.

Overall, FDA agrees that adjuvant nivolumab 480 mg IV Q4W demonstrated a statistically significant and clinically meaningful improvement in RFS compared with placebo in patients with completely resected Stage IIB or IIC melanoma. Study CA20976K met its primary endpoint of RFS in the interim analysis at 88% information fraction (HR: 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001). The alpha-controlled key secondary endpoint OS was not mature, and no formal analysis was conducted for OS.

An HR in favor of nivolumab arm in DMFS was observed; however, the Type I error is not controlled for DMFS per the multiplicity plan, (b) (4) .

Although no pediatric patients (<18 years) were enrolled to Study CA20976K, the effectiveness of nivolumab IV in pediatric patients was based on extrapolation from other studies which characterize the clinical pharmacology and safety in this population. Refer to Section 10 for more information.

The results support approval of this indication.

8.2. Review of Safety

The Applicant's Position:

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The safety profile of nivolumab in this setting was similar to previous experience with nivolumab across other studies in varied tumor types and/or disease settings and no new safety concerns were identified. Although overall frequencies of all-causality and drug-related aEs, SAEs and discontinuations due to treatment-related adverse events were higher with nivolumab than with placebo, the results are consistent with the known safety profile of nivolumab.

The FDA's Assessment:
The data supporting FDA's assessment of the safety of nivolumab comes from Study CA20976K, a randomized, double-blind study designed to evaluate the use of adjuvant immunotherapy with nivolumab (n=524) vs placebo (n=264) after complete resection of Stage IIB or IIC melanoma in adult patients and pediatric patients ≥ 12 years old. The safety analysis population consists of patients enrolled to the blinded phase of the study who received at least one dose of 480 mg nivolumab IV or placebo as a 30-minute IV infusion. Study treatment continued for up to 12 months, until unacceptable toxicity, disease progression, withdrawal of consent or the end of study.

The safety of nivolumab IV as a single agent has been well characterized in studies of adult patients with melanoma and other tumor types. Based on the available data from this trial, there were no new safety signals associated with single agent nivolumab IV in patients with completely resected Stage IIB or IIC melanoma. As there were no pediatric patients enrolled in Study CA20976K, the safety of nivolumab IV in the pediatric population is based on extrapolation from studies of nivolumab IV in adult patients, the known similarities between adolescent melanoma and adult melanoma; comparable exposure profiles of nivolumab IV in pediatric and adult patients with solid tumors and hematological malignancies; and the relatively flat exposure-response curve for efficacy for nivolumab and review of safety data submitted from Study CA209070.

8.2.1. Safety Review Approach

The Applicant's Position:
Safety analyses were conducted by arm in all treated subjects who received at least 1 dose of study drug. Safety presentations were based on all treated subjects as follows:

- AEs, SAEs, AEs leading to discontinuation, and laboratory abnormalities used a safety window of 30 days after last dose. The 30-day safety window was intended to provide a characterization of the safety experience of nivolumab and placebo regimens without the influence of AEs associated with subsequent therapies.
- AEs leading to death used safety windows of 30 days and 100 days after last dose.
- Drug-related AEs leading to death (study-drug toxicities) used safety windows of 30 days, 100 days, and > 100 days after last dose.
- IMAE analyses with extended safety follow-up (using a 100-day window), as well as results of OESIs, are provided in the "Safety Results, Significant Adverse Events" subsection(s).

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The FDA's Assessment:
FDA agrees with the Applicant's summary of the safety analyses and data that was submitted to the sBLA. Safety was assessed for patients enrolled in the blinded phase and the study. Safety data from the open-label extension (OLE), the optional on-protocol administration of nivolumab to patients with recurrence events, was not included in the FDA assessment of safety.

The FDA safety review focused on analyses of the incidence of key adverse event (AR) categories including fatal and nonfatal SAEs, ARs resulting in permanent discontinuation of treatment, common AEs, Grade ≥3 AEs, and IMAEs. FDA also notes that the FDA review of adverse events includes the use of a list of grouped terms that are highly related and are thought to provide a more comprehensive description of the AE profile. During the review of this application (b) (4), some of the Applicant's frequency of AEs has changed due to incorporation of the FDA OOD grouped term list.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

Data:

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Table 17: Applicant - Cumulative Dose and Relative Dose Intensity Summary - Blinded Phase - All Treated Subjects in CA20976K

	Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
NUMBER OF DOSES RECEIVED		
MEAN (SD)	10.3 (4.01)	11.5 (3.06)
MEDIAN (MIN - MAX)	12.0 (1 - 14)	13.0 (1 - 14)
CUMULATIVE DOSE (MG)		
MEAN (SD)	4919.0 (1924.41)	N.A.
MEDIAN (MIN - MAX)	5760.0 (480 - 6720)	N.A.
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	N.A.
90% TO < 110%	470 (89.7)	N.A.
70% TO < 90%	51 (9.7)	N.A.
50% TO < 70%	3 (0.6)	N.A.
< 50%	0	N.A.

Last dose date and start dose date are dose dates relative to study phase.
The following subjects received unknown dose(s): (b) (6) in Cycle 10, (b) (6) in Cycle 12, (b) (6) in Cycle 13, (b) (6) in Cycle 14, (b) (6) in Cycle 7, (b) (6) in Cycle 14.
The following subjects received either 1 cycle of the wrong treatment ((b) (6) in Cycle 2, (b) (6) in Cycle 5) or site manually dispensed nivolumab from a different study but considered as Placebo in database ((b) (6)) or subject skipped one treatment cycle but considered as Placebo in database ((b) (6)).
All above doses are not counted in dosing summary in the Nivolumab arm nor in the Placebo arm.

The Applicant's Position:

In the blinded phase, 97.5% of all treated subjects in the nivolumab arm received the first dose of treatment within 0 to 3 days of randomization. The median number of nivolumab doses received was 12 (range: 1–- 14) and the median number of placebo doses received was 13 (range: 1-14) (Table 17). The proportion of treated subjects who received ≥ 90% of the planned nivolumab dose intensity was 89.7%. The median duration of therapy was 11.04 months in the nivolumab arm and 11.07 months in the placebo arm.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the duration of exposure in Study CA20976K for the blinded phase of the trial. Overall, the number of doses of study drug received was similar across study arms. FDA notes that the median duration of exposure to study drug in CA20976K was 11.04 months. This is comparable to that observed in CHECKMATE-238 in patients with completely resected Stage IIIB, IIIC or Stage IV melanoma (median duration of exposure 11.5 months) and longer than that observed in studies of patients with unresectable or metastatic melanoma (range 2.8 to 6.5 months).

8.2.2.2. Relevant characteristics of the safety population

The Applicant's Position:

See Sections 8.1.2.5 and 8.1.2.6 for baseline demographic and disease characteristics, respectively, of the all randomized population, which included 2 additional subjects compared with the treated population.

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The FDA's Assessment:
Of the 526 patients randomized to the nivolumab IV arm, there were two patients who were not treated due to suspected autoimmune disease (sarcoidosis) in one patient and elevated liver enzymes in the other patient. Most patients in Study CA20976K were male, white and non-Hispanic; the distribution of the study population by sex and racial and ethnic subgroups appeared generally consistent that of the US patient population with melanoma. The median age of patients in Study CA20976K was 62 years. The is slightly higher than the median age that has been reported for patients in the AJCC melanoma staging database with Stage I and II melanoma (Black 2013)..

8.2.2.3. Adequacy of the safety database

The Applicant's Position:
The population studied in CA20976K is representative of a resected Stage IIB/C melanoma population; this is supported by the study population's demographic, disease, and other baseline characteristics. With a 12-month course of study therapy and an established drug regimen with a well characterized safety profile in many other populations, the exposure to study drug in Study CA20976K is sufficient to characterize the safety of nivolumab in the resected Stage IIB/C melanoma population. The routine clinical and laboratory evaluations performed in the study were appropriate to evaluate and characterize the safety profile of nivolumab.

The FDA's Assessment:
FDA agrees that the safety database is adequate in regard to size, study treatment exposure and duration of treatment. Although there were a limited number of patients that identified as Black, Asian, Pacific Islander, America Indian/Alaskan Native, the study population appears to generally represent the relevant US population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
Continuous data quality review was performed throughout the study to ensure data completeness, accuracy, and integrity (see Section 8.1.2). An external DMC with multi-disciplinary representation was established to evaluate on a periodic basis AEs, laboratory measurements, and safety assessments, to ensure the ongoing safety of study subjects.

On 02-Sep-2021, BMS discovered that an automated process for republishing documents from the document management system/ (b) (4) to the SIP experienced delays due to intermittent system failures. Upon investigation (QE-030565), 21% of SUSARs were delayed (1553/7478), of which 18% (278/1553) were initial SUSARs. In addition, 15 blinded SUSAR reports and 10 executive summaries of DSURs that had not been communicated in a timely manner to clinical investigators.

