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.

OPDIVO (nivolumab) Supplemental BLAs 125554/117, 118 and 119
[FDA will complete this section.]

Application Type	Efficacy supplemental Biologic License Applications (sBLAs)
Application Number(s)	sBLA 125554.117, 118, and 119
Priority or Standard	Priority
Submit Date(s)	August 11, 2022
Received Date(s)	August 11, 2022
PDUFA Goal Date	February 11, 2022
Division/Office	Division of Oncology 3
Review Completion Date	February 14, 2023
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 every 2 weeks or 480 mg every 4 weeks As a single agent for pediatric patients weighing <40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks In combination: nivolumab 1 mg/kg every 3 weeks with ipilimumab 3 mg/kg intravenously for a maximum of 4 doses
Applicant Proposed Indication(s)/Population(s)	OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma. OPDIVO is indicated for the 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.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	

Table of Contents

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Table of Tables

Table of Figures

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[FDA will complete this section.]

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OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Planning

Glossary

ABCDE	Asymmetrical, Border, Color, Diameter, Evolving
AC	advisory committee
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
AdjPPK	adjuvant PPK analysis
AdvPPK	advanced PPK analyses
AE	adverse event
AJCC	American Joint Cancer Committee
AST	aspartate aminotransferase
AUC(0-T)	AUC from time zero to the last tie of the last quantifiable concentration
AUC(TAU)	AUC in one dosing interval
BLA	biologics license application
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRAF	B-rapidly accelerated fibrosarcoma
BRF	Benefit Risk Framework
BW	body weight
CAEPR	comprehensive adverse events and potential risks
Cavg4	time-averaged concentration at Day 4
Cavgss	time-averaged concentration at steady state
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
Cmax	maximum observed serum concentration
Cmaxss	peak concentration at steady state
CMC	chemistry, manufacturing, and controls
Cmin4	minimum serum concentration at Day 4
Cmin	Predose trough serum concentration
Cminss	trough concentration at steady state
CNS	central nervous system
COG	Children's Oncology Group
COGC	Children's Oncology Group Chair

COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
Ctau	Serum concentration achieved at the end of dosing interval
CTEP	Cancer Therapy Evaluation Program
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CV	coefficient of variation
DBL	database lock
DL1	dose level 1
DL2	dose level 2
DLT	dose limiting toxicity
DMC	data monitoring committee
DMFS	Distant Metastasis Free Survival
DOR	duration of response
ECG	electrocardiogram
eCTD	electronic common technical document
EMA	European Medicines Agency
E-R	exposure response
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	fixed dose combination
FU	follow up
GCP	good clinical practice
Geo. Mean	geometric mean
GLP	good laboratory practice
GRMP	good review management practice
GR2	Grade 2
GVHD	graft-versus-host disease
HL	Hodgkin lymphoma
ICH	International Conference on Harmonization
IFN α-2b	Interferon-Alpha 2b
IMAE	immune mediated adverse events
IMM	immune-modulating medications
IND	Investigational New Drug
Ipi	ipilimumab
Ipi mono	ipilimumab monotherapy

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
LLN	lower limit of normal
LPFV	last patient first visit
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MEL	melanoma
mg	milligram
MIBG	meta-iodobenzylguanidine
mITT	modified intent to treat
mm	millimeter
MTD	maximum tolderated dose
N	number
N1I3	nivolumab 1 mg/kg plus ipilimumab 3 mg/kg
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI/CTEP	Clinical Trials Evaluation Program of the National Cancer Institute
NDA	new drug application
NED	no evidence of disease
NHL	Non-hodgkin's lymphoma
Nivo	nivolumab
Nivo mono	nivolumab monotherapy
Nivo + Ipi	nivolumab plus ipilimumab
NME	new molecular entity
NOS	other tumor types not included in the previous solid tumor categories
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OESI	other events of special interest
OPQ	Office of Pharmaceutical Quality
OR	objective response
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-1	programmed death-1

PD-L1	programmed death-ligand 1
PEP-CTN	Pediatric Early Phase Clinical Trials Network
PI	prescribing information
pIND	pediatric investigational new drug
PIP	pediatric investigation plans
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PNET	primitive neuroectodermal tumor
PP	persistent positive
PPI	patient package insert
PPK	population pharmacokinetic(s)
PPSR	proposed pediatric study request
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWR	pediatric written request
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RFS	recurrence free survival
RMS	Rhabdomyosarcoma
RP2D	recommended Phase 2 dose
R/R	recurrent or refractory
RRA	request for rapid amendment
RSS	Regulatory Support System
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
SD	stable disease
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TERT	telomerase reverse transcriptase
Tmax	Time of maximum observed serum concentration
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States

USPI	United States Prescribing Information
UV	ultraviolet
VC	volume of distribution of the central compartment
WHO	World Health Organization

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, administered as an intravenous infusion, was approved on December 22, 2014 (BLA 125554) 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 now approved as monotherapy and in combination with other anti-cancer therapies for the treatment of 11 cancers, including traditional approval for the treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86.

Ipilimumab, administered as an intravenous infusion, was approved on March 25, 2011 (BLA 125377) for the treatment of unresectable or metastatic melanoma. Ipilimumab is now approved as monotherapy and in combination with other anti-cancer therapies for the treatment of 7 cancers, including traditional approval in the adjuvant setting for the treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenopathy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The safety and effectiveness of nivolumab as a single agent or in combination with ipilimumab for the treatment of adult patients with unresectable or metastatic melanoma has been previously demonstrated in multiple studies:

CHECKMATE-037 was a multicenter, open-label trial of adult patients with unresectable or metastatic melanoma who progressed after anti-CTLA-4 treatment. Patients were randomized (2:1) to receive nivolumab 3 mg/kg intravenously every 2 weeks or investigator's choice of chemotherapy, either single agent dacarbazine 1000 mg/m2 every 3 weeks or the combination of carboplatin AUC 6 intravenously every 3 weeks and paclitaxel 175 mg/m2 intravenously every 3 weeks. The ORR was 32% (95% confidence

interval [CI]: 23, 41), consisting of 4 complete responses and 34 partial responses in nivolumab-treated patients. The median duration of OS was 15.7 months (95% CI: 12.9, 19.9) in nivolumab-treated patients compared to 14.4 months (95% CI: 11.7, 18.2) (HR 0.95; 95.54% CI: 0.73, 1.24) in patients assigned to investigator's choice of treatment.

CHECKMATE-066 was a multicenter, double-blind, randomized (1:1) trial in 418 adult patients with previously untreated BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either nivolumab 3 mg/kg by IV infusion every 2 weeks or dacarbazine 1000 mg/m2 IV every 3 weeks until disease progression or unacceptable toxicity. This study demonstrated a statistically significant improvement in OS (HR 0.42; 95% CI: 0.30, 0.60) for the nivolumab arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS.

CHECKMATE-067 was a multicenter, double-blind trial in 945 adult patients with previously untreated, unresectable or metastatic melanoma that randomized (1:1:1) patients to one of the following arms: nivolumab and ipilimumab, nivolumab alone, or ipilimumab alone. This study demonstrated statistically significant improvements in OS (HR 0.55; 95% CI 0.44, 0.69 for the nivolumab and ipilimumab arm and HR 0.63; 95% CI: 0.50, 0.78 for the nivolumab monotherapy arm) and PFS (HR 0.42; 95% CI: 0.34, 0.51 for the nivolumab and ipilimumab arm and HR 0.57; 95% CI: 0.47, 0.69 for the nivolumab monotherapy arm) for patients randomized to either nivolumab-containing arm compared with the ipilimumab arm. The median PFS was 11.5 months (95% CI: 8.9, 16.7) in the nivolumab and ipilimumab arm, 6.9 months (95% CI: 4.3, 9.5) in the nivolumab arm, and 2.9 months (2.8, 3.4) in the ipilimumab arm. The median OS was not reached in the nivolumab and ipilimumab arm (95% CI: 38.2, NR). The median OS was 36.9 months (95% CI: 28.3, NR) in the nivolumab arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Data from these studies supported the approval of nivolumab as a single agent or in combination with ipilimumab for the treatment of adult patients with unresectable or metastatic melanoma.

The safety and effectiveness of nivolumab for the treatment of adult patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting has been previously demonstrated in CHECKMATE-238. This study was a double-blind trial in 906 adult patients with completely resected Stage IIIB/C or Stage IV melanoma who were randomized (1:1) to receive nivolumab 3 mg/kg IV every 2 weeks or ipilimumab 10 mg/kg IV every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. The study demonstrated a statistically significant improvement in RFS (HR 0.65; 95% CI: 0.53, 0.80) for patients randomized to the nivolumab arm compared with the ipilimumab arm.

Data from this study supported the approval of nivolumab for the treatment of adult patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

To support the supplemental biologics licensing applications (sBLAs) intended to expand the Opdivo and Yervoy melanoma indications to pediatric patients 12 years and older, the Applicant provided data from Study CA209070 (Children's Oncology Group (COG) Study ADVL 1412). This study is a multicenter, open-label, single arm, dose confirmation and dose expansion study conducted in pediatric (12 months to <18 years) and young adult (≥ 18 years to ≤ 30 years old) patients with relapsed and/or refractory solid tumors and lymphoma includingmelanoma. Study CA209070 provided safety and pharmacokinetic data to support the extrapolation of the the adult data to pediatric patients.

Study CA209070 enrolled a total of 110 pediatric patients with solid tumor malignancies; 60 received nivolumab as a single agent, and 46 received nivolumab in combination with ipilimumab. Among the 58 efficacy evaluable patients who received nivolumab as a single agent, no responses were observed. Among the 43 efficacy evaluable pediatric patients who received nivolumab in combination with ipilimumab the ORR was 4.7% (95% CI: 0.6, 15.8), including 2 partial responses [patient with Ewing sarcoma and patient with rhabdomyosarcoma].

A total of 22 pediatric patients with hematological tumors were enrolled; 20 received nivolumab as a single agent and none received nivolumab in combination with ipilimumab. Among the 17 efficacy evaluable pediatric patients who received single agent nivolumab, 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]. Among all treated patients, the median duration of treatment with single agent nivolumab was 0.84 months and the median duration of treatment with nivolumab in combination with ipilimumab was 0.72 months.

In addition to data from Study CA209070, the Applicant provided supportive clinical evidence from 3 trials as follows: CA209067 provided supportive data from nivoluman as a single agent and in combination in patients with advanced melanoma; CA209915 provided supportive data for the use of single agent nivolumab as adjuvant treatment for melanoma (this trial enrolled 3 adolescent patients); CA209238 provided supportive data for single agent nivolumab for the adjuvant treatment of melanoma. The sBLA submissions also contained pharmacokinetic analyses including population PK model-based simulations to support the extrapolation of adult data to pediatric patients. These analyses demonstrated that the proposed dosages of nivolumab as a single agent and nivolumab in combination with ipilimumab in pediatric patients achieved exposures similar to those produced in adult patients with the recommended nivolumab single-agent dosing regimen.

Based on the evidence of the safety and efficacy of nivolumab and ipilimumab in the treatment

of adult patients with melanoma; the known similarities between adolescent melanoma and adult melanoma; comparable exposure profiles of nivolumab and ipilimumab in pediatric and adult patients with solid tumor and hematological malignancies; and the relatively flat exposure-response curve for efficacy for nivolumab, ipilimumab, and nivolumab and ipilimumab in combination, the review team concluded that the Applicant had met the evidentiary requirements to support approval of the sBLAs. The review team recommends approval of nivolumab as a single agent and in combination with ipilimumab and, of ipilimumab in combination with nivolumab, for the treatment of pediatric patients 12 years and older with unresectable or metastatic melanoma. The review division also recommends approval of nivolumab for pediatric patients 12 years and older with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

The Applicant requests approval for an extension of Opdivo and Yervoy indications for the treatment of melanoma, to pediatric patients 12 years and older. The proposed indications, as amended, are as follows:

- OPDIVO (nivolumab), as a single agent or in combination with YERVOY (ipilimumab), is indicated for the treatment of **adult and pediatric patients 12 years and older** with unresectable or metastatic melanoma
- OPDIVO (nivolumab) is indicated for the 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.
- YERVOY (ipilimumab), in combination with OPDIVO (nivolumab), is indicated for the treatment of unresectable or metastatic melanoma in **adult and pediatric patients 12 years and older**.

The proposed dosing regimen for nivolumab in pediatric patients aged 12 years and older and weighing 40 kg or more is 240 mg every 2 weeks or 480 mg every 4 weeks via intravenous (IV) infusion over 30 minutes and 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks via IV infusion over 30 minutes in pediatric patients aged 12 years and older who weigh less than 40 kg is.

The proposed dosing regimen when nivolumab and ipilimumab are administered in combination in pediatric patients aged 12 years and older is nivolumab 1 mg/kg via IV infusion and ipilimumab 3 mg/kg via IV infusion over 30 minutes for a maximum of 4 doses.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

There are approximately 99,780 cases of melanoma estimated to be diagnosed in the US in 2022; this represents almost 5.2% of all new cancer diagnoses with a 5-year overall survival (OS) rate of 93.7% (SEER 17 2012-2018). According to SEER data, patients with regional disease have a 5-year survival of 70.6% while those with metastatic disease have a 5-year survival of 31.9%. Patients younger than 20 years of age represent 0.3% of new cases of melanoma. There are several FDA-approved therapies for the treatment of adult patients with resectable, unresectable, or metastatic melanoma. However, due to the rarity of melanoma in the pediatric population therapies currently approved for the treatment of pediatric patients with melanoma were granted approval based upon extrapolation of data from adult patients. YERVOY (ipilimumab) and OPDUALAG (nivolumab and relatlimab-rmbw FDC) are approved for the treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older and KEYTRUDA (pembrolizumab) is approved for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.

The Applicant submitted data from Study CA209070 and supportive clinical evidence from 3 trials (CA209067 provided supportive data from nivolumab as a single agent and in combination in patients with advanced melanoma; CA209915 provided supportive data for the use of single agent nivolumab as adjuvant treatment for melanoma (this trial enrolled 3 adolescent patients); CA209238 provided supportive data for single agent nivolumab for the adjuvant treatment of melanoma) to support approval of nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab for the treatment of pediatric patients 12 years and older with unresectable or metastatic melanoma and nivolumab for the treatment of pediatric patients 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, in the adjuvant setting. Similarities in the pathophysiology between adult and adolescent melanoma have been demonstrated and treatment responses similar to those observed in studies of adult patients are also expected in the adolescent melanoma population. The pharmacokinetic analyses, including population PK model-based simulations, support the extrapolation of adult data to pediatric patients and demonstrated that the proposed dosages of nivolumab as a single agent and nivolumab in combination with ipilimumab in pediatric patients achieved exposures similar to those produced in adult patients with the recommended nivolumab single-agent dosing regimen.

The safety of nivolumab and ipilimumab as single agents and in combination has been well characterized in the treatment of patients with

resectable, unresectable, and metastatic melanoma. Although there was limited safety data available in the Study CA209070 due to the short duration of study treatment, the types of adverse events observed in the pediatric population were generally consistent with the known safety profile of nivolumab. The incidence of immune-mediated adverse events (IMAEs) associated with single agent nivolumab was numerically higher in the pediatric study CA209070 compared to what is reported in the US prescribing information (USPI) for nivolumab as a single agent. In Study CA209070 IMAEs were defined/identified by preferred term and not defined in the same way as IMAES reported in the USPI, as events without alternate etiologies that were managed by corticosteroids. This difference in defining IMAEs should be considered when comparing IMAEs in Study CA209070 with the USPI. In addition, based on E-R safety analyses the probability of Grade 2+ IMAEs in pediatric patients (12 years and older) is expected to be similar to or lower than that in adults. Although nivolumab has been associated with severe and life-threatening immune-mediated toxicity, the observed clinical efficacy and potential for benefit in a pediatric population with a serious and life-threatening disease supports the use of these drug products in this population.

The safety and efficacy of nivolumab and ipilimumab in the treatment of adult patients with melanoma; the known similarities between adolescent melanoma and adult melanoma; comparable exposure profiles of nivolumab and ipilimumab in pediatric and adult patients with solid tumor and hematological malignancies; and the relatively flat exposure-response curve for efficacy for nivolumab, ipilimumab, and nivolumab in combination with ipilimumab support the approval of the sBLAs. The review team recommends that nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab be approved for the treatment of pediatric patients 12 years and older with unresectable or metastatic melanoma. The review division also recommends that nivolumab be approved for the treatment of pediatric patients 12 years and older with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Melanoma accounts for 5.2% of all cancers. • It is estimated that there were 99,780 new cases of melanoma in the US in 2022; and 7,650 people will have died of this disease (Seer 17 2012 – 2018). • Patients younger than 20 years represent 0.3% of new cases of melanoma.	Melanoma is a serious and life-threatening condition. Although its course and prognosis is similar between adult and pediatric patients, the disease occurs significantly less frequently in patients less than 20 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Melanoma is known to be similar between adolescent and adult patients. As has been observed in adults, stage at diagnosis is a key predictor of outcomes in pediatric patients (Clin Derm 2009)	
Current Treatment Options	• There have been several FDA approval drugs findicated for the treatment of adult patients with melanoma. However, only 3 are indicated for the treatment of melanom in pediatric patients. • Pembrolizumab is the only therapy that has been approved for the adjuvant treatment of pediatric patients with Stage IIB, IIC, or III melanoma. This approval was based on data from KEYNOTE-716 and KEYNOTE-054 which demonstrated a statistically significant improvement in RFS for patients randomized to the pembrolizumab arm. • Adjuvant interferon has not demonstrated consistent survival benefits but has been observed to have a better toxicity profile in pediatric patients (UpToDate 2022). • Therapies for the treatment of unresectable or metastatic melanoma that have a pediatric indication include ipilimumab (demonstrated OS benefit, HR 0.66 [0.51, 0.87]) and nivolumab relatlimab-rmbw FDC (demonstrated a PFS benefit, HR 0.75 [0.62, 0.92]).	Treatment for pediatric melanoma represents an unmet medical need due to the limited treatment options for pediatric patients with melanoma in both the adjuvant and the unresectable or metastatic setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Study CA209067 demonstrated statistically significant improvements in OS (HR 0.55; 95% CI 0.44, 0.69 for the nivolumab and ipilimumab arm and HR 0.63; 95% CI: 0.50, 0.78 for the nivolumab monotherapy arm) and PFS (HR 0.42; 95% CI: 0.34, 0.51 for the nivolumab and ipilimumab arm and HR 0.57; 95% CI: 0.47, 0.69 for the nivolumab monotherapy arm) for patients randomized to either nivolumab-containing arm compared with the ipilimumab arm. This study supports the approval of nivolumab as a single agent and nivolumab and ipilimumab in combination for the treatment of adult patients with advanced melanoma. • CA209238 demonstrated a statistically significant improvement in RFS (HR 0.65; 95% CI: 0.53, 0.80) for patients randomized to the nivolumab arm compared with the ipilimumab arm. This study provided supportive data for single agent nivolumab for the adjuvant treatment of melanoma • CA209915 did not demonstrate significant improvement in the primary endpoint of RFS in the nivolumab amd ipilimumab arm compared with the nivolumab arm (median RFS: not reached in both groups; HR = 0.92 (97.295% CI, 0.77, 1.09); p = 0.269). However efficacy resultsfor the single agent nivolumab arm were consistent with results observed for the single agent nivolumab arm in Study CA209238. Ca209915 provided supportive data for the use of single agent nivolumab as adjuvant	Based on the evidence of the safety and efficacy of nivolumab and ipilimumab in the treatment of adult patients with melanoma; the known similarities between adolescent melanoma and adult melanoma; comparable exposure profiles of nivolumab and ipilimumab in pediatric and adult patients with solid tumor and hematological malignancies; and the relatively flat exposure-response curve for efficacy for nivolumab, ipilimumab, and nivolumab and ipilimumab in combination, the review team concluded that an extrapolation of adult data to an adolescent population is acceptable to support approval of these sBLAs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment for melanoma. • Based on the similarities between melanoma in adult and adolescent patients, it is expected that pediatric patients with melanoma will experience the same disease responses that have been demonstrated in studies with adults. • Pharmacokinetic analyses, including population PK model-based simulations, demonstrated that the proposed dosages of nivolumab as a single agent and nivolumab in combination with ipilimumab in pediatric patients achieved exposures similar to those produced in adult patients with the approved adult dosing regimen. • Adult approved dosing regimens for nivolumab monotherapy and nivolumab and ipilimumab in combination in advanced melanoma or nivolumab monotherapy in the adjuvant treatment of melanoma resulted in an E-R safety analysis that predicted lower median Grade 2+ IMAEs for nivolumab monotherapy or nivolumab + ipilimumab combination therapy in pediatric patients than that in adults. • Pharmacokinetic analyses demonstrated a relatively flat E-R efficacy fir nivolumab, ipilimumab, and nivolumab and ipilimumab in combination.	
Risk and Risk Management	• The median duration of treatment with single agent nivolumab was 0.84 months and the median duration of treatment with nivolumab in combination with ipilimumab was 0.72 months for patients enrolled in Study CA209070;	The safety of nivolumab and ipilimumab has been well-characterized and the risks are considered acceptable considering the risk of recurrence or progression of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	no new safety signals were identified. • The adverse events observed on Study CA209070 were generally consistent with what has been observed with nivolumab and ipilimumab as single agents, and when used in combination. • While there was a numerically higher incidence of IMAEs associated with single agent nivolumab in the pediatric study CA209070 compared to the USPI for nivolumab, the adjudication of IMAEs was conducted differently and included all events that were described using a prespecified list of IMAE preferred terms. IMAEs in trials of adult patients defined immune-mediated events as those without alternative etiology that were managed with corticosteroids. This difference in how IMAEs were defined may account for difference in incidence. • The incidence of IMAEs associated with nivolumab in combination with ipilimumab in the pediatric study CA209070 was comparable to what is reported in the nivolumab and ipilimumab USPIs for the combination when nivolumab is administered at 1 mg/kg and ipilimumab at 3 mg/kg.	disease in an adolescent patient population. Routine pharmacovigilance for late toxicities is warranted.

1.4. Patient Experience Data

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

					Section where discussed, if applicable
☐	The patient experience data that was submitted as part of the application, include:				
	☐	Clinical outcome assessment (COA) data, such as			
		☐	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			
	☐	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 _____

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Melanoma is a rare diagnosis in the pediatric population accounting for 3% of all pediatric cancers. While the incidence is very low in the first decade of life (between 0.7 and 0.8 cases per million), this rises sharply to over 10 cases per million in the second decade, consistent with sun exposure as the primary driver.[1,2,3,4] In the US, melanoma is the deadliest form of skin cancer and is the second leading cause of cancer in adolescents and young adults aged 15 to 29 years. According to the US SEER program data, the age-adjusted incidence rates from 2015 to 2019 were 21.5 per 100,000 for all ages and 0.3 per 100,000 for ages < 20 years. The incidence rates by age at diagnosis were: 0.1 per 100,000 for the category of 1-4 years, 0.1 per 100,000 for 5-9 years, 0.3 per 100,000 for 10-14 years, and 0.8 per 100,000 for 15-19 years. The US prevalence (number of people alive with melanoma) on 01-Jan-2019 was 1462 for ages < 20 years.[5] In a retrospective review of SEER data (1988 to 2007) in pediatric subjects, 85% of melanoma cases age <18 years of age were non-Hispanic white, 5% were Hispanic, 2% were Asian/Pacific Islanders, 1% were African American, and 7% were reported as other or unknown race/ethnicity.[6]

Pediatric melanoma shares many similarities with adult melanoma. As in adults, most pediatric cases (about 75%) are localized and have an excellent outcome. The majority of childhood and adolescent melanoma occurs sporadically, with most attributed to UV pathophysiology exposure, especially in adolescents. Familial cases account for only 1% of melanoma cases in children, but approximately 25% of pediatric patients have a preexisting condition known to be associated with melanoma. The strongest risk factor for melanoma in adolescents is the presence of more than 100 nevi with a diameter greater than 2 mm.[7] The genomic landscape of conventional melanoma in children is represented by many of the genomic alterations that are found in adults with melanoma. A report from the Pediatric Cancer Genome Project observed that 15 cases of conventional melanoma had a high burden of somatic single-nucleotide variations, TERT promoter mutations (12 of 13), and activating BRAF V600 mutations (13 of 15), as well as a mutational spectrum signature consistent with UV light damage.[8]

Pediatric melanoma presents a clinical and histopathological challenge due to its rarity and atypical presentations that make early diagnosis difficult. Up to 60% of diagnoses in patients younger than 10 years and 40% in patients betweeen 11 to 19 years do not meet traditional ABCDE criteria (asymmetry, border irregularity, color variation, diameter > 6 mm, and evolution). A modified ABCDE criteria was proposed to evaluate suspicious skin lesions in children and adolescents: amelanotic, bleeding or bump, color uniformity, de novo and any diameter, and evolution.[9] Melanomas affecting pediatric patients can be classified in 3

subtypes: Spitzoid melanoma, melanoma arising in congenital melanocytic nevi, and conventional (adult-type) melanoma. In general, melanomas presenting in children younger than 11 years have higher rates of ulceration, thickness, mitotic activity, and positive sentinel lymph nodes, albeit these findings do not translate into higher mortality rates. Moreover, they are more often located on the head and neck region and on the extremities and belong to the Spitzoid subtype. In patients 11 years and older, conventional melanoma is the prevailing subtype, which shares morphologic (superficial spreading and nodular) and molecular features with adult melanoma and is mainly located on the trunk.[10]

Similar to adults, the main predictor of outcomes in melanoma is the stage at the time of diagnosis.[11] Five-year overall survival for all stages is 87% to 95%. Data collected in 219 pediatric melanoma patients from 2002 to 2012 by the European Cooperative Study Group reported a 3-year OS rate of 100% for Stage I, 90.0% for Stage II, 92.1% for Stage III, and 57.1% for Stage IV tumors.[1] Data from the 2004-2016 National Cancer Database collected from 1903 pediatric melanoma patients reported a 5-year OS rate is greater than 90% for Stage I-III tumors and 34.4% for Stage IV tumors.[12]

The FDA's Assessment:

FDA agrees with the Applicant's assessment of pediatric melanoma.

2.2. Analysis of Current Treatment Options

Data:

Table 1: Applicant - FDA Approved Treatments (Checkpoint Inhibitors) for Pediatric Patients - Advanced or Adjuvant Melanoma

Product (s) Name	Year/ Type of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
Ipilimumab (YERVOY)	2017/ Full	Unresectable or metastatic melanoma in adults and pediatric patients 12 years and older	Ipilimumab 3 mg/kg every 3 weeks for a maximum of 4 doses	No new safety signals were observed in pediatric patients in two studies (NCT01445379 and NCT01696045), which included a total of 45 pediatric patients.	Of the 17 patients ≥12 years of age with melanoma treated with YERVOY across both studies, 2 patients experienced objective responses, including one partial response that was sustained for 16 months. Evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacokinetic data

					demonstrate the exposure at doses of 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable.
Nivolumab and Relatlimab-rmbw (OPDUALAG)	2022/Full	Unresectable or metastatic melanoma in adult patients and pediatric patients 12 years and older	Pediatric patients 12 years of age and older who weigh at least 40 kg: 480 mg nivolumab and 160 mg relatlimab intravenously every 4 weeks	Use of OPDUALAG is supported by evidence from an adequate and well-controlled study in adults[13] and additional data analyses that suggest that nivolumab and relatlimab exposures in pediatric patients 12 years of age who weigh at least 40 kg are expected to result in similar safety and efficacy to that of adults.	The pharmacokinetics of monoclonal antibodies and the course of unresectable or metastatic melanoma are sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data from adult patients to pediatric patients 12 years of age or older (who weigh at least 40 kg).
Pembrolizumab (KEYTRUDA)	2021/Full	Adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection	For pediatric use: 2 mg/kg (up to 200 mg) intravenously every 3 weeks	In KEYNOTE-051, [14] 161 pediatric patients (99 aged 12-17 years) with advanced melanoma, lymphoma, or PD-L1 positive solid tumors received KEYTRUDA. Adverse reactions or laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients vs adults were pyrexia (33%), vomiting (30%), upper respiratory tract infection (29%), headache (25%),	Use of KEYTRUDA in pediatric patients for approved indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

				leukopenia (30%), neutropenia (26%), and Grade 3 anemia (17%).	

The Applicant's Position:

Pediatric melanoma is still poorly studied and underrepresented in clinical trials. There is clearly a need for more prospective testing of therapeutic strategies in the pediatric population. Melanoma in adolescents and adults is generally regarded as an analogous disease and is treated similarly using multimodal therapy including surgery, systemic therapy, and in some cases, radiation. As such, current treatment strategies for pediatric and adolescent melanoma are based on clinical guidelines for adult patients,[15,16,17,18] and there are limited clinical studies evaluating treatment outcomes in these age groups. Despite the small number of patients, results of these studies showed that safety profiles and treatment effects (such as objective responses or PD effects of immunotherapy) in pediatric patients are comparable with adult patients. In NCCN guidelines, there are no differences in treatment options recommended for melanoma by variables such as sex, race, ethnicity, or age.[15]

The mainstay of treatment of pediatric cutaneous melanoma is cure by surgical resection. This process includes full-thickness biopsy for diagnosis, wide local excision with margins based on lesion depth, and selective use of sentinel lymph node biopsy and completion lymph node dissection. Given the lack of pediatric-specific clinical trials guiding surgical management, adult guidelines are applied to children with some modifications based on expected differences in cosmetic and functional outcomes in younger patients.[7]

Pediatric patients with Stages III and IV melanoma are considered for additional therapy. Prior to 2011, approved therapies were limited to dacarbazine chemotherapy and IL-2 immunotherapy as treatment of metastatic melanoma and IFN α-2b as adjuvant treatment. Since then, three distinct therapeutic classes have been developed with demonstrated efficacy in adult adjuvant and advanced settings: checkpoint inhibitors targeting the PD-1, LAG-3 inhibitory receptor, and CTLA-4 coinhibitory receptor pathways and targeted therapies inhibiting tyrosine kinase signaling pathways (such as BRAF and MEK inhibitors).[19] Approved checkpoint inhibitor therapies are summarized in Table 1.

Treatment of Advanced (Unresectable or Metastatic) Melanoma

The checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab and the BRAF- (dabrafenib, vemurafenib, and encorafenib) and MEK- (trametinib, cobimetinib, and binimetinib) targeted therapies were evaluated in adult unresectable and metastatic melanoma. The 3 checkpoint inhibitors (ipilimumab, nivolumab, and pembrolizumab) and the nivolumab plus ipilimumab (nivo + ipi) combination were approved in adults in the US and EU. Nivolumab and relatlimab fixed-dose combination was approved in the US and received CHMP positive opinion on 21-Jul-2022 in the EU. Three BRAF-MEK inhibitor combinations were approved in US and EU for adult use in advanced melanoma (dabrafenib + trametinib,

vemurafenib + cobimetinib, and encorafenib + binimetinib), with little to indicate whether one combination would be better suited to pediatric use than another. [15,17]

Despite the availability of new treatment options for advanced melanoma in adults, current experience with immunotherapy, and checkpoint inhibitors in particular in the pediatric setting is very limited. Ipilimumab has received FDA and EMA approval for treatment of unresectable or metastatic melanoma in pediatric patients 12 years and older (extension of the adult indication). Nivolumab and relatlimab fixed -dose combination (Opdualag®) was approved by the FDA for adult and pediatric patients 12 years and older with unresectable or metastatic melanoma based on RELATIVITY-047 Phase 2/3 study[13] and PK-based extrapolations of efficacy to adolescent patients.

Pembrolizumab monotherapy was evaluated in 154 pediatric patients, including patients with advanced melanoma (5.2%), lymphoma (13.0%), and PD-L1 positive advanced, relapsed/refractory solid tumors. Pooled efficacy results for the 136 subjects in the solid tumors cohort reported an ORR of 5.9%, with no CR and 8 PRs (no melanoma patients). The safety profile was generally similar to that seen in adults.[14] To date, there are limited data on the safety and efficacy of BRAF-targeted therapies (eg, vemurafenib and dabrafenib) in adolescent melanoma patients (≥ 12 to < 18 years).[20] Real world data from the Dutch melanoma treatment registry (N = 3775) showed that the proportion of adolescents and young adults (N = 210) initially treated with BRAF or MEK inhibitors and immune checkpoint inhibitors in the Netherlands were 35.2% and 33.8%, respectively.[21]

Adjuvant Therapy of Resected High-risk Melanoma

Pediatric patients with melanoma have been absent from most of the prospective trials, and current treatment strategies for younger patients must extrapolate from adult data.[22] Adjuvant therapy for adult melanoma has changed dramatically in the past five years. Interferon α-2b has essentially been replaced by the adjuvant use of PD-1 inhibitors (nivolumab and pembrolizumab) as well as the adjuvant use of BRAF and MEK inhibitors. The combination of the BRAF (dabrafenib) and MEK (trametinib) inhibitors was approved by the FDA and EMA for adult BRAF-mutant Stage III melanoma following complete resection.[15,17] The FDA and recently EMA approved the expanded indication of pembrolizumab for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB, IIC, based on KEYNOTE-716 study[23], and and Stage III melanoma based on KEYNOTE-054 study[24] following complete resection.