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Based on assessment, BMS determined there was no impact to patient safety as the processes to timely report to health authorities and ethics committees were not affected. Also, the signal detection and mechanisms to inform investigators and subjects of changes to the risk benefit profile through updates to the IB and the Informed Consent remained unchanged. This incident was reported as a potential serious breach due to the systemic nature and the potential to impact patient safety as the CA20976K investigators may not have received timely notification of SUSARs and SASUSARs; however, it was confirmed not to be a serious breach.

BMS republished the documents between 09-Sep-2021 and 12-Oct-2021. The documents were received in SIP and distributed to the CA20976K investigators. BMS has successfully implemented the SIP/ (b) (4) API upgrade and, as of 14-Oct-2021, all failed documents which should have been published to study/sites have been successfully published/ re-published. In addition, BMS IT has implemented a proactive manual daily monitoring of the SIP/ (b) (4).

In an effort to prevent such future distribution issues, automated programmatic checks and detailed error logs to verify uploaded documents from (b) (4) and SIP are distributed to the study sites will be instituted. An effectiveness check was performed on 31-May-2022; a safety document monitoring report provided by (b) (4) (IT vendor) showed all files since 14-Oct-2021 successfully passed from (b) (4) to SIP.

The COVID-19 pandemic had limited impact on study conduct and data integrity. Measures taken to minimize the impact of COVID-19 on the conduct of the clinical study and analysis of data included:

- A "Dear Investigator Letter" was prepared and sent to the FDA and all sites participating in this study on 19-Mar-2020. The letter describes the proactive steps taken to protect the safety of study subjects, employees and staff at clinical trial sites while also ensuring regulatory compliance and the scientific integrity of trial data. A second "Dear Investigator Letter" was sent to the sites on 09-Apr-2020 to provide additional updates regarding patient enrollment, ongoing patient treatment, and reporting of confirmed COVID-19 cases to BMS.
- Impact on data integrity: All critical CRF data entry was completed and all critical queries were addressed. Due to on-site monitoring visit restrictions during the COVID-19 pandemic, there were minimal issues regarding critical CRF data entry SDV'd prior to the DBL.
- Protocol deviations: There were 65 COVID-19 related protocol deviations reported.
- A COVID-19 Safety Surveillance Plan was created by BMS, and newly released MedDRA version 23.0 (effective date 04-May-2020) was adopted to retrospectively search for AEs related to COVID-19 in the database.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA considers it unlikely that the automated delay in the process for republishing documents from the document management system/ (b) (4) to the SIP had a clinically meaningful impact on the interpretation of study safety.

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8.2.3.2. Categorization of Adverse Event

The Applicant's Position:
Adverse events in CA20976K were categorized by system organ class and preferred term using the MedDRA version 25.0 and by severity grade using NCI CTCAE version 5.0.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.3.3. Routine Clinical Tests

The Applicant's Position:
Standard laboratory tests (eg, liver, renal, thyroid, metabolic) and pregnancy tests were conducted at the screening visit, each treatment visit, and the post-adjuvant therapy Visits 1 and 2. Laboratory tests were graded using the NCI CTCAE, version 5.0.

The FDA's Assessment:
FDA agree with the Applicant's approach for routine clinical testing.

8.2.4. Safety Results - Study CA20976K

Data:

Table 18 - Applicant: Summary of Safety - Blinded Phase - All Treated Subjects in CA20976K

	No. of Subjects (%)			
Safety Parameters	**Nivolumab 480 mg IV Q4W N = 524**		**Placebo IV Q4W N = 264**	
Deaths	13[a] (2.5)		8 (3.0)	
Primary Reason for Death				
Disease	3[a] (0.6)		4 (1.5)	
Study Drug Toxicity	1[b] (0.2)		0	
Unknown	1 (0.2)		1 (0.4)	
Other	8[c] (1.5)		3 (1.1)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	74 (14.1)	55 (10.5)	29 (11.0)	20 (7.6)
≥ 0.6% of Subjects in Any Treatment Group				
COVID-19	4 (0.8)	2 (0.4)	1 (0.4)	1 (0.4)
Alanine aminotransferase increased	3 (0.6)	3 (0.6)	0	0
Aspartate aminotransferase increased	3 (0.6)	3 (0.6)	1 (0.4)	1 (0.4)
Pulmonary embolism	3 (0.6)	2 (0.4)	0	0
Melanoma recurrent	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.4)
Invasive breast carcinoma	0	0	2 (0.8)	2 (0.8)
Drug-related SAEs	25 (4.8)	23 (4.4)	3 (1.1)	2 (0.8)
≥ 0.4% of Subjects in Any Treatment Group				
Colitis	2 (0.4)	2 (0.4)	0	0
Diarrhea	2 (0.4)	2 (0.4)	0	0

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Table 18 - Applicant: Summary of Safety - Blinded Phase - All Treated Subjects in CA20976K

	No. of Subjects (%)			
	Nivolumab 480 mg IV Q4W N = 524		Placebo IV Q4W N = 264	
Safety Parameters				
Adrenal insufficiency	2 (0.4)	2 (0.4)	0	0
Rhabdomyolysis	0	0	1 (0.4)	1 (0.4)
Myocarditis	2 (0.4)	2 (0.4)	0	0
Hepatitis	0	0	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Interstitial lung disease	0	0	1 (0.4)	0
All-causality AEs leading to DC	91 (17.4)	37 (7.1)	9 (3.4)	2 (0.8)
≥ 1% of Subjects in Any Treatment Group				
Arthralgia	9 (1.7)	0	0	0
Diarrhea	6 (1.1)	3 (0.6)	0	0
Colitis	5 (1.0)	2 (0.4)	0	0
Alanine aminotransferase increased	6 (1.1)	3 (0.6)	2 (0.8)	0
Aspartate aminotransferase increased	6 (1.1)	4 (0.8)	2 (0.8)	1 (0.4)
Rash	5 (1.0)	3 (0.6)	0	0

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Reference ID: 5260748

Table 18 - Applicant: Summary of Safety - Blinded Phase - All Treated Subjects in CA20976K

Safety Parameters	No. of Subjects (%)			
	Nivolumab 480 mg IV Q4W N = 524		Placebo IV Q4W N = 264	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Drug-Related AEs leading to DC	77 (14.7)	29 (5.5)	7 (2.7)	2 (0.8)
≥ 1% of Subjects in Any Treatment Group				
Arthralgia	9 (1.7)	0	0	0
Diarrhea	6 (1.1)	3 (0.6)	0	0
Colitis	5 (1.0)	2 (0.4)	0	0
Alanine aminotransferase increased	5 (1.0)	2 (0.4)	2 (0.8)	0
Aspartate aminotransferase increased	5 (1.0)	3 (0.6)	2 (0.8)	1 (0.4)
Rash	5 (1.0)	3 (0.6)	0	0
All-causality AEs	502 (95.8)	115 (21.9)	229 (86.7)	32 (12.1)
≥ 10% of Subjects in Any Treatment Arm				
Fatigue	137 (26.1)	1 (0.2)	66 (25.0)	1 (0.4)
Diarrhea	118 (22.5)	6 (1.1)	40 (15.2)	0
Pruritus	105 (20.0)	1 (0.2)	29 (11.0)	0
Arthralgia	86 (16.4)	2 (0.4)	30 (11.4)	1 (0.4)
Nausea	74 (14.1)	0	29 (11.0)	0
Rash	65 (12.4)	4 (0.8)	25 (9.5)	1 (0.4)
Headache	60 (11.5)	1 (0.2)	33 (12.5)	2 (0.8)
Hypothyroidism	60 (11.5)	0	0	0
Asthenia	59 (11.3)	1 (0.2)	25 (9.5)	0
Blood creatine phosphokinase increased	55 (10.5)	10 (1.9)	31 (11.7)	1 (0.4)
Drug-related AEs	433 (82.6)	54 (10.3)	142 (53.8)	6 (2.3)
≥ 10% of Subjects in Any Treatment Arm				
Fatigue	106 (20.2)	0	53 (20.1)	1 (0.4)
Pruritus	97 (18.5)	1 (0.2)	25 (9.5)	0
Diarrhea	80 (15.3)	4 (0.8)	25 (9.5)	0
Rash	57 (10.9)	4 (0.8)	18 (6.8)	0
Arthralgia	54 (10.3)	1 (0.2)	15 (5.7)	0
Hypothyroidism	54 (10.3)	0	0	0
All-causality Select AEs				
Endocrine	116 (22.1)	9 (1.7)	14 (5.3)	0
Gastrointestinal	122 (23.3)	8 (1.5)	41 (15.5)	0
Hepatic	86 (16.4)	18 (3.4)	35 (13.3)	3 (1.1)
Pulmonary	10 (1.9)	2 (0.4)	1 (0.4)	0
Renal	30 (5.7)	2 (0.4)	10 (3.8)	0
Skin	217 (41.4)	6 (1.1)	64 (24.2)	1 (0.4)
Hypersensitivity/Infusion Reactions	33 (6.3)	0	2 (0.8)	0