The FDA's Assessment:

FDA agress with the Applicant's summary of available therapies for the treatment of melanoma, including for the treatment of melanoma in pediatric patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nivolumab (nivo) monotherapy was first approved by the US FDA for the treatment of unresectable or metastatic melanoma (adults) on 22-Dec-2014; nivo is now also approved (as monotherapy and in combination with other agents) for multiple additional tumor types, including the use of nivolumab as a monotherapy (for MSI-H/dMMR CRC) and in combination with relatlimab (for unresectable or metastatic melanoma) in pediatric patients 12 years and older.

Ipilimumab (ipi) was approved in the US for advanced melanoma on 25-Mar-2011; this indication was expanded to include pediatric patients ≥ 12 years old in 2017.

The combination of nivo + ipi was first approved by FDA on 30-Sep-2015 for the treatment of unresectable or metastatic melanoma (adults); the combination is now also approved for multiple additional tumor types, including the use of nivolumab in combination with ipilimumab in pediatric patients 12 years and older for MSI-H/dMMR CRC.

Development in pediatric populations for nivolumab and ipilimumab included submission of a proposed pediatric study report (PPSR), discussions with and feedback received from the FDA, followed by issuance of a PWR by the FDA for both nivolumab and ipilimumab. As of 20-Jul-2017, the FDA determined that the PWR for ipilimumab was fulfilled. The current nivolumab PWR, which includes Amendment 03, lists a request for non-clinical biomarker studies in pediatric tumor tissues, a clinical study (Study 1: ADVL1412/ CA209070), and pharmacokinetic analyses to establish pediatric dosing recommendations for nivolumab alone and in combination with ipilimumab in advanced melanoma. In the present sBLA, BMS requests determination of pediatric exclusivity for nivolumab, based on the results of the studies (non-clinical biomarker studies, CA209070, and pharmacokinetic analyses) conducted according to the nivolumab PWR.

Additionally, in the present sBLA, BMS requests the extension of the approved adult melanoma indications to include pediatric patients 12 years and older:

- OPDIVO (nivolumab), as a single agent in combination with YERVOY (ipilimumab), is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma
- OPDIVO (nivolumab) is indicated for the 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.
- YERVOY (ipilimumab), in combination with OPDIVO (nivolumab), is indicated for the treatment of unresectable or metastatic melanoma in adult and pediatric patients 12 years and older.

Clinical efficacy and safety data for the filing comprise of:

- Pivotal study CA209070 (ADVL1412), a Phase 1/2 open-label trial of nivolumab in children, adolescents, and young adults with recurrent or refractory solid or hematological tumors as a single agent and in combination with ipilimumab.
    - CA209070 included 1 adolescent subject with melanoma (treated with nivolumab monotherapy [nivo mono]).
- Supportive data from the following Phase 3 studies conducted in adult melanoma patients:
    - CA209067, supportive data from nivo mono arm and nivo+ipi arm for advanced melanoma
    - CA209915, supportive data from nivo mono arm for the adjuvant treatment of melanoma
        - 3 adolescent subjects with melanoma were treated in CA209915 (2 with nivo mono and 1 with nivo + ipi)
    - CA209238, supportive data from nivo mono arm for the adjuvant treatment of melanoma.

With a similarity of the disease in adult and adolescent patients with melanoma, a similarity in the response to treatment is expected that justifies the efficacy extrapolation approach from adult clinical studies with melanoma to support the requested indication expansion for adolescent patients. A PK-based extrapolation of efficacy in adolescents (≥ 12 years to < 18 years), supported by modeling and simulations, was used to predict nivolumab exposures in adolescent subjects for comparison with corresponding exposures from the target efficacious dose in the adult population.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the regulatory interactions

The original Written Request was issued on September 11, 2014. Amendments to the Written Request are summarized below:

- Amendment #1, dated April 11, 2016
    - This amendment included revisions to specify that the dose finding portion for the combination regimen would consist of nivolumab 1 mg/kg or nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks until progression. The original Written Request stated that nivolumab 1 mg/kg would be evaluated with ipilimumab at a dose of either 1 mg/kg or 3 mg/kg.

- Amendment #2, dated July 3, 2018
    - This amendment included revisions to include study stopping rules for Grade 3-5 hyperacute graft-versus-host disease (GVHD) and to include acute and chronic GVHD criteria for removal from protocol therapy.
    - Three additional cohorts were added to Part B (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and melanoma expansion cohorts) and a new Part D with 6 arms/cohorts was added.

- o The final study report submission date was also amended to allow additional time for accrual and analysis of results of the newly added study arms.

- Amendment #3, dated November 9, 2020
  - o This amendment included revisions to remove Study 2 based on the results of Study 1 (CA209070) which demonstrated no responses in the solid tumor cohorts treated with nivolumab monotherapy and minimal activity observed in pediatric patients with solid tumors treated with nivolumab in combination with ipilimumab. The request to remove Study 2 was also supported by publicly available results of other PD-1/PD-L1 studies in pediatric tumors demonstrating limited activity.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of the key regulatory history milestones in the development of nivolumab in advanced melanoma, nivo + ipi in advanced melanoma, nivolumab in the adjuvant treatment of melanoma, as well as the nivolumab pediatric written request is provided in Table 2.

Table 2: Applicant - Key Regulatory Milestones Related to Nivolumab & Ipilimumab for Melanoma, and Nivolumab Pediatric Written Request

Date	Regulatory Milestone
07-Mar-2013	Nivolumab intravenous (IV) pediatric study plan submitted to Food and Drug Administration (FDA) (IND 100,052 Seq. 0232).
19-Dec-2013	BMS submitted nivolumab IV proposed pediatric study request (PPSR) (pediatric investigational new drug [pIND] 120,909 Seq.0000).
07-Apr-2014	Submission of revised nivolumab IV PPSR that incorporates FDA comments (pIND 120,909 Seq.0001).
11-Sep-2014	FDA issued formal pediatric written request (PWR) for nivolumab IV.
22-Dec-2014	FDA approved nivolumab for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
10-Mar-2015	Proposal to change PWR to reflect updated dosing for the second dose level of nivolumab (pIND 120,909 Seq.0005).
30-Sep-2015	FDA approved nivo + ipi for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.
23-Jan-2016	FDA expanded the indication of nivolumab as a single agent and in combination with ipilimumab for the treatment of patients with unresectable or metastatic melanoma.
11-Apr-2016	FDA issued Amendment 1 to PWR.

Table 2: Applicant - Key Regulatory Milestones Related to Nivolumab & Ipilimumab for Melanoma, and Nivolumab Pediatric Written Request

Date	Regulatory Milestone
20-Dec-2017	FDA approved nivolumab for the treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
03-Jul-2018	FDA issued Amendment 2 to PWR.
08-Aug-2018	Submission of agreed nivolumab PWR Amendment 2, which includes: • Incorporation of all FDA changes to align with nivolumab approvals and current protocol of Study ADVL1412 (pIND 120,909 Seq.0014).
26-Jun-2020	Type C Meeting Request submitted to discuss the results of Study 1 (CA209070/ ADVL1412) and to inquire on the need for inclusion of Study 2 in the nivolumab IV PWR.
27-Aug-2020	FDA preliminary comments for Type C Meeting received. Based on the clear feedback from FDA's preliminary comments, a formal meeting was cancelled. FDA agreed to BMS' proposal to amend the nivolumab IV PWR to remove Study 2 based on available results from CA209070, publicly available results of other PD-1/PD-L1 studies in pediatric tumors demonstrating limited activity, as well as from expert consensus.
28-Sep-2020	Submission of proposed Amendment 3 to PWR which included: • Revision to PWR to remove Study 2 in alignment with the feedback received in the preliminary meeting comments (pIND 120,909 Seq.0023).
09-Nov-2020	FDA issued Amendment 3 to PWR which includes removal of Study 2.
19-Oct-2021	Type B Meeting Request submitted to discuss BMS' proposal to (b) (4)
03-Dec-2021	FDA preliminary comments for Type B Meeting received. Based on the clear feedback from FDA's preliminary comments, a formal meeting was cancelled. FDA did not agree with BMS' proposal to (b) (4)
24-Mar-2022	Type B pre-sBLA Meeting Request submitted to discuss the adequacy of the data from pediatric patients treated in Study CA209070, other supportive clinical studies and modeling & simulation to support extrapolation from adult to pediatric patients to support updates to the nivolumab and ipilimumab package inserts. BMS also requested FDA feedback on the planned request for pediatric exclusivity determination for nivolumab, and the proposed Opdivo and Yervoy sBLA submissions to fulfill the PWR. (pIND 120,909 Seq.0028)
20-June-2022	FDA preliminary comments for Type B, pre-sBLA Meeting received. Based on the clear FDA feedback from FDA's preliminary comments, a formal meeting was cancelled. FDA was in general agreement with the proposed filing strategy and content for the sBLAs.

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

The FDA's Assessment:
FDA agrees with the Applicant's summary of the regulatory activity.

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 (DO3) reviewed the enrollment characteristics, patterns of protocol violations reported for the sites, efficacy reporting, and reporting of serious adverse events and did not identify any issues in any of the participating sites in Study CA209070; therefore, OSI was not consulted. In addition, considering the safety and efficacy of nivolumab and ipilimumab has been demonstrated in other indications and the inspection history for investigators who participated in Study CA209070, clinical site inspections were not deemed necessary for these sBLAs.

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 devie or a companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

The results of study report Expression of PD-L1, and Characterization of Tumor Infiltrating Immune Cells in Tumors of Pediatric Origin are submitted in Module 4.2.1.1. This nonclinical biomarker report is provided in this submission to fulfill the nivolumab PWR and PIP01, and no corresponding Module 2 non-clinical summaries are included in this application, as the pediatric non-clinical study results are out of the scope of the proposed extension of the approved adult indications of nivolumab as a single agent or in combination with ipilimumab for the treatment of melanoma to include pediatric (12 years and older) patients.

The FDA's Assessment:
FDA agrees with the Applicant's summary of nonclinical data submitted with these sBLAs.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Opdivo® (nivolumab) Injection was initially approved by FDA 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. Yervoy® (ipilimumab) Injection was initially approved by FDA on March 25, 2011. BMS submitted three efficacy supplements (S-117, S-118, and S-119) for Opdivo® (nivolumab) proposing to extend the the current indications for the treatment of unresctable or metastatic melanoma and for adjuvant treatment of melanoma with lymph node involvement or metastatic disease who have undergone complete resection, to pediatric patients (12 years and older). BMS also submitted an efficacy supplement (S-129) for Yervoy® (ipilimumab) to also extend the current indication of ipilimumab in combination with nivolumab for the treatment for unresectable or metastatic melanoma, to pediatric patients (12 years and older). Data from Study CA209070 (Children's Oncology Group (COG) Study ADVL 1412) are included in all four efficacy supplements .

The adult dosing regimens are proposed to be used in pediatric patients 12 years and older who weigh 40 kg or more for nivolumab as a single agent (1) for the treatment of advanced melanoma and (2) for the adjuvant treatment of melanoma; and for nivolumab and ipilimumab combination therapy (3) for the treatment of advanced melanoma. For pediatric patients 12 years and older and weighing < 40 kg receiving nivolumab as a single agent, body weight-based dosing is proposed. To support the proposed pediatric dosing regimens, BMS submitted

updated population PK (PPK) analyses of nivolumab and iplimumab for pediatric patients with advanced melanoma, PPK analysis of nivolumab for pediatric patients with adjuvant treatment of melanoma, and exposure-response (E-R) analyses for safety.

The Applicant employed PK-based extrapolation to demonstrate that the established efficacy in adults would be applicable to pediatric patients (12 years and older) for treatment of advanced melanoma and for the adjuvant treatment of melanoma based on 1) disease similarity; 2) comparable exposure profiles; and 3) relatively flat E-R efficacy.

The proposed recommended dosages for nivolumab and ipilimumab in pediatric patients (12 years or older) are acceptable because

1) PPK analyses with the proposed pediatric dosages predicted higher nivolumab and or ipilimumab exposure in pediatric patients than adults
2) Higher exposures in pediatric patients are still well below the exposures observed with the clinically tolerated dosage of nivolumab 10 mg/kg Q2W and ipilimumab 10 mg/kg Q3W in adults.
3) The E-R safety analysis predicted numerically lower median $Gr2^{+}$ IMAEs with overlapping 90% PIs for pediatric patients compared to adults when using the approved adult dosing regimens.

The Office of Clinical Pharmacology has reviewed the information contained in NDA 125554 supplement 117, 118, 119, and NDA 125388 supplement 129 and determined that it is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Table 3: Applicant - Proposed Dosing Regimens for the Treatment of Melanoma in Adolescents (Advanced and Adjuvant Melanoma)

Indication	Approved Adult Dosing Regimen	Proposed Dosing Regimen for Adolescents
Nivo mono for Advanced MEL	Nivo 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
Nivo+Ipi combo for Advanced MEL	Nivo 1 mg/kg followed by Ipi 3 mg/kg on same day Q3W for 4 doses, followed by Nivo 240 mg Q2W or 480 mg Q4W	**≥ 40 kg**: Nivo 1 mg/kg followed by Ipi 3 mg/kg on same day Q3W for 4 doses, then Nivo 240 mg Q2W or 480 mg Q4W **< 40 kg***: Nivo 1 mg/kg followed by Ipi 3 mg/kg on same day Q3W for 4 doses, then Nivo 3 mg/kg Q2W or 6 mg/kg Q4W

Table 3: Applicant - Proposed Dosing Regimens for the Treatment of Melanoma in Adolescents (Advanced and Adjuvant Melanoma)

Indication	Approved Adult Dosing Regimen	Proposed Dosing Regimen for Adolescents
Nivo mono for Adjuvant Treatment of MEL	Nivo 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

Nivolumab and ipilimumab are administered by intravenous infusion.
*BW dosing is recommended for adolescents <40 kg since nivolumab exposures are predicted to continue to increase at BW < 40 kg with flat dosing and could exceed 10 mg/kg Q2W exposures observed in adults.

Advanced Melanoma - Nivolumab Monotherapy

Table 4: Applicant - Predicted Nivolumab Exposures for Adolescents with Solid Tumors at Doses of 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W and Adult MEL Subjects at 240 mg Q2W

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
Cavgss	30-40	100	83.4(42.3)	Yes	NA	NA	63.6 - 132
	40-50	100	165(42.7)	NO(25%)	100	132(45.5)	
	50-60	100	145(45.2)	NO(9.85%)	100	124(44.2)	
	60-70	100	125(47.4)	Yes	100	110(46)	
	70-80	100	119(43.1)	Yes	100	92.3(43.8)	
	80-90	100	104(39.2)	Yes	100	82.2(54.1)	
	90-100	100	96(47.3)	Yes	100	85(43.6)	
	100-110	100	103(45.7)	Yes	100	77.4(40.1)	
	≥ 110	100	81.8(50.1)	Yes	100	63.6(43.7)	
Cminss	30-40	100	65.7(50.4)	Yes	NA	NA	48.4 - 104
	40-50	100	131(50.4)	NO(26%)	100	104(54.2)	
	50-60	100	115(53.3)	NO(10.6%)	100	98.9(52.3)	
	60-70	100	97.6(56.4)	Yes	100	86.6(54.9)	
	70-80	100	94.7(51.1)	Yes	100	71.8(52.4)	
	80-90	100	82.5(46.3)	Yes	100	63.7(65.6)	
	90-100	100	74.1(57.1)	Yes	100	66.8(52.1)	
	100-110	100	81.2(55)	Yes	100	60.3(48.2)	
	≥ 110	100	64.1(59.3)	Yes	100	48.4(53.2)	
Cmaxss	30-40	100	128(32.1)	Yes	NA	NA	97.1 - 190
	40-50	100	250(33.8)	NO(31.6%)	100	190(34.7)	
	50-60	100	217(35.3)	NO(14.2%)	100	178(34.6)	
	60-70	100	194(35)	NO(2.11%)	100	159(35.8)	
	70-80	100	179(32.7)	Yes	100	136(33.1)	
	80-90	100	158(30.5)	Yes	100	122(39.6)	
	90-100	100	150(34.2)	Yes	100	125(34.1)	
	100-110	100	155(33.5)	Yes	100	115(30.6)	
	≥ 110	100	125(39.2)	Yes	100	97.1(32.8)	

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01-supp/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-mono-240.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

Table 5: Applicant - Predicted Nivolumab Exposures for Adolescents with Solid Tumors at Doses of 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W and Adult MEL Subjects at 480 mg Q4W

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
Cavgss	30-40	100	91.5(55.3)	Yes	NA	NA	78.5 - 131
	40-50	100	174(53.9)	NO(32.8%)	100	128(51.7)	
	50-60	100	147(52.6)	NO(12.2%)	100	131(47.1)	
	60-70	100	145(51.4)	NO(10.7%)	100	107(54)	
	70-80	100	124(52.7)	Yes	100	99.1(47.4)	
	80-90	100	116(58.5)	Yes	100	91.1(50.8)	
	90-100	100	106(47.4)	Yes	100	91.7(57.3)	
	100-110	100	98.1(53.9)	Yes	100	84.7(51.3)	
	≥ 110	100	90.4(54.4)	Yes	100	78.5(47.1)	
Cminss	30-40	100	59.6(72.8)	Yes	NA	NA	52.4 - 86
	40-50	100	113(68.5)	NO(31.4%)	100	79.7(70.2)	
	50-60	100	96.4(69.1)	NO(12.1%)	100	86(62.9)	
	60-70	100	94.1(67.6)	NO(9.42%)	100	66.6(72.8)	
	70-80	100	79.5(69.6)	Yes	100	63.6(63.2)	
	80-90	100	75.7(76)	Yes	100	57.9(68.2)	
	90-100	100	68.1(63.8)	Yes	100	58.3(76.7)	
	100-110	100	61.5(72.3)	Yes	100	55.9(67.5)	
	≥ 110	100	58.6(71.4)	Yes	100	52.4(61.1)	
Cmaxss	30-40	100	187(36.3)	Yes	NA	NA	145 - 257
	40-50	100	363(37.5)	NO(41.2%)	100	257(31.9)	
	50-60	100	299(35.1)	NO(16.3%)	100	246(31.4)	
	60-70	100	300(33.2)	NO(16.7%)	100	218(33.4)	
	70-80	100	258(33.3)	NO(0.389%)	100	188(30.3)	
	80-90	100	236(36.1)	Yes	100	177(32.9)	
	90-100	100	220(30.7)	Yes	100	177(36)	
	100-110	100	208(33.7)	Yes	100	159(33.5)	
	≥ 110	100	186(36.4)	Yes	100	145(34.2)	

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01-supp/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-mono-480.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

Table 6: Applicant - Predicted Median Probability (90% PI) of Gr2+ IMAEs at Select Times for Nivolumab 240 mg Q2W in Adults, Nivolumab 240 mg in Adolescents (with Adolescents < 40 kg 3 mg/kg) and Nivolumab 3 mg/kg with/without Cap in Adolescents with Advanced Melanoma

Time	Adult 240 mg	Adolescent 240 mg	Adolescent 3 mg/kg	Adolescent Cap 3 mg/kg
6 Month	0.207 (0.17, 0.267)	0.164 (0.105, 0.224)	0.164 (0.106, 0.226)	0.165 (0.106, 0.226)
1 Year	0.286 (0.237, 0.364)	0.229 (0.149, 0.307)	0.229 (0.15, 0.311)	0.23 (0.15, 0.311)
2 Year	0.365 (0.305, 0.456)	0.295 (0.195, 0.39)	0.295 (0.197, 0.393)	0.296 (0.197, 0.393)

Note: Cap, dose cap of 240 mg applied to nivolumab.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/export/ mono240advtable.csv

Table 7: Applicant - Predicted Median Probability (90% PI) of Gr2+ IMAE at Select Times for Nivolumab 480 mg Q4W in Adults, Nivolumab 480 mg in Adolescents (with Adolescents < 40 kg 6 mg/kg) and Nivolumab 6 mg/kg with/without Cap in Adolescents with Advanced Melanoma

Time	Adult 480 mg	Adolescent 480 mg	Adolescent 6 mg/kg	Adolescent Cap 6 mg/kg
6 Month	0.207 (0.17, 0.267)	0.164 (0.105, 0.223)	0.164 (0.106, 0.225)	0.165 (0.106, 0.227)
1 Year	0.286 (0.237, 0.364)	0.229 (0.149, 0.307)	0.229 (0.15, 0.311)	0.23 (0.151, 0.312)
2 Year	0.365 (0.305, 0.457)	0.295 (0.195, 0.39)	0.295 (0.197, 0.393)	0.297 (0.198, 0.394)

Note: Cap, dose cap of 480 mg applied to nivolumab.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/export/ mono480advtable.csv

Advanced Melanoma - Nivolumab in Combination with Ipilimumab

Table 8: Applicant - Predicted Nivolumab Exposures for Adolescents with Solid Tumors at Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 Doses then Nivo 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
Cavg4	30-40	100	10.5(31)	Yes	NA	NA	9.91 - 13.4
	40-50	100	11.8(29.4)	Yes	100	9.91(31.1)	
	50-60	100	12(29.4)	Yes	100	10.2(30.5)	
	60-70	100	13.3(29.8)	Yes	100	11.5(28.3)	
	70-80	100	13.5(30)	NO(0.746%)	100	11.4(30.6)	
	80-90	100	14.7(31)	NO(9.7%)	100	11.9(30.8)	
	90-100	100	15.4(32.1)	NO(14.9%)	100	12.9(27.8)	
	100-110	100	15.5(32.4)	NO(15.7%)	100	12.8(29.6)	
	≥ 110	100	15.5(30)	NO(15.7%)	100	13.4(28.5)	
Cmin4	30-40	100	6.05(44.4)	Yes	NA	NA	5.80 - 7.56
	40-50	100	7(42.4)	Yes	100	6.04(43.1)	
	50-60	100	6.95(43.4)	Yes	100	5.8(44.9)	
	60-70	100	7.81(45)	NO(3.31%)	100	6.81(42.4)	
	70-80	100	7.81(44.9)	NO(3.31%)	100	6.64(45.8)	
	80-90	100	8.63(43.6)	NO(14.2%)	100	6.99(45.1)	
	90-100	100	9.02(43.5)	NO(19.3%)	100	7.38(43.3)	
	100-110	100	8.69(48.9)	NO(14.9%)	100	7.36(43.7)	
	≥ 110	100	8.6(45.1)	NO(13.8%)	100	7.56(44)	
Cmax4	30-40	100	25.7(26.1)	Yes	NA	NA	20.8 - 31.0
	40-50	100	27.2(24.1)	Yes	100	20.8(26.3)	
	50-60	100	28.9(23.9)	Yes	100	22.9(25.9)	
	60-70	100	32.6(27)	NO(5.16%)	100	25(23.4)	
	70-80	100	33.3(26.5)	NO(7.42%)	100	24.9(24.6)	
	80-90	100	35.7(28)	NO(15.2%)	100	26.6(26.2)	
	90-100	100	37.5(30)	NO(21%)	100	29.2(22.7)	
	100-110	100	38.2(27.8)	NO(23.2%)	100	28.7(26.4)	
	≥ 110	100	39.1(26.8)	NO(26.1%)	100	31(22.5)	
Cavgss	30-40	100	67.9(55.1)	Yes	NA	NA	56.3 - 111

Table 8: Applicant - Predicted Nivolumab Exposures for Adolescents with Solid Tumors at Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 Doses then Nivo 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
Cminss	40-50	100	140(44.1)	NO(26.1%)	100	111(46.7)	41.1 - 83.7
	50-60	100	111(45.6)	Yes	100	94.4(46.7)	
	60-70	100	103(49.2)	Yes	100	94.8(43.4)	
	70-80	100	91.1(49.8)	Yes	100	81(41.3)	
	80-90	100	87.6(46.1)	Yes	100	71.5(46.9)	
	90-100	100	86.1(51)	Yes	100	72.5(55.4)	
	100-110	100	74.4(49.5)	Yes	100	63.9(47.9)	
	≥ 110	100	62(50.5)	Yes	100	56.3(46.3)	
Cmaxss	30-40	100	49.9(67.5)	Yes	NA	NA	91.5 - 170
	40-50	100	106(53.3)	NO(26.6%)	100	83.7(56.3)	
	50-60	100	81.4(56.2)	Yes	100	68.7(57.4)	
	60-70	100	75.4(61.7)	Yes	100	71.9(53.8)	
	70-80	100	67(61.7)	Yes	100	61.1(50.9)	
	80-90	100	64.5(56.1)	Yes	100	53.1(58)	
	90-100	100	64.6(60.7)	Yes	100	53.5(67.8)	
	100-110	100	53.7(61.4)	Yes	100	47.1(59)	
	≥ 110	100	44.6(62.7)	Yes	100	41.1(57.9)	
	30-40	100	114(38.6)	Yes	NA	NA	
	40-50	100	224(32.6)	NO(31.8%)	100	170(36)	
	50-60	100	186(31.4)	NO(9.41%)	100	151(33.6)	
	60-70	100	177(33.1)	NO(4.12%)	100	146(31.1)	
	70-80	100	155(35.7)	Yes	100	124(30.3)	
	80-90	100	149(34.3)	Yes	100	114(33.4)	
	90-100	100	143(38.6)	Yes	100	115(39.1)	
	100-110	100	127(34.4)	Yes	100	101(34.9)	
	≥ 110	100	107(35.1)	Yes	100	91.5(30.9)	

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-combo-240.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups

Table 9: Applicant - Predicted Nivolumab Exposures for Adolescents with Solid Tumors at Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 Doses then Nivo 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult N	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]
Cavgss	30-40	100	72.8(55.5)	Yes	NA	NA	62.4 - 104
	40-50	100	138(53.9)	NO(32.7%)	100	102(51.8)	
	50-60	100	117(52.7)	NO(12.5%)	100	104(47.3)	
	60-70	100	115(51.6)	NO(10.6%)	100	85.3(54.1)	
	70-80	100	98.3(52.8)	Yes	100	78.8(47.4)	
	80-90	100	92.4(58.8)	Yes	100	72.4(50.9)	
	90-100	100	84.3(47.5)	Yes	100	72.9(57.8)	
	100-110	100	78(54.1)	Yes	100	67.3(51.5)	
	≥ 110	100	71.9(54.5)	Yes	100	62.4(47.2)	
Cminss	30-40	100	42.3(77.6)	Yes	NA	NA	37.4 - 61.2
	40-50	100	80(72.1)	NO(30.7%)	100	56(74.9)	
	50-60	100	68.7(73.4)	NO(12.3%)	100	61.2(67.2)	
	60-70	100	66.9(71.9)	NO(9.31%)	100	46.7(77.7)	
	70-80	100	56.4(73.9)	Yes	100	45(67.2)	
	80-90	100	53.9(80.5)	Yes	100	40.9(72.6)	
	90-100	100	48.3(68)	Yes	100	41.1(82.3)	
	100-110	100	43.3(77.2)	Yes	100	39.8(72.1)	
	≥ 110	100	41.6(75.8)	Yes	100	37.4(64.7)	
Cmaxss	30-40	100	169(34.7)	Yes	NA	NA	129 - 232
	40-50	100	328(35.9)	NO(41.4%)	100	232(30.1)	
	50-60	100	270(33.8)	NO(16.4%)	100	220(30.1)	
	60-70	100	272(31.7)	NO(17.2%)	100	197(31.4)	
	70-80	100	233(31.7)	NO(0.431%)	100	168(28.8)	
	80-90	100	213(33.9)	Yes	100	159(31)	
	90-100	100	199(29.7)	Yes	100	159(33.9)	
	100-110	100	188(32)	Yes	100	142(31.8)	
	≥ 110	100	168(34.8)	Yes	100	129(33.1)	

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01-supp/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-combo-480.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

Table 10: Applicant - Predicted Ipilimumab Exposures for Adolescents with MEL at Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 Doses

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	Adult N	Adult Geo. Mean (%CV)	If within Adult Range[a]	Adult Low - High Geo. Mean[b]
Cavg4	30-40	100	30.5(30.6)	100	21.5(36)	Yes	21.5 - 38.2
	40-50	100	34(32.5)	100	27.3(33.9)	Yes	
	50-60	100	36.2(31.8)	100	27.5(37.5)	Yes	
	60-70	100	39.7(32)	100	28.6(31.5)	NO(3.93%)	
	70-80	100	40.2(36.2)	100	32.1(32.7)	NO(5.24%)	
	80-90	100	46.2(27.9)	100	32(33.3)	NO(20.9%)	
	90-100	100	47(33.5)	100	33.8(35.8)	NO(23%)	
	100-110	100	50.7(33.2)	100	33.5(34.5)	NO(32.7%)	
	≥ 110	100	53.1(36.7)	100	38.2(39.6)	NO(39%)	
Cmin4	30-40	100	18.2(43.1)	100	11.8(54.1)	Yes	11.8 - 21.1
	40-50	100	20.8(45.8)	100	14.7(51.4)	Yes	
	50-60	100	22.1(46)	100	14.8(53.7)	NO(4.74%)	
	60-70	100	24.1(46)	100	15.5(46.9)	NO(14.2%)	
	70-80	100	24.1(51.8)	100	17.8(48.7)	NO(14.2%)	
	80-90	100	29.1(40.1)	100	17.7(48.2)	NO(37.9%)	
	90-100	100	28.6(48)	100	18.3(52.6)	NO(35.5%)	
	100-110	100	31(46.1)	100	17.8(52.4)	NO(46.9%)	
	≥ 110	100	32.8(50.9)	100	21.1(57.7)	NO(55.5%)	
Cmax4	30-40	100	74.5(24.2)	100	52.7(25.9)	Yes	52.7 - 91.6
	40-50	100	79.3(24.2)	100	68(25)	Yes	
	50-60	100	84.6(22)	100	69.2(28.6)	Yes	
	60-70	100	94.3(22.7)	100	70.3(22.4)	NO(2.95%)	
	70-80	100	96.3(29.4)	100	77.9(23.7)	NO(5.13%)	
	80-90	100	105(21.4)	100	76.4(23.7)	NO(14.6%)	
	90-100	100	112(24.3)	100	83.3(23.6)	NO(22.3%)	
	100-110	100	119(26.7)	100	83.8(22.1)	NO(29.9%)	
	≥ 110	100	124(27.6)	100	91.6(28.4)	NO(35.4%)	

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-ipi/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation-ipi.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-combo-3mpk.csv

[a] Values in the parenthesis indicate the percent difference between geometric mean of adolescent exposure and geometric mean of adult exposure.

[b] The range of lowest to highest geometric mean exposure in adults across body weight groups.

Table 11: Applicant - Model Predicted Median Probability (90% PI) of Gr2+ IMAEs at Select Times for Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W (4 Doses) with Q2W Maintenance Dose with/without Cap in Adults and Adolescents with Advanced Melanoma

Time	Adult 240 mg	Adolescent 240 mg	Adolescent Cap 3 mg/kg
6 Month	0.635 (0.553, 0.743)	0.525 (0.371, 0.653)	0.536 (0.381, 0.662)
1 Year	0.667 (0.585, 0.773)	0.555 (0.396, 0.684)	0.566 (0.406, 0.694)
2 Year	0.752 (0.671, 0.846)	0.646 (0.474, 0.769)	0.656 (0.483, 0.778)

Notes: cap, dose cap of 80 mg applied to nivolumab and 240 mg applied to ipilimumab.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/export/ combo240table.csv

Table 12: Applicant - Model Predicted Median Probability (90% PI) of Gr2+ IMAEs at Select Times for Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W (4 Doses) with Q4W Maintenance Dose with/without Cap in Adults and Adolescents with Advanced Melanoma

Time	Adult 480 mg	Adolescent 6 mg/kg	Adolescent Cap 6 mg/kg
6 Month	0.629 (0.548, 0.739)	0.521 (0.368, 0.648)	0.531 (0.376, 0.657)
1 Year	0.662 (0.581, 0.77)	0.553 (0.392, 0.681)	0.562 (0.401, 0.69)
2 Year	0.748 (0.667, 0.843)	0.644 (0.472, 0.766)	0.653 (0.479, 0.775)

Notes: cap, dose cap of 80 mg applied to nivolumab and 480 mg applied to ipilimumab.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/export/ combo480table.csv

Adjuvant Treatment of Melanoma - Nivolumab Monotherapy

Table 13: Applicant - Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W and Adults with Adjuvant Treatment of Melanoma at 240 mg Q2W

Exposure (µg/mL)	Body Weight (kg)	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]	Adult 10 mg/kg Geo. Mean*
Cavgss	30-40	95.4 (30.8)	Yes	NA	89.7-167	261
	40-50	183 (29.5)	No (9.58%)	167 (32.3)		
	50-60	170 (32.5)	No (1.8%)	152 (32.1)		
	60-70	147 (29.5)	Yes	136 (28.5)		
	70-80	138 (30.7)	Yes	120 (29.6)		
	80-90	123 (29.3)	Yes	107 (28)		
	90-100	116 (30.7)	Yes	102 (32.4)		
	100-110	116 (31.5)	Yes	91.7 (25.6)		
	≥ 110	90.6 (36.2)	Yes	89.7 (29.7)		
Cminss	30-40	78 (35.9)	Yes	NA	74.1-137	200
	40-50	150 (33.9)	No (9.49%)	137 (38)		
	50-60	141 (37)	No (2.92%)	128 (36)		
	60-70	121 (34.3)	Yes	113 (32.8)		
	70-80	115 (35.4)	Yes	99.2 (34.4)		
	80-90	102 (33.2)	Yes	87.9 (32.8)		
	90-100	95.5 (35.5)	Yes	84.5 (36.8)		
	100-110	96.4 (36.4)	Yes	75.2 (29.8)		
	≥ 110	74.2 (41.5)	Yes	74.1 (34.2)		
Cmaxss	30-40	137 (26.1)	Yes	NA	123-231	385
	40-50	260 (27.2)	No (12.6%)	231 (27.7)		
	50-60	235 (28.9)	No (1.73%)	202 (30.3)		
	60-70	208 (25.5)	Yes	189 (24.4)		
	70-80	191 (26.9)	Yes	166 (25.4)		
	80-90	171 (26.3)	Yes	149 (23.7)		
	90-100	163 (26.9)	Yes	142 (28.3)		
	100-110	163 (28)	Yes	127 (22.5)		
	≥ 110	128 (32.5)	Yes	123 (26.9)		

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
R-Program Source: Analysis-Directory/R/scripts/5-simulation-nivo.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-mono-240.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.
*Adults with advanced melanoma

Table 14: Applicant - Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W and Adults with Adjuvant Treatment of Melanoma at 480 mg Q4W

Exposure (µg/mL)	Body Weight (kg)	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]	Adult 10 mg/kg Geo. Mean
Cavgss	30-40	104 (32.3)	Yes	NA	83.2-172	261
	40-50	198 (35.1)	No (15.1%)	172 (30.4)		
	50-60	176 (31.5)	No (2.33%)	149 (29.7)		
	60-70	162 (33.1)	Yes	136 (31.9)		
	70-80	146 (30.5)	Yes	115 (29.3)		
	80-90	129 (33.9)	Yes	101 (29.4)		
	90-100	116 (29.5)	Yes	96.5 (26.5)		
	100-110	108 (30.1)	Yes	93.9 (34.2)		
	≥ 110	96 (30.8)	Yes	83.2 (29.3)		
Cminss	30-40	73.8 (40.4)	Yes	NA	57.4-123	200
	40-50	141 (44.2)	No (14.6%)	123 (38.6)		
	50-60	129 (39)	No (4.88%)	104 (39.3)		
	60-70	115 (41.3)	Yes	94.6 (41.5)		
	70-80	105 (38.3)	Yes	81.4 (36.9)		
	80-90	92.2 (43.7)	Yes	69.1 (39.2)		
	90-100	81.4 (38.7)	Yes	66.4 (36.4)		
	100-110	75.2 (39.5)	Yes	64.6 (46.2)		
	≥ 110	66.9 (40.3)	Yes	57.4 (37.5)		
Cmaxss	30-40	190 (30.4)	Yes	NA	153-298	385
	40-50	371 (30.5)	No (24.5%)	298 (26.8)		
	50-60	311 (29.9)	No (4.36%)	263 (25.1)		
	60-70	302 (29.1)	No (1.34%)	245 (27)		
	70-80	266 (26.5)	Yes	204 (26.3)		
	80-90	235 (26.4)	Yes	184 (26.7)		
	90-100	218 (27.5)	Yes	176 (22.7)		
	100-110	205 (25.2)	Yes	172 (27.3)		
	≥ 110	182 (26.6)	Yes	153 (28.6)		

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
R-Program Source: Analysis-Directory/R/scripts/5-simulation-nivo.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-mono-480.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

Table 15: Applicant - Predicted Median Probability (90% PI) of Gr2+ IMAEs at Select Times for Nivolumab 240 mg in Adults, Nivolumab 240 mg in Adolescents (with Adolescents < 40 kg 3 mg/kg) and Nivolumab 3 mg/kg with/without Cap in Adolescents with Adjuvant Treatment of Melanoma

Time	Adult 240 mg	Adolescent 240 mg	Adolescent 3 mg/kg	Adolescent Cap 3 mg/kg
6 Month	0.162 (0.128, 0.209)	0.125 (0.0795, 0.172)	0.125 (0.0804, 0.173)	0.126 (0.0804, 0.174)
1 Year	0.225 (0.18, 0.287)	0.175 (0.113, 0.239)	0.175 (0.114, 0.24)	0.176 (0.114, 0.241)

Notes: Cap, dose cap of 240 mg applied to nivolumab.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/plots/ mono240adjtable.csv

Table 16: Applicant - Predicted Median Probability (90% PI) of Gr2+ IMAEs at Select Times for Nivolumab 480 mg dose in Adults, Nivolumab 480 mg in Adolescents (with Adolescents < 40 kg 6 mg/kg) and Nivolumab 6 mg/kg with/without cap dose in Adolescents with Adjuvant Treatment of Melanoma

Time	Adult 480 mg	Adolescent 480 mg	Adolescent 6 mg/kg	Adolescent Cap 6 mg/kg
6 Month	0.162 (0.128, 0.209)	0.125 (0.0793, 0.172)	0.125 (0.0803, 0.173)	0.124 (0.0797, 0.172)
1 Year	0.225 (0.18, 0.287)	0.175 (0.113, 0.238)	0.175 (0.114, 0.24)	0.175 (0.113, 0.239)

Notes: Cap, dose cap of 480 mg applied to nivolumab.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/plots/ mono480adjtable.csv

The Applicant's Position:

Adolescent Dosing Recommendations: The adult dosing regimens are recommended for adolescent subjects for nivo mono in advanced and adjuvant melanoma $\geq$ 40 kg, and for nivo + ipi in advanced melanoma across all body weight ranges (Table 3). For subjects weighing < 40 kg receiving monotherapy and after combination dosing in the maintenance phase, body weight-based dosing is recommended, which will maintain efficacy and avoids the potential for further exposure increases with flat dosing in low body weight adolescent subjects that have potential to exceed the well tolerated adult exposures for the 10 mg/kg dose..
The dosing recommendations are based on the extrapolation principles outlined in FDA guidance,[25] similarities in disease in adolescent and adult and the totality of the data from comprehensive, pooled population PK and E-R safety (Gr2+ IMAEs) analyses across adult and pediatric studies.

Pediatric Studies: The efficacy and safety of nivolumab alone or in combination therapies have been evaluated in pediatric studies, including CA209070 (nivo mono and nivo+ipi in multiple tumors), CA209744 (nivo + brentuximab vedotin in cHL), and CA209908 (nivo mono and

nivo+ipi in CNS tumors), and the adult/adolescent study CA209915 (nivo mono and nivo+ipi in adjuvant treatment of melanoma, with 3 adolescent melanoma subjects treated in the adjuvant setting). The efficacy and safety of ipilimumab alone or in combination therapies have been evaluated in pediatric studies, including CA184070 (ipi mono in multiple tumors), CA184178 (ipi mono in advanced melanoma), CA209070, and CA209908. CA209070 is a Phase 1/2 study of nivolumab in young pediatric (1 to < 12 years), adolescents (≥ 12 to < 18 years) and young adults (from 18 to ≤ 30 years) with advanced solid tumors (including 1 subject with melanoma) as a single therapeutic agent and in combination with ipilimumab, or in Hodgkin lymphoma/non-Hodgkin lymphoma as a single therapeutic agent.[26]

PK-based Efficacy Extrapolation

Population PK Supporting Adolescent Advanced Melanoma (advPPK)**.** Population PK (PPK) analyses for nivolumab and ipilimumab were conducted using PK data from CA209070 and other adult and pediatric studies (outlined in Table 3.1-1 of Adv PPK report).[27] On the basis of similarity of the disease in adult and adolescent patients with advanced melanoma,[1,28,29,30,31,32,33,34] and the expected similarity in the E-R of efficacy to nivolumab and nivo + ipi treatment, a PK-based extrapolation approach was used to extend the favorable benefit and risk characterization of these nivolumab-based regimens from adults to adolescents with advanced melanoma. Model-based simulations were conducted to identify dosing regimens for nivolumab and nivo + ipi in adolescent subjects with advanced melanoma that are predicted to achieve a similar benefit: risk profile to those in adults.

Population PK Supporting Adolescent Adjuvant Treatment of Melanoma (adjPPK). A PPK analysis was conducted to characterize the PK of nivolumab in adolescent subjects (≥ 12 to <18 years) with the adjuvant treatment of melanoma. The PPK report includes PK data from nivolumab studies with a focus on adjuvant treatment of melanoma (including Studies CA209238 [adult patients, nivo mono and ipi mono] and CA209915 [adult and adolescent patients, nivo+ipi and nivo mono]).[35] The results from the PPK report are primarily used to characterize the PK of nivolumab in adolescent subjects in the adjuvant treatment of melanoma setting, including the effect of covariates on PK parameters, and to provide dosing recommendations for nivo mono using model-based simulations.

Adolescent PK. The adolescent nivolumab population PK analyses to support advanced melanoma indicated adolescents with advanced solid tumors have a 20% lower CL and a 24% lower VC compared to adults with advanced melanoma (Adv PPK)[27] after accounting for the effects of body weight. These findings were confirmed again in the second PPK analyses that focused on the adjuvant setting (Adv PPK).[35] The second PPK analyses indicated that adolescents treated in the adjuvant setting, also had a 19% lower CL than adults treated in the adjuvant setting. Consistent with nivolumab CL and VC lowering relative to adult, the adolescent ipilimumab PPK analysis to support advanced melanoma indicated adolescents with melanoma had a 29% lower CL and a 19% lower VC than adults with melanoma after accounting for the effects of body weight.

E-R Safety Analysis Supporting Dosing Regimens: An E-R analysis of safety was conducted to evaluate the potential impact of higher nivolumab and/or ipilimumab exposures in adolescents with melanoma on safety when using the approved adult dosing regimens for melanoma.[36] An E-R efficacy analysis was not conducted for this submission given i) higher predicted exposures for adolescents with the approved adult dosing regimen, ii) similarity of disease in adults versus adolescents, and iii) the relatively flat E-R efficacy for nivolumab, ipilimumab, and nivolumab in combination with ipilimumab.[37] The E-R relationship for safety was characterized with respect to Grade 2 or greater immune-mediated adverse events (Gr2+ IMAEs). The endpoint of time to Gr2+ IMAEs is more sensitive to exposure changes and informs on more proximal mechanistic, immunomodulatory effects on safety compared with Gr3+ AEs and Gr2+ TRAEs.[38] The E-R Gr2+ IMAE relationship was characterized in a pooled analysis with data from nivo mono, ipilimumab monotherapy (ipi mono), and nivo + ipi combination therapy studies in adult, young pediatric (1 to < 12 years) and adolescent (≥ 12 to < 18 years) subjects across solid tumors, including advanced melanoma and melanoma treated in the adjuvant setting. Model predictions of Gr2+ IMAEs were used to recommend nivo mono dosing regimens for the treatment of advanced melanoma or adjuvant treatment of melanoma as well as nivo + ipi dosing regimens for the treatment of advanced melanoma in adolescent subjects.

Data Supporting the Dose Recommendation for Nivolumab Monotherapy in Adolescent Advanced Melanoma

Adult flat dosing exposures were used as the reference. Simulation results indicate that for adolescents ≥ 40 kg with advanced solid tumors receiving the flat dosing of 240 mg Q2W, nivolumab steady state exposures were expected to exceed the adult exposure range, resulting in up to 25.0%, 26.0% and 31.6% higher Cavgss, Cminss, and Cmaxss, respectively (Table 4). It should be noted that the upper range of the exposure differences is expected in only the lowest body weight band (40 to 50 kg) in adolescents and supports the rationale to use body weight-based dosing for subjects < 40 kg. However, for adolescents ≥ 40 kg, flat dosing is still appropriate despite the higher adolescent exposures (versus adult exposures) given that the adolescent exposures are still well below the exposures observed with the clinically tolerated dose of nivolumab 10 mg/kg Q2W in adults. Similar findings were observed with the Q4W regimens of 480 mg (Table 5).

The supporting pooled E-R safety analysis across adult and pediatric subjects predicted numerically lower median Gr2+ IMAEs for adolescents compared with adults with overlapping 90% pediction intervals (PI) (adults versus adolescents) for both the Q2W and Q4W flat dosing regimens(Table 6 and Table 7). Model predicted Gr2+ IMAEs for adolescents receiving nivolumab 3 mg/kg Q2W (< 40 kg), 240 mg Q2W (≥ 40 kg), or nivolumab 3 mg/kg Q2W with or without a dose cap are similar and both numerically lower than that for adults using the approved 240 mg Q2W dosing regimen. Similarly, model predicted Gr2+ IMAEs for adolescents receiving nivolumab 6 mg/kg Q4W (< 40 kg), 480 mg Q4W (≥ 40 kg), or nivolumab 6 mg/kg Q4W with or without a dose cap are similar and numerically lower than that for adults using the approved 480 mg Q4W dosing regimen. The numerically lower median Gr2+ IMAE prediction

for adolescents versus adults may be due to age and body weight being notable baseline predictors in the E-R safety analysis, with higher risk of Gr2+ IMAEs associated with higher body weight and older age subjects. The flat nivolumab E-R is also an additional contributing factor for the lack of a meaningful increase in Gr2+ IMAEs in adolescents, despite the higher predicted exposure in adolescents compared to adults. Therefore, the moderate increase in the adolescent exposures relative to adults when using the approved adult dosing regimens is not predicted to result in an increased risk of Gr2+ IMAEs for adolescents.

Data Supporting the Dose Recommendation for Nivolumab in Combination with Ipilimumab in Adolescent Advanced Melanoma

Nivolumab

Adult body weight-based dosing was used as the reference. Nivolumab simulated exposures following the 4th dose of the combination treatment in adolescents were predicted to be higher compared to those in adults treated with the same weight-based regimen. Nivolumab Cavg4, Cmin4 and Cmax4 were up to 15.7%, 19.3% and 26.1% higher, respectively, in adolescents than in adults treated with the same weight-based dosing, with the highest differences seen in higher body weight bands (Table 8). The adolescent exposure increase relative to adult is not expected to be clinically relevant and is also supported by somewhat lower predicted median and overlapping Gr2+ IMAEs for adolescents versus adults (Table 11 and Table 12). As described above for nivo mono, the finding that higher baseline body weight and older age are predicted to result in higher Gr2+ IMAEs applies to the combination therapy as well and is contributed to the lower Gr2+ IMAE predictions for adolescents versus adults for the combination. Nivolumab steady-state exposures during the nivolumab flat dosing monotherapy maintenance were also higher in adolescents than adults with similar magnitudes to those predicted following nivolumab 240 mg Q2W(Table 8) or 480 mg Q4W (Table 9) “de novo” monotherapy.[27]

Ipilimumab

Adult body weight-based dosing was used as the reference. The results of the ipilimumab simulations in adolescents performed with the approved adult combination regimen of nivolumab 1 mg/kg followed by ipilimumab 3 mg/kg on the same day Q3W suggested higher ipilimumab exposures following the 4th dose of the combination treatment in adolescents with advanced melanoma compared with adults (Table 10). Ipilimumab Cavg4, Cmin4 and Cmax4 were up to 39.0%, 55.5% and 35.4% higher, respectively, in adolescents compared to adult values, with the highest differences in higher body weight bands (ref table above). The higher exposure in adolescents relative to adults is not expected to be clinically relevant and is supported by a lower predicted median and overlapping Gr2+ IMAEs for adolescents vs adults (Table 11 and Table 12).

In summary, Gr2+ IMAEs for the combination were predicted from the pooled E-R safety analysis across adult and pediatric subjects that included both nivolumab and ipilimumab exposure measures. Model-predicted Gr2+ IMAEs for adolescents receiving N1I3 combination therapy followed by nivolumab Q2W or Q4W maintenance with or without dose cap are similar

and both with a lower predicted median and overlapping Gr2+ IMAEs than that for adults using the approved N1I3 dosing regimen followed by nivolumab maintenance. Higher Gr2+ IMAEs predicted for adult may be due to body weight being a significant predictor, with higher risk associated with higher body weight and older age subjects. On the other hand, the effect of both nivolumab and ipilimumab exposures when dosed in combination is relatively flat. Therefore, the moderate exposure increase in adolescent subjects relative to adults is not predicted to result in an increased risk of Gr2+ IMAEs for adolescents.

Data Supporting the Dose Recommendation for Nivolumab Monotherapy in Adolescent Adjuvant Treatment of Melanoma

Adult flat dosing exposures were used as a reference. Results of the nivolumab simulations indicate that for adolescents ≥ 40 kg with advanced solid tumors receiving the flat dosing of 240 mg Q2W, nivolumab steady state exposures were expected to exceed the adult exposure range, resulting in up to 9.6%, 9.5% and 12.6% higher Cavgss, Cminss, and Cmaxss, respectively (Table 13). It should be noted that the upper range of the exposure difference is expected in only the lowest body weight band (40 to 60 kg) in adolescents and supports the rationale to use body weight based dosing for subjects < 40 kg. However, for adolescents ≥ 40 kg flat dosing is still recommended despite the higher adolescent exposures versus adult exposures, since adolescent exposures are still well below the exposures observed with the clinically tolerated dose of nivolumab 10 mg/kg Q2W in adults. Similar findings were observed with the Q4W regimens of 480 mg (Table 14).

The supporting E-R safety analysis predicted numerically lower median Gr2+ IMAEs with overlapping 90% PIs for adolescents compared to adults when using the approved adult dosing regimens (Table 15 and Table 16). Model-predicted Gr2+ IMAEs for adolescents receiving nivolumab 3 mg/kg Q2W (< 40 kg), 240 mg (≥ 40 kg) Q2W or nivolumab 3 mg/kg Q2W with or without a dose cap are similar and both lower than that for adults using the approved 240 mg Q2W dosing regimen (Table 15). Similarly, model predicted Gr2+ IMAEs for adolescents receiving nivolumab 6 mg/kg Q4W (< 40 kg), 480 mg (≥ 40 kg) Q4W or nivolumab 6 mg/kg Q4W with or without a dose cap (Table 16) are similar and both lower than that for adults using the approved 480 mg Q4W dosing regimen.

The FDA's Assessment:

FDA agrees with the Applicant's position.

The Applicant's approach and assessment involving PK-based extrapolation from adults to pediatric patients (12 years and older) with unresectable or metastatic melanoma and with melanoma with lymph node involvement or metastatic disease that has been completely resected was found acceptable based on

1) similarity of disease in adults versus in adolescent patients
2) comparable or <40% higher predicted nivolumab and ipilimumab exposures for pediatric patients with the approved adult dosing regimen. Higher exposures in pediatric patients (12

years and older) are still well below the exposures observed with the clinically tolerated dosages of nivolumab 10 mg/kg Q2W and ipilimumab 10 mg/kg Q3W in adults.

3) the relatively flat E-R efficacy for nivolumab, ipilimumab, and nivolumab in combination with ipilimumab.

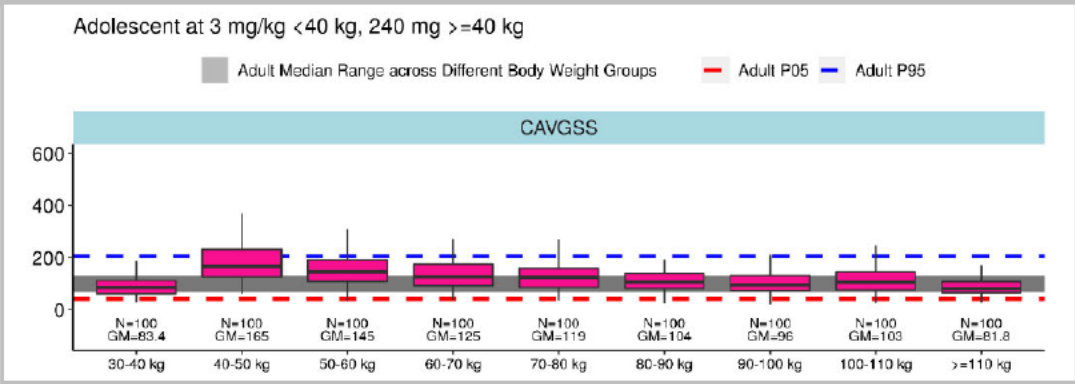
The adult dosing regimens are proposed for adolescent patients (12 years and older) in the following settings:

- Nivolumab monotherapy in pediatric patients weighing ≥40 kg with advanced melanoma or adjuvant treatment of melanoma.
- Nivolumab + ipilimumab combination therapy in pediatric patients with advanced melanoma across all body weight ranges.

For pediatric patients (12 years and older) who weigh < 40 kg receiving nivolumab monotherapy or monotherapy in the maintenance phase after nivolumab + ipilimumab combination therapy, body weight-based dosing is proposed. The Applicant supported the proposed recommended dosages in pediatric patients based on the following data:

1) PPK analysis for nivolumab monotherapy in pediatric patients with advanced melanoma

The PPK analysis results showed that nivolumab steady-state exposure for pediatric patients (12 years and older) weighing ≥ 40 kg receiving flat dosage of 240 mg Q2W for nivolumab was expected to be comparable to or exceed the adult exposure range, resulting in up to 25%, 26% and 32% higher Cavgss, Cminss, and Cmaxss, respectively (**Figure 1**). The upper range of the exposure difference is expected in only the lowest body weight band of 40 to 60 kg.



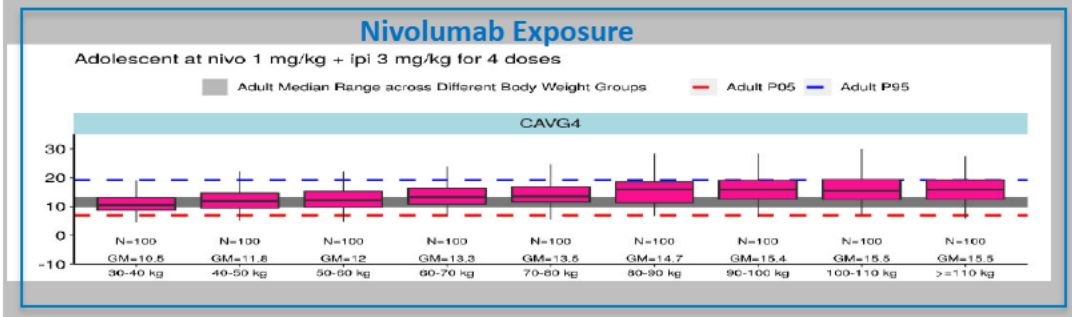
Source: Reproduced from the Summary of Clinical Pharmacology in Module 2.7.2 of Supplement 117

Figure 1. Predicted Nivolumab Exposure [Steady state Caverage (Cavg,ss)] in Pediatric Patients at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W Nivolumab Monotherapy

2) PPK analysis for nivolumab + ipilimumab combination therapy in pediatric patients

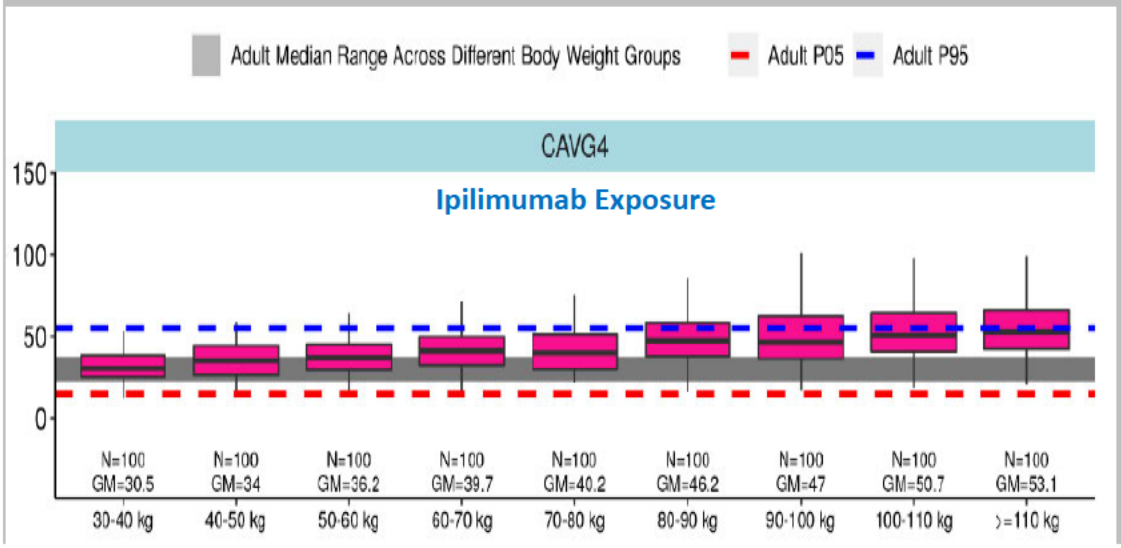
with advance melanoma

The predicted nivolumab and ipilimumab exposures after 4 dosages in pediatric patients (12 years and older) weighing ≥ 40 kg in advanced melanoma receiving nivolumab 1 mg/kg + ipilimumab 3 mg/kg were expected to be comparable to or exceed the adult exposure range (**Figure 2** and **Figure 3,** respectively). The upper range of the exposure difference is expected in higher body weight pediatric patients. This higher nivolumab or ipilimumab exposures at higher body weight band pediatric patients with nivolumab + ipilimumab combination therapy could be due to the drug-drug interaction between nivolumab and ipilimumab. The higher actual dose of nivolumab for pediatric patients with body weight ≥ 80 kg might have greater impact on the exposure of ipilimumab as compared to those for pediatric patients with body weight < 80 kg; and vice versa for the nivolumab exposure with the higher actual dose of ipilimumab with weight-based dosage of 3 mg/kg Q3W.



Source: Reproduced from the Summary of Clinical Pharmacology in Module 2.7.2 of Supplement 117

Figure 2. Predicted Nivolumab Exposure [Fourth-dose Cavg (Cavg4)] in Pediatric Patients with Nivolumab + Ipilimumab Combination Therapy following Fourth Dose of Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W for 4 doses

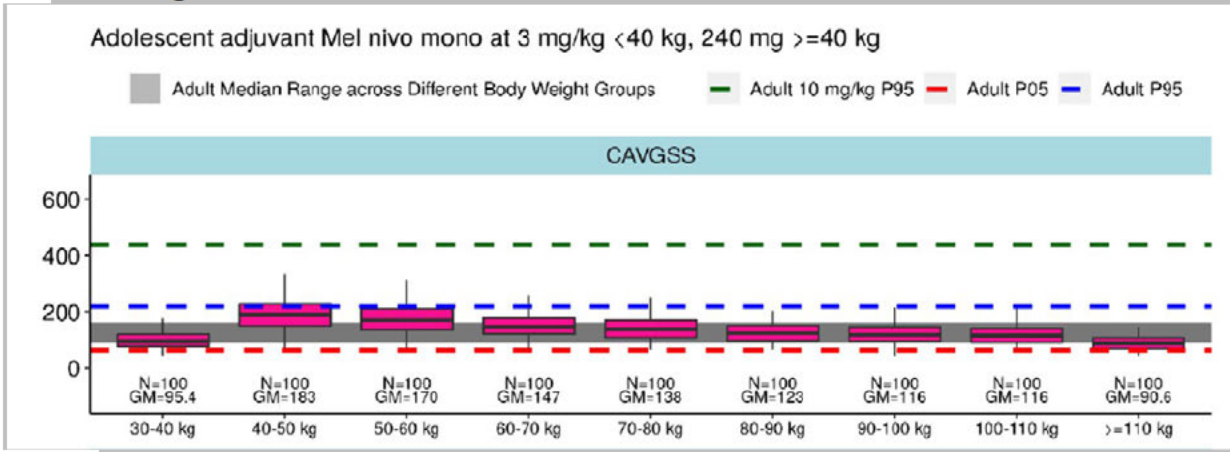


Source: Reproduced from the Summary of Clinical Pharmacology in Module 2.7.2 of Supplement 117

Figure 3. Predicted Ipilimumab Exposure (Cavg4) in Pediatric Patients with Nivolumab + Ipilimumab Combination Therapy following Fourth Dose of Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W for 4 doses

3) PPK analysis for nivolumab monotherapy in pediatric patients with adjuvant treatment of melanoma

The predicted nivolumab steady-state exposure for pediatric patients (12 years and older) weighing ≥ 40 kg in adjuvant treatment of melanoma receiving flat dosage of 240 mg Q2W was expected to be comparable to or exceed the adult exposure range (**Figure 4**). The upper range of the exposure difference is expected in pediatric patients with body weight band of 40 – 60 kg.



Source: Reproduced from the Summary of Clinical Pharmacology in Module 2.7.2 of Supplement 117

Figure 4. Predicted Nivolumab Exposure (Cavg,ss) for Pediatric Patients with Adjuvant Treatment of Melanoma at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W Nivolumab Monotherapy

The higher exposures of nivolumab and ipilimumab in pediatric patients (12 years and older) weighing ≥40 kg are not clinically relevant because:

i. The higher exposures of nivolumab in pediatric patients are still well below the exposures observed with the clinically tolerated dosage of nivolumab 10 mg/kg Q2W in adults.

ii. The E-R safety analysis for nivolumab and ipilimumab predicted numerically lower median Gr2+ IMAEs with overlapping 90% PIs for adolescents compared to adults when using the approved adult dosing regimens for nivolumab and ipilimumab.

These data support the Applicant's proposed flat adult dosages (nivolumab 240 mg Q2W or 480 mg Q4W) for nivolumab in pediatric patients (12 years and older) weighing ≥40 kg, and body weight-based dosing regimens (3 mg/kg Q2W or 6 mg/kg Q4W) for nivolumab and 1 mg/kg

Q2W for ipilimumab in pediatric patients weighing <40 kg.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Proposed Dosage and Administration

Recommended doses and schedules are presented in Table 3.

Confirmation of the selected Doses and Regimens

- **Clinical efficacy and safety results:** The recommended dosing regimens were supported by the nivolumab and ipilimumab PPK and E-R safety analyses to support the PK-based efficacy extrapolation from adult pivotal efficacy studies to adolescents in advanced melanoma and adjuvant treatment of melanoma.
- **PPK analysis:** The PK of nivolumab is adequately characterized by a 2 compartment, zero-order IV infusion PK model with time-varying CL for advanced melanoma and solid tumor, and with stationary CL for adjuvant treatment of melanoma. The PK of ipilimumab is also adequately characterized by a 2 compartment, zero-order IV infusion PK model with time-varying CL for advanced melanoma and solid tumors. Details of the PPK assessments to characterize adolescent PK for nivolumab and ipilimumab are provided in section 6.3 and the Appendix.
- **Exposure-Response safety analysis:**
  Dosing Recommendation for Advanced Melanoma Nivolumab Monotherapy
  Despite higher exposures predicted for adolescents versus adults when given the adult approved dosing regimens (exposures exceeding the adult range up to 25.0%, 26.0% and 31.6% higher Cavgss, Cminss, and Cmaxss, respectively for 240 mg Q2W and up to 32.8%, 31.4% and 41.2% higher Cavgss, Cminss, and Cmaxss, respectively for 480 mg Q4W), the pooled E-R safety analysis predicted lower median Gr2+ IMAEs with overlapping 90% PIs in adolescents versus adults when using the approved adult dosing regimens (Table 6 and Table 7). Body weight-based dosing for adolescent < 40 kg is recommended and avoids the potential for higher exposure in low body weight subjects using adult flat dosing.
  Dosing Recommendation for Advanced Melanoma Nivolumab in Combination with Ipilimumab
  Despite higher exposures predicted for adolescents versus adults when given the adult approved dosing regimens (exposures exceeding the adult range up to 15.7%, 19.3%, and 26.1% higher Cavg4, Cmin4, and Cmax4, respectively for nivolumab and up to 39%, 56%, and 35% higher Cavg4, Cmin4, and Cmax4, respectively for ipilimumab), the pooled E-R safety analysis predicted lower median Gr2+ IMAEs with overlapping 90% PIs in adolescent versus adult when using the approved adult dosing regimens (Table 11 and Table 12). Nivolumab maintenance dosing after the combination uses the same dosing recommendations for nivo mono.