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Table 18 - Applicant: Summary of Safety - Blinded Phase - All Treated Subjects in CA20976K

Safety Parameters	No. of Subjects (%)			
	Nivolumab 480 mg IV Q4W N = 524		Placebo IV Q4W N = 264	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Drug-Related Select AE				
Endocrine	108 (20.6)	9 (1.7)	13 (4.9)	0
Gastrointestinal	85 (16.2)	6 (1.1)	25 (9.5)	0
Hepatic	59 (11.3)	14 (2.7)	16 (6.1)	2 (0.8)
Pulmonary	7 (1.3)	1 (0.2)	1 (0.4)	0
Renal	9 (1.7)	2 (0.4)	0	0
Skin	181 (34.5)	6 (1.1)	47 (17.8)	0
Hypersensitivity/Infusion Reactions	31 (5.9)	0	2 (0.8)	0
All-causality IMAEs within 100 days of last dose Treated with Immune Modulating Medication				
Diarrhea/Colitis	24 (4.6)	6 (1.1)	2 (0.8)	1 (0.4)
Hepatitis	22 (4.2)	14 (2.7)	1 (0.4)	0
Pneumonitis	4 (0.8)	1 (0.2)	2 (0.8)	0
Nephritis/Renal Dysfunction	3 (0.6)	2 (0.4)	1 (0.4)	0
Rash	45 (8.6)	4 (0.8)	4 (1.5)	0
Hypersensitivity/Infusion Reactions	7 (1.3)	0	0	0
All-causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication				
Adrenal Insufficiency	12 (2.3)	3 (0.6)	3 (1.1)	0
Hypophysitis	9 (1.7)	5 (1.0)	2 (0.8)	0
Hypothyroidism/Thyroiditis	64 (12.2)	0	0	0
Hyperthyroidism	40 (7.6)	1 (0.2)	4 (1.5)	0
Diabetes Mellitus	3 (0.6)	3 (0.6)	0	0
All-causality OESIs within 100 days of last dose With or Without Immune Modulating Medication				
Uveitis	2 (0.4)	0	0	0
Myocarditis	3 (0.6)	2 (0.4)	0	0
Pancreatitis	8 (1.5)	2 (0.4)	0	0
Encephalitis	0	0	0	0
Myositis/Rhabdomyolysis	8 (1.5)	5 (1.0)	2 (0.8)	1 (0.4)
Guillain-Barré Syndrome	0	0	0	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Graft Versus Host Disease	0	0	0	0
Autoimmune Cytopenia	0	0	0	0

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Table 18 - Applicant: Summary of Safety - Blinded Phase - All Treated Subjects in CA20976K

	No. of Subjects (%)			
Safety Parameters	Nivolumab 480 mg IV Q4W N = 524		Placebo IV Q4W N = 264	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Autoimmune Eye Disorder	0	0	0	0
Immune Mediated Arthritis	0	0	0	0

[a]One additional death due to disease occurred prior to data cutoff, but was reported after DBL, in the nivolumab arm for a total of 14 deaths with 4 deaths due to disease. This subject had a disease recurrence prior to death and this was captured as an RFS event prior to data cutoff.

[b]The causes of death per investigator were heart failure and acute kidney failure.

[c]The causes of death due to "other" reasons were as follows: in the nivolumab arm: COVID-19 lung infection, diverticulitis, circulatory failure, suicide, pulmonary embolism, HSV-1 encephalitis, potential allergic reaction during TEP scanner, and acute cardiac ischemic event not related to therapy (1 subject each); in the placebo arm: multi organ failure, sudden death, and COVID-19 infection (1 subject each).

MedDRA version 25.0. CTCAE version 5.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

8.2.4.1. Deaths

The Applicant's Position:

As of the 28-Jun-2022 data cutoff, 13 (2.5%) treated subjects in the nivolumab IV arm and 8 (3.0%) in the placebo arms had died (Table 18). One additional death occurred in the nivolumab arm prior to the data cutoff but was reported after the DBL for a total of 14 (2.7%) deaths. The death rates reported within 30 days and 100 days of last dose were similar in both treatment arms.

"Other" reason was the most common cause of death in the nivolumab IV arm. The verbatim terms for death attributed to "other" were consistent with events expected in the population under study and none were considered related to study drug. Disease progression was the most common cause of death in the placebo arm.

There was 1 subject (0.2%) who died due to study drug toxicity in the nivolumab IV arm. The subject discontinued treatment 1 week after the first dose of nivolumab IV, following a Grade 3 skin rash (vasculitis) event, and a few weeks later deterioration of renal functions leading to a Grade 4 acute kidney injury and an acute cardiac event leading to heart failure. The patient died 123 days after the first and only dose of nivolumab, and the cause of death was reported as heart failure and acute kidney failure.

The FDA's Assessment:

[FDA generally agrees with the Applicant's summary of death events in Study CA20976K. Of the 14 deaths that occurred in the nivolumab IV arm, the cause of death reported for four patients was progression of disease. The cause of death reported for eight of the patients who died in the nivolumab IV arm was "other" and the cause of death of one patient was reported as

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"unknown." A brief summary of the death narratives for the patients with a cause of death reported as "other" or "unknown" is provided below. Upon review of the safety narratives, FDA agrees with the Applicant's assessment of the one death considered to be related to study treatment.

Table 19: Description of Deaths in Nivolumab IV Arm Reported as "Other" or "Unknown"

COVID-19	This patient was diagnosed with COVID-19 infection on Day 136 (23 days after the 5th nivolumab infusion). The patient died on Day 166.	Reviewer assessment is that this death is unlikely to be drug related.
Diverticulitis	This patient was admitted to the hospital on Day 71 (70 days after the 1st nivolumab infusion) due to Grade 2 diverticulitis. Patient died on Day 101 due to diverticulitis.	Reviewer assessment is that this death is unlikely to be drug related.
Circulatory collapse s/p appendicitis and surgery	This patient was hospitalized on Day 206 (37 days after the 7th nivolumab infusion) due to Grade 3 appendicitis and underwent appendectomy on the same day. Patient was discharged on Day 211. The patient died on Day 212, No additional details were available regarding the patient's death. The Applicant was not aware as to whether an autopsy had been performed.	Reviewer assessment is that this death is unlikely to be drug related.
Suicide	Patient died on Day 868 (559 days after the last nivolumab infusion).	Reviewer assessment is that this death is unlikely to be drug related.
Pulmonary embolism	This patient was admitted to the hospital on Day 24 (24 days after the 1st nivolumab infusion) due to a Grade 4 pulmonary embolism. The patient died on Day 34.	There was insufficient information provided regarding other potential risk factors for this death event. It is unclear to the reviewer whether this death is drug related.
HSV encephalitis	This patient was admitted to the hospital on Day 177 (8 days after the 7th nivolumab infusion) due to Grade 3 herpes simplex encephalitis. The hospital course was complicated by hospital acquired pneumonia on Day 188. The patient died on Day 214.	There was insufficient information provided regarding other potential risk factors for this death event. It is unclear to the reviewer whether this death is drug related.

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Contrast media allergy	The patient died on Day 345 (9 days after the 12th nivolumab infusion) during a PET scan.	Reviewer assessment is that this death is unlikely to be drug related.
Acute myocardial ischemia	This patient died on Day 30 (29 days after the first nivolumab infusion). The Applicant was not aware as to whether an autopsy had been performed.	There was insufficient information provided regarding other potential risk factors for this death event. It is unclear to the reviewer whether this death is drug related.
Unknown	This patient was LTFU and died 468 days after last dose of study treatment	There is insufficient information to determine whether this death is drug related; however, the death is unlikely related given the timing of the patient's death with respect to treatment.

8.2.4.2. Serious Adverse Events

The Applicant's Position:

The frequencies of any Grade and Grade 3-4 SAEs (all-causality and drug-related) were numerically higher with nivolumab than with placebo; the most common preferred terms are provided in Table 18. The frequency of all reported individual SAEs was < 1% in both the nivolumab and placebo arms. The majority of SAEs in both treatment arms were considered not drug-related by the investigator.

The FDA's Assessment:

FDA conducted an independent assessment of SAEs using the FDA OOD list of grouped terms and determined that serious adverse events occurred in 18% of patients in the nivolumab IV arm and 14% of patients in the placebo arm. FDA notes these incidence rates differ from information provided in the Applicant's Table 18. The frequency of all reported individual SAEs was ≤1% in both treatment arms. The most commonly reported (>2 patients) SAEs in the nivolumab IV arm are included below.

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Table 20: Most Common (>2 patients) SAEs in Nivolumab Arm

	NIVOLUMAB 480 MG IV Q4W N = 524 N (%)	PLACEBO IV Q4W N = 264 N (%)
Patients with serious AEs	**95 (18)**	**37 (14)**
Infections And Infestations		
Covid-19	4 (0.8)	1 (0.4)
Diverticulitis	3 (0.6)	0 (0.0)
Gastrointestinal Disorders		
Diarrhea (GT)	5 (1.0)	2 (0.8)
Respiratory, Thoracic And Mediastinal Disorders		
Pulmonary Embolism	4 (0.8)	0 (0.0)
Endocrine Disorders		
Adrenal Insufficiency	3 (0.6)	0 (0.0)
Investigations		
Alanine Aminotransferase Increased	4 (0.8)	0 (0.0)
Aspartate Aminotransferase Increased	4 (0.8)	1 (0.4)
Hepatic Enzyme Increased	1 (0.2)	0 (0.0)
Renal And Urinary Disorders		
Acute Kidney Injury (GT)	3 (0.6)	1 (0.4)

Group Diarrhea (GT) includes PT terms COLITIS, DIARRHOEA, AUTOIMMUNE COLITIS, ENTEROCOLITIS,
Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY,
Source: ADSL (Subject-Level Analysis Dataset) - 2022-12-13, ADAE (Adverse Events Analysis Dataset) - 2022-12-13. Variables used: USUBJID, TRT01A, SAFFL, TR01E2FL, AEDECOD, AETOXGRN, APERIODC, AEACN, AEBODSYS, AESER

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8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

The frequencies of any Grade and Grade 3-4 AEs leading to discontinuation (all-causality and drug-related) were numerically higher with nivolumab IV than with placebo; the most common preferred terms are provided in Table 18.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of AEs that resulted in permanent

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treatment discontinuation presented in Table 18. Treatment discontinuation was more common in the nivolumab IV arm (17%) compared to the placebo arm (3.4%). Upon reevaluation of the adverse events using the standard FDA grouped term list, the most common (>1%) AEs that resulted in permanent treatment discontinuation were musculoskeletal pain (primarily arthralgia), rash (1.7% each), and diarrhea (1.1%).

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8.2.4.4. Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:
Dose reductions were not permitted with nivolumab IV or placebo treatment as per protocol. Adverse events (all causality) leading to a dose delay were reported in 129 (24.6%) subjects in the nivolumab arm and 35 (13.3%) subjects in the placebo arm. Drug-related AEs leading to a dose delay were reported in 82 (15.6%) subjects in the nivolumab IV arm and 12 (4.5%) subjects in the placebo arm.

The FDA's Assessment:
FDA agrees with the Applicant's summary of adverse events that resulted in dose interruption. Dose interruptions due to AEs were more common in the nivolumab IV arm. Overall, the incidence of any single reported AE that resulted in dose interruption was low with the most commonly reported (>1%) AEs leading to dose interruption were COVID-19 infection, infusions related reactions, diarrhea, musculoskeletal pain (primarily arthralgia), and ALT increased.

Dose reductions of nivolumab IV were not allowed on study.

8.2.4.5. Significant Adverse Events

The Applicant's Position:
Immune-mediated Adverse Events: IMAEs are a predefined list of specific events (or groups of PTs describing specific events) known to have an immunologic etiology. They were identified by the investigator as IMAEs with no clear alternate etiology and an immune mediated component. IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose of blinded adjuvant therapy (ie, with extended follow-up). These analyses were limited to subjects who received IMM for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

IMAEs were reported more frequently in the nivolumab arm than the placebo arm (Table 18). Overall, most IMAEs were Grade 1-2, excluding hepatitis, nephritis, hypophysitis, and diabetes mellitus. The most frequently reported IMAEs (any grade) by category in each treatment arm are provided in Table 18.

Across IMAE categories, most non-endocrine IMAEs were manageable using established algorithms, with resolution occurring when immune-modulating medication (commonly

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systemic corticosteroids) was administered. Except for hyperthyroidism, many endocrine IMAEs were not considered resolved at time of DBL.

Other Events of Special Interest: OESIs are events that do not fulfill all criteria to qualify as select AEs or IMAEs. They may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100-day window). OESI categories: uveitis, myocarditis, pancreatitis, encephalitis, myositis/rhabdomyolysis, Guillain-Barré syndrome, myasthenic syndrome, demyelination, Graft Versus Host Disease, autoimmune cytopenia, autoimmune eye disorder, and immune-mediated arthritis.

OESIs were only reported in the pancreatitis, uveitis, myocarditis, and myositis/rhabdomyolysis categories (Table 18). Frequency of all OESI categories (any grade; any causality) with nivolumab were < 1%, except for myositis/rhabdomyolysis (1.5%) and pancreatitis (1.5%). Most of the OESIs in the nivolumab arm were considered drug-related by the investigator.

The FDA's Assessment:
There was no new information presented in this sBLA to change the understanding of the type or severity of IMAEs in patients treated with single agent nivolumab IV. The FDA conducted an independent analysis of IMAEs. FDA identified a total of 180 patients (168 patients in the nivolumab IV arm and 12 patients in the placebo arm) that were reported as having a protocol-defined IMAE in the blinded phase of the study. Of the patients who experienced IMAEs, there were 88 patients in the nivolumab IV arm (52%) and 6 patients on the placebo arm (50%) who had ongoing protocol-defined IMAEs at the time of the database lock (August 17, 2022). FDA notes some differences compared to the Applicant's report in the incidences of IMAEs (requiring immune mediating therapy) in the nivolumab IV arm with the most common (≥10 patients) IMAEs as follows: hypothyroidism (11%), rash (8%), hyperthyroidism (7%), autoimmune colitis or diarrhea (4.4%), and adrenal insufficiency (1.9%). IMAEs appear to have occurred at a higher incidence in patients treated with IV nivolumab in Study CA20976K compared to the incidence of IMAEs reported in Section 5 (Warnings and Precautions) of the USPI. However, there are likely multiple factors that have not been unaccounted for including but not limited to size of the respective populations and duration of exposure to nivolumab which may contribute to this difference. Of note, the median duration of exposure in studies of patients with unresectable or metastatic melanoma reported in the USPI (CHECKMATE-037, CHECKMATE-066, and CHECKMATE-067) ranges from 2.8 to 6.5 months. The median duration of exposure to nivolumab IV in patients with completely resected Stage IIIB, IIIC or Stage IV melanoma in CHECKMATE-238 was 11.5 months. The median duration of exposure to nivolumab IV in Study CA20976K was 11.04 months.

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8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Data:

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Reference ID: 5260748

Table 21: Applicant - Adverse Reactions Occurring in ≥ 10% of OPDIVO-Treated Patients - CA20976K

Adverse Reaction	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	37	0.4	35	0.4
Skin and Subcutaneous Tissue				
Rash[b]	24	1.3	14	0.4
Pruritus	20	0.2	11	0
Gastrointestinal				
Diarrhea	23	1.1	15	0
Nausea	14	0	11	0
Musculoskeletal and connective tissue				
Musculoskeletal pain[c]	18	0	19	0
Arthralgia	16	0.4	11	0.4
Nervous system				
Headache	12	0.2	13	0.8
Endocrine				
Hypothyroidism[d]	12	0	0	0

Toxicity was graded per NCI CTCAE version 5.0.

[a] Includes asthenia.

[b] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis psoriasiform, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular.

[c] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, sacral pain and pain in extremity.

[d] Includes autoimmune hypothyroidism.

The Applicant's Position:

For (b) (4) adverse reactions (grouped by system organ class and presented by CTCAE grade) (b) (4) that were reported in ≥ 10% of subjects treated with nivolumab in CA20976K (b) (4); see (Table 21). The most common adverse reactions (reported in ≥ 20% of patients) were fatigue, rash, diarrhea, and pruritis. There were no Grade 3 or 4 adverse reactions that occurred in ≥ 2% of patients.

The FDA's Assessment:

[Using the standard list of FDA OOD grouped terms, the FDA analysis of TEAEs resulted in the same overall list of TEAEs with a slightly different incidence of the individual events. The incidence of Grade 3-4 AEs were more common in the nivolumab IV arm (22%) compared to the placebo arm (12%). The most frequently reported Grade 3-4 AEs in the nivolumab arm were blood creatinine phosphokinase increased (1.9%) and ALT increased, AST increased, and hypertension (1.5% each).