Dosing Recommendation for Adjuvant Treatment of Melanoma Nivolumab monotherapy
Despite higher exposures predicted for adolescents versus adults when given the adult approved dosing regimens (up to 9.6%, 9.5% and 12.6% higher Cavgss, Cminss, and Cmaxss, respectively for 240 mg Q2W and up to 15.1%, 14.6% and 24.5%% higher Cavgss, Cminss, and Cmaxss, respectively for 480 mg Q4W), the pooled E-R safety analysis predicted lower median Gr2+ IMAEs with overlapping 90% PIs in adolescent versus adult when using the approved adult dosing regimens (Table 15 and Table 16). Body weight-based dosing for adolescent < 40 kg is recommended and avoids the potential for higher exposure in low body weight subjects using adult flat dosing.

The FDA's Assessment:
FDA agrees with the Applicant's position. FDA's assessment of the proposed recommended pediatric dosages has been summarized in section 6.1.1 above.

Despite the higher exposures predicted for pediatric patients (12 years and older) when given the adult approved dosing regimens for nivolumab monotherapy and nivolumab + ipilimumab in advanced melanoma or nivolumab monotherapy in the adjuvant treatment of melanoma, the E-R safety analysis predicted lower median Gr2+ IMAEs for nivolumab monotherapy or nivolumab + ipilimumab combination therapy in pediatric patients than that in adults. It should also be noted that the higher exposures for nivolumab and ipilimumab in pediatric patients are still well below the exposures observed with the clinically tolerated dosage of nivolumab 10 mg/kg Q2W and ipilimumab 10 mg/kg Q3W in adults.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:
For adolescent subjects who are ≥ 12 years old and weigh < 40 kg, body weight-based dosing (3 mg/kg Q2W or 6 mg/kg Q4W) is recommended for nivo mono in the advanced and adjuvant setting and for nivolumab maintenance dosing after the nivo + ipi combination in advanced melanoma.

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

In this submission, the Applicant proposed the adult approved flat dosages for use in pediatric patients (12 years and older)weighing ≥40 kg, and body weight-based dosing regimen (3 mg/kg Q2W or 6 mg/kg Q4W) for nivolumab in nivolumab monotherapy in pediatric patients with advanced melanoma and pediatric patients with adjuvant treatment of melanoma. The Applicant also proposed body weight-based dosing regimen of 1 mg/kg Q2W for ipilimumab in pediatric patients weighing <40 kg in nivolumab + ipilimumab combination therapy. This proposed therapeutic individualization for nivolumab and ipilimumab is supported by the Applicant's PPK analyses and E-R safety analyses for nivolumab and ipilimumab in nivolumab

monotherapy, or in combination with ipilimumab in pediatric patients with advanced melanoma, and for nivolumab in nivolumab monotherapy in pediatric patients with adjuvant treatment of melanoma. See section 6.1.1 for FDA's detailed justifications for acceptability of the proposed dosages for nivolumab and ipilimumab.

6.2.2.3. Outstanding Issues

The Applicant's Position:
Not applicable

The FDA's Assessment:
FDA agrees with the Applicant's position that there are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

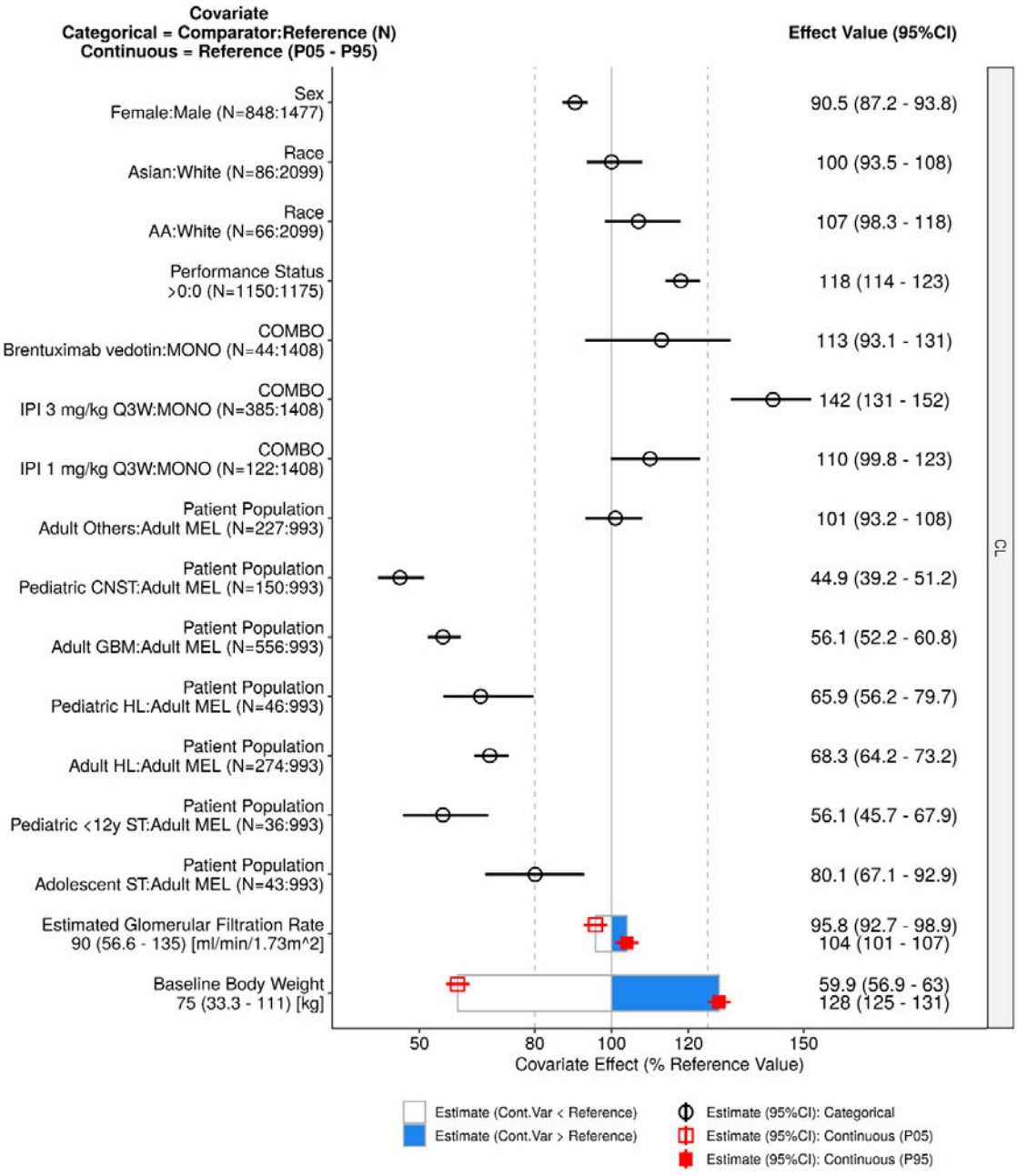
Data:

APPEARS THIS WAY ON ORIGINAL

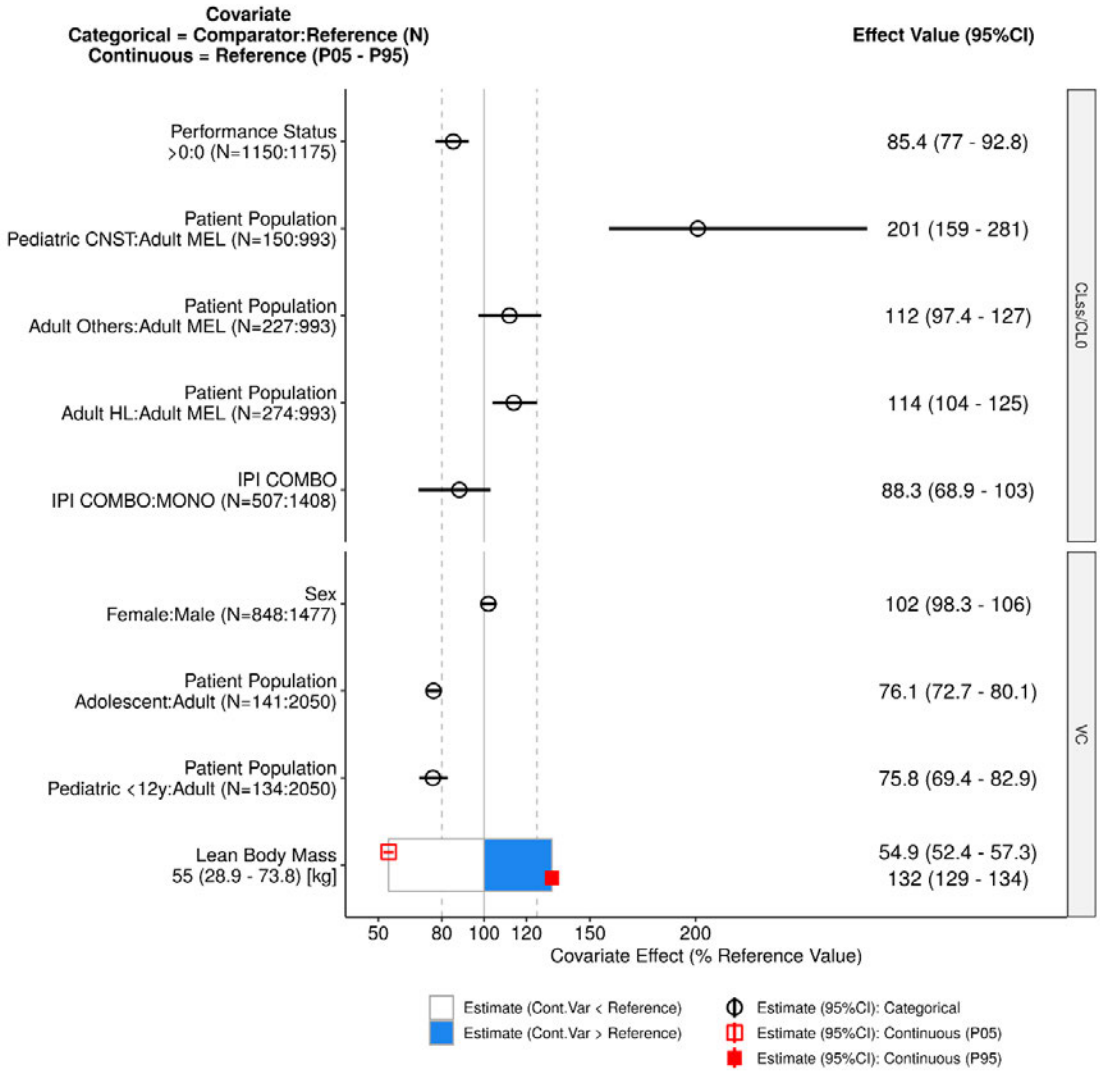
Nivolumab PPK Supporting Advanced Melanoma

Figure 1: Applicant - Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters

A) Covariate Effects on CL



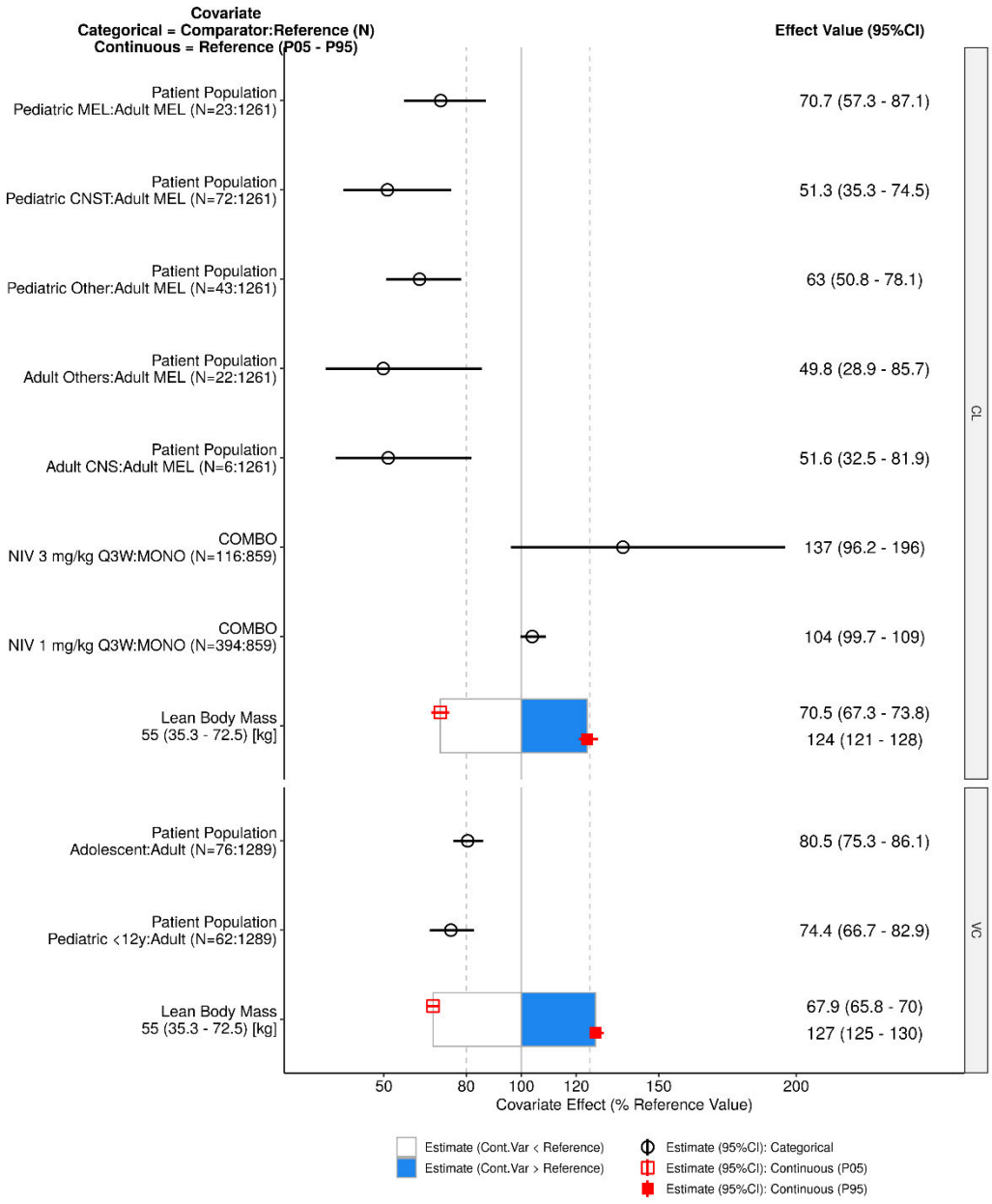
B) Covariate Effects on CL_{SS}/CL_0 and VC



Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd
Source: Analysis-Directory/R/plots/ggcoveff-full1c-cl.png, ggcoveff-full1c-emax-vc.png
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is a 60-year old male, white/other race, WTB = 75 kg, LBM = 55 kg, PS = 0, baseline eGFR = 90 mL/min/1.73 m^2, received nivo mono, and with MEL. Parameter estimate in a reference subject is considered as 100% (vertical solid line), and dashed vertical lines are at 80% and 125% of this value.
Note 4: Confidence Interval values are taken from bootstrap calculations (966 successful out of a total of 1,000).
Note 5: The effect of WTB and LBM was also added on Q and VP, respectively, and their estimates were fixed to be similar to that CL and VC, respectively.
Note 6: CLss/CL0 = e^{EMAX}

Ipilimumab PPK Supporting Advanced Melanoma

Figure 2: Applicant - Covariate Effects on Full Ipilimumab Pharmacokinetic Model Parameters



Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-ipi/final/
Program Source: Analysis-Directory/R/scripts/2-model-dev-ipi.Rmd
Source: Analysis-Directory/R/plots/ggcoveff-full1.png
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

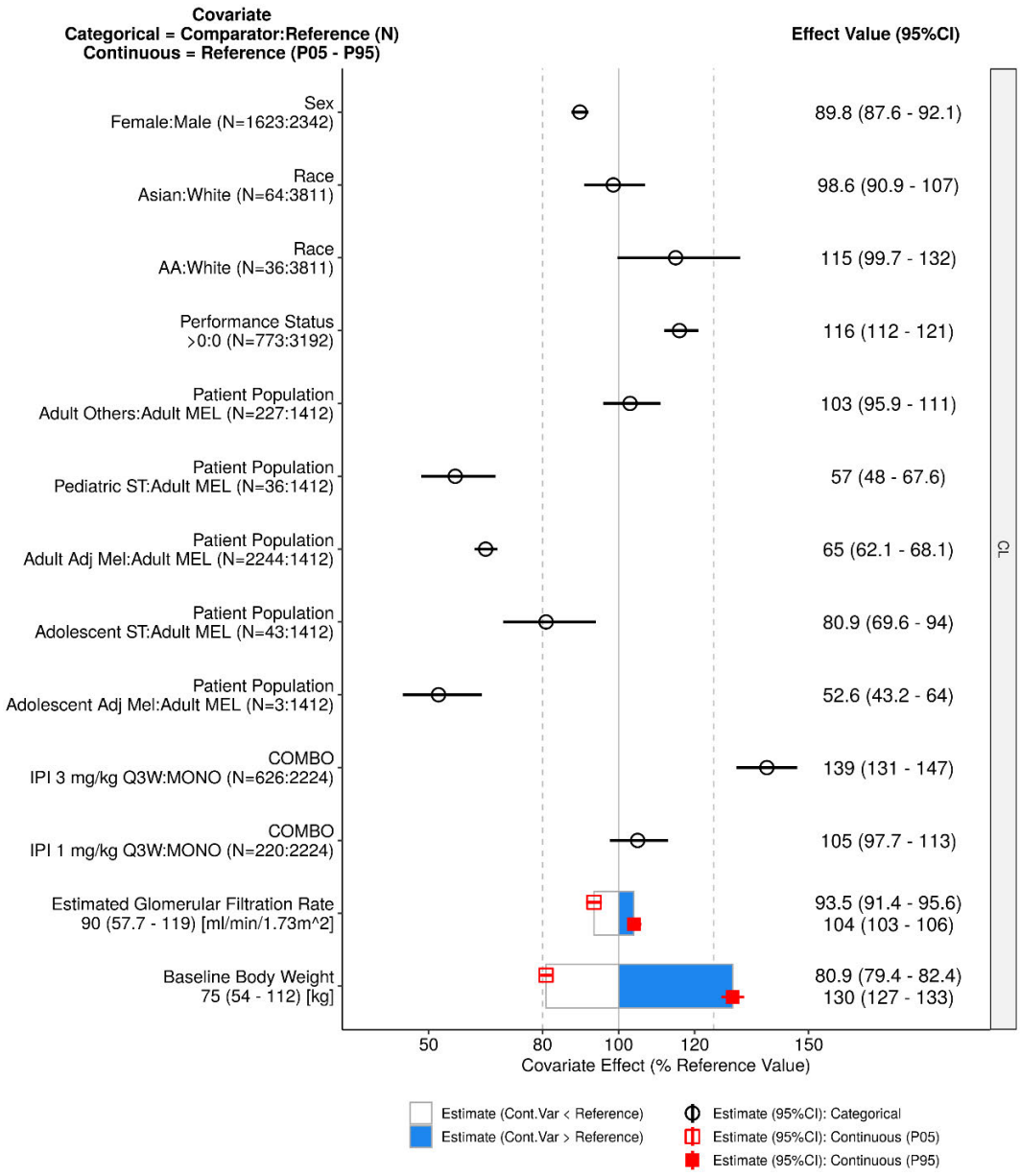
Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Note 3: Reference subject is a 60-year old male, LBM = 55 kg, ipil mono, and with MEL. Parameter estimate in a reference subject is considered as 100% (vertical solid line), and dashed vertical lines are at 80% and 125% of this value.
Note 4: Confidence Interval values are taken from bootstrap calculations (982successful out of a total of 1,000).
Note 5: The effect of LBM was also added on Q and VP, respectively, and their estimates were fixed to be similar to that CL and VC, respectively.

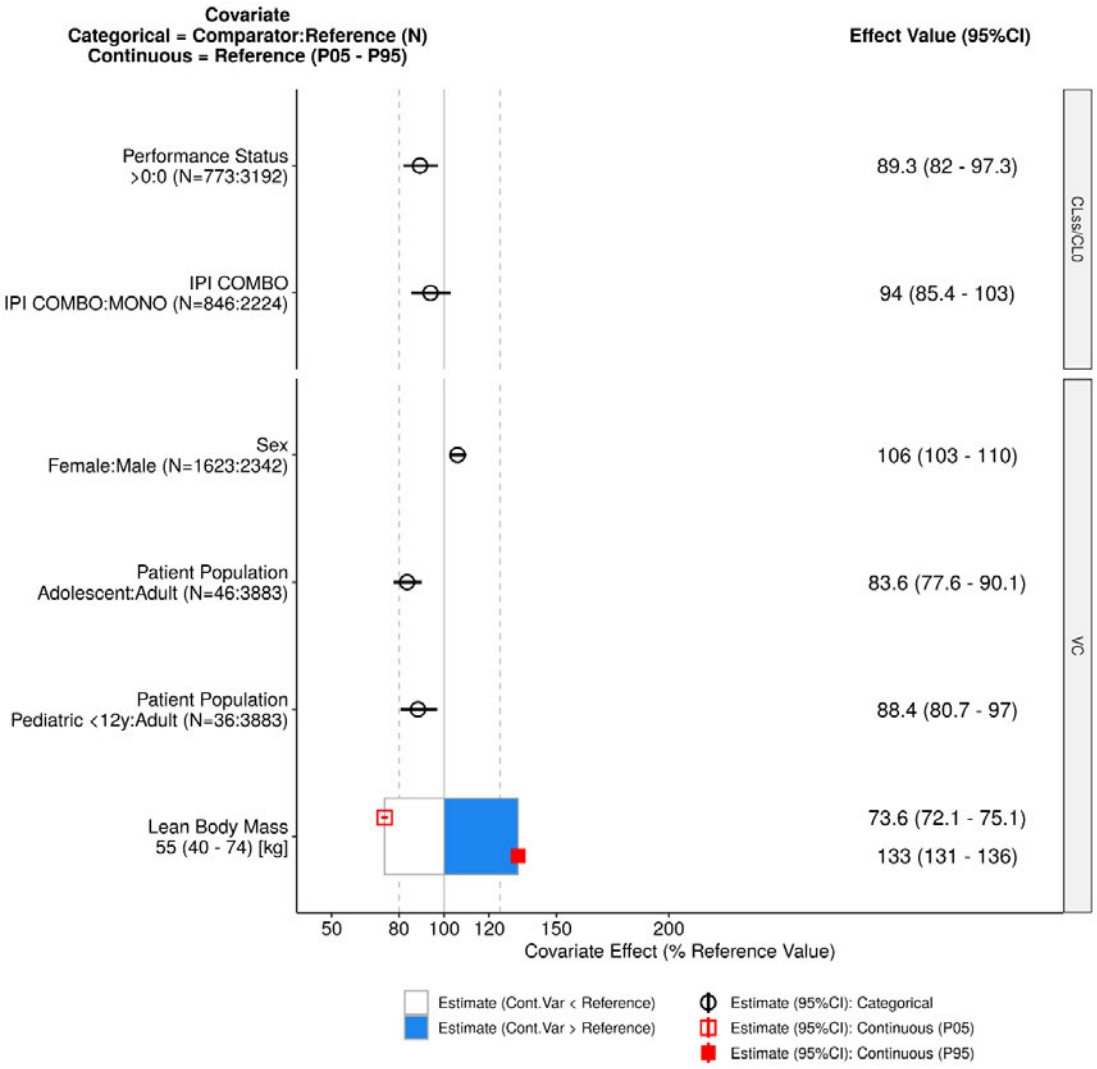
Nivolumab PPK Supporting Adjuvant Treatment of Melanoma

Figure 3: Applicant - Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters

A) Covariate Effects on CL



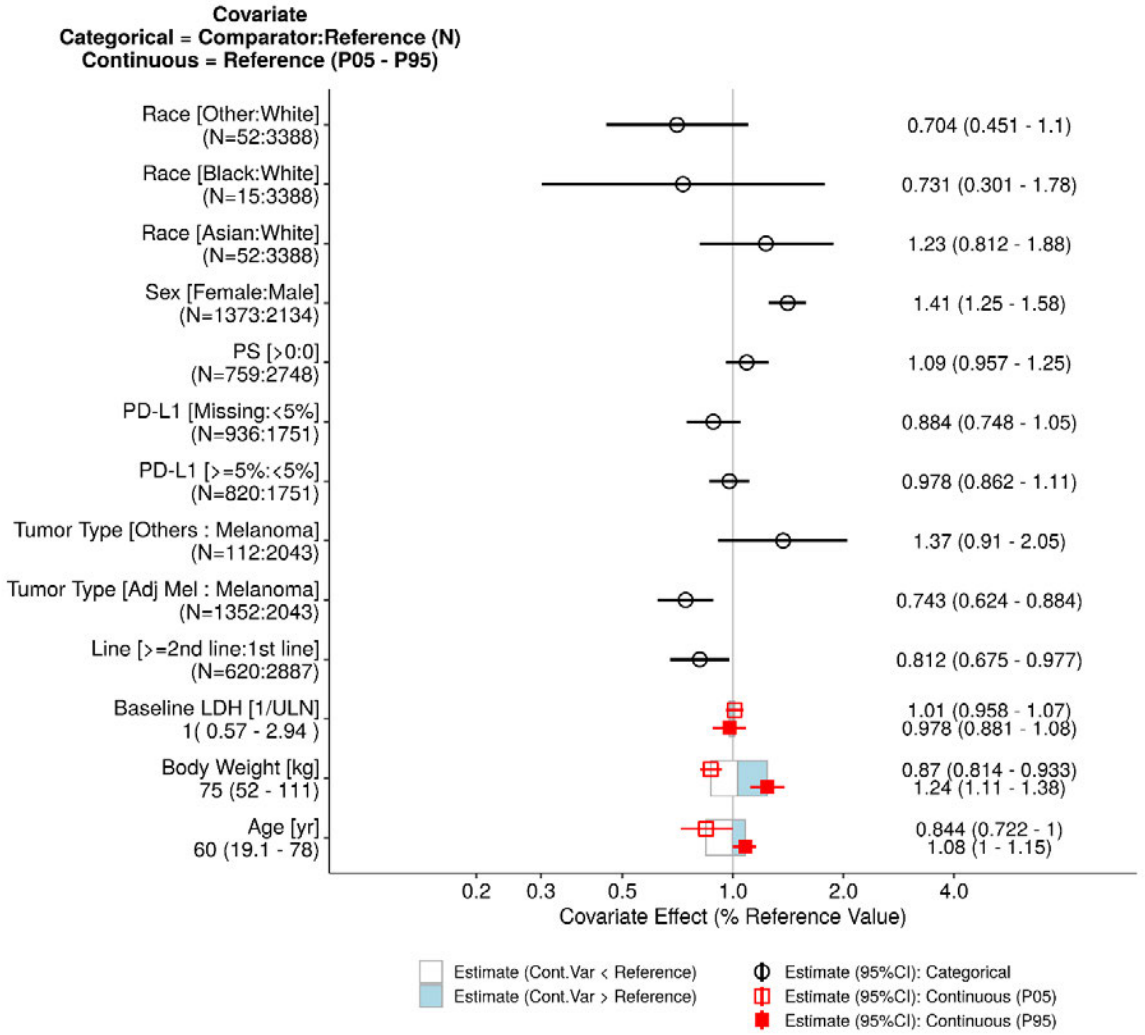
B) Covariate Effects on CL_{SS}/CL_0 and VC



Program Source: Analysis-Directory/R/scripts/ 2-model-dev.Rmd
Source: Analysis-Directory/R/plots/ggcoveff-full5-cl.png, ggcoveff-full5-emax-vc.png
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is a 60-year old male, white/other race, WTB = 75 kg, LBM = 55 kg, PS = 0, baseline eGFR = 90 mL/min/1.73 m^2, received nivo mono, and with melanoma. Parameter estimate in a reference subject is considered as 100% (vertical solid line), and dashed vertical lines are at 80% and 125% of this value.
Note 4: The effect of WTB and LBM was also added on Q and VP, respectively, and their estimates were fixed to be similar to that CL and VC, respectively.
Note 5: CLss/CL0 = eEMAX

Pooled E-R Safety Analysis Supporting Nivolumab Monotherapy in Adjuvant and Advanced Melanoma and Nivo + Ipi in Advanced Melanoma

Figure 4: Applicant - Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Full Model)



Note 1: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 2: Reference subject: male who had median value of LDH (normalized) = 1, body weight = 75 kg, age = 60 yr, performance score = 0, with 1st line advanced melanoma, tumor cell PD-L1 < 5%, and white.
Note 3: The dataset includes a much larger number of adult subjects compared to adolescent and young pediatric subjects. Therefore, the 5th to 95th percentile for age is from 19.1 to 78 years.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/2-model-tv-imae-dev-final.Rmd
Source: Analysis-Directory/R/scripts/2-model-tv-imae-dev-final.html

The Applicant's Position:

Adolescent PK was characterized using a population PK (PPK) approach for nivo mono and in combination with ipilimumab and for ipili mono and in combination with nivolumab to support the dosing recommendations for adolescents in advanced melanoma for nivo mono and in combination with ipilimumab, respectively and referred to as advanced PPK analyses (AdvPPK).[27] Adolescent PK was also characterized for nivo mono in the adjuvant setting to support the dosing recommmendation for adolescents treated in the adjuvant melanoma setting, referred to as adjuvant PPK analysis (AdjPPK).[35]

Advanced Melanoma PPK Analysis- Nivolumab (Covariate Effect Plot Figure 1)

Nivolumab PK data from Study CA209070 (young pediatric, adolescent, and young adult with multiple recurrent or refractory cancers) were pooled with data from 12 other studies in adult and pediatric subjects with advanced melanoma and other advanced solid tumors (including CNS tumors), and hematological malignancies treated with nivo mono or nivo+ipi combination therapy. The dataset was robust, with nivolumab PK data from 2325 subjects including 2050 adult subjects and 275 pediatric subjects (n=1 advanced melanoma pediatric subject). **Error! Bookmark not defined.** Pediatric PK characterization in the current analysis extended the previous pediatric PK analysis for the nivolumab+relatlimab FDC by i) including pediatric subjects across studies and indications, ii) investigating which body size parameters (lean body mass, body surface area and body weight) best characterized the pediatric effect on CL and VC, iii) evaluating numerical and categorical effects of age on CL and VC, and iv) evaluating PK differences across pediatric indications (model development details in PK report).[27]

The PK of nivolumab is adequately characterized by a 2-compartment, zero-order IV infusion PK model with time-varying CL for advanced melanoma and solid tumor, and with stationary CL for adjuvant treatment of melanoma.

Effects of covariates on nivolumab CL:

- Adult adjuvant treatment of melanoma (35% lower), adolescent adjuvant treatment of melanoma (47% lower), young pediatric subjects (1 to < 12 years) with advanced solid tumor (43% lower), adolescent subjects (≥ 12 to < 18 years) with advanced solid tumor (19% lower) have lower baseline CL than that of adult advanced melanoma subjects.
- Adolescent adjuvant treatment of melanoma subjects have lower CL (19% lower) compared with adult adjuvant treatment of melanoma.
- The effects of eGFR, PS, and sex on nivolumab baseline CL are statistically significant, however they are not considered clinically relevant (< 20%).
- Race (Asian vs White; African American vs White) does not have a significant effect on nivolumab CL.
- There is a covariate effect of baseline body weight on CL (19% lower CL at 5th percentile of body weight than median body weight).
- Coadministration with ipilimumab 3 mg/kg Q3W is associated with ~39% higher nivolumab CL than nivo mono. However, coadministration with ipilimumab 1 mg/kg Q3W has no

significant impact on nivolumab CL.