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Table 22: TEAEs in ≥10% of Patients Treated with Nivolumab

Adverse Reaction	OPDIVO IV (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	36	0.4	34	0.4
Musculoskeletal and connective tissue				
Musculoskeletal pain[b]	30	0.4	26	0.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.1	15	0.4
Pruritus	20	0.2	11	0
Gastrointestinal				
Diarrhea[d]	23	1.3	16	0
Nausea	14	0	11	0
Endocrine				
Hypothyroidism[e]	14	0	2.3	0
Nervous system				
Headache[f]	12	0.2	14	0.8

Toxicity was graded per NCI CTCAE v5.

[a] Includes asthenia.

[b] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, spinal pain, pain in extremity.

[c] Includes dermatitis, dermatitis acneiform, dyshidrotic eczema, eczema, eczema asteatotic, eyelid rash, genital rash, pemphigoid, penile rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, toxic skin eruption.

[d] Includes autoimmune colitis, colitis, diarrhea, enteritis, enterocolitis

[e] Includes autoimmune hypothyroidism, blood thyroid stimulating hormone increased.

[f] Includes cluster headache, migraine.

Source: ADAE dataset]

8.2.4.7. Laboratory Findings

Data:

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Table 23: Applicant - Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥ 10% of OPDIVO-Treated Patients - CA20976K

Laboratory Abnormality	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	19	0	14	0
Lymphopenia	17	1.1	17	1.7
Neutropenia	10	0	10	0.4
Chemistry				
Increased AST	25	2.2	16	0.4
Increased Lipase	22	2.9	21	2.3
Increased ALT	20	2.1	15	0.4
Increased Amylase	17	0.4	9	0
Increased Creatinine	15	0.4	13	0
Hyponatremia	13	0.6	11	0.4
Hyperkalemia	13	1.0	15	1.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 262 to 513 patients) and placebo group (range: 138 to 261 patients).

The Applicant's Position:
Laboratory abnormalities were primarily Grade 1 or 2 in severity in both treatment arms. The majority of subjects did not have laboratory tests that worsened to Grade 3 or 4 relative to baseline (Table 23).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of laboratory findings. Although there was a slight numerical increase in the incidence of some laboratory findings (anemia, Increased AST, Increased ALT, Increased Amylase, Increased Creatinine, and Hyponatremia), the increase was considered to nominal.

8.2.4.8. Vital Signs

The Applicant's Position:
Vital signs were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:
FDA agrees with the Applicant's description of vital sign assessment.

8.2.4.9. Electrocardiograms (ECGs)

The Applicant's Position:
ECG testing was conducted at Screening as a part of eligibility assessments for study participation. Routine ECG testing (as part of study safety assessments) was not performed during the on-treatment and follow-up visits.

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The FDA's Assessment:
No new information or data pertaining to ECGs were submitted with this application.

8.2.4.10. QT

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

8.2.4.11. Immunogenicity

The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:
No new information was submitted in this review.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position: Not applicable.

The FDA's Assessment:
FDA did not identify submission-specific safety issues that required further analysis.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position: PRO data were collected regarding patient bother from side effects of treatment using the one-item FACIT-GP5 questionnaire. Overall, in responding to FACIT-GP5 "I am bothered by side effects of treatment", few subjects treated with nivolumab reported a lot of bother (ie, responded "Quite a Bit" or "Very Much") during treatment, and the proportions were similar to placebo-treated subjects.

In the nivolumab arm, ≤ 3.1% of subjects responded "Quite a Bit" and ≤ 1.0% of subjects responded "Very Much" through Week 53. In the placebo arm, ≤ 2.5% of subjects responded "Quite a Bit" and ≤ 0.6% of subjects responded "Very Much" through Week 53. In both treatment arms, the highest proportion of patients responding "Quite a Bit" or "Very Much" to bother by side effects of treatment came after treatment ended, during Follow-up Visits 1 and 2, where the nivolumab arm had a combined rate of 10.8% at Follow-up Visit 1 and 8.6% at Follow-up Visit 2, and the placebo arm had a combined rate of 4.4% at Follow-up Visit 1 and 2.2% at Follow-up Visit 2.

The FDA's Assessment:
COAs were exploratory endpoints and were not formally evaluated in the safety analysis of Study CA20976K. See Section 8.1.2.14 for additional discussion of PRO endpoints.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

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Table 24: Applicant - Drug-Related Adverse Events Classified by Worst CTCAE Grade and by Age, Sex, Race, and Region - Blinded Phase - All Treated Subjects in CA20976K

	Drug-related AEs (n [%])							
	Nivolumab Arm 480 mg Q4W				Placebo Arm Q4W			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	524	433 (82.6)	54 (10.3)	0	264	142 (53.8)	6 (2.3)	0
By Age (years)								
< 65	305	253 (83.0)	29 (9.5)	0	155	94 (60.6)	3 (1.9)	0
≥ 65 and < 75	139	115 (82.7)	17 (12.2)	0	77	36 (46.8)	3 (3.9)	0
≥ 75 and < 85	77	62 (80.5)	8 (10.4)	0	30	11 (36.7)	0	0
≥ 85	3	3 (100.0)	0	0	2	1 (50.0)	0	0
≥ 65	219	180 (82.2)	25 (11.4)	0	109	48 (44.0)	3 (2.8)	0
By Sex								
Male	320	264 (82.5)	39 (12.2)	0	161	87 (54.0)	4 (2.5)	0
Female	204	169 (82.8)	15 (7.4)	0	103	55 (53.4)	2 (1.9)	0
By Race								
White	513	422 (82.3)	53 (10.3)	0	262	140 (53.4)	6 (2.3)	0
Black or African American	2	2 (100.0)	0	0	1	1 (100.0)	0	0
Asian	1	1 (100.0)	0	0	0	0	0	0
Other	7	7 (100.0)	1 (14.3)	0	1	1 (100.0)	0	0
By Region								
US and Canada	97	90 (92.8)	16 (16.5)	0	46	35 (76.1)	2 (4.3)	0
Western Europe	301	241 (80.1)	30 (10.0)	0	160	80 (50.0)	4 (2.5)	0
Eastern Europe	58	39 (67.2)	3 (5.2)	0	28	8 (28.6)	0	0
Australia	68	63 (92.6)	5 (7.4)	0	30	19 (63.3)	0	0

MedDRA Version: 25.0; CTCAE version 5.0; Includes events reported between first dose and 30 days after last dose of study therapy.

The Applicant's Position:

In the blinded phase, the frequencies of all-causality and drug-related AEs in the nivolumab IV and placebo arms for subgroups of gender, race, and age, were similar to AE frequencies reported for the overall study population by treatment (Table 24).

By Age

- Frequencies of all-causality AEs and drug-related AEs were comparable by age category (< 65, ≥ 65 - < 75, and ≥ 75 - < 85) within each treatment arm.
- Due to a very small sample size of subjects in the ≥ 85 age category in nivolumab IV and placebo arms, the interpretability is limited.

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By Sex

- Frequencies of all-causality AEs and Grade 3-4 AEs were slightly higher in males than females in the nivolumab arm.
- The drug-related AE rates were generally similar by sex in both nivolumab and placebo arms.

By Race

- For subgroups based on race, most of the subjects were classified as "White" with frequencies of all-causality AEs and drug-related AEs of any grade and Grade 3-4 consistent with that reported in the overall study population.
- Very low sample sizes in other categories of race, such as "Black" or "African American", "Asian" and "Other", limit the interpretability of potential differences.

By Region

- Subgroup analyses by region showed that most of the subjects were located in Western Europe with frequencies of all-causality AEs and drug-related AEs of any grade and Grade 3-4 consistent with those reported in the overall study population.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. FDA conducted an independent analysis of all causality adverse events by age, sex, race, and region. Frequencies of all-causality adverse events were relatively balanced across the subgroups based on age and sex; however FDA notes that there were very few patients aged 85 years or older enrolled to CA20976K and therefore no conclusions can be made regarding a balance or imbalance of adverse events in this age group. As the majority of patients treated on Study CA20976K were White with very few patients treated who were Black, Asian, or "other" race, limited conclusions can be made on the incidence of adverse events across racial groups. However, the distribution of the study population by racial and ethnic subgroups appeared generally consistent that of the US patient population with melanoma. Although the frequency of all-causality all grade adverse events appeared relatively balanced across region, there were some differences in the frequency of Grade 3 and 4 adverse events most notably a numerically lower frequency of high-grade events in patients in the nivolumab arm in Eastern Europe. There was also a numerically lower frequency of all grade and Grade 3-4 AEs in the placebo arm in patients in Eastern and Western Europe. Considering Study CA20976K is randomized, the enrollment across region was generally balanced between the nivolumab IV and placebo arms, and patients treated in Eastern Europe (who had the largest numerical differences in AE frequency) account for only 11% of the total study population, this numerical difference in the frequency of AEs is unlikely to have a significant impact on the interpretation of study results.

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Table 25: Summary of Adverse Events by Age

	NIVOLUMAB 480 MG IV Q4W				PLACEBO IV Q4W			
	>= 18 AND < 65 N = 305 N (%)	>= 65 AND < 75 N = 139 N (%)	>= 75 AND < 85 N = 77 N (%)	>= 85 N = 3 N (%)	>= 18 AND < 65 N = 155 N (%)	>= 65 AND < 75 N = 77 N (%)	>= 75 AND < 85 N = 30 N (%)	>= 85 N = 2 N (%)
All-Grade TEAEs	293 (96)	135 (97)	71 (92)	3 (100)	133 (86)	68 (88)	26 (87)	2 (100)
Grade 3-4 TEAEs	60 (20)	32 (23)	22 (29)	1 (33)	13 (8)	12 (16)	6 (20)	1 (50)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-12-13, ADAE (Adverse Events Analysis Dataset) - 2022-12-13. Variables used: USUBJID, TRT01A, SAFFL, AGEGR2, TR01EFL, AETOXGRN, APERIODC

Table 26: Summary of Adverse Events by Sex

	NIVOLUMAB 480 MG IV Q4W		PLACEBO IV Q4W	
	MALE N = 320 N (%)	FEMLAE N = 204 N (%)	MALE N = 161 N (%)	FEMALE N = 103 N (%)
All-Grade TEAEs	313 (98)	189 (93)	140 (87)	89 (86)
Grade 3-4 TEAEs	83 (26)	32 (16)	19 (12)	13 (13)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-12-13, ADAE (Adverse Events Analysis Dataset) - 2022-12-13. Variables used: USUBJID, TRT01A, SAFFL, SEX, TR01EFL, AETOXGRN, APERIODC

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Table 27: Summary of Adverse Events by Race

	NIVOLUMAB 480 MG IV Q4W				PLACEBO IV Q4W		
	WHITE N = 513 N (%)	OTHER N = 7 N (%)	BLACK OR AFRICAN AMERICAN N =2 N (%)	ASIAN N =1 N (%)	WHITE N = 262 N (%)	BLACK OR AFRICAN AMERICAN N = 1 N (%)	OTHER N = 1 N (%)
All-Grade TEAEs	491 (96)	7 (100)	2 (100)	1 (100)	227 (86)	1 (100)	1 (100)
Grade 3-4 TEAEs	114 (22)	1 (14)	0 (0)	0 (0)	31 (12)	1 (100)	0 (0)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-12-13, ADAE (Adverse Events Analysis Dataset) - 2022-12-13. Variables used: USUBJID, TRT01A, SAFFL, RACE, TR01EFL, AETOXGRN, APERIODC

Table 28: Summary of Adverse Events by Geographic Region

	NIVOLUMAB 480 MG IV Q4W				PLACEBO IV Q4W			
	US AND CANADA N = 97 N (%)	WESTERN EUROPE N = 301 N (%)	EASTERN EUROPE N = 58 N (%)	AUSTRALIA N = 68 N (%)	US AND CANADA N = 46 N (%)	WESTERN EUROPE N = 160 N (%)	EASTERN EUROPE N = 28 N (%)	AUSTRALIA N = 30 N (%)
All-Grade TEAEs	96 (99)	287 (95)	53 (91)	66 (97)	44 (96)	137 (86)	19 (68)	29 (97)
Grade 3-4 TEAEs	30 (31)	61 (20)	5 (9)	17 (25)	8 (17)	13 (8)	4 (14)	6 (20)

Source: ADSL (Subject-Level Analysis Dataset) - 2022-12-13, ADAE (Adverse Events Analysis Dataset) - 2022-12-13. Variables used: USUBJID, TRT01A, REGION1, TR01EFL, AETOXGRN

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:
FDA agrees.

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8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

The Applicant's Position:
There were no findings related to human carcinogenicity for nivolumab IV in Study CA20976K.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.9.2. Human Reproduction and Pregnancy

The Applicant's Position:
There was one patient who became pregnant in CA20976K, a 32 year old female in the Nivolumab arm. This was reported as an adverse event 26 days after the 1st dose of nivolumab, and the patient subsequently withdrew consent for any further treatment and participation in the study.

The FDA's Assessment:
No information regarding the effect of nivolumab on human reproduction and pregnancy was provided in this application.

8.2.9.3. Pediatrics and Assessment of Effects on Growth

The Applicant's Position: Not applicable, see Section10.

The FDA's Assessment:
Although Study CA20976K was open to the enrollment of adolescent patients none were enrolled to the study. No information regarding the effect of nivolumab IV on growth were provided in this supplemental BLA. Refer Section Pediatrics10 for additional information regarding the assessment of nivolumab IV in the pediatric population.

8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There is no information on overdose or drug abuse. No cases of withdrawal symptoms related to nivolumab were reported in CA20976K.

The FDA's Assessment:
Drug overdose or abuse is not expected to occur with an anti-PD-1 monoclonal antibody and there were no reports to the FDA of these events. Drug withdrawal or rebound effects are also not expected with an anti-PD-1 monoclonal antibody.

8.2.10. Safety in the Postmarket Setting

8.2.10.1. Safety Concerns Identified Through Postmarket Experience

The Applicant's Position: Not applicable.

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The FDA's Assessment:
FDA analysis of postmarketing safety reports suggests that the overall safety of nivolumab IV is consistent with the current labeling information.

8.2.10.2. Expectations on Safety in the Postmarket Setting

The Applicant's Position: Not applicable.

The FDA's Assessment:
Safety in the postmarketing setting is expected to be similar to that observed in Study CA20976K.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
Safety data from 524 subjects treated with nivolumab in CA20976K demonstrate that the safety profile of adjuvant nivolumab 480 mg IV Q4W in completely resected Stage IIB/C melanoma was manageable and consistent with the safety of nivolumab across other studies in different tumor types and/or disease settings of approved indications. No new safety concerns were identified.

In summary, the totality of the safety data supports the use of nivolumab IV as adjuvant therapy for subjects with completely resected Stage IIB/C melanoma.

The FDA's Assessment:
The assessment of nivolumab IV as a single agent for the adjuvant treatment of adult patients and pediatric patients 12 year of age and older with completely resected Stage IIB or IIC melanoma was based primarily on data from Study CA20976K. The clinical review of safety was based on the 788 patients treated with at least one dose of either single agent nivolumab IV or placebo in Study CA20976K. The safety database for Study CA20976K was determined to be adequate for the safety review of this sBLA. The toxicity profile of nivolumab IV has been well characterized in other studies of single agent nivolumab IV used for the treatment of adult patients with melanoma and other malignancies. The safety of single agent nivolumab IV in pediatric patients was determined though extrapolation of data from studies of nivolumab IV in adult patients and from the review of data submitted in supplements 117, 118, and 119 from Study CA209070 (Children's Oncology Group (COG) Study ADVL 1412), which evaluated nivolumab IV as a single agent or in combination with ipilimumab IV in pediatric patients aged 1 to 27 years with relapsed or refractory solid tumors (neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma/Peripheral PNET, melanoma, and solid tumors not otherwise specified) and lymphoma (non-Hodgkin lymphoma and Hodgkin lymphoma); this study showed an ORR of 4.7% (95% CI: 0.6, 15.8) in the efficacy evaluable patients with solid tumors that were treated with nivolumab IV in combination with ipilimumab IV and an ORR of 23.5% (95% CI: 6.8, 49.9) in the efficacy evaluable patients with hematologic tumor that were treated with single agent nivolumab IV. FDA notes that adverse events, discontinuations, dose interruptions were more commonly observed in the nivolumab IV arm which is expected in a

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trial with a placebo control arm. The absolute increase in adverse events compared to placebo did not suggest unacceptable toxicity associated with single agent nivolumab IV and overall the safety profile of nivolumab IV in Study CA20976K appeared consistent to what has been reported in the USPI and the literature.

The clinical review team has determined that the risks of treatment with nivolumab 240 mg intravenously (IV) every 2 weeks or 480 mg IV every 4 weeks in adult patients and pediatric patients age 12 years and older and weighing 40 kg or more and 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks in pediatric patients age 12 years and older and weighing less than 40 kg for the adjuvant treatment of completely resected Stage IIB or IIC melanoma are considered acceptable.]

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues with this application. The pivotal study CA20976K showed a statistically significant improvement in favor of the nivolumab IV arm with respect to the primary endpoint RFS (stratified HR=0.42 [95% CI: 0.30, 0.59]; stratified log-rank p value<0.0001) based on an interim analysis conducted at 88% information fraction. At the time of the interim analysis of RFS, the key secondary endpoint of OS (b) (4) . The descriptive OS results do not indicate excess harm or detriment to survival at this time.