Effects of covariates on nivolumab VC:

- The young pediatric (1 to < 12 years) (12% lower) and adolescent (≥ 12 to < 18 years) subjects (16% lower) both have lower VC than adult subjects.
- There is a covariate effect of lean body mass on VC (26% lower VC at 5th percentile of lean body mass than median lean body mass). Sex has no effect on VC.

Advanced Melanoma PPK Analysis- Ipilimumab (Covariate Effect Plot Figure 2)

Ipilimumab PK data from Study CA209070 were pooled with data from 9 other studies with adult and pediatric subjects with advanced melanoma and other tumors treated with ipi mono or nivo+ipi combination therapy. The dataset was robust, with ipilimumab PK data from 1427 subjects including 1289 adult subjects and 138 pediatric subjects (n=3 pediatric advanced melanoma, and n=20 adolescent advanced melanoma).[27] Pediatric effects on CL and VC after accounting body weight were also observed for ipilimumab.

The conclusions from this analysis are summarized below. Consistent with previous analyses in adults, the PK of ipilimumab, alone and in combination with nivolumab, was characterized by a 2-compartment, zero-order IV infusion PK model first-order elimination.

Effects of covariates on ipilimumab CL:

- Pediatric subjects with melanoma (< 18 years) had 29% lower CL than adult melanoma subjects.
- Pediatric subjects with CNST (< 18 years) had 49% lower CL than adult melanoma, similarly, adults with CNST had 48% lower CL than adult melanoma.
- There was a covariate effect of LBM on CL (29% lower CL at 5th percentile of LBM than median LBM).
- Combination therapy with nivolumab, either as nivolumab 3 mg/kg or nivolumab 1 mg/kg, showed no significant impact on ipilimumab CL as 95% CI included 1.

Effects of covariates on ipilimumab VC:

- The adolescent (≥ 12 to < 18 years) and young pediatric subjects (< 12 years) had 19% and 26% lower VC than adult subjects, respectively.
- There was a covariate effect of LBM on VC (32% lower VC at 5th percentile of LBM than median LBM).

Adjuvant Melanoma PPK Analysis- Nivolumab (Covariate Effect Plot Figure 3)

Nivolumab PK data from Study CA209070 (young pediatric, adolescent, and young adult with recurrent or refractory cancer) were pooled with data from 10 other studies in adult and pediatric subjects with advanced melanoma, other advanced solid tumors, and adjuvant melanoma treated with nivo mono or nivo+ipi combination therapy. To note, subjects with hematological malignancies or CNS tumors were not included in the dataset to focus on the PK in solid tumors which are more similar to melanoma than other malignancies. In addition, study CA209238 (nivo mono) and CA209915 (nivo + ipi and nivo mono) were not included in the advanced melanoma PPK analysis described above, but were included in the adjuvant

treatment of melanoma PPK analysis as these 2 studies were in the adjuvant treatment of melanoma setting. The dataset was robust, with nivolumab PK data from 3965 subjects including 3883 adult subjects (n=2244 adult melanoma subjects treated in the adjuvant setting) and 82 pediatric and adolescent subjects (n= 3 adolescent melanoma subjects treated in the adjuvant setting).[35] Pediatric effects on CL and VC were also identified in the adjuvant treatment of melanoma.

The conclusions from this analysis are summarized below. Consistent with previous analyses in adults, the PK of nivolumab is adequately characterized by a 2-compartment, zero-order IV infusion PK model with time-varying CL for advanced melanoma and advanced solid tumor, and with stationary CL for adjuvant treatment of melanoma.

Effects of covariates on nivolumab CL:

- Adult adjuvant treatment of melanoma (35% lower), adolescent adjuvant treatment of melanoma (47% lower), young pediatric subjects (1 to < 12 years) with advanced solid tumor (43% lower), adolescent subjects (≥ 12 to < 18 years) with advanced solid tumor (19% lower) have lower baseline CL than adult advanced melanoma subjects.
- Adolescents undergoing adjuvant treatment of melanoma have lower CL (19% lower) compared with adult adjuvant treatment of melanoma.
- The effects of eGFR, PS, and sex on nivolumab baseline CL are statistically significant, however they are not considered clinically relevant (< 20%).
- Race (Asian vs White; African American vs White) does not have a significant effect on nivolumab CL.
- There is a covariate effect of baseline body weight on CL (19% lower CL at 5th percentile of body weight than median body weight).
- Coadministration with ipilimumab 3 mg/kg Q3W is associated with ~39% higher nivolumab CL than nivo mono. However, coadministration with ipilimumab 1 mg/kg Q3W has no significant impact on nivolumab CL.

Effects of covariates on nivolumab VC:

- The young pediatric (1 to < 12 years) (12% lower) and adolescent (≥ 12 to < 18 years) subjects (16% lower) both have lower VC than adult subjects.
- There is a covariate effect of lean body mass on VC (26% lower VC at 5th percentile of lean body mass than median lean body mass). Sex has no effect on VC.

E-R Safety Analysis- (Covariate Effect Plot Figure 4)

The E-R safety analysis was performed with data from 3507 subjects with advanced or adjuvant treatment of melanoma from 15 studies who were treated with nivolumab, ipilimumab, or nivo+ipi combination therapy. There were 42 young pediatric subjects (< 12 years) and 55 adolescent (≥ 12 to < 18 years) subjects included in the dataset.[36]

The conclusions from this analysis are summarized below:

The E-R model for Gr2+ IMAEs provides an adequate description of the cumulative probability of the time to first occurrence of a Gr2+ IMAE in adult and adolescent subjects with adjuvant treatment of melanoma or advanced melanoma.

The risk of Gr2+ IMAEs is significantly associated with ipilimumab exposure and interaction between nivolumab and ipilimumab exposure. In addition, the combination therapy leads to a higher baseline probability of Gr2+ IMAEs, resulting in a higher risk in combination therapy compared to either monotherapy.

The magnitude of the impact of ipilimumab exposure-response and interaction of ipilimumab and nivolumab exposure on the risk of Gr2+ IMAEs for the nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W combination is predicted to be minimal; The range of predicted probabilities of Gr2+ IMAEs is narrow at Week 12 with a median (P05, P95) of 0.526 (0.490, 0.558) across the range of nivolumab and ipilimumab daily Cavgs for this N1I3 combination regimen.

Effect of other covariates:

- The risk of Gr2+ IMAEs is significantly associated with the following baseline covariates:
    - Sex: females have 41% higher risk than males
    - Tumor setting: advanced melanoma has 26% higher risk than adjuvant treatment of melanoma
    - Line of therapy: first line therapy has 19% higher risk than previously treated
    - Higher BW increases risk (hazard ratio 0.87 for 5th percentile BW vs median BW or 1.24 for 95th percentile BW vs median BW)
    - Older age increases risk (hazard ratio 0.844 for 5th percentile age vs median age or 1.08 for 95th percentile age vs median age)
- Risk of time to first Gr2+ IMAE is independent of race, baseline LDH, PD-L1, and PS

The FDA's Assessment:
FDA agrees with the Applicant's PK characterization of nivolumab as a single agent and in combination with ipilimumab for the treatment of advanced melanoma and of nivolumab single agent forthe adjuvant treatment of melanoma based on the PPK and E-R safety analyses, as well as the Applicant's PK characterization of ipilimumab in nivolumab + ipilimumab combination therapy in advanced melanoma.

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 nivolumab and ipilimumab clinical pharmacology profile (based on PPK and E-R safety analysis) in conjunction with the understanding of similarity of disease, support the proposed dosing recommendations for nivo mono or nivo + ipi combination therapy for adolescent patients

with advanced melanoma, or nivo mono for adolescent patients for the adjuvant treatment of melanoma.

The FDA's Assessment:
FDA agrees with the Applicant's position. Based on PPK and E-R safety analyses, the Clinical Pharmacology program identified that:

- Nivolumab and ipilimumab exposures in pediatric patients are within range of those in adults;
- Any differences in CL are not considered to be clinically relevant based on comparable and relatively flat E-R relationships for safety in advanced melanoma and adjuvant treatment of melanoma;
- The probability of Gr2+ IMAEs in pediatric patients (12 years and older) is expected to be similar to or lower than that in adults

Therefore, the Clinical Pharmacology program agreed with the Applicant's proposed recommended dosages of nivolumab and ipilimumab for the pediatric patients with advanced melanoma and pediatric patients with completely resected melanoma in the adjuvant setting.

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, for adolescent patients ≥ 40 kg, the dosing recommendations for advanced melanoma for nivo mono and nivo + ipi or for adjuvant treatment of melanoma for nivo mono are identical to those recommended for adult patients for the same indication. For adolescent patients < 40 kg, a body weight-based approach is recommended for nivolumab to replace the flat dosing regimen (ie, 3 mg/kg to replace 240 mg Q2W, and 6 mg/kg to replace 480 mg Q4W) for nivo mono or during the nivolumab maintenance phase after nivo+ipi combination therapy. This combination dose regimen was selected based on the totality of clinical data from the nivolumab program as well as the pharmacometric results (PPK and E-R) described above.

The FDA's Assessment:
FDA agrees with the Applicant's position. The appropriateness of the proposed dosages for nivolumab and ipilimumab is supported by available PK data in pediatric patients and the PPK and E-R analyses in in addition to the following:

- The higher predicted exposures of nivolumab and ipilimumab in pediatric patients (12 years and older) are still below the exposure with the clinically tolerated dosage for nivolumab and ipilimumab.
- Lower predicted Gr2+ IMAEs with the proposed dosages for nivolumab and ipilimumab in pediatric patients (12 years and older) than adults based on E-R safety analysis support the proposed body weight-based dosing regimens for both nivolumab and ipilimumab for

pediatric patients weighing < 40 kg.
- Approved flat adult dosages for pediatric patients with body weight ≥ 40 kg.

Refer to Section 6.1.1. for more 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:
Yes. For adolescents ≥ 12 years old and weighing < 40 kg, body weight based dosing (3 mg/kg Q2W or 6 mg/kg Q4W) is recommended for nivo mono and for nivolumab maintenance dosing after the combination as described in Section 6.2.2.2.
Age and race were evaluated as covariates in both PPK and exposure-response safety analyses. (See Section 6.3.1 for interpretation of covariate effects, and Sections 19.4.1 and 19.4.2 for detailed distributions in the analysis datasets).

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

The Applicant's PPK analyses were conducted in patients with age range 1 to <12 years, 12 to <18 years and 18 to ≤30 years. Pediatric patients (12 years and older) with advanced solid tumors have lower CL and VC for both nivolumab and ipilimumab than adults with melanoma after accounting for the effect of body weight. This higher nivolumab exposure in pediatric patients (12 years and older) is expected only in the lowest body weight band (40-60 kg) and supports a body weight-based dosing regimens for pediatric patients weighing < 40 kg. The higher nivolumab or ipilimumab exposures at higher body weight band (weighing >80 kg) for pediatric patients (12 years and older) treated with nivolumab + ipilimumab combination therapy could be due to the drug-drug interactions between nivolumab and ipilimumab. Refer to Section 6.1.1. for more details.

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:
No. There are no clinical studies evaluating food-drug interactions, as nivolumab is an IgG4 kappa immunoglobin. There are no drug-drug interactions with nivo mono and nivo + ipi, via PPK evaluation.

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

X X

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Division of Cancer Pharmacology II

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Clinical Pharmacology Team Leader
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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 17: Applicant - Table of Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route for this application	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
Pivotal Clinical Study								
CA209070/ ADVL1412 Phase 1/2, Ongoing	NCT02304458	5-part dose-escalation/expansion study: Part A: estimation of nivo RP2D Part B: activity of nivo in expanded cohorts with different tumor types Part C: estimation of nivo + ipi RP2D Part D: activity of nivo + ipi in expanded cohorts with different tumor types Part E: alternative dosing of nivo + ipi in rhabdomyosarcoma or Ewing	Parts A, B: nivo 3 mg/kg IV Days 1,15 Q4W Parts C, D: nivo IV + ipi IV Day 1 Q3W C1-4 (induction), then nivo IV Days 1,15 Q4W (maintenance) (Part C DL1: nivo 1 mg/kg + ipi 1 mg/kg); (Part C DL2 and Part D: nivo 3 mg/kg + ipi 1 mg/kg) Part E: nivo 1 mg/kg + ipi 3 mg/kg	Primary: safety, antitumor effects (ORR, TTR, DOR, OS), PK, immunogenicity Secondary: vaccinated antibodies, PD-L1 status	Nivolumab (Parts A-B): The mimimum follow-up (time from LPFV date to data cutoff date) was > 24.0 months (except for Part B6). Nivo + Ipi (Parts C-D): The mimimum follow-up was 28.3 months.	N = 126 treated (Parts A-D); 8 treated Part E (In total: 100 subjects < 18 yrs and 34 subjects 18-30 yrs) **1 adolescent with advanced melanoma (nivo monotherapy) enrolled and was treated**	Pediatric and young adult subjects with solid tumors (melanoma, neuroblastoma, Ewing sarcoma/ peripheral PNET, osteosarcoma, rhabdomyosarcoma, solid tumor NOS), lymphoma (HL, non HL)	Nivolumab treatment group, 23 sites in the United States (US) Nivo + ipi treatment group 1 site in Canada and 19 sites in the US

Table 17: Applicant - Table of Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route for this application	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
		sarcoma/peripheral PNET						
Trial Identity	**NCT no.**	**Trial Design**	**Regimen/ schedule/ route for this application**	**Study Endpoints**	**Treatment Duration/ Follow Up**	**No. of patients enrolled**	**Study Population**	**No. of Centers/ Countries**
Supportive Clinical Studies								
CA209067/Phase 3 /Ongoing	NCT01844505	Multicenter, double-blind trial in patients randomized (1:1:1) to one of the following arms: nivo + ipi, nivolumab, or ipilimumab	Nivo group: nivo 3 mg/kg IV Q2W Nivo + ipi group: nivo 1 mg/kg + ipi 3 mg/kg Q3W x 4 doses followed by nivo 3 mg/kg Q2W Ipi group: ipi 3 mg/kg Q3W x 4 doses	Primary: PFS, OS (nivo vs ipi and nivo + ipi vs ipi) Secondary: ORR, PD-L1 expression as predictive biomarker, HRQoL, and PFS, OS and ORR (nivo + ipi vs nivo)	Final CSR (DBL: 13-Sep-2016): Minimum f/u = 28 months Addendum 02 CSR (DBL: 10-May-2018): Minimum f/u = 48 months Addendum 03 CSR (DBL: 02-Jul-2019): Minimum f/u = 60 months	N = 945 randomized Nivo group: 316 Nivo+ipi group: 314 Ipi group: 315	Adult subjects with previously untreated, unresectable or metastatic melanoma **No subjects < 18 years were enrolled**	137 sites in 21 countries (45 sites in the US)
CA209915/Phase 3 /Complete	NCT03068455	Randomized, double-blind study of nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (hereafter nivo + ipi) versus nivo mono 480 mg every 4 weeks	**Adults:** Nivo + ipi group: nivo 240 mg Q2W and ipi 1 mg/kg Q6W Nivo group: 480 mg Q4W **Adolescents (≥ 12 to < 18 yrs):** Nivo + ipi group: 3 mg/kg Q2W up to a	Primary: RFS in patients with tumor PD-L1 expression <1% and in the ITT population Secondary: Association between tumor PD-L1 expression and	Clinical database on 25-Oct-2019 RFS in subjects with tumor PD-L1 expression level of < 1% had minimum follow-up time for this analysis approximately	N = 1943 randomized Nivo + ipi group: 920 Nivo group: 924 Ipi group: 99 **3 adolescents (2 nivo and 1 nivo + ipi)**	Adult and adolescent (≥ 12 yrs) subjects with completely resected Stage IIIb/c/d or Stage IV NED melanoma	122 sites in 19 countries (34 sites in the US)

Table 17: Applicant - Table of Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route for this application	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
			max of 240 mg and ipi 1 mg/kg Q6W Nivo group: 6 mg/kg Q4W up to a max of 480 mg	RFS, PFS on next-line systemic therapy, time to next treatment, time to second next treatment, time from next treatment to second next treatment	14 months. Clinical database on 08-Sep-2020 for RFS in all randomized subjects had minimum follow-up time for this analysis approximately 24 months	**enrolled and were treated**		
CA209238/Phase 3 /Ongoing	NCT02388906	Randomized (1:1), double-blind study of nivolumab vs ipilimumab	Nivo group: nivo 3 mg/kg IV Q2W Ipi group: ipi 10 mg/kg IV Q3W x 4 doses then Q12W starting at Week 24	Primary: RFS Secondary: OS, safety, PD-L1 expression as predictive biomarker, HRQoL	12-Jun-2017 interim CSR DBL included primary and secondary efficacy objectives results (except for OS) with a minimum of 18-month follow-up	N = 906 randomized Nivo group: 453 Ipi group: 453	Adult and adolescent (≥ 15 yrs) subjects with completely resected Stage IIIb/c or Stage IV NED melanoma **No subjects < 18 years were enrolled**	130 sites in 25 countries (35 sites in the US)

Source: Table 1.3.3-1 in the Clinical Overview (Module 2.5), [39] and Appendix 1.5 in the CA209070[26], CA209067[40], CA209915[41], and CA209238[42] CSRs

The Applicant's Position:

Data from the pivotal CA209070 study conducted in pediatric and young adult subjects with solid tumors or lymphomas are presented to support the use of nivolumab alone or in combination with ipilimumab in pediatric patients. The application is further supported by Study CA209067 conducted in adult subjects with unresectable or metastatic melanoma, Study CA209915 in adolescent (≥ 12 years) and adult subjects with completely resected Stage IIIb/c/d or Stage IV melanoma, and Study CA209238 in adult subjects with completely resected Stage IIIb/c or Stage IV melanoma (Table 17).

Limited clinical data are available in adolescent melanoma subjects, ie, 1 adolescent subject with advanced melanoma treated with nivolumab in Study CA209070 and 3 adolescent subjects (2 subjects who received nivo mono and 1 subject who received nivo+ipi) in CA209915.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the studies submitted to support the use of nivolumab as a single agent or in combination with ipilimumab, and ipilimumab in combination with nivolumab in pediatric patients 12 years and older with melanoma.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

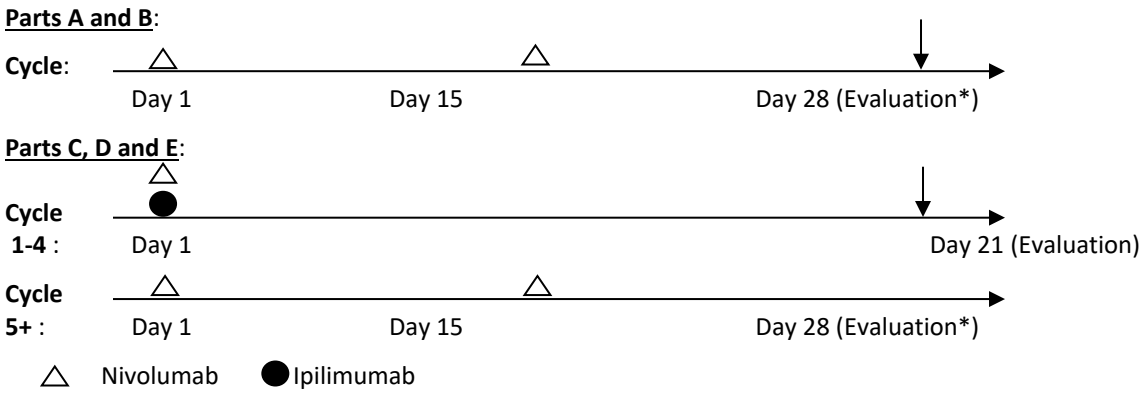
8.1.1. CA209070

Trial Design

The CA209070 Interim CSR reports results from Parts A-D only. Unless otherwise stated, CA209070 efficacy and safety results reported in this Assessment Aid reflect Parts A-D (results for the now closed Part E are described in a COG Progress Report [13-Jul-2020][43] and are briefly summarized in Section 8.1.1.1 and Section 8.2.5.

Trial Design

Figure 5: Applicant - Study Design



Therapy was to be discontinued if there was evidence of progressive disease or drug related dose-limiting toxicity that required removal from therapy. Cycle length for Parts A and B was 28 days. Cycle length for Parts C, D, and E in cycle 1-4 (combination therapy) was 21 days, and 28 days for subsequent cycles (nivolumab alone).

The Applicant's Description:

The pivotal CA209070 study (sponsor's protocol number ADVL1412) is a multicenter, open-label, single-arm, dose-confirmation and dose-expansion, Phase 1/2 study of nivolumab as a single agent and in combination with ipilimumab in pediatric subjects (12 months to < 18 years old) and young adults (≥ 18 years to ≤ 30 years old) with R/R solid and lymphoma tumors. Study CA209070 was sponsored by the NCI/CTEP and was designed and conducted by the Children's Oncology Group (COG) in the US and Canada.

CA209070 consisted of 5 parts:

- **Part A** was to define the RP2D, which is a tolerable dose of nivolumab that provides systemic exposure similar to that achieved by the RP2D in adults. Part A enrolled at least 6 evaluable children with measurable or evaluable recurrent or refractory solid tumors, excluding brain tumors.
- **Part B** was to evaluate the activity of nivolumab at its RP2D in expanded cohorts for patients with measurable disease for neuroblastoma (Part B1), osteosarcoma (Part B2), rhabdomyosarcoma (Part B3), Ewing sarcoma (Part B4), HL(Part B5), NHL(Part B6), measurable or evaluable disease for melanoma (Part B7), and MIBG evaluable disease without measurable disease in patients with neuroblastoma (Part B8). The primary objective of Part B was to identify histologic subtypes where there was a signal for anti-tumor activity, using a Simon's optimal two-stage design, with the exception of Part B7, which was a non-statistical access cohort for the rare diagnosis of melanoma, and remained open to enrollment until Parts B1-B6, B8 were completed.
- **Part C** enrolled all histologies with the same eligibility criteria as Part A with the goal of identifying the RP2D of the combination of nivo + ipi using a rolling 6 design. Patients were monitored for response and toxicity using standard criteria.
- **Part D** was to evaluate the dose of nivolumab in combination with ipilimumab determined in Part C in selected disease cohorts (neuroblastoma, rhabdomyosarcoma, NHL, osteosarcoma, or Ewing sarcoma) using a Simon's optimal two-stage design only if there is insufficient activity in the initial stage of the Simon's optimal two-stage design in Part B.
- **Part E** was to evaluate alternative dosing, which is nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) in rhabdomyosarcoma (Part E3) or Ewing sarcoma/Peripheral PNET (Part E4).

The study was initially planned with 3 parts (Part A, Part B, and Part C), and per Amendments 4 and 8B, Parts D and E were added later. Part E was outside the scope of the nivolumab PWR. Study subjects were required to have adequate organ function (including neutrophils ≥ 750/mm^3, transfusion independent platelet count for 7 days ≥ 75,000/mm^3, bilirubin ≤ 1.5 x ULN for age, AST ≤ 135 U/L, lipase ≤ ULN, no evidence of dypnea at rest and pulse oximetry > 92% on room air), recovered from the acute toxic effects of prior anticancer therapies, and adequate performace status (Karnofsky ≥ 50% for subjects > 16 years of age or Lansky ≥ 60 for

subjects ≤ 16 years of age). Subjects with known CNS metastases or CNS tumors, those requiring daily systemic corticosteroids or those who had received systemic corticosteroids within 7 days prior to enrollment were ineligible.

Study treatments were administered IV as follows:

- **Part A**: nivolumab 3 mg/kg Q2W (DL1) that can be de-escalated to 1 mg/kg if not tolerated. DLTs are defined in Section 5.4 of the study protocol (CA209070 Clinical Study Report, Appendix 1.1). The single-agent RP2D of Part A was determined to be 3 mg/kg nivolumab.[44]
- **Part B**: nivolumab 3 mg/kg Q2W.
- **Part C**: nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W for cycles 1 to 4 followed by nivolumab 3 mg/kg Q2W for cycles 5 and more (5+) until progression or unacceptable toxicity at DL1, and nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for cycles 1 to 4 followed by nivolumab 3 mg/kg Q2W for cycles 5+ until progression or unacceptable toxicity at DL2. The RP2D of nivolumab in combination with ipilimumab from Part C was determined to be 3 mg/kg nivolumab and 1 mg/kg ipilimumab.
- **Part D**: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for cycles 1 to 4 followed by nivolumab 3 mg/kg Q2W for cycles 5+ until progression or unacceptable toxicity.
- **Part E**: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for Cycles 1 to 4 followed by nivolumab 3 mg/kg for Cycles 5+ until progression or unacceptable toxicity.

Once the MTD or RP2D had been defined in Part A, Parts B and C were to open concurrently. In the event a cohort in a given disease group in Part B was completed after Stage 1, a corresponding cohort in the same disease group was to open for select disease types in Part D at the RP2D determined in Part C. A safety monitoring rule was stated for Part E: if at least one Cycle 1 DLT occurred among the first 10 subjects or 4 subjects with DLT among 20, then the study was to be closed and concluded that Part E dose was too toxic.

Study therapy was discontinued if there was evidence of progressive disease, withdrawal of consent, or drug-related DLT that required removal from therapy.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study design.

Eligibility Criteria

The Applicant's Description:
See Table 17 and Section 8.1.1 for eligibility requirements related to study population criteria, tumor types, and age for Parts A-D.
Pregnant or breast-feeding women were not eligible due to risks of fetal and teratogenic AEs, as there is yet no available information regarding human fetal or teratogenic toxicities. Patients requiring daily systemic corticosteroids were not eligible. Patients must not have received systemic corticosteroids within 7 days prior to enrollment. If used to modify immune adverse

events related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid. Patients who were currently receiving another investigational drug were not eligible. Patients with CNS tumors or known CNS metastases were excluded due to concerns regarding pseudo-progression in the CNS. Patients with a history of CNS metastases that were previously treated were eligible if sequential imaging showed no evidence of active disease. Patients with extra axial disease [e.g. skull (bone) metastasis that did not invade the dura] were eligible if there was no evidence for CNS edema associated with the lesion. Patients who had received prior anti-PD1 directed therapy (monoclonal antibody [mAb] or small molecule) were not eligible. For Parts C and D, patients who had received prior ipilimumab were not eligible.

The FDA's Assessment:

FDA agrees with the Applican't summary of key eligibility criteria.

Study Endpoints

The Applicant's Description:

Key endpoints for CA209070 are listed in Table 18.

Table 18: Applicant - Study CA209070 Objectives and Endpoints

Objective	Endpoint	Endpoint Description
Primary Objectives		
Determine the tolerability, and define and describe the toxicities of nivolumab administered as a single agent in children with R/R solid tumors at the adult recommended dose of 3 mg/kg.	Overall safety and tolerability	The assessment of safety was based on the incidence of AEs, SAEs, AEs leading to discontinuation, select AEs, OESIs, and deaths. The use of immune modulating concomitant medication were also summarized. In addition, clinical laboratory tests, and immunogenicity were analyzed.
Determine the MTD and/or RP2D and define and describe the toxicities of nivo + ipi administered to children with R/R solid tumors.	Determine RP2D and MTD	RP2D or MTD was assessed based on DLT. The number of subjects with DLTs were tabulated once specifically for DLT assessment for Parts A and C (separately). The DLT evaluation period consisted of the first dose of study drug through the first 28 days for Part A and 21 days for Part C of treatment. DLT definitions were provided in Section 3.4.5.1 of the protocol.
Assess antitumor effects of nivolumab across selected childhood solid tumors in 7 expansion cohorts (Parts B1-B6, B8); neuroblastoma (2 cohorts: measurable disease; MIBG positive only non-measurable disease), osteosarcoma, RMS, Ewing sarcoma, HL, and NHL. A non-statistical access cohort for the	ORR, TTR, DOR, and OS	**Objective Response Rate (ORR)** was defined as the number of responders divided by the sum of the number of responders and non-responders, multiplied by 100. Eligible patients who received at least 1 dose of protocol therapy were considered evaluable for response. Evaluable patients who demonstrated a CR or PR confirmed by central review before receiving non-protocol anticancer therapy were considered a responder. All other evaluable patients were considered non-responders. Each patient was classified according to their "best response" for the purposes of analysis of treatment effect.

Objective	Endpoint	Endpoint Description
rare diagnosis of melanoma (Part B7) remained open to enrollment until Parts B1-B6, B8 are complete B7 to preliminarily define the antitumor effects of nivolumab within the confines of a Phase 1/2 study. Assess antitumor effects of nivolumab in combination with ipilimumab across selected childhood solid tumors in two dose combinations (Part D).		**Time to Response (TTR)** was defined as the time from the date of first dose of study medication to the first response date (CR or PR, whichever occurred first), as assessed by the investigator and confirmed by Central Review. TTR was evaluated for responders only. Note that when confirmation was required, it was the time from the first study dose date to the date the response was first observed (the initial response date). **Duration of Response (DOR)** was defined as the time between the first response date (CR or PR whichever is recorded first), as determined by the investigator and confirmed by Central Review, to the date of the first documented tumor progression or death due to any cause, whichever occurred first. Subjects who died without a reported prior progression were considered to have progressed on the date of their death. For subjects who neither progressed nor died, DOR was censored on the date of their last evaluable tumor assessment. DOR was evaluated for responders only. When confirmation of response was required, the first date when initial response was observed was used. **Overall survival (OS)** was defined as the time from the date of first dose of study medication to the date of death from any cause. For subjects that were alive, their survival time was censored at the date of last contact date (or "last known alive date").
Characterize the PK of nivolumab alone and in combination with ipilimumab, including AUC, Cmax, Cmin, using intensive sampling.[a]	PK	The following PK parameters of nivolumab alone and in combinations with ipilimumab was derived: **Cmax:** Maximum observed serum concentration **Tmax:** Time of maximum observed serum concentration **Ctau:** Serum concentration achieved at the end of dosing interval **Cmin:** Predose trough serum concentration **AUC(TAU):** AUC in one dosing interval **AUC(0-T):** AUC from time zero to the last time of the last quantifiable concentration
Assess immunogenicity of nivolumab alone and in combination with ipilimumab by measuring ADA levels.	Immuno-genicity	Immunogenicity interpretation was evaluated from the detection of nivolumab and ipilimumab ADA and characterization of neutralizing antibodies. A subject's immunogenicity status was assessed using the follow criteria to determine the incidence of ADA development: **Baseline ADA Positive**: A subject with baseline ADA-positive sample; **ADA Positive**: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (≥) than baseline positive titer) at any time after initiation of treatment; **Persistent Positive (PP)**: ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart; **Not PP-Last Sample Positive**: Not persistent but with ADA-positive sample at the last sampling timepoint; **Other Positive**: Not persistent but some ADA-positive samples with the last

Objective	Endpoint	Endpoint Description
		sample being negative; **Neutralizing Positive**: At least one ADA-positive sample with neutralizing antibodies detected post-baseline; **ADA Negative**: A subject with no ADA-positive sample after initiation of treatment.
Secondary Objectives		
Conduct exploratory studies of the phenotypic and functional effects of nivolumab (alone and in combination with ipilimumab), as well as changes in antibodies to previously vaccinated viruses, in serum samples.	Vaccinated antibodies	Exploratory analysis on effects of nivolumab (alone and in combination with ipilimumab) on changes in antibodies to previously vaccinated viruses were performed. Serum samples for these analyses were collected in accordance with Protocol Appendix IV (at baseline and prior to Cycle 2, Day 1 nivolumab infusion). Antibody titers for mumps, measles, rubella, and varicella was considered for this analysis.
Explore whether correlations exist between PD-L1 expression on tumor and antitumor effects of nivolumab (alone and in combination with ipilimumab) in pediatric solid tumors.	PD-L1 status	PD-L1 expression was defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry assay. This was referred to as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it is further classified as: Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor tissue sample and not because of improper sample preparation or handling. Not evaluable: Tumor tissue sample was not optimally collected or prepared and PD-L1 expression was neither quantifiable nor indeterminate. Not evaluable could be determined from H&E process before the tumor biopsy specimen was sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation. Subjects with missing PD-L1 expression were subjects with no tumor tissue sample available for evaluation.

a All available PK concentration data from Parts A, B, C, and D were reported. PK parameters (Cmax, AUC, Cmin) were only reported for nivolumab for subjects in Parts A and B when intensive PK samples were collected with evaluable concentrations. Cmax and AUC were not reported for nivolumab or ipilimumab when administered in combination as intensive PK samples were not collected in Parts C and D, only Cmin was reported.
Abbreviations: ADA = antidrug antibody, AE = adverse event, BOR = best overall response, DLT = dose limiting toxicity, DOR = duration of response, MTD = maximum tolerated dose, OESI = other events of special interest, ORR = objective response rate, OS = overall survival, PD-L1 = programmed death-ligand 1, RP2D =recommended Phase 2 dose , SAE = serious adverse event, SAP = statistical analysis plan, TTR = time to response.
Source: CA209070 Protocol, Appendix 1.1 and Appendix 1.11

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints. ORR and DOR are considered appropriate endpoints to characterise anti-tumor activity. Time-to-event endpoints, such as OS, are not considered interpretable in single-arm trials.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Overall, a maximum of 375 subjects were planned to be treated (Table 19). Simon's optimal two-stage design was used for expansion Parts B1-B6, B8, D, and E. Assuming that the study did not stop early for occurrence of a DLT, a total of 10 response-evaluable subjects was to be enrolled into Stage 1. If at least 1 response was observed among 10 evaluable subjects, then stage 2 was to be opened for enrollment of 10 additional subjects.

Table 19: Applicant - Sample Size for Study CA209070

Part	Minimum	Maximum
A	4 (2 by dose level)	36 (20% inevaluable)
B	60	170 (10% inevaluable)
C	2 (2 by dose level)	36 (20% inevaluable)
D	0	110 (10% inevaluable)
E	2	23 (10% inevaluable)

Statistical Analyses: For CA209070, unless otherwise noted, all analyses were performed using all treated subjects by cohort (A, B1-B8, C1, C2, D2-D4), and also pooled nivo mono versus nivo + ipi (A + B vs C + D), overall, and split by solid tumors versus hematologic malignancies (HL and NHL). Analysis by disease indication were also performed, pooling subjects with same disease diagnosis from Parts A and B (nivo mono), and from Parts C and D (nivo + ipi). Indications consisted of HL, NHL, Neuroblastoma, Ewing sarcoma, Osteosarcoma, RMS, Melanoma, and Solid tumor NOS (other tumor types not included in the previous solid tumor categories). Efficacy endpoints that are based on tumor response data were derived using assessments from investigators (plus central review when required per protocol) per RECIST 1.1 response criteria, when relevant given the disease indication. Time-to-event variables (eg, time-to resolution) were analyzed using the KM technique. When specified, the median was reported along with 95% CI using Brookmeyer and Crowley method (using log-log transformation for constructing the CIs). CIs for binomial proportions were derived using the Clopper-Pearson method and the method of Chang. Descriptive analyses were performed for safety data. The evaluation of safety focused on the incidence of AEs, SAEs, adverse events leading to discontinuation, select AEs, other OESIs, and deaths.

Post-hoc Exploratory Efficacy Analyses: Post-hoc analyses, using the same methodologies as for prespecified analyses, were conducted for this application based on the interim CSR DBLs for Parts A to D subjects (30-Sep-2019 for Parts A-B and 30-Jun-2020 for Parts C-D) and include:

- ORR analyses in pediatric < 18 years subjects
- OS analyses for subjects < 18 years and subjects ≥ 12 to < 18 years old age groups

The FDA's Assessment:
FDA agrees with the summary of the statistical analysis plan (SAP) of CA209070 described by the Applicant. In general, the SAP is deemed acceptable.

Protocol Amendments

The Applicant's Description:

The original protocol for this study was dated 16-Jan-2015 and there were a total of 12 global amendments (Table 20).

Table 20: Applicant - Summary of Key Changes to CA209070 Protocol

Document (Amendment) Date	Summary of Key Changes
Original Protocol 16-Jan-2015	Not applicable.
Amendment 1A 03-Mar-2015	To clarify the correlative sample processing instructions with details provided by the drug company. Additionally, after discussions with Cancer Therapy Evaluation Program (CTEP) and the drug company, the Endocrine and Autoimmune observations have been modified and the total required blood volumes have been significantly reduced. Administrative revisions have also been made for clarity and consistency throughout the protocol.
Amendment 2C 30-Oct -2015	For management of pleural effusion as well as to add an additional cohort to Part B for enrollment of patients with relapsed or refractory neuroblastoma who are evaluable only for meta-iodobenzylguanidine (MIBG) response. Administrative revisions have also been made for clarity and consistency throughout the protocol. Also, a non-statistical cohort for melanoma patients was added.
Amendment 3 02-Mar-2016	The protocol was revised in response to the the updated request for rapid amendment (RRA) from the Primary Investigator (PI), dated 01-Mar-2016. Additional administrative edits have been made for clarity within the protocol.
Amendment 4 07-Jul-2016	To add Part D. Since response rates to combination nivolumab/ipilimumab are higher in melanoma than with single agent nivolumab, it is important to determine if the combination regimen might show efficacy in pediatric solid tumors. Hence, for select disease cohorts in Part B that do not meet criteria to proceed beyond Stage 1 due to lack of objective responses to single agent nivolumab, the combination of nivolumab (3 mg/kg) with ipilimumab (1mg/kg) was to be examined in selected disease specific cohorts. The combination of nivolumab (3 mg/kg) with ipilimumab (1 mg/kg) was determined to be tolerable and is the recommended Phase 2 dose (RP2D) of the same schedule utilized in Part C. Additionally, the eligibility criteria have been modified to permit enrollment of patients with lymphoma who have previously received an allogeneic stem cell transplant.
Amendment 5A 17-Jan-2017	To reflect modified risk information for both BMS-93658 (nivolumab) and ipilimumab. The comprehensive adverse events and potential risks (CAEPR) list for BMS-93648 nivolumab has been updated to version 2.2, 15-Nov-2016.The CAEPR list for ipilimumab has been updated to version 2.8, 21-Dec-2016.
Amendment 6 24-Feb-2017	Amendment in response to the Food and Drug Administration review of Amendment #4 to ADVL1412. In addition to changes made in response to the FDA, changes have also been made to address comments from Bristol-Myers Squibb and CTEP recommendations. This included clarification of correlative study procedures involving vaccinated antibody responses. Stopping

Table 20: Applicant - Summary of Key Changes to CA209070 Protocol

Document (Amendment) Date	Summary of Key Changes
	rules were added for the incidence of graft-versus-host disease (GVHD) in lymphoma patients who enrolled following allogeneic stem cell transplant. Also, assessment of cardiac function, was added given the occurrence of myocarditis in patients using combination Ipilimumab/Nivolumab in other studies.
Amendment 7A 09-Aug-2018	Amendment in response to two RRAs from CTEP. The first was dated 17-Jul-2018 for BMS-936558 (Nivolumab, MDX-1106, NSC 748726); the second was dated for 25-Jul-2018 for Ipilimumab (MDX010, NSCs 732442 and 720801). In this amendment, the revised toxicity profile (BMS-936558, CAEPR version 2.3, dated 18-Jun-2018) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised accordingly. The revised toxicity profile (Ipilimumab, CAEPR version 2.9, dated 20-Dec-2017) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised accordingly. This amendment also reflected the conversion of the protocol to common terminology criteria for adverse events (CTCAE) version 5.0.
Amendment 8B 02-Apr-2019	Amendment in response to a Request for Amendment from PI, dated 20-Dec-2018 that includes administrative changes to reflect the transition from Children's Oncology Group Chair (COGC) to Pediatric Early Phase Clinical Trials Network (PEP-CTN). This amendment also added a new arm (Part E) to explore a different combination of nivolumab and ipilimumab in patients with rhabdomyosarcoma or Ewing sarcoma/peripheral primitive neuroectodermal tumor (PNET).
Amendment 9 23-May-2019	Amendment in response to a RRA from PI, dated 08-May-2019. In this amendment the revised CAEPR for ipilimumab has been inserted in the protocol, and the associated risk information in the informed consent documents has been revised accordingly.
Amendment 10 31-Jul-2019	To update the infusion time of nivolumab from 60 min to 30 min. Ipilimumab was infused over 90 min.
Amendment 10C 20-Feb-2020	This was a combined amendment that addressed CTEP recommendations from the approval of amendment 8B. It also addressed the Request for Amendment from the Pharmaceutical Management Branch, in which nivolumab drug information has been updated. The amendment also included the addition of preclinical biomarker study information that has been agreed upon by the Pediatric Committee of the European Medicines Agency.
Amendment 11 30-Mar-2020	This amendment was administrative in nature and included the addition of off-study criteria for Part E patients.

Source: CA209070 Interim CSR, Protocol Amendments in Appendix 1.1[26]

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments; the amendments are not considered by FDA to have an clinically significant impact on the the study results.

8.1.1.1. Study Results

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 International Council for Harmonisation and in accordance with the ethical principles underlying European Union 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 Institutional Review Board/Independent Ethics Committee 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. All data management activities regarding trial oversight, trial build, conduct, and closeout, as well as all associated documentation of such activities, were owned and managed by COG.

CA209070 was an open-label study in children, adolescents, and young adults with recurrent or refractory solid or hematological tumors treated with nivolumab or nivo + ipi. In this study, Part A determined the RP2D for Part B. Similarly, Part C determined the RP2D for Part D. Measures to minimize bias included aspects of the study design and the use of third parties for critical activities. Specifically, these included:

- Patient Management - Treatment management guidance was provided in Sections 3.4.9.1, 5.0 , and 6.0 of the protocol.
- Use of Centralized Vendors - Individual pharmacokinetic, and Human Anti-Human Antibodies (HAHA) assessments were performed by PPD and analyzed by BMS. To ensure consistency with pediatric laboratory normal values across the study, standardized normal ranges for alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), and alkaline phosphatase were used for calculating toxicity grades.
- Independent Data Monitoring Board - The Data Monitoring Committee (DMC) for this study convened approximately every 6 months. The DMC was consulted on an ad-hoc basis as a safety signal emerged and convened an ad-hoc meeting on its own initiative. A separate DMC charter described the activities of this committee. The DMC had access to reports of study data including analyses addressing population characteristics, dosing, safety, and efficacy updated as available prior to each of its meetings.
- System Controls - Measures to control dissemination of data included procedural and technical controls. Specifically, measures included procedural and technical access controls on systems used in data handling to limit access. These systems included UNIX (statistical computing environment) where patient-level data were stored.
- Data Integrity - Use of Secure File Transfer Protocol (sFTP) for Transferring Data: sFTP was used exclusively to transfer datasets to third-parties.

After review of 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 of non compliance with good clinical practices during the conduct of Study CA209070.

Financial Disclosure

The Applicant's Position:

Due to NCI/CTEP (CA209070 study sponsor) policy precluding provision of Financial Disclosure Forms to pharmaceutical companies, BMS proposed that financial disclosure information for CA209070 shall be provided directly from NCI/CTEP to FDA upon request by the FDA. FDA agreed with this proposal (IND 120909 Preliminary Meeting Comments; Reference ID: 5001702) and therefore, BMS is not providing financial disclosure information for CA209070 in this application.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Given the limited duration of study treatment and the absence of clinically meaningful anti-tumor activity in the relapsed/refractory solid tumor populationin Study CA209070, FDA concluded that the Investigator's financial disclosures are unlikely to have biased the interpretation of the study results.

Patient Disposition

The Applicant's Position:

This study was conducted at 24 sites in 2 countries, all subjects and sites from the US except 1 subject from 1 site in Canada. Overall, 132 subjects were enrolled in Parts A to D of the study and 126 subjects (age from 1 to 27 years; 97 subjects < 18 years old, including 53 subjects ≥ 12 to < 18 years old) were treated with nivo mono (N = 80; 12 subjects in Part A and 68 subjects in Part B) or nivo+ipi (N = 46; 18 subjects in Part C and 28 subjects in Part D). Overall, the 97 (77.0%) subjects who were less than 18 years of age were treated with nivo mono (N = 64: 12 subjects in Part A and 52 subjects in Part B), or nivo+ipi (N = 33; 18 subjects in Part C and 15 subjects in Part D).

Nivolumab Monotherapy (Combined Cohorts of Parts A and B):

At the time of the DBL, only 1 (1.3%) of the subjects treated with nivo in Cohort B5 with HL was still on treatment. The most common reason for treatment discontinuation was clinical or radiographic evidence of progressive disease of > 40% increase in target lesions (43.8%), physician determination of patients best interest (18.8%), and clinical or radiographic evidence of progressive disease > 12 weeks after start of protocol therapy (13.8%).

Nivo + Ipi (Combined Cohorts of Parts C and D):

At the time of the DBL, none of the subjects treated with nivo + ipi across cohorts were still on treatment. The most common reason for treatment discontinuation was clinical or radiographic evidence of progressive disease of > 40% increase in target lesions (65.2%) and clinical or radiographic evidence of progressive disease > 12 weeks after start of protocol therapy (17.4%).

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Ninety-five percent of patients enrolled in Study CA209070 were treated. At the time of the database lock 99% of treated patients had discontinued study treatment due to either clinical or radiographic progression.

Protocol Violations/Deviations

The Applicant's Position:
No relevant protocol deviations were reported in this study. Relevant protocol deviations are deviations related to inclusion or exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results; they are predefined in the SAP.

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

Table of Demographic Characteristics

Data:

Table 21: Applicant - Demographic Characteristics by Treatment, All Treated (Parts A-D)

	Nivo N = 80	Nivo + Ipi N = 46
AGE (YEARS)		
N	80	46
MEAN	13.0	15.0
MEDIAN	13.5	15.0
MIN , MAX	1 , 27	4 , 27
SD	6.1	5.8
	Number of Subjects (%)	
AGE CATEGORIZATION 1 (%)		
>= 1 TO < 6 YEARS	11 (13.8)	3 (6.5)
>= 6 TO < 12 YEARS	20 (25.0)	10 (21.7)
>= 12 TO < 18 YEARS	33 (41.3)	20 (43.5)
>= 18 YEARS	16 (20.0)	13 (28.3)
AGE CATEGORIZATION 2 (%)		
< 12 YEARS	31 (38.8)	13 (28.3)
>= 12 YEARS	49 (61.3)	33 (71.7)
AGE CATEGORIZATION 3 (%)		
< 18 YEARS	64 (80.0)	33 (71.7)
>= 18 YEARS	16 (20.0)	13 (28.3)
SEX (%)		
MALE	49 (61.3)	30 (65.2)
FEMALE	31 (38.8)	16 (34.8)
RACE (%)		

WHITE	60 (75.0)	33 (71.7)
BLACK OR AFRICAN AMERICAN	9 (11.3)	4 (8.7)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (2.2)
ASIAN	6 (7.5)	2 (4.3)
UNKNOWN	4 (5.0)	3 (6.5)
NOT REPORTED	1 (1.3)	3 (6.5)
ETHNICITY (%)		
HISPANIC OR LATINO	11 (13.8)	8 (17.4)
NOT HISPANIC OR LATINO	68 (85.0)	36 (78.3)
UNKNOWN	1 (1.3)	0
NOT REPORTED	0	2 (4.3)
COUNTRY BY GEOGRAPHIC REGION (%)		
NORTH AMERICA	80 (100.0)	46 (100.0)
CANADA	0	1 (2.2)
UNITED STATES OF AMERICA	80 (100.0)	45 (97.8)
KARNOFSKY PERFORMANCE STATUS (SUBJECTS > 16 YEARS OF AGE) (A)		
N OF SUBJECTS > 16 YEARS OF AGE	23	17
50	0	0
60	0	0
70	3 (13.0)	1 (5.9)
80	5 (21.7)	5 (29.4)
90	9 (39.1)	8 (47.1)
100	6 (26.1)	3 (17.6)
LANSKY PERFORMANCE STATUS (SUBJECTS <= 16 YEARS OF AGE) (A)		
N OF SUBJECTS <= 16 YEARS OF AGE	57	29
60	4 (7.0)	1 (3.4)
70	2 (3.5)	2 (6.9)
80	10 (17.5)	6 (20.7)
90	24 (42.1)	11 (37.9)
100	17 (29.8)	9 (31.0)

	Nivo N = 80	Nivo + Ipi N = 46
	Number of Subjects (%)	
KARNOFSKY OR LANSKY PERFORMANCE STATUS (B)		
50	0	0
60	4 (5.0)	1 (2.2)
70	5 (6.3)	3 (6.5)
80	15 (18.8)	11 (23.9)
90	33 (41.3)	19 (41.3)
100	23 (28.8)	12 (26.1)
PRIOR SURGERY		
YES	37 (46.3)	32 (69.6)
NO	43 (53.8)	14 (30.4)
PRIOR RADIOTHERAPY		
YES	52 (65.0)	31 (67.4)
NO	28 (35.0)	15 (32.6)
BASELINE DISEASE DIAGNOSIS		
NEUROBLASTOMA	20 (25.0)	1 (2.2)
OSTEOSARCOMA	13 (16.3)	13 (28.3)
RHABDOMYOSARCOMA	11 (13.8)	10 (21.7)
EWING SARCOMA/PERIPHERAL PNET	11 (13.8)	10 (21.7)
HODGKIN LYMPHOMA	10 (12.5)	0
NON-HODGKIN LYMPHOMA	10 (12.5)	0
MELANOMA	1 (1.3)	0
SOLID TUMOR, NOS (C)	4 (5.0)	12 (26.1)
BASELINE HEMOGLOBIN		
< LLN	54 (67.5)	26 (56.5)
>= LLN	26 (32.5)	20 (43.5)

BASELINE PD-L1+ STATUS BASED ON A 1% CUT OFF*		
>= 1%	22 (27.5)	7 (15.2)
< 1%	41 (51.3)	32 (69.6)
NOT EVALUABLE	2 (2.5)	2 (4.3)
NOT TESTED	2 (2.5)	0
NOT REPORTED	13 (16.3)	5 (10.9)

(A) Percent out of the number of subjects in the relevant age group.
(B) Percent out of the number of subjects in the total population.
(C) Solid NOS include other tumor types not included in the previous solid tumor categories (undifferentiated sarcoma, epithelioid sarcoma, 8800-3 sarcoma, renal cell carcinoma, myxoid liposarcoma,8010-3 carcinoma, myofibroblastic tumor, synovial sarcoma, desmoplastic small round cell sarcoma, adrenal cortical adenoma, yolk sac tumor, hepatoblastoma, and nephroblastoma
[a] Not tested: If the enrolled subjects had missing PDL1 expression and with no result. Not reported: If the enrolled subjects did not have any records of PDL1 data.
Source (ADaM datasets): CA209070 Interim CSR, Table S.3.2.1.3 (adsl.xpt) and Table S.3.2.7.3 (addx.xpt, adsl.xpt)

The Applicant's Position:

Baseline demographics in all treated subjects were balanced between the nivo and nivo + ipi treatment groups. Overall, among the treated population, 97 subjects were pediatric subjects from 12 months to < 18 years of age and 29 subjects were adults ≥ 18 years of age with a refractory or relapsed solid or hematological tumor, including advanced and metastatic melanoma, that is refractory or relapsed after at least one accepted standard of care regimen and for whom no effective treatment is known.

Study CA209070 took into account adequate representation of children of ethnic and racial minorities. The racial and ethnic representation of subjects enrolled in CA209070 was as expected based on the the epidemiology data among pediatric subjects with melanoma, per SEER (see Section 2.1). All sites were in the US, with the exception of 1 site in Canada.

The FDA's Assessment:

FDA agrees with the data presented in this section for the demographic and baseline disease characteristics of the treated population in Study CA209070. The median age of patients who received nivolumab as a single agent was 13.5 years and the median age of patients who received nivolumab in combination with ipilimumab was 15 years. Melanoma occurs predominantly in individuals who report White race (i.e., approximately 94% of all cases diagnosed in the US [CDC 2012-2016]).

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

Data and The Applicant's Position of "Other Baseline Characteristics" are provided above and in Table 21. Information on concomitant therapy is provided below.

The FDA's Assessment:

See FDA assessment of demographic characteristics. FDA has no additional comments.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position

Treatment Compliance: All study medication was administered by trained medical personnel, and each treatment was recorded on the subject's CRF. Treatment compliance was monitored by drug accountability. The start date and stop time of the cycle, and total dose (mg) delivered were recorded on the CRF.

Nivolumab Monotherapy

In combined cohorts of Parts A and B, most subjects received all doses of study medications without a cycle delay or infusion interruption. A total of 4 (5.0%) subjects had at least 1 cycle delayed, and 13 (16.3%) subjects had at least 1 cycle infusion interrupted.

Nivolumab + Ipilimumab

In combined cohorts of Parts C and D, most subjects received all doses of study medications without a cycle delay or infusion interruption. One (2.2%) subject had at least 1 cycle delayed, and 4 (8.7%) subjects had at least 1 cycle interrupted.

Concomitant Therapy: 77 (96.3%) subjects treated with nivolumab (combined cohorts of Parts A and B), and 42 (91.3%) subjects treated with nivo + ipi (combined cohorts of Parts C and D) received concomitant non-study medications.

Immune-Modulating Concomitant Medications for Management of Adverse Events:

IMMs were recommended for the treatment of certain AEs. The list of IMMs was derived from the WHO Drug Dictionary, and included all drugs belonging to the following categories: corticosteroids, immune modulating agents, immunosuppressive agents, and glucocorticoids.

Nivolumab Monotherapy

In combined cohorts of Parts A and B, 18 (22.5%) subjects received concomitant IMMs. The most frequently used IMMs were corticosteroids for ophthalmological use and corticosteroids for systemic use (16.3% each).

- Solid Tumors: 11 (18.3%) subjects received concomitant IMMs.
- Hematology Tumors: 7 (35.0%) subjects received concomitant IMMs.

Nivolumab + Ipilimumab

In combined cohorts of Parts C and D, 9 (19.6%) subjects received concomitant IMMs. The most frequently used IMMs were corticosteroids for dermatological use, corticosteroids for ophthalmological use, and corticosteroids for systemic use (15.2% each).

Rescue Medication Use: Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's summary of treatment compliance and concomitant medication use. There was a nominally higher incidence of concomitant immune-modulating medication use in patient who received nivolumab as a single agent.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 22: Applicant - Efficacy Summary - Nivolumab and Nivo + Ipi - All Treated Subjects in Study CA209070 (Parts A-D)

	Nivolumab			Nivo + Ipi
	Solid Tumor N = 60	**Hematology Tumor N =20**	**Total N =80**	**Solid Tumor N = 46**
ORR and BOR[a]				
Response-evaluable Subjects	58	17	75	43
CR	0	1 (5.9)	1 (1.3)	0
PR	0	3 (17.6)	3 (4.0)	2 (4.7)
SD	15 (25.9)	6 (35.3)	21 (28.0)	7 (16.3)
PD	38 (65.5)	6 (35.3)	44 (58.7)	32 (74.4)
Unable to determine	5 (8.6)	1 (5.9)	6 (8.0)	2 (4.7)
ORR (%)[b]	0/58	4/17 (23.5)	4/75 (5.3)	2/43 (4.7)
(95% CI)	(0.0, 6.2)	(6.8, 49.9)	(1.5, 13.1)	(0.6, 15.8)
OS				
# Events/#Subjects (%)	34/60 (56.7)	4/20 (20.0)	38/80 (47.5)	27/46 (58.7)
Median OS (Months) (95% CI)[c]	7.00 (5.98, 14.06)	NA	11.07 (6.37, 27.63)	8.87 (5.75, 18.50)
6-month OS Rate (95% CI)[c]	62.5 (47.8, 74.2)	78.0 (51.5, 91.1)	66.6 (54.3, 76.4)	64.6 (46.3, 78.0)
12-month OS rate (95% CI)[c]	36.4 (22.0, 50.9)	78.0 (51.5, 91.1)	48.1 (35.0, 60.1)	42.8 (25.0, 59.4)
24-month OS rate (95% CI)[c]	NA	NA	NA	16.0 (4.3, 34.4)

[a] Per RECIST 1.1 Other response criteria could be used for HL, NHL, neuroblastoma, or other cohorts as relevant in those disease indications in compliance with section 12 of the protocol.

[b] CR + PR. ORR calculated based on response evaluable subjects. For nivo monotherapy, the subject with CR had Hodgkin lymphoma, and the 3 subjects with PR had HL (2 subjects) and NHL (1 subject). For nivo+ipi, the 2 subjects with PR had Ewing sarcoma/peripheral PNET and rhabdomyosarcoma (1 subject each).

[c] Based on Kaplan-Meier estimates

Source: CA209070 Interim CSR, Table S.5.5.1.1 (adefresp.xpt, adsl.xpt)(ORR), Table S.5.22.1 (adefttes.xpt, adsl.xpt)(OS), Table S.5.23.1 (adefttes.xpt, adsl.xpt)(OS rate), Table S.5.5.1.2 (adefresp.xpt, adsl.xpt)(ORR by tumor type)

Table 23: Applicant - ORR and BOR by Age Subgroups - Nivolumab and Nivo+Ipi - All Treated Response Evaluable Subjects in CA209070 (Parts A-D)

	Nivolumab (Total)			Nivo+Ipi		
Age Subgroups (years)	**≥ 12 to < 18**	**< 18**	**≥ 18**	**≥ 12 to < 18**	**< 18**	**≥ 18**
Response-evaluable Subjects, N	31	60	15	19	30	13
CR	1 (3.2)	1 (1.7)	0	0	0	0
PR	1 (3.2)	2 (3.3)	1 (6.7)	0	0	2 (15.4)
SD	9 (29.0)	17 (28.3)	4 (26.7)	4 (21.1)	5 (16.7)	2 (15.4)
PD	16 (51.6)	35 (58.3)	9 (60.0)	15 (78.9)	25 (83.3)	7 (53.8)
Unable to determine	4 (12.9)	5 (8.3)	1 (6.7)	0	0	2 (15.4)
ORR%[b] (95% CI)	6.5 (0.8, 21.4)	5.0 (1.0, 13.9)	6.7 (0.2, 31.9)	0 (0.0, 17.6)	0 (0.0, 11.6)	15.4 (1.9, 45.4)

[a] BOR per RECIST 1.1.

[b] CR + PR. ORR calculated based on response evaluable subjects.

Source: CA209070 Interim CSR, Table S.5.5.2.1 (adefresp.xpt, adsl.xpt)

Table 24: Applicant - OS by Age Subgroups - Nivolumab and Nivo+Ipi - All Treated Subjects in CA209070 (Parts A-D)

	Nivolumab (Total)			Nivo+Ipi		
Age Subgroups (years)	**≥ 12 to < 18 n = 33**	**< 18 n = 64**	**≥ 18 n = 16**	**≥ 12 to < 18 n = 20**	**< 18 n = 33**	**≥ 18 n = 13**
#event/#subjects (%)	15/33 (45.5)	30/64 (46.9)	8/16 (50.0)	10/20 (50.0)	19/33 (57.6)	8/13 (61.5)
mOS, months (95% CI)[a]	6.67 (4.99, N.A.)	6.67 (5.98, N.A.)	14.06 (7.00, N.A.)	8.87 (5.62, 33.08)	8.25 (5.45, 16.95)	19.91 (5.16, N.A.)
OS rate (95% CI),[a] %						
6-month	65.3 (44.5, 79.9)	60.7 (46.3, 72.4)	87.1 (57.3, 96.6)	72.8 (41.5, 89.2)	64.1 (41.3, 79.9)	66.6 (33.1, 86.1)
12-month	46.6 (26.2, 64.7)	45.5 (30.6, 59.3)	57.1 (27.9, 78.2)	45.5 (17.5, 70.1)	37.4 (17.3, 57.5)	55.5 (22.8, 79.1)
24-month	N.A.	N.A.	N.A.	30.3 (6.1, 60.1)	15.0 (2.7, 36.7)	18.5 (1.0, 53.8)

[a] Based on Kaplan-Meier estimates

Source: Summary of Clinical Efficacy[45], Appendix 2, Table S.8.1.2 (adefttes.xpt, adsl.xpt), and Table S.9.1.2 (adefttes.xpt, adsl.xpt).

The Applicant's Position:

Overall Efficacy Summary

Efficacy analyses were descriptive in nature. The minimum follow-up (time from LPFV date to data cutoff date) was > 24.0 months for all subjects treated with nivo mono in Parts A and B except Cohort B6 (N = 80). The minimum follow-up was 28.3 months for all subjects treated with nivo + ipi treatment.

Efficacy results for all treated subjects are summarized by tumor type for nivo mono (pooled solid tumor and hematological tumor) and for nivo + ipi (solid tumor) in Table 22.

Nivolumab Monotherapy

- Among all treated response-evaluable subjects, antitumor activity was observed with nivolumab in hematology tumors (ORR: 23.5% [95% CI: 6.8, 49.9]; 1 CR (subject with HL) and 3 PRs [2 with HL and 1 with NHL]), while no responses were observed for the common, non-lymphoma, pediatric solid tumors studied. Across all tumor types, 21 subjects showed SD as the BOR (15 with solid tumors and 6 with hematology tumors). Among the 4 responders with hematology tumors, TTR ranged from 1.9 to 8.6 months and DOR ranged from 1.0 to 2.8 months. For 1 NHL subject with PR, DOR was censored on the date of their last evaluable tumor assessment.
- Among all treated subjects, the 12-month OS rate was 48.1% (95% CI 35.0%, 60.1%). For nivo treatment, 42/80 (52.5%) subjects were censored for OS at DBL. Of the censored subjects, only 1 subject with hematological tumor was still on-treatment, 25 (31.3%) subjects were in follow-up, and 16 (20.0%) subjects were off study.

Nivolumab + Ipilimumab

- Among all treated response-evaluable subjects, limited antitumor activity (ORR: 4.7% [95% CI: 0.6, 15.8]) was observed with nivo+ipi in subjects with non-lymphoma, pediatric solid tumors. 2 subjects had PRs (1 pediatric Ewing sarcoma/peripheral PNET and 1 adult rhabdomyosarcoma). Across all tumor types, 7 subjects showed SD as the BOR. Among the 2 responders (PR) with solid tumors, TTR was 2.1 months in each responder, and DOR was 0.8 month and < 0.1 month (1 responder each). For both responders, DOR was censored on the date of their last evaluable tumor assessment.
- Among all treated subjects, 12-month OS rate was 42.8% (95% CI: 25.0%, 59.4%). For nivo + ipi treatment, 19/46 (41.3%) subjects were censored for OS at DBL. Of the censored subjects, no subjects were still on-treatment, 5 (10.9%) subjects were in follow-up, and 14 subjects (30.4%) were off study.

Efficacy results are presented by age subgroups in Table 23 and Table 24. No major differences in OS and ORR were observed among the age subgroups (≥ 12 to < 18 years, < 18 years, and ≥ 18 years).

The only adolescent subject with melanoma enrolled in CA209070 was a 15-year-old, Asian, female who received 2 doses (C1D1 and C1D15) of nivolumab 3 mg/kg. The subject had a Lansky performance status of 90, received prior lines of anticancer immunotherapies (including

cellular therapy) and underwent surgery (3 resections). The subject's BOR was PD. During treatment, the only AE experienced by the subject was Grade 1 constipation. The subject discontinued treatment due to PD and the subject died due to disease progression 137 days after receiving the last dose of nivolumab.

In additional subgroup analyses of efficacy (ORR), no meaningful differences in response were noted in male compared with female subjects. Among nivolumab-treated subjects, ORR was observed in 2/45 (4.4%) males (1 CR and 1 PR), and 2/30 in females (2 PR). Among nivo+ipi-treated subjects, ORR was observed in 1/30 (3.3%) male (1 PR), and 1/13 in female (1 PR). For subgroups based on race or ethnicity, most subjects were clustered in a single category (White or Not Hispanic/Not Latino), which limited the interpretability of potential differences. Among nivolumab-treated subjects, for subgroups based on race, ORR was observed in 2/56 (3.6%) White subjects (2 PR), and 2/9 (22.2%) Black or African American subjects (1 CR and 1 PR). For subgroups based on ethnicicty, ORR was observed in 1/10 (10.0%) Hispanic or Latino subjects (1 PR), and 3/65 (4.6%) Not Hispanic or Latino subjects (1 CR and 2 PR). Among nivo+ipi-treated subjects, for subgroups based on race, ORR was observed in 1/30 (3.3%) White subjects (1 PR), and 1/3 (33.3%) Not Reported (1 PR). For subgroups based on ethnicity, ORR was observed in 1/33 (3.0%) Not Hispanic or Latino subjects (1 PR), and 1/2 (50.0%) Not Reported (1 PR).