8.4. Conclusions and Recommendations

The FDA's Assessment:

[The data submitted has provided substantial evidence for the effectiveness of nivolumab IV at the recommended dosage, for treatment of Stage IIB and Stage IIC melanoma in adult and pediatric patients 12 years of age and older. The Applicant provided data supporting a favorable risk-benefit ratio of nivolumab IV over placebo when administered for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected with Stage IIB or IIC melanoma.

The results of Study CA20976K at the interim analysis for RFS demonstrated that patients treated with nivolumab IV had a statistically significant and clinically relevant improvement in Investigator-assessed RFS compared to patients treated with placebo (HR: 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001). The descriptive summary of OS at the interim analysis did not indicate any detriment on survival for nivolumab versus placebo in the patient population.

The safety profile is manageable and no new safety signals were identified during the review. The adverse reactions associated with nivolumab IV are described in the USPI and the risks of

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severe and serious adverse reactions are adequately described in the Warnings and Precautions and Dosage Modifications sections of the product labeling. The safety profile of nivolumab IV treatment in the adjuvant setting, including immune-mediated adverse reactions, was consistent with the known safety profile of nivolumab in other approved melanoma settings. Although treatment with nivolumab IV is associated with a risk of serious and/or prolonged immune-mediated adverse events in a minority of patients, the review team has concluded that the benefit-risk profile of adjuvant nivolumab IV is favorable. Therefore, the review team recommends regular approval.

X X

Yiming Zhang, PhD
Primary Statistical Reviewer

Joyce Cheng, PhD
Statistical Team Leader

X X

Jamie R. Brewer, MD
Primary Clinical Reviewer
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
The Division did not refer the application to the Oncologic Drugs Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this supplemental BLA as no significant review issues were identified during the review.

10 Pediatrics

The Applicant's Position:
Pediatric Stage IIB/C melanoma patients ≥ 12 years old were eligible for CA20976K; however, no pediatric subjects were enrolled due to rarity of the disease. The youngest patient treated was 19 years old at enrollment. Based on the biologic similarity of melanoma in adult and adolescent (≥ 12 years to < 18 years old) patients, as well as previous PPK modeling in the advanced and Stage III/IV adjuvant settings, safety and efficacy can be extrapolated from adult subjects enrolled in CA20976K to pediatric patients ≥ 12 years old.

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The FDA's Assessment:
Although no pediatric patients were enrolled to Study CA20976K, safety and efficacy data extrapolated from the adult population of this study, adult populations treated with single agent nivolumab IV in other studies, and safety and pharmacokinetic data submitted in Supplements 117, 118, and 119 from Study CA209070 (Children's Oncology Group (COG) Study ADVL 1412) support the extension of the proposed indication for the adjuvant treatment of patients with Stage IIB or IIC melanoma to include adolescent patients. Study CA209070 is a multicenter, open-label, single-arm, dose-confirmation, and dose expansion study of nivolumab IV as a single agent and in combination with ipilimumab IV in pediatric patients aged 1 to 27 years with relapsed or refractory solid tumors (neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma/peripheral primitive neuroectodermal tumors (PNET), and other stolid tumors not otherwise specified (NOS)) and lymphoma (non-Hodgkin and Hodgkin lymphoma). Study CA209070 enrolled a total of 110 pediatric patients with solid tumor malignancies; 60 received nivolumab IV as a single agent. Among the 58 efficacy evaluable patients who received nivolumab IV as a single agent, no responses were observed. A total of 22 pediatric patients with hematological tumors were enrolled; 20 received nivolumab IV as a single agent. Among the 17 efficacy evaluable pediatric patients who received single agent nivolumab IV, the ORR was 23.5% (95% CI: 6.8, 49.9), including one complete response in a patient with HL and three PRs [two patients with HL; 1 patient with NHL].

Based on the evidence of the safety and efficacy of nivolumab IV in the treatment of adult patients with melanoma; the known similarities between adolescent melanoma and adult melanoma; comparable exposure profiles of nivolumab IV in pediatric and adult patients with solid tumor and hematological malignancies; and the relatively flat exposure-response curve for efficacy for nivolumab IV, the review team concludes that the Applicant had met the evidentiary requirements to support inclusion of pediatric patients in the proposed indication.
]

11 Labeling Recommendations

Data:

Table 29: Applicant - Summary of Significant Labeling Changes for OPDIVO (High Level Changes and Not Direct Quotations)

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
INDICATIONS AND USAGE (1)	OPDIVO is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, IIC, III, or IV melanoma.	Minor edit to align with labeling practice for describing multiple stages in indication statement.
DOSAGE AND ADMINISTRATION (2.2)	Adult and pediatric patients (12 years and older) ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks.	FDA agrees.

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	Pediatric patients (12 years and older) (b) (4) 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.	
ADVERSE REACTIONS (6.1)	Addition of clinical safety data from the CA20976K study, including: a brief summary of the serious and most common adverse reactions; tables of the adverse reactions occurring at an incidence of 10% or greater; and tables of laboratory abnormalities occurring at an incidence of 10% or greater.	Edited to include current format for SAR, dosage interruptions, and dose delays due to SAR. Updated most common adverse reactions to add musculoskeletal pain.
CLINICAL PHARMACOLOGY (12.6 Immunogenicity)	Immunogenicity sub-section moved from 6.2 to 12.6 per Clinical Pharmacology guidance	Minor edits to present data in table for readability
EFFICACY (14.2)	Addition of standard study information, efficacy table with RFS data, and Figure with K-M curve related to Study CA209076K.	Minor edits for consistency with current oncology labeling.
CLINICAL STUDIES (14.3)	Addition of clinical efficacy data from the CA20976K study, including: a brief description of the study design and treatment groups; inclusion/exclusion criteria of the study; patient demographics; primary and key secondary efficacy endpoints.	FDA agrees.

Other Prescription Drug Labeling for OPDIVO:

The OPDIVO Medication Guide was updated to include the following additional information in patient-friendly language:

- Under "What is OPDIVO" - Revision of present text regarding melanoma to identify treatment in adults and adjuvant treatment in adults and children 12 years and older, consistent with the proposed indication in the Full Prescribing Information.
- Under "What is OPDIVO" - Section titled " (b) (4) children younger than 12 years of age (b) (4) .

The Applicant's Position:

The clinical data provided in this supplemental BLA submission demonstrate the clinical benefit and safety of the use of nivolumab IV for the treatment of patients with completely resected Stage IIB/C melanoma. Based on these data, the table above provides a high-level summary of the proposed changes to the labeling for OPDIVO (nivolumab).

The FDA's Assessment:

FDA agrees with the high level summary of labeling changes to the USPI and the Medication Guide with additional clarification regarding labeling changes provided by FDA in (b) (4). See the final approved prescribing information for OPDIVO (nivolumab) accompanying the approval letter for more information.

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12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of nivolumab IV as adjuvant treatment of patients with Stage IIB or IIC melanoma given the experience of the medical oncology community with this drug product and in managing immune-mediated adverse reactions. Recommendations for the safe and effective use of nivolumab IV, including monitoring for immune-related adverse events, are provided in the US prescribing information as well as in the patient medication guide.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
[No PMC/PMR are required for this application.]

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

14 Division Director (DHOT) (NME ONLY)

X

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15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

'Lola Fashoyin-Aje

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

'Lola Fashoyin-Aje

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Reference ID: 5260748

19 Appendices

19.1. References

The Applicant's References:
References are provided at the end of this document in Section 19.5.

The FDA's References:

1. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. [updated: 2023 Jul 31; cited 2023 Sep 25]. Available from: https://seer.cancer.gov/statistics-network/explorer/.
2. Ives NJ, Suciu S, Eggermont AMM, Kirkwood J, Lorigan P, Markovic SN, et al. Adjuvant int erferon-α for the treatment of high-risk melanoma: an individual patient data meta-analysis. Eur J Cancer. 2017 Sep;82:171-83.
3. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. Expert Rev Anticancer Ther. 2018 Aug; 18(8): 775–784.
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5. Black CM, Soong S, Gershenwald JE, Thompson JF, Coit DG, et al. Age as a Prognostic Factor in Patients with Localized Melanoma and Regional Metastases. Ann Surg Oncol. 2013 Nov; 20(12): 3961-3968.

19.2. Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA20976K clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:
FDA reviewed the financial disclosure information submitted for all study investigators (Primary Investigators and Sub-investigators). The Applicant reported that all investigators signed the BMS Financial Disclosure Forms (FDFs). There was a total of 1217 investigators of which 1198 investigators (98%) did not have significant financial disclosures to report. There were 19 investigators with disclosable financial interests or arrangements. Cumulatively, the study sites that these 19 investigators were associated with enrolled 34 patients of which 29 were randomized to receive study treatment. In all, 3.6% of the total 790 patients were randomized at the study sites of investigators reporting financial disclosures.

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- One investigator associated with site (b) (6) disclosed significant payments totaling $288,000.00 received by their institution for laboratory research. This site enrolled (b) (6) patients and randomized (b) (6) patients which is (b) (6)% of the total 790 patients randomized to the study.
- One investigator associated with site (b) (6) disclosed significant payments totaling $536,000.00 received by their institution in the form of research grants. This site (b) (6) in the study.
- (b) (6) associated with site (b) (6) disclosed significant payments totaling $3,544,500.00 received by their institution due to involvement in the Bristol Myers Squibb and/or Ono Pharmaceutical Co., Ltd International Immuno-Oncology Network (II-ON). This site randomized (b) (6) which is less than (b) (6)% of the total 790 patients randomized to the study.
    - One investigator also reported equity in BMS stock valued at $65,000.00.
    - One investigator also reported receiving significant payments of other sorts from BMS and/or Ono Pharmaceutical Co., Ltd for speaking and consulting services in the amount of $45,000.00.
- One investigator associated with site (b) (6) disclosed significant payments as a consultant and member of the speaking bureau totaling $37,424.48. This site enrolled (b) (6) patients and randomized (b) (6) patients which is less than (b) (6)% of the total 790 patients randomized to the study.
- One investigator associated with site (b) (6) reported equity in Bristol Myers Squibb and/or Ono Pharmaceutical Co., Ltd stock valued at $190,000.00. This site enrolled and randomized (b) (6) patients which is less than (b) (6)% of the total 790 patients randomized to the study.

Based on the information provided by the Applicant, FDA considers it unlikely that the outcome of the analyses were biased in any meaningful way by investigators with disclosable interests. None of the study sites that the investigators with disclosures are associated with randomized more than 2% of the total study population. The use of a double-blind study design with blinded independent central review of the primary RFS endpoint limits the likelihood of bias. In addition, the secondary endpoint of OS would not be influenced or affected by any specific study investigator.

Covered Clinical Study (Name and/or Number):* CA20976K

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1217		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

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19		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 16 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position: Not applicable.

The FDA's Assessment:
[Not applicable.]

19.4. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
[No additional safety analyses were conducted by FDA.]

19.5. References

[1] Ossio R, Marin-Roldan R, Martinez-Said H, et al. Melanoma: a global perspective. Nature Reviews – Cancer. 2017;17:393-394.

[2] Gershenwald J, Scolyer R, Hess K, et al. Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. CA Cancer J Clin. 2017;67(6):472–492.

[3] Poklepovic AS, Luke JJ. Considering adjuvant therapy for stage II melanoma. Cancer. 2020;126(6):1166-1174.

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Reference ID: 5260748

[4] Garbe C, Keim U, Amaral T, et al. Prognosis of Patients With Primary Melanoma Stage I and II According to American Joint Committee on Cancer Version 8 Validated in Two Independent Cohorts: Implications for Adjuvant Treatment. J Clin Oncol 2022.
[5] Leonardi G, Falzone L, Salemi R, et al. Cutaneous melanoma: From pathogenesis to therapy (Review). Int J of Oncol. 2018;52:1071-1080.
[6] Centers for Disease Control and Prevention. Melanoma Incidence and Mortality, United States–2012–2016. U.S. Cancer Statistics data brief, no 9. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2019.
[7] Austin MT, Xing Y, Hayes-Jordan AA, et al. Melanoma incidence rises for children and adolescents: an epidemiologic review of pediatric melanoma in the United States. J Pediatr Surg. 2013 Nov;48(11):2207-13.
[8] Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol. 2005;23(21):4735.
[9] National Comprehensive Cancer Network (NCCN) guideline: Melanoma: Cutaneous v3. 2022 - 11-Apr-2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
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[11] Hamuro L, Statkevich P, Bello A, Roy A, Bajaj G. Nivolumab Clearance Is Stationary in Patients With Resected Melanoma on Adjuvant Therapy: Implications of Disease Status on Time-Varying Clearance. Clin Pharmacol Ther. 2019 Nov;106(5):1018-1027.
[12] Sanghavi K, Vuppala P, Ivaturi V, Hamuro L, Roy A, Suryawanshi S. Nivolumab exposure-response analysis for adjuvant treatment of melanoma supporting a change in posology. CPT Pharmacometrics Syst Pharmacol. 2021 Jul;10(7):748-759.
[13] Zhao X, Shen J, Ivaturi V, et al. Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. Ann Oncol 2020;31:302-309.
[14] Bi Y, Liu J, Furmanski B, et al. Model-informed drug development approach supporting approval of the 4-week (Q4W) dosing schedule for nivolumab (Opdivo) across multiple indications: a regulatory perspective. Ann Oncol 2019;30:644-51
[15] Module 2.7.2 Nivolumab Summary of Clinical Pharmacology - Advanced Melanoma. Bristol-Myers Squibb Company; 2014. Document Control No. (b) (4).
[16] Pharmacometric Analyses To Predict Nivolumab Exposures, Efficacy, and Safety with Flat Doses of Nivolumab 240 mg Q2W and 480 mg Q4W for the Adjuvant Treatment of Melanoma. Bristol-Myers Squibb Company; 2019. Document Control No. (b) (4).
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[18] Module 2.7.2 Nivolumab and Nivolumab in Combination with Ipilimumab Summary of Clinical Pharmacology. Bristol Myers Squibb Company, 2022. Document Control No. (b) (4).
[19] Final Clinical Study Report for Study CA209238: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence. Bristol Myers Squibb Company; 2020. Document Control No. (b) (4).
[20] Primary Clinical Study Report for Study CA209915: A Phase 3 Randomized Study of Adjuvant Immunotherapy with Nivolumab Combined with Ipilimumab versus Nivolumab Monotherapy After Complete Resection of Stage IIIB/C/D or Stage IV Melanoma. Bristol Myers Squibb Company; 2020. Document Control No. (b) (4).
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[23] U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2021. Available from: https://gis.cdc.gov/Cancer/USCS/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcancer%2Fdataviz%2Findex.htm#/RaceEthnicity/.

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Jamie Brewer, M.D.	Division of Oncology 3	Sections: All	**Select one:** ☒Authored ☐Approved
	Signature: Refer to final assessment aid electronic signature.			
Clinical Team Leader	Jamie Brewer, M.D.	Division of Oncology 3	Sections: All	**Select one:** ☒Authored ☒Approved
	Signature: Refer to final assessment aid electronic signature.			
Statistics Reviewer	Yiming Zhang, Ph.D.	Division of Biometrics 5	Sections: 1, 8	**Select one:** ☒Authored ☐Approved
	Signature: Yiming Zhang -S Digitally signed by Yiming Zhang -S Date: 2023.09.19 16:44:37 -04'00'			
Statistics Team Leader	Joyce Cheng, Ph.D.	Division of Biometrics 5	Sections: 1, 8	**Select one:** ☒Authored ☒Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2023.09.19 16:28:07 -04'00'			
Statistics Division Director	Shenghui Tang, Ph.D.	Division of Biometrics 5	Sections: 1, 8	**Select one:** ☐Authored ☒Approved
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Clinical Pharmacology Reviewer	Lauren Price, Pharm.D.	Division of Cancer Pharmacology II	Sections: 6, 19.4	**Select one:** ☒Authored ☐Approved
	Signature: Lauren Price -S Digitally signed by Lauren Price -S Date: 2023.09.22 15:46:51 -04'00'			

Clinical Pharmacology Team Leader	Jason Moore, Pharm.D.	Division of Cancer Pharmacology II	Sections: 6, 19.4	**Select one:** ☒Authored ☒Approved
	Signature: Jason N. Moore Jr -S Digitally signed by Jason N. Moore Jr -S Date: 2023.09.22 17:02:40 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, Ph.D.	Division of Cancer Pharmacology II	Sections: 6, 19.4	**Select one:** ☐Authored ☒Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2023.09.23 14:12:02 -04'00'			
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Associate Director for Labeling (ADL)	Doris Auth, PharmD	Office of Oncologic Diseases	Sections: Prescribing Information, Medication Guide	**Select one:** ☒Authored ☒Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2023.09.26 07:00:00 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Jamie Brewer, M.D.	Division of Oncology 3	Sections: All	**Select one:** ☒Approved
	Signature: Refer to final assessment aid electronic signature.			
Deputy Division Director	'Lola Fashoyin-Aje, M.D., M.P.H.	Division of Oncology 3	Sections: All	**Select one:** ☒Approved
	Signature: Refer to final assessment aid electronic signature.			

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/

JAMIE R BREWER
10/13/2023 04:28:54 PM

STEVEN J LEMERY on behalf of IBILOLA A FASHOYIN-AJE
10/13/2023 04:48:25 PM