The FDA's Assessment:

Pediatric patients treated in Study CA209070 did not experience high rates of tumor response. In the 60 patients with solid tumors who were treated with nivolumab as a single agent no responses to treatment were observed in 58 efficacy evaluable patients. In the 46 patients with solid tumors who were treated with nivolumab in combination with ipilimumab an ORR of 4.7% (95% CI: 0.6, 15.8), including 2 partial responses [patient with Ewing sarcoma and patient with rhabdomyosarcoma], was observed among 43 efficacy evaluable patients. In the 20 pediatric patients with hematological tumors who were treated with nivolumab as a single agent the ORR was 23.5% (95% CI: 6.8, 49.9), including 1 complete response in a patient with HL and 3 PRs [two patients with HL and 1 patient with NHL], among 17 efficacy evaluable patients. There were no pediatric patients with hematologic malignancies treated with nivolumab in combination with ipilimumab. Given the limited number of patients treated with each regimen and the overall lack of responses, no definitive conclusions can be made regarding anti-tumor activity in any study subgroups. Time-to-event endpoints, such as OS, are not interpretable on single arm studies.

Data Quality and Integrity

The Applicant's Position:

Data collection for this study was done through the (b) (4) clinical data management system. Access to the trial in (b) (4) was granted through the (b) (4) application to all persons with the appropriate roles assigned in Regulatory Support System (RSS)

All data management activities regarding trial oversight, trial build, conduct, and closeout, as well as all associated documentation of such activities, was owned and managed by COG.

The FDA's Assessment:
FDA did not identify issues regarding data integrity and submission quality during review of this application.

Efficacy Results – Secondary and other relevant endpoints

Data regarding PD-L1 status are provided in Table 21 and association with response is discussed below.

The Applicant's Position

Nivolumab Monotherapy

Of the 80 subjects treated with nivo mono, 22 (27.5%) subjects had baseline PD-L1 expression ≥ 1%, 41 (51.3%) subjects had PD-L1 expression < 1%, and 17 (21.3%) subjects were without quantifiable PD-L1 at baseline. 3 pediatric subjects (2 with HL, 1 with NHL) in the PD-L1 ≥ 1% subgroup had PR, and 1 pediatric subject (with HL) in the PD-L1 missing subgroup had CR (. No subjects from the PD-L1 < 1% subgroup had either CR or PR. Small subgroup sizes preclude firm conclusions.

Nivolumab + Ipilimumab

Of the 46 subjects treated with nivo + ipi treatment, 7 (15.2%) subjects had baseline PD-L1 expression ≥ 1%, 32 (69.6%) subjects had PD-L1 expression < 1%, and 7 (15.2%) subjects were without quantifiable PD-L1 at baseline. 1 pediatric subject in the PD-L1 ≥ 1% subgroup with Ewing sarcoma/peripheral PNET and 1 adult subject in the PD-L1 < 1% subgroup with rhabdomyosarcoma had PR, and no subjects from the PD-L1 missing subgroup had either CR or PR. Small subgroup sizes preclude firm conclusions.

The FDA's Assessment:
FDA agrees with the Applicant's description of the PD-L1 subgroups. Given the small number of patients in each PD-L1 subgroup, no definitive conclusions can be made about the impact of PD-L1 expression levels on anti-tumor activity.

Dose/Dose Response

The Applicant's Position:
E-R analyses support the CA209070 clinical efficacy results. See Section 6.2 for details.

The FDA's Assessment:
See the Clinical Pharmacology Review in Section 6.2.

Durability of Response

The Applicant's Position:
See below for Persistence of Effect.

The FDA's Assessment:
See FDA response below.

Persistence of Effect

The Applicant's Position:
In CA209070 (all treated subjects), for nivolumab treated subjects with solid tumors, minimum follow-up ranged from 27.8 to 49.2 months and for nivolumab treated subjects hematology tumors, minimum follow-up ranged from 14.0 to 31.0 months. For nivo+ipi treated subjects with solid tumors, minimum follow-up ranged from 28.3 to 58.3 months. DOR among responders and OS are reported above. CA209070 is ongoing to follow-up on longer term safety and efficacy of nivolumab and nivo+ipi in pediatric subjects with advanced solid and hematological tumors.

The FDA's Assessment:
[In the four patients with hematologic tumors who were treated with nivolumab as a single agent and had responses the duration of responses ranged from 1.0 to 2.8 months. In the two patients with solid tumors who were treated with nivolumab in combination with ipilimumab and had responses the duration of responses were 0.8 month and <0.1 month (I patient each).]

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
The Applicant's Position: Not applicable.
The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

Data and The Applicant's Position:
As of 30-Jun-2020, 8 subjects were enrolled and treated with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg in Parts E3 (N = 5; rhabdomyosarcoma) and Part E4 (N = 3; Ewing sarcoma) of the study. Three subjects were less than 18 years of age. No objective response was observed and all treated subjects discontinued treatment at the time of DBL. Enrollment to Part E was closed after the first DLT was observed, per the prespecified safety monitoring rule.[43] Limited data from Part E preclude definitive conclusions regarding efficacy.
The FDA's Assessment:
FDA agrees no conclusions can be made based on the limited data from Part E.

8.1.2. Supportive Studies for Treatment of Advanced Melanoma

8.1.2.1. CA209067

Study CA209067 provides data for nivo mono and nivo+ipi in subjects ≥ 18 years in the approved advanced melanoma indication in adult patients. Data in adults are proposed to be

applicable to the requested indication expansion for adolescent patients based on disease similarity.

Trial Design

The Applicant's Description:

Trial design for CA209067 is summarized in Table 17.

Study Population

The Applicant's Description:

1296 subjects were enrolled at 137 sites in 21 countries from Australia, Europe, Israel, New Zealand, and US, and 945 subjects were randomized in the nivolumab group (N = 316), nivo+ipi group (N = 314), and ipilimumab group (N = 315).

Study CA209067 did not enroll any adolescent subjects. However, the study provides data for nivo mono and nivo + ipi in advanced melanoma in adult subjects. The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥ 5% tumor cell membrane expression as determined by the clinical trial assay (46%); and prior adjuvant therapy (22%).

Efficacy results provided below reflect the data presented in the current approved USPI. CA209067 has been analyzed for the primary endpoints per pre-specified plans as well as for additional, longer-term follow-up.

The FDA's Assessment:

FDA agrees with the Applicant's description of Study CA209067.

Efficacy Summary

The Applicant's Position:

Study CA209067 demonstrated statistically significant improvements in OS (based on the primary OS analysis with 28 months of minimum follow-up) and PFS (based on the primary PFS analysis with 18 months of minimum follow-up) for patients randomized to either nivolumab-containing arm as compared with the ipilimumab arm (HR = 0.55 [95% CI = 0.44, 0.69; p < 0.0001] and HR = 0.42 [95% CI = 0.34, 0.51; p < 0.0001] for OS and PFS, respectively, for the nivo + ipi arm compared to the ipilimumab arm and HR = 0.63 [95% CI = 0.50, 0.78; p < 0.0001] and HR = 0.57 [95% CI = 0.47, 0.69; p < 0.0001] for OS and PFS, respectively, for the nivolumab arm compared to the ipilimumab arm). The trial was not designed to assess whether adding ipilimumab to nivolumab improves PFS or OS compared to nivolumab as a single agent. Efficacy results are shown in Table 48 and Figure 3 of the nivolumab USPI.[46] Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the nivolumab+ipilimumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the nivolumab arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Long-term results for CA209067 based on minimum follow-up of 48 months months are described in the sBLA dossier; results remained consistent over time with results of the primary analysis. CA209067 is ongoing for further long term follow-up.

The FDA's Assessment:

FDA agrees with the Applicant's description of the efficacy results for Study CA209067. The study was previously reviewed by FDA and supports the approved indications for nivolumab as as a single agent and in combination with ipilimumab and the approved indication for ipilimumab in combination with nivolumab for the treatment of adult patients with unresectable or metastatic melanoma. Based on the similarities between melanoma in adolescent and adult patients, FDA considers this study to serve as the primary basis for concluding benefit in the pediatric population and for extending the nivolumab and ipilimumab melanoma indications in unresectable or metastatic melanoma to include pediatric patients 12 years of age and older.

8.1.3. Supportive Studies for the Adjuvant Treatment of Resected Melanoma

8.1.3.1. CA209915

Study CA209915 (double-blind, randomized CA209915 Phase 3 study (CheckMate-915) of nivo + ipi vs nivo mono in adult and adolescent (≥ 12 years of age) subjects after complete resection of Stage IIIb/c/d or Stage IV NED melanoma) was further designed to evaluate adjuvant treatment with nivolumab vs nivo+ipi in adult and adolescent melanoma and enrolled 3 adolescent melanoma subjects.

CA209915 provides safety and PK data for nivo mono and nivo + ipi in adolescent and adult subjects with completely resected melanoma. This study includes 3 adolescent subjects ≥ 12 to < 18 years of age (2 who received nivo mono and 1 subject who received nivo + ipi).

Trial Design

The Applicant's Description:

Trial design for CA209915 is summarized in Table 17.

Study Population

The Applicant's Position:

In total, 1943 subjects were randomized at 122 sites in 19 countries from Australia, Brazil, Canada, Europe, Israel, New Zealand and US (920 subjects to nivo+ipi, 924 subjects to nivolumab, and 99 subjects to ipilimumab [Arm C]). Of the 1844 subjects randomized to nivo+ipi or nivolumab, 1833 (99.4%) were treated (916 with nivo+ipi, 917 with nivolumab). Three adolescents (≥ 12 to < 18 years of age) were randomized and treated with nivolumab (N = 2) or nivo+ipi (N = 1).

Overall Population: Baseline characteristics for all randomized subjects were well balanced between the nivolumab and nivo+ipi groups. Overall, the majority of randomized subjects were male (57.0%), White (98.6%), with an ECOG PS of 0 (92.2%); the median age was 55.0 years (range, 15 to 89 years). A total of 52.6% of subjects had Stage IIIc disease, 30.7% had a BRAF

mutation, and 57.5% had PD-L1 status ≥ 1%. Median time from surgical resection to randomization was 9.57 weeks (range 0.1 to 18.7).

Adolescent Subjects: The 3 adolescent (≥ 12 to < 18 years) patients treated were:

Nivolumab Monotherapy:

- A 15-year old, White (Caucasian),male with PD-L1 status ≥ 5%, was randomized to nivolumab This subject had been treated with wide local excision, resective surgery, and complete lymph node dissection prior to the study. This subject completed the treatment period.
- A 16-year old White female with PD-L1 status < 1%, was randomized to nivolumab . The subject had been treated with resective surgery and complete lymph node dissection prior to the study. This subject completed the treatment period.

Nivolumab +Ipilimumab:

- A 16-year old White male with PD-L1 status < 1%, was randomized to nivo+ipi The subject had been treated with resective surgery and complete lymph node dissection prior to the study. This subject died of disease progression.

The FDA's Assessment:

FDA agrees with the Applicant's description of Study CA209915.

Efficacy Summary

The Applicant's Position:

Overall Population: Nivo+ipi did not demonstrate significant improvement in the primary endpoint RFS vs nivolumab (median RFS: not reached in both groups; HR = 0.92 (97.295% CI, 0.77, 1.09); p = 0.269). The results in the PD-L1 < 1% population were consistent with those in the overall population with no improvement in RFS with nivo+ipi vs nivolumab (HR = 0.91 [95% CI, 0.73, 1.14]). There was also no improvement in DMFS with nivo+ipi vs nivolumab.

Efficacy results for the nivo mono arm in CA209915 were consistent with results observed for nivo mono in Study CA209238.

Adolescent Subjects: Due to small sample size, no definitive conclusion can be drawn about efficacy of nivo+ipi or nivolumab in adolescents with completely resected Stage IIIb/c/d or Stage IV NED melanoma. The efficacy results in the adolescent subjects are summarized briefly below:

Nivolumab Monotherapy:

- Subject 15-year old, who was randomized to nivolumab, was censored at 30.4 months in the follow-up period (data cutoff), and had no recurrence of disease.
- Subject 16-year old, who was randomized to nivolumab, had RFS of 11.2 months, and a PFS on next-line systemic therapy of 27.2 months.

Nivolumab +Ipilimumab:

Subject 16-year old, who was randomized to nivo+ipi, had RFS of 16.9 months, and a PFS on next-line systemic therapy of 17.2 months.

The FDA's Assessment:
FDA agrees with the Applicant's description of the efficacy results for Study CA209915 and considered this study and Study CA209238 to serve as the primary basis for concluding benefit in the pediatric population and for extending the nivolumab adjuvant melanoma indication to adolescents. Given the current approval of nivolumab in the adjuvant setting; the negative results of Study CA209915; and the comparable efficacy in the nivolumab arm in Study CA209915 compared to the nivolumab arm in CA209238, FDA did not independently verify the results of this study during the review of this supplemental BLA.

8.1.3.2. CA209238

Study CA209238 provides data for nivo mono in subjects ≥ 18 years in the approved adjuvant melanoma indication in adult patients. Data in adults are proposed to be applicable to the requested indication expansion for adolescent patients based on disease similarity.

Trial Design
The Applicant's Description:
Trial design for CA209238 is summarized in Table 17.

Study Population
The Applicant's Position:
906 subjects were randomized at 130 sites in 25 countries from Europe, North America, and Rest of the World (953 subjects to nivolumab group and 453 subjects to ipilimumab group) and 905 subjects were treated.

Study CA209238 did not enroll any adolescent subjects. However, the study provides data for nivo mono in adult subjects with resected melanoma. The trial population characteristics were: median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

Data presented below for Study CA209238 reflect data presented in the the nivolumab USPI.[46] Recurrence-free survival data are based on the interim analysis (primary analysis for RFS) that used a clinical cut-off of 15-May-2017 with minimum follow-up of 18 months, while OS data are based on the 48-month follow-up data included in the final analysis, which used a clinical cut-off of 26-Nov-2019.

The FDA's Assessment:
FDA agrees with the Applicant's description of Study CA209238.

Efficacy Summary
The Applicant's Position:

CA209238 demonstrated a statistically significant improvement in recurrence-free survival (RFS) for patients randomized to the nivolumab arm compared with the ipilimumab 10 mg/kg arm (HR = 0.65 [95% CI: 0.53, 0.80 p < 0.0001]). Efficacy results are presented in Table 49 of the nivolumab USPI, and a Kaplan-Meier curve of RFS is provided in Figure 4 of the nivolumab USPI.

Long-term results for CA209238 based on minimum follow-up of 48 months are described in the sBLA dossier. At a minimum follow-up of 48 months (final OS and updated RFS analysis), CA209238 continued to demonstrate improvement in RFS with nivolumab vs ipilimumab. Median OS was not reached in either arm.

The FDA's Assessment:

FDA agrees with the Applicant's description of the efficacy results for Study CA209238. The study was previously reviewed by FDA and supports the approved indication for nivolumab as a single agent for the adjuvant treatment of adult patients with completely resected melanoma with lymph node involvement or metastatic disease. Based on the similarities between melanoma in adolescent and adult patients, FDA considers this study and Study CA209915 to serve as the primary basis for concluding benefit in the pediatric population and for extending the nivolumab and ipilimumab melanoma indications in the adjuvant setting to include pediatric patients 12 years of age and older.

8.1.4. Integrated Review of Effectiveness

The Applicant's Position:

Data from the pivotal CA209070 study conducted in pediatric and young adult subjects with solid tumors or lymphoma are presented to support the efficacy of nivolumab alone or in combination with ipilimumab in pediatric patients. Limited clinical data are available in adolescent melanoma subjects, ie, 1 adolescent subject with advanced melanoma treated with nivolumab in Study CA209070 and 3 adolescent subjects (2 subjects who received nivo mono and 1 subject who received nivo+ipi) in Study CA209915.

Nivolumab ± ipilimumab has established efficacy in adults in the proposed adolescent indications, demonstrated in Study CA209067 in advanced melanoma and CA209238 (nivo mono) for the adjuvant treatment of resected Stage III/IV melanoma. Based on the similarity of disease biology, genetic makeup, and phenotypic traits of melanoma in adults and adolescents, treatment outcomes in adolescent patients are expected to be similar to adults, allowing for PK-based extrapolation of efficacy.

The FDA's Assessment:

The analysis of the efficacy of nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab in pediatric patients age 12 years and older was based on a review of data from the pivotal trial CA209070 in the context of FDA's findings of the effectiveness of nivolumab and ipilimumab in advanced melanoma, based on studies CA209915, CA209067 and CA209238. Based on a prior demonstration of efficacy in adult patients in the adjuvant setting with completely resected Stage IIIB/C and IV melanoma and adult patients with unresectable or metastatic melanoma; population PK model-based

simulation that demonstrated comparable exposures in adult and pediatric patients; and the known similarities between adolescent and adult melanoma, FDA determined that there was sufficient information to support the extension of the melanoma indications for nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab to pediatric patients 12 years of age and older.

8.2. Review of Safety

The Applicant's Position:

The overall safety profile of nivo mono and nivo+ipi in pediatric and young adult subjects in the pivotal study CA209070 was consistent with previous data for these agents, with no new safety signals identified. CA209070, together with supportive studies CA209067, CA209915, and CA209238 comprises the population for the evaluation of safety for the requested expansion of indications in approved melanoma to include adolescent patients.

The FDA's Assessment:

The safety of nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab has been well characterized in studies of adult patients with melanoma and other tumor types. Pediatric safety data was provided from the pivotal trial CA209070, however patients on study had a limited exposure to study treatment. The median number of nivolumab single agent and nivolumab in combination with ipilimumab doses received was 2. The median duration of treatment was 0.84 months for nivolumab as a single agent and 0.72 months for nivolumab in combination with ipilimumab. Based on the available data from this trial, there were no new safety signals or increased risk of death identified in pediatric patients treated with nivolumab or nivolumab in combination with ipilimumab.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety data are from the pivotal CA209070 study conducted in pediatric and young adult subjects with solid tumors or lymphoma, and the supportive studies CA209915, CA209067, and CA209238.

AEs from the pivotal study CA209070 were evaluated. Safety analyses were conducted for AEs, SAEs, AEs leading to discontinuation, select AEs, modified IMAEs, and OESIs reported up to 100 days after the last dose of study treatment. Tolerability was assessed via DLTs. An analysis of adverse events was conducted by age subgroups (< 12 years, ≥ 12 years to < 18 years, and ≥ 18 years of age) in CA209070.

Study CA209067 provides data for nivo mono and nivo+ ipi in the approved advanced melanoma indication in adult patients.

Study CA209915 provides adjuvant melanoma data in adult patients and in 3 adolescents (2 treated with nivo monotherapy; 1 treated with nivo+ipi). Study CA209238 provides data for nivo mono in the approved adjuvant melanoma indication in adult patients.

Data in adults are proposed to be applicable to the requested indication expansion for adolescent patients based on disease similarity.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the general safety review approach. As the safety of nivolumab and ipilimumab has been previously reviewed and characterized in adult patients with resectable, unresectable and metastatic melanoma and also in other tumor types, FDA did not conduct an in depth analysis of the data from Studies CA209067, CA209915 or CA209238 during the review of this supplemental BLA. Safety results of Studies CA209067 and CA209238 served as the basis for prior approvals of nivolumab and ipilimumab and therefore have previously been reviewed in detail.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

In the pivotal study CA209070, 80 subjects received at least 1 dose of nivo, and 46 subjects received at least 1 dose of nivo + ipi.

Advanced Melanoma: In the supportive study CA209067, 313 subjects recieved at least 1 dose of nivo, and 313 subjects received at least 1 dose of nivo + ipi. No subjects in CA209067 were < 18 years old.

Adjuvant Melanoma: In the supportive study CA209915 which included 3 adolescent subjects with melanoma, 2 subjects < 18 years recieved at least 1 dose of nivo, and 1 subject < 18 years recieved at least 1 dose of nivo + ipi. Among the overall population in CA209915, 917 subjects recieved at least 1 dose of nivo and 916 subjects received at least 1 dose of nivo + ipi.

In the supportive study CA209238, 452 subjects received at least 1 dose of nivo. No subjects in CA209238 were < 18 years old.

The FDA's Assessment:

The median duration of study treatment on Study CA209070 was 0.84 months for patients treated with nivolumab as a single agent and 0.72 months for patients treated with nivolumab in combination with ipilimumab. The median number of single agent nivolumab doses received was 2 (range: 1, 89) and the median number of doses received for patients treated with nivolumab in combination with ipilimumab was 2.0 (range: 1, 24) for nivolumab and 2.0 (range: 1, 4) for ipilimumab. Based on the limited exposure to study treatment safety data from Study CA209070 was not used to further inform the nivolumab or ipilimumab prescribing information.

Relevant characteristics of the safety population:

The Applicant's Position:

See CA209070 Demographics Table 21, and Study Population in Sections 8.1.2.1, 8.1.3.1, and 8.1.3.2 for Studies CA209067, CA209915, and CA209238, respectively.

The FDA's Assessment:

FDA agrees with the study demographic data presented for the treated population in Study CA209070 in Section 8.1.1.1 and Table 21. Refer to this sections for the FDA Assessment.

Adequacy of the safety database:

The Applicant's Position:

The population studied in CA209070 is representative of a pediatric and young adult population with R/R solid and hematological tumors; this is supported by the study population's demographic, disease, and other baseline characteristics. With the established drug regimens and follow-up including the entirety of expected safety data up to 100 days reporting window of last subject, the exposure to study treatment in CA209070 is sufficient to characterize the safety of nivolumab and nivo+ipi. The routine clinical and laboratory evaluations performed were appropriate to evaluate and characterize the safety profile of nivolumab and nivo+ipi.

Supportive studies CA209067, CA209915, and CA209238 are Phase 3, well-controlled clinical trials with adequate exposure to study drug, clinical evaluations, and follow up to characterize the safety of nivolumab ± ipilimumab in adults and limited number of adolescent subjects.

The FDA's Assessment:

Patients enrolled to Study CA209070 had a limited duration of time on treatment and therefore limited exposure to study treatment. It is difficult to make a definitive assessment of the safety of nivolumab and ipilimumab in a pediatric melanoma population based solely on the results of this study. FDA considers the safety data from the pivotal trial CA209070 and the well characterized safety profile of nivolumab and ipilimumab in an adult melanoma population, as well as the population PK data and E-R safety analysis that supports the recommended doses to be sufficient to support the extension of the approved nivolumab and ipilimumab adult melanoma indications to a pediatric population 12 years of age and older.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The Applicant's Position:

All data management activities regarding trial oversight, trial build, conduct, and closeout, as well as all associated documentation of such activities, was owned and managed by COG. No issues with data quality and integrity have been identified.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Categorization of Adverse Events

The Applicant's Position:

Adverse events in the pivotal and supportive studies were categorized by system organ class

and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 and by severity grade using NCI CTCAE:

- CA209070 - MedDRA version 23.0 and NCI CTCAE V4 and V5.
- CA209067 - MedDRA version 19.0 and NCI CTCAE V4.
- CA209915 - MedDRA version 23.0 and NCI CTCAE V4.
- CA209238 - MedDRA version 22.1 and NCI CTCAE V4.

The FDA's Assessment:

FDA agrees with the Applicant's summary.

Routine Clinical Tests

The Applicant's Position:

Standard laboratory tests (eg, liver, hepatic, renal, thyroid, metabolic) were conducted at the screening visit, weekly during Cycle 1, weekly prior to subsequent cycles, 100 days after last dose, every 6 months up to 24 months, and annually up to 60 months. Pregnancy tests were conducted at screening. Laboratory tests were graded using the NCI CTCAE, version 4.0 or 5.0.

The FDA's Assessment:

FDA agrees with the Applicant's summary.

8.2.4. Safety Results

APPEARS THIS WAY ON ORIGINAL

Data:

Table 25: Applicant - Overall Safety Summary- Pooled Analysis: Solid vs. Hematology vs. Total for Nivolumab Monotherapy and Nivo + Ipi - All Treated Subjects in CA209070 (Parts A-D)

	Number of Subjects (%)							
	Nivo						Nivo + Ipi	
	Solid N = 60		Hemato N = 20		Total N = 80		Solid N = 46	
Deaths	34 (56.7)		4 (20.0)		38 (47.5)		27 (58.7)	
Primary Reasons for Death								
Due to This Disease	34 (56.7)		3 (15.0)		37 (46.3)		26 (56.5)	
Due to Other Cause (A)	0		1 (5.0)		1 (1.3)		0	
Not Reported	0		0		0		1 (2.2)	
Deaths Within 30 Days of Last Dose	4 (6.7)		1 (5.0)		5 (6.3)		2 (4.3)	
Deaths Within 100 Days of Last Dose	15 (25.0)		3 (15.0)		18 (22.5)		8 (17.4)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	32 (53.3)	22 (36.7)	11 (55.0)	10 (50.0)	43 (53.8)	32 (40.0)	20 (43.5)	12 (26.1)
Drug-related SAEs	13 (21.7)	8 (13.3)	4 (20.0)	4 (20.0)	17 (21.3)	12 (15.0)	9 (19.6)	7 (15.2)
All-causality AEs Leading To Discontinuation	10 (16.7)	6 (10.0)	5 (25.0)	4 (20.0)	15 (18.8)	10 (12.5)	6 (13.0)	3 (6.5)
All-causality AEs	60 (100.0)	40 (66.7)	20 (100.0)	15 (75.0)	80 (100.0)	55 (68.8)	46 (100.0)	23 (50.0)
Drug-related AEs	53 (88.3)	15 (25.0)	19 (95.0)	12 (60.0)	72 (90.0)	27 (33.8)	46 (100.0)	16 (34.8)
[3] 20% of Total Subjects in either Treatment Group								
Anaemia	25 (41.7)	2 (3.3)	10 (50.0)	3 (15.0)	35 (43.8)	5 (6.3)	19 (41.3)	2 (4.3)
Lymphocyte count decreased	13 (21.7)	6 (10.0)	9 (45.0)	4 (20.0)	22 (27.5)	10 (12.5)	20 (43.5)	6 (13.0)
Fatigue	23 (38.3)	0	7 (35.0)	0	30 (37.5)	0	16 (34.8)	0
White blood cell count decreased	15 (25.0)	2 (3.3)	9 (45.0)	1 (5.0)	24 (30.0)	3 (3.8)	10 (21.7)	1 (2.2)
Aspartate aminotransferase increased	13 (21.7)	1 (1.7)	9 (45.0)	0	22 (27.5)	1 (1.3)	8 (17.4)	2 (4.3)
Neutrophil count decreased	15 (25.0)	0	7 (35.0)	4 (20.0)	22 (27.5)	4 (5.0)	8 (17.4)	1 (2.2)
Alanine aminotransferase increased	9 (15.0)	1 (1.7)	9 (45.0)	0	18 (22.5)	1 (1.3)	11 (23.9)	2 (4.3)
Platelet count decreased	7 (11.7)	0	7 (35.0)	2 (10.0)	14 (17.5)	2 (2.5)	11 (23.9)	1 (2.2)
Nausea	12 (20.0)	0	2 (10.0)	0	14 (17.5)	0	10 (21.7)	1 (2.2)
C-reactive protein increased	12 (20.0)	0	2 (10.0)	0	14 (17.5)	0	9 (19.6)	0

	Number of Subjects (%)							
	Nivo						Nivo + Ipi	
	Solid N = 60		Hemato N = 20		Total N = 80		Solid N = 46	
Decreased appetite	13 (21.7)	0	2 (10.0)	0	15 (18.8)	0	6 (13.0)	1 (2.2)
Preferred Term	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hypocalcaemia	6 (10.0)	0	5 (25.0)	0	11 (13.8)	0	1 (2.2)	0
Hypoalbuminaemia	5 (8.3)	0	4 (20.0)	1 (5.0)	9 (11.3)	1 (1.3)	6 (13.0)	0
Hypokalaemia	5 (8.3)	0	4 (20.0)	1 (5.0)	9 (11.3)	1 (1.3)	5 (10.9)	0
Hypophosphataemia	5 (8.3)	0	4 (20.0)	0	9 (11.3)	0	3 (6.5)	0
Headache	7 (11.7)	0	4 (20.0)	0	11 (13.8)	0	4 (8.7)	0
All-causality Select AEs								
Endocrine	17 (28.3)	0	7 (35.0)	0	24 (30.0)	0	13 (28.3)	0
Gastrointestinal	16 (26.7)	1 (1.7)	5 (25.0)	1 (5.0)	21 (26.3)	2 (2.5)	11 (23.9)	1 (2.2)
Hepatic	36 (60.0)	8 (13.3)	18 (90.0)	3 (15.0)	54 (67.5)	11 (13.8)	28 (60.9)	7 (15.2)
Pulmonary	0	0	0	0	0	0	3 (6.5)	1 (2.2)
Renal	20 (33.3)	4 (6.7)	6 (30.0)	0	26 (32.5)	4 (5.0)	15 (32.6)	2 (4.3)
Skin	26 (43.3)	3 (5.0)	11 (55.0)	0	37 (46.3)	3 (3.8)	17 (37.0)	2 (4.3)
Hypersensitivity/ Infusion Reactions	3 (5.0)	0	3 (15.0)	0	6 (7.5)	0	2 (4.3)	0
Drug-related Select AEs								
Endocrine	14 (23.3)	0	5 (25.0)	0	19 (23.8)	0	11 (23.9)	0
Gastrointestinal	5 (8.3)	0	1 (5.0)	0	6 (7.5)	0	3 (6.5)	0
Hepatic	19 (31.7)	1 (1.7)	13 (65.0)	0	32 (40.0)	1 (1.3)	13 (28.3)	2 (4.3)
Pulmonary	0	0	0	0	0	0	1 (2.2)	0
Renal	4 (6.7)	0	3 (15.0)	0	7 (8.8)	0	7 (15.2)	0
Skin	13 (21.7)	1 (1.7)	3 (15.0)	0	16 (20.0)	1 (1.3)	11 (23.9)	1 (2.2)
Hypersensitivity/ Infusion Reactions	2 (3.3)	0	2 (10.0)	0	4 (5.0)	0	2 (4.3)	0

MedDRA Version: 23.0, CTC Version CTCAE V4 and V5

Includes events reported between first dose and 100 days after last dose of study therapy.

(A) Other cause was reported as intraparenchymal hematoma with intracranial pressure secondary to disease progression in 1 subject with NHL

Source: CA209070 CSR, Table S.6.15.1 (adsl.xpt)(deaths), Table S.6.1.32.3 (adae.xpt, adsl.xpt)(all-causality SAEs), Table S.6.1.32.4 (adae.xpt, adsl.xpt)(drug-related SAEs), Table S.6.1.31.1 (adae.xpt, adsl.xpt)(all causality AEs leading to discontinuation), Table S.6.1.32.1 (adae.xpt, adsl.xpt)(all-causality AEs), Table S.6.1.32.2 (adae.xpt, adsl.xpt)(drug-related AEs), Table S.6.5.1.3.1 (adae.xpt, adsl.xpt, aeosi.xpt)(all-causality non-endocrine select AEs), Table S.6.5.1.3.2 (adae.xpt, adsl.xpt, aeosi.xpt)(drug-related non-endocrine select AEs), Table S.6.5.1.3.5 (adae.xpt, adsl.xpt)(all-causality endocrine select AEs), and Table S.6.5.1.3.6 (adae.xpt, adsl.xpt)(drug-related endocrine select AEs)

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

Deaths

The Applicant's Position:

Nivolumab Monotherapy

As of the database lock (Parts A and B on 30-Sep-2019, Parts C and D on 30-Jun-2020), in the pooled analysis for nivo mono treated subjects who died (N = 80): a total of 38 deaths were reported in the pooled nivo mono group, of which 34/60 (56.7%) subjects were in the solid tumor group, and 4/20 (20.0%) subjects were in the hematology tumor group. The most common cause of death was disease progression, including within 30 days and 100 days of the last dose. One subject with relapsed or refractory non-Hodgkin tumor died due to intraparenchymal hematoma, 57 days after the last dose. No deaths were attributed to study drug toxicity.

Nivolumab + Ipilimumab

In the pooled analysis for subjects with solid tumors treated with nivo + ipi (N = 46), 27 (58.7%) subjects died. Disease progression was the most common cause of death, including within 30 days and 100 days of the last dose. The cause of death was not reported for 1 subject who died 1307 days after the last dose of study drug. There were no deaths due to study drug toxicity per investigator assessment.

The FDA's Assessment:

FDA agrees with the Applicant's summary of deaths. In the nivolumab monotherapy group 37 out of 38 deaths were due to progression of disease. The remaining death occurred in a patient with Non-Hodgkin Lymphoma was due to intraparenchymal hematoma that was attributed to disease progression. In the nivolumab and ipilimumab combination arm 26 out of 27 deaths were due to progression of disease. The cause of the remaining death was not reported.

Serious Adverse Events

The Applicant's Position:

Event rates and most common PTs were consistent with the known profiles of the study treatments.

Nivolumab Monotherapy

All-causality any-grade SAEs (within 100 days of last dose) were reported in 43 (53.8%) subjects treated with nivo. Grade 3-4 SAEs were reported in 32 (40.0%) subjects. Grade 5 SAEs were reported in 9 (11.3%) subjects (8 disease progression and 1 cardiac arrest).

- The most frequently reported all-causality any-grade SAEs (≥ 5%) were pyrexia (16.3%), disease progression and tumor pain (10.0% each), pleural effusion (8.8%), dyspnea, and febrile neutropenia (6.3% each).
- The most frequently reported all-causality Grade 3-4 SAEs (≥ 5%) were tumor pain (10.0%), febrile neutropenia (6.3%), dyspnea, and pleural effusion (5.0% each).

Drug-related any-grade SAEs (within 100 days of last dose) were reported in 17 (21.3%) subjects treated with nivo. Drug-related Grade 3-4 SAEs were reported in 12 (15.0%) subjects. There were no drug-related Grade 5 SAEs.

- Only drug-related SAE (any-grade) reported in ≥ 5.0% of subjects was pyrexia (6.3%).
- Drug-related Grade 3-4 SAEs reported in ≥ 2 (2.5%) subjects were febrile neutropenia and pleural effusion (2.5% each).

Nivolumab + Ipilimumab

All-causality any-grade SAEs (within 100 days of last dose) were reported in 20 (43.5%) subjects treated with nivo + ipi. All-causality Grade 3-4 SAEs were reported in 12 (26.1%) subjects. Grade 5 SAEs were reported in 4 (8.7%) subjects (2 disease progression and 2 respiratory failure).

- The most frequently reported all-causality any-grade SAEs (≥ 5%) were pleural effusion (10.9%), hypoxia (6.5%), pain in extremity, dehydration, and AST (6.5% each).
- The most frequently reported all-causality Grade 3-4 SAEs (≥ 5%) were AST increased, hypoxia, and pleural effusion (6.5% each).

Drug-related any-grade SAEs (within 100 days of last dose) were reported 9 (19.6%) subjects treated with nivo + ipi. Drug-related Grade 3-4 SAEs were reported in 7 (15.2%) subjects. There were no drug-related Grade 5 SAEs.

- Only drug-related any-grade SAE reported in ≥ 5% of subjects was pleural effusion (8.7%).
- Drug-related Grade 3-4 SAE reported in ≥ 2 subjects were ALT increased, AST increased, hyponatremia, and pleural effusion (4.3% each).

The FDA's Assessment:

FDA agrees with the Applicant's summary of SAEs. The incidence of any grade (53.8% vs 43.5%) and Grade 3-4 (40% vs 26.1) SAEs was higher on the nivolumab arm compared to the nivolumab and ipilimumab arm in Study CA209070. The incidence of SAEs in Study CA209070 appear comparable to that observed in a previously treated metastatic melanoma population (CHECKMATE-037: single agent nivolumab 41%) and previously untreated metastatic melanoma population (CHECKMATE-066: single agent nivolumab 36%; CHECKMATE-067: nivolumab plus ipilimumab 74%, single agent nivolumab 44%).

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 26: Applicant - Any Adverse Events Leading to Study Drug Discontinuation Summary by Worst CTC Grade - Graded with CTCAE V4 - 100 Days Safety Window - Pooled Analysis: Solid vs. Hematology vs. Total for Each Treatment - All Treated Subjects in CA209070 (Parts A-D)

System Organ Class (%) Preferred Term (%)	Nivo Solid N = 60		Nivo Hemato N = 20		Nivo Total N = 80		Nivo + Ipi Solid N = 46	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	10 (16.7)	6 (10.0)	5 (25.0)	4 (20.0)	15 (18.8)	10 (12.5)	6 (13.0)	3 (6.5)
General disorders and administration site conditions	2 (3.3)	0	0	0	2 (2.5)	0	0	0
Disease progression	2 (3.3)	0	0	0	2 (2.5)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.3)	2 (3.3)	0	0	2 (2.5)	2 (2.5)	0	0
Tumour pain	2 (3.3)	2 (3.3)	0	0	2 (2.5)	2 (2.5)	0	0
Gastrointestinal disorders	1 (1.7)	1 (1.7)	1 (5.0)	0	2 (2.5)	1 (1.3)	1 (2.2)	1 (2.2)
Upper gastrointestinal haemorrhage	1 (1.7)	1 (1.7)	0	0	1 (1.3)	1 (1.3)	0	0
Duodenitis	0	0	0	0	0	0	1 (2.2)	1 (2.2)
Nausea	0	0	1 (5.0)	0	1 (1.3)	0	0	0
Investigations	1 (1.7)	1 (1.7)	2 (10.0)	2 (10.0)	3 (3.8)	3 (3.8)	3 (6.5)	2 (4.3)
Lipase increased	1 (1.7)	1 (1.7)	1 (5.0)	1 (5.0)	2 (2.5)	2 (2.5)	1 (2.2)	1 (2.2)
Alanine aminotransferase increased	0	0	0	0	0	0	1 (2.2)	1 (2.2)
Amylase increased	0	0	0	0	0	0	1 (2.2)	1 (2.2)
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (2.2)	1 (2.2)
Blood creatinine increased	0	0	0	0	0	0	1 (2.2)	0
Neutrophil count decreased	0	0	1 (5.0)	1 (5.0)	1 (1.3)	1 (1.3)	0	0
Musculoskeletal and connective tissue disorders	1 (1.7)	1 (1.7)	0	0	1 (1.3)	1 (1.3)	0	0
Bone pain	1 (1.7)	1 (1.7)	0	0	1 (1.3)	1 (1.3)	0	0
Nervous system disorders	1 (1.7)	0	0	0	1 (1.3)	0	0	0
Peripheral sensory neuropathy	1 (1.7)	0	0	0	1 (1.3)	0	0	0
Reproductive system and breast	1 (1.7)	0	0	0	1 (1.3)	0	0	0

disorders								
Oedema genital	1 (1.7)	0	0	0	1 (1.3)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (1.7)	1 (1.7)	0	0	1 (1.3)	1 (1.3)	2 (4.3)	0
Pleural effusion	1 (1.7)	1 (1.7)	0	0	1 (1.3)	1 (1.3)	1 (2.2)	0
Cough	0	0	0	0	0	0	1 (2.2)	0
Dyspnoea	0	0	0	0	0	0	1 (2.2)	0
Respiratory failure	0	0	0	0	0	0	1 (2.2)	0
Blood and lymphatic system disorders	0	0	1 (5.0)	1 (5.0)	1 (1.3)	1 (1.3)	0	0
Febrile neutropenia	0	0	1 (5.0)	1 (5.0)	1 (1.3)	1 (1.3)	0	0
Immune system disorders	0	0	1 (5.0)	1 (5.0)	1 (1.3)	1 (1.3)	0	0
Autoimmune disorder	0	0	1 (5.0)	1 (5.0)	1 (1.3)	1 (1.3)	0	0
Infections and infestations	0	0	1 (5.0)	0	1 (1.3)	0	0	0
Enterocolitis infectious	0	0	1 (5.0)	0	1 (1.3)	0	0	0

MedDRA Version: 23.0

CTC Version CTCAE V4

Includes events reported between first dose and 100 days after last dose of study therapy.

In the nivo group, 2 subjects (both solid tumors) were reported as Grade 5 event leading to discontinuation (disease progression in both subjects). In the nivo + ipi group, 1 subject was reported as having Grade 5 event leading to discontinuation (respiratory failure).

Source: CA209070 CSR, Table S.6.1.31.1 (adae.xpt, adsl.xpt)

The Applicant's Position:

Nivolumab Monotherapy

All-causality any-grade AEs leading to discontinuation were reported in 15 (18.8%) subjects treated with nivolumab. All-causality Grade 3-4 AEs leading to discontinuation were reported in 10 (12.5%) subjects (Table 26). Two (2.5%) subjects were reported as having Grade 5 AEs leading to discontinuation (disease progression in both subjects).

- All-causality AEs (any grade) leading to discontinuation reported in 2 (2.5%) subjects each were disease progression, lipase increased, and tumor pain. All other AEs leading to discontinuation occurred in single subjects.

Nivolumab + Ipilimumab

All-causality any-grade AEs leading to discontinuation were reported in 6 (13.0%) subjects treated with nivo + ipi. All-causality Grade 3-4 AEs leading to discontinuation were reported in 3 (6.5%) subjects. One (2.2%) subject was reported as having Grade 5 AE leading to discontinuation (respiratory failure).

- All AEs (any grade) leading to discontinuation occurred in single subjects.

The FDA's Assessment:

FDA agrees with the Applicant's summary of treatment discontinuations due to adverse events. Based on the overall low incidence and types of adverse events that occurred on each treatment arm, no conclusions can be made regarding association with study treatment. will complete this section.

Significant Adverse Events

The Applicant's Position:

Select AEs included the following categories: endocrine, gastrointestinal, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reactions.

A summary of all-causality and drug-related select AEs observed with nivolumab or nivo + ipi (100 days safety window - pooled analysis: solid vs. hematology vs. total for each treatment) is provided in Table 25. Event rates and most common PTs were consistent with the known profiles of the study treatments.

Nivolumab Monotherapy

In subjects treated with nivolumab, most select AEs (all-causality and drug-related) were Grade 1-2 .

- The most frequently reported (≥ 10%) drug-related select AE categories (any grade) were hepatic (40.0%), endocrine (23.8%), and skin (20.0%).
- The most frequently reported (≥ 10%) drug-related select AEs by PT (any grade) were AST increased (27.5%), ALT increased (22.5%), hypothyroidism (12.5%), and rash maculopapular (10.0%).
- The drug-related serious select AEs reported were: diarrhea , ALT increased, AST increased, and blood bilirubin increased, and Stevens-Johnson syndrome (1.3% each).

Nivolumab + Ipilimumab

In subjects treated with nivo + ipi, most select AEs (all-causality and drug-related) were Grade 1-2.

- The most frequently reported (≥ 10%) drug-related select AE categories (any grade) were hepatic (28.3%), skin and endocrine (23.9% each), and renal (15.2%).
- The most frequently reported (≥ 10%) drug-related select AEs by PT (any grade) were ALT increased (23.9%), AST increased (17.4%), rash maculo-papular (17.4%), blood creatinine increased and hypothyroidism (15.2% each).
- The drug-related serious select AEs reported were: ALT increased, AST increased, and gammaglutamyl transferase increased (4.3% each), and rash maculopapular (2.2%).

Immune mediated adverse events: IMAEs could not be derived for CA209070 based on the CRF design. Therefore, a listing of modified IMAEs was generated, which consisted of a listing of AEs up to 100 days after the last dose that had PTs in the list of "IMAE PTs" regardless of whether or not the subject received immune-modulating medication. Event rates and most common PTs were consistent with the known profiles of the study treatments.

Nivolumab Monotherapy

Among the 80 subjects treated with nivolumab, any-grade modified IMAEs reported in ≥ 20% of subjects were as follows:

- Hepatitis events:49 (61.3%) subjects,
- Nephritis and renal dysfunction events: 24 (30.0%) subjects,
- Rash events: 23 (28.8%) subjects, and
- Diarrhea/colitis events: 21 (26.3%) subjects.

Grade 3-4 modified IMAEs reported in ≥ 5% of subjects were as follows:

- Hepatitis events: 7 (8.8%) subjects, and
- Nephritis and renal dysfunction events: 4 (5.0%) subjects.

No pneumonitis, adrenal insufficiency, thyroiditis, diabetes, or hypophysitis events were reported in subjects treated with nivolumab.

Nivolumab + Ipilimumab

Among the 46 subjects treated with nivolumab + ipilimumab, any-grade modified IMAEs reported in ≥ 20% were as follows:

- Hepatitis events: 23 (50.0%) subjects,
- Nephritis and renal dysfunction events: 15 (32.6%) subjects,
- Rash events: 12 (26.1%) subjects, and
- Diarrhea/colitis events: 11 (23.9%) subjects.

Grade 3-4 modified IMAEs reported in ≥ 5% of subjects were as follows:

- Hepatitis events: 6 (13.0%) subjects.

No adrenal insufficiency, thyroiditis, diabetes, or hypophysitis events were reported in subjects treated with nivolumab + ipilimumab.

Other events of special interest: OESIs are are events that do not fulfill all criteria to qualify as select AEs or IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. OESIs included the following categories: demyelination, encephalitis, graft-versus-host disease, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis/rhabdomyolysis, pancreatitis, and uveitis. Analyses of OESIs had extended follow up (100 days window).

Event rates and types were consistent with the known profiles of the study treatments.

Nivolumab Monotherapy

- Among the 80 subjects treated with nivolumab, 3 (3.8%) experienced an OESI: 1 subject with drug-related Grade 2 AE of pancreatitis, 1 with drug-related Grade 2 AE of pancreatitis, and 1 with unrelated Grade 3 AE of graft-versus-host disease in the setting of allogeneic transplant. All cases were resolved.

Nivolumab + Ipilimumab

- Among the 46 subjects treated with nivo + ipi, 2 (4.3%) experienced an OESI: 1 subject with drug-related Grade 2 AE of uveitis and 1 with drug-related Grade 3 SAE of pancreatitis. Both cases were resolved.

The FDA's Assessment:

The Applicant's approach to categorizing select AEs, immune-mediated AEs, and OESIs is generally acceptable. FDA notes that while the types of IMAES that occurred in Study CA209070 appear consistent with what has been presented in the USPI from other studies of nivolumab and ipilimumab the incidence of IMAEs associated with single agent nivolumab were numerically higher in the pediatric population in Study CA209070 compared to what is reported in the USPI for single agent nivolumab. However, it should be noted that the characterization of IMAEs in this study included all events that were consistent with a specified list of IMAE PTs. IMAEs were not defined as events that required use of corticosteroids and having no clear alternate etiology as they are defined in the nivolumab US prescribing information. The incidence of IMAEs associated with nivolumab in combination with ipilimumab in the pediatric study CA209070 was comparable to what is reported in the nivolumab and ipilimumab USPIs for the combination when nivolumab is administered at 1 mg/kg and ipilimumab at 3 mg/kg.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Event rates and most common PTs were consistent with the known profiles of the study treatments.

Nivolumab Monotherapy

Drug-related any-grade AEs were reported in 72 (90.0%) subjects treated with nivolumab. Drug-related Grade 3-4 AEs were reported in 27 (33.8%) subjects treated with nivolumab. There were no drug-related Grade 5 AEs.

- The most frequently reported drug-related any-grade AE (≥ 20%) was anemia (43.8%), fatigue (37.5%), white blood cell count decreased (30.0%), AST increased (27.5%), lymphocyte count decreased (27.5%), neutrophil count decreased (27.5%), and ALT increased (22.5%).
- The most frequently reported drug-related Grade 3-4 AEs (≥ 5%) were lymphocyte count decreased (12.5%), anemia (6.3%), and neutrophil count decreased (5.0%).

Nivolumab + Ipilimumab

Drug-related any-grade AEs were reported in 46 (100.0%) subjects treated with nivo + ipi. Drug-related Grade 3-4 AEs were reported in 16 (34.8%) subjects treated with nivo + ipi. There were no drug-related Grade 5 AEs.

- The most frequently reported drug-related any-grade AEs (≥ 20%) were lymphocyte count decreased (43.5%), anemia (41.3), fatigue (34.8%), ALT increased (23.9%), platelet count decreased (23.9%), and white blood cell count decreased and nausea (21.7% each).
- The most frequently reported drug-related Grade 3-4 AEs (≥ 5%) were lymphocyte count decreased (13.0%), lipase increased (8.7%), and hyponatremia (6.5%).

The FDA's Assessment:

FDA considers the occurrence of all adverse events that occur on study treatment when characterizing the adverse reactions that occur on study treatment. One hundred percent of patients in both the single agent nivolumab arm and the nivolumab in combination with ipilimumab arm had treatment emergent adverse events.

Laboratory Findings

The Applicant's Position:

The data presented here is summarized based on laboratory parameters, whereas laboratory abnormalities that were reported AEs by the investigator are presented in other sections. The observed laboratory abnormalitieswere consistent with the known profiles of the study treatments.

Hematology

Nivolumab Monotherapy

- Among the 79 subjects with on-treatment hematology test results, hematologic abnormalities were primarily Grade 1 or 2.
- Grade 3-4 hematologic abnormalities reported were as follows: decreased hemoglobin (8.9% Grade 3), decreased leukocytes (5.1% Grade 3, 1.3% Grade 4), decreased absolute neutrophil count (1.3% Grade 3, 2.5% Grade 4), and decreased platelet count (1.3% Grade 3, 1.3% Grade 4).

Nivolumab + Ipilimumab

- Among the 46 subjects with on-treatment hematology laboratory test results, hematologic abnormalities were primarily Grade 1 or 2.

- Grade 3-4 hematologic abnormalities reported were as follows: decreased hemoglobin (10.9% Grade 3), decreased leukocytes (2.2% Grade 3), and decreased absolute neutrophil count (2.2% Grade 3).

Chemistry

Nivolumab Monotherapy

- ***Liver Tests:*** Among the 79 subjects with on-treatment liver function test results, abnormalities in ALT, AST, and bilirubin (all increases) occurred at low frequencies and were all Grade 1 or 2. No subjects had concurrent ALT or AST > 3 x´ ULN with total bilirubin > 2 x´ ULN within 1 day and within 30 days.
- ***Thyroid Function Tests:*** TSH increases (> ULN) from baseline (≤ ULN) were reported in 9 (26.5%) subjects in the nivolumab arm, and there were no decreases (< LLN) from baseline (≥ LLN) reported.
- ***Kidney Function Tests:*** The majority of subjects with at least 1 on-treatment measurement had normal creatinine values. The abnormalities in creatinine (increase) in subjects in the nivolumab arm were primarily Grade 2 in severity (12.7%). Grade 1 (2.5%) and Grade 3 (1.3%) abnormalities were also reported; there were no Grade 4 abnormalities.
- ***Pancreatic Function Tests:*** The majority of subjects in the nivolumab arm with at least 1 on-treatment measurement had normal amylase and lipase levels (31/33 [93.9%] subjects). Two subjects had Grade 1 amylase abnormality and 2 subjects had Grade 1 lipase abnormality. There were no Grade 2, 3, or 4 abnormalities for either amylase or lipase.
- ***Electrolytes and Glucose:*** Among the 79 subjects in the nivolumab arm with on-treatment results for blood sodium, potassium, calcium and magnesium, abnormalities were mostly Grade 1 or 2. Grade 3 4 abnormalities observed were hyponatremia (2.5% Grade 3), hyperkalemia (1.3% Grade 3), and hypokalemia (6.3% Grade 3). Among the 71 subjects with on-treatment results for blood glucose, 2 (2.8%) subjects had Grade 1 hypoglycemia.

Nivolumab + Ipilimumab

- ***Liver Tests:*** Among the 46 subjects with on-treatment liver function test results, abnormalities in ALT, AST, and bilirubin (all increases) occurred at low frequencies and were all Grade 1 or 2. No subjects had concurrent ALT or AST > 3 × ULN with total bilirubin > 2 × ULN within 1 day and within 30 days.
- ***Thyroid Function Tests:*** TSH increases (> ULN) from baseline (≤ ULN) were reported in 5 (16.1%) subjects in the nivo + ipi arm, and decreases (< LLN) from baseline (≥ LLN) were reported in 1 (3.2%) subject.
- ***Kidney Function Tests:*** The majority of subjects with at least 1 on-treatment measurement had normal creatinine values. The abnormalities in creatinine (increase) in subjects in the nivo + ipi arm were Grade 1 (8.7%) or Grade 2 (10.9%). There were no Grade 3 or 4 abnormalities.
- ***Pancreatic Function Tests:*** The majority of subjects in the nivo + ipi arm with at least 1 on-treatment measurement had normal amylase and lipase levels (24/30 [80.0%] subjects). Five subjects had Grade 1 amylase abnormality and 1 subject had Grade 2 amylase

abnormality; there were no Grade 3 or 4 amylase abnormalities. One subject had Grade 2 lipase abnormality and 3 subjects had Grade 3 lipase abnormality. There were no Grade 1 or Grade 4 lipase abnormalities.

- ***Electrolytes and Glucose:*** Among the 46 subjects in the nivo + ipi arm with on-treatment results for blood sodium, potassium, calcium and magnesium, abnormalities were mostly Grade 1 or 2. Grade 3-4 abnormalities observed were hyponatremia (2.2% Grade 3) and hypokalemia (1.3% Grade 3). Among the 41 subjects with on-treatment results for blood glucose, 1 (2.4%) subject had Grade 1 hypoglycemia.

The FDA's Assessment:

FDA agrees with the Applicant's description of laboratory abnormalities on Study CA209070. The observed laboratory abnormalities observed in both the nivolumab arm and the nivolumab in combination with ipilimumab arm were primarily Grade 1 or 2.

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 the vital sign assessment.

Electrocardiograms (ECGs)

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

QT

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Immunogenicity

The Applicant's Position:

Immunogenicity was evaluated in Study CA209070 from the detection of nivolumab and ipilimumab ADA and characterization of NAb. Samples from CA209070 were analyzed for nivolumab and ipilimumab ADAs and NAb using validated immunoassay methods. The main results were:

- In combined cohorts treated with nivo mono, 3/51 (5.9%) subjects were tested positive for ADA at baseline, and 1/51 (2.0%) subject was tested positive post baseline but was not persistently positive or NAb positive.
- In combined cohorts treated with nivo+ipi, − 2/35 (5.7%) subjects were tested positive for nivolumab ADA at baseline, and 1/35 (2.9%) subject was tested positive post baseline but was not persistently positive or NAb positive.
- 1/33 (3.0%) subject was tested positive for ipilimumab ADA at baseline, and no subjects were tested positive post baseline.
- The low number of ADA positive and ADA evaluable subjects precluded meaningful assessment of the impact of immunogenicity on the efficacy and safety of tested regimens, respectively.

The low incidence of immunogenicity observed in this pediatric study is consistent with the generally low incidence rate observed in adults for both antibodies.

The FDA's Assessment:
See Section 6. FDA agrees that the incidence of treatment-emergent (TE) ADA and Nab were low in study CA209070. . Due to their low incidences, no conclusions can be made on the impact of TE-ADAs and TE-Nabs on the safety of nivolumab.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 CA209070 - Part E

Data and The Applicant's Position:
Eight subjects were treated with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg in Part E of the study. Of the 7 evaluable subjects for toxicity, one 12-year-old subject experienced Cycle 1 DLTs (fever and rash maculo-papular) and 2 young adult (22-and 25-years old) subjects experienced Cycle 2 DLTs (diarrhea in 1 subject and alkaline phosphatase increased, AST increased, and hyperthyroidism in the second). Per protocol safety monitoring rule, enrollment to Part E was closed after first DLT was observed.[Error! Bookmark not defined.] Limited data from Part E preclude definitive conclusions regarding safety.

The FDA's Assessment:
Given the limited number of patients enrolled and the overall short duration of treatment on study, no definitive conclusions can be made about the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg regimen that was administered in Part E of Study CA209070. Due to the observances of DLT, enrollment to this part of the study was closed.

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

The Applicant's Position: Not applicable.

The FDA's Assessment:
Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

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Table 27: Applicant - Any Adverse Events Summary (in ≥ 20% Subjects in Age < 18 Years Subgroup) by Worst CTC Grade by Age with 100 Days Safety Window - All Treated Subjects in CA209070 (Parts A-D)

	Age ≥ 12 years to < 18 years				Age < 18 years				Age ³ 18 years			
	Nivo		Nivo+Ipi		Nivo		Nivo+Ipi		Nivo		Nivo+Ipi	
SOC (%)	Total (N=33)		Solid (N=20)		Total (N=64)		Solid (N=33)		Total (N=16)		Solid (N=13)	
PT (%)	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4
Total subjects with an event	**33 (100.0)**	**22 (66.7)**	**20 (100.0)**	**11 (55.0)**	**64 (100)**	**42 (65.6)**	**33 (100)**	**15 (45.5)**	**16 (100)**	**13 (81.3)**	**13 (100)**	**8 (61.5)**
Metabolism and nutrition disorders	**32 (97.0)**	**11 (33.3)**	**19 (95.0)**	**8 (40.0)**	**63 (98.4)**	**20 (31.3)**	**31 (93.9)**	**12 (36.4)**	**16 (100)**	**2 (12.5)**	**12 (92.3)**	**3 (23.1)**
Hyponatraemia	20 (60.6)	4 (12.1)	13 (65.0)	4 (20.0)	36 (56.3)	6 (9.4)	19 (57.6)	6 (18.2)	8 (50.0)	1 (6.3)	5 (38.5)	1 (7.7)
Hypocalcaemia	18 (54.5)	0	7 (35.0)	1 (5.0)	34 (53.1)	0	13 (39.4)	1 (3.0)	6 (37.5)	0	2 (15.4)	0
Hypoalbuminaemia	19 (57.6)	2 (6.1)	9 (45.0)	1 (5.0)	34 (53.1)	3 (4.7)	15 (45.5)	1 (3.0)	8 (50.0)	1 (6.3)	4 (30.8)	0
Hyperglycaemia	15 (45.5)	0	7 (35.0)	1 (5.0)	28 (43.8)	2 (3.1)	11 (33.3)	1 (3.0)	4 (25.0)	0	6 (46.2)	0
Decreased appetite	13 (39.4)	1 (3.0)	4 (20.0)	0	23 (35.9)	3 (4.7)	9 (27.3)	0	6 (37.5)	1 (6.3)	8 (61.5)	2 (15.4)
Hypokalaemia	12 (36.4)	2 (6.1)	8 (40.0)	2 (10.0)	27 (42.2)	8 (12.5)	12 (36.4)	4 (12.1)	6 (37.5)	1 (6.3)	4 (30.8)	0
Hypophosphataemia	11 (33.3)	2 (6.1)	7 (35.0)	1 (5.0)	26 (40.6)	5 (7.8)	11 (33.3)	2 (6.1)	5 (31.3)	0	3 (23.1)	1 (7.7)
Hyperkalaemia	7 (21.2)	2 (6.1)	1 (5.0)	0	14 (21.9)	3 (4.7)	2 (6.1)	0	2 (12.5)	0	2 (15.4)	0
Hypomagnesaemia	10 (30.3)	0	5 (25.0)	0	18 (28.1)	0	6 (18.2)	0	4 (25.0)	0	1 (7.7)	0
Hypermagnesemia	5 (15.2)	0	4 (20.0)	0	13 (20.3)	0	6 (18.2)	1 (3.0)	2 (12.5)	0	1 (7.7)	0
General disorders and administration site conditions	**29 (87.9)**	**3 (9.1)**	**13 (65.0)**	**2 (10.0)**	**56 (87.5)**	**6 (9.4)**	**22 (66.7)**	**2 (6.1)**	**14 (87.5)**	**0**	**12 (92.3)**	**2 (15.4)**
Fatigue	18 (54.5)	1 (3.0)	8 (40.0)	1 (5.0)	38 (59.4)	1 (1.6)	14 (42.4)	1 (3.0)	11 (68.8)	0	9 (69.2)	1 (7.7)
Pyrexia	13 (39.4)	1 (3.0)	9 (45.0)	1 (5.0)	32 (50.0)	4 (6.3)	14 (42.4)	1 (3.0)	6 (37.5)	0	6 (46.2)	0
Pain	8 (24.2)	2 (6.1)	2 (10.0)	0	19 (29.7)	4 (6.3)	4 (12.1)	0	2 (12.5)	0	2 (15.4)	1 (7.7)
Disease progression	7 (21.2)	0	3 (15.0)	0	15 (23.4)	0	5 (15.2)	0	2 (12.5)	0	1 (7.7)	0
Investigations	**30 (90.9)**	**21 (63.6)**	**20 (100.0)**	**9 (45.0)**	**60 (93.8)**	**40 (62.5)**	**32 (97.0)**	**14 (42.4)**	**15 (93.8)**	**12 (75.0)**	**13 (100)**	**7 (53.8)**
Platelet count decreased	21 (63.6)	9 (27.3)	10 (50.0)	3 (15.0)	39 (60.9)	18 (28.1)	14 (42.4)	4 (12.1)	9 (56.3)	5 (31.3)	3 (23.1)	1 (7.7)
White blood cell count decreased	19 (57.6)	8 (24.2)	7 (35.0)	2 (10.0)	39 (60.9)	14 (21.9)	10 (30.3)	3 (9.1)	10 (62.5)	6 (37.5)	4 (30.8)	1 (7.7)

Table 27: Applicant - Any Adverse Events Summary (in ≥ 20% Subjects in Age < 18 Years Subgroup) by Worst CTC Grade by Age with 100 Days Safety Window - All Treated Subjects in CA209070 (Parts A-D)

	Age ≥ 12 years to < 18 years				Age < 18 years				Age ³ 18 years			
	Nivo		Nivo+Ipi		Nivo		Nivo+Ipi		Nivo		Nivo+Ipi	
SOC (%)	**Total (N=33)**		**Solid (N=20)**		**Total (N=64)**		**Solid (N=33)**		**Total (N=16)**		**Solid (N=13)**	
PT (%)	**Any**	**G3-4**	**Any**	**G3-4**	**Any**	**G3-4**	**Any**	**G3-4**	**Any**	**G3-4**	**Any**	**G3-4**
Lymphocyte count decreased	17 (51.5)	13 (39.4)	12 (60.0)	6 (30.0)	35 (54.7)	22 (34.4)	18 (54.5)	7 (21.2)	15 (93.8)	10 (62.5)	10 (76.9)	6 (46.2)
Neutrophil count decreased	14 (42.4)	10 (30.3)	5 (25.0)	2 (10.0)	35 (54.7)	19 (29.7)	7 (21.2)	3 (9.1)	9 (56.3)	9 (56.3)	4 (30.8)	1 (7.7)
AST increased	12 (36.4)	1 (3.0)	5 (25.0)	2 (10.0)	28 (43.8)	4 (6.3)	11 (33.3)	3 (9.1)	8 (50.0)	0	4 (30.8)	2 (15.4)
ALT increased	15 (45.5)	2 (6.1)	9 (45.0)	1 (5.0)	28 (43.8)	5 (7.8)	13 (39.4)	1 (3.0)	6 (37.5)	0	5 (38.5)	2 (15.4)
Blood creatinine increased	7 (21.2)	2 (6.1)	9 (45.0)	0	16 (25.0)	3 (4.7)	12 (36.4)	0	7 (43.8)	0	3 (23.1)	0
C-reactive protein increased	8 (24.2)	0	4 (20.0)	0	15 (23.4)	0	6 (18.2)	0	4 (25.0)	0	5 (38.5)	0
Weight decreased	6 (18.2)	0	7 (35.0)	0	13 (20.3)	1 (1.6)	10 (30.3)	1 (3.0)	6 (37.5)	0	7 (53.8)	1 (7.7)
Blood alkaline phosphatase increased	6 (18.2)	2 (6.1)	7 (35.0)	1 (5.0)	10 (15.6)	3 (4.7)	8 (24.2)	1 (3.0)	7 (43.8)	1 (6.3)	3 (23.1)	0
Lipase increased	1 (3.0)	0	3 (15.0)	1 (5.0)	6 (9.4)	3 (4.7)	7 (21.2)	3 (9.1)	1 (6.3)	0	3 (23.1)	2 (15.4)
Gastrointestinal disorders	**25 (75.8)**	**5 (15.2)**	**12 (60.0)**	**1 (5.0)**	**51 (79.7)**	**15 (23.4)**	**17 (51.5)**	**4 (12.1)**	**12 (75.0)**	**5 (31.3)**	**11 (84.6)**	**1 (7.7)**
Nausea	18 (54.5)	1 (3.0)	7 (35.0)	0	32 (50.0)	2 (3.1)	9 (27.3)	1 (3.0)	6 (37.5)	1 (6.3)	7 (53.8)	1 (7.7)
Vomiting	12 (36.4)	1 (3.0)	7 (35.0)	0	30 (46.9)	6 (9.4)	12 (36.4)	1 (3.0)	6 (37.5)	0	8 (61.5)	0
Constipation	12 (36.4)	0	6 (30.0)	0	24 (37.5)	0	8 (24.2)	0	6 (37.5)	0	3 (23.1)	0
Abdominal pain	6 (18.2)	0	5 (25.0)	1 (5.0)	23 (35.9)	3 (4.7)	8 (24.2)	2 (6.1)	3 (18.8)	1 (6.3)	5 (38.5)	1 (7.7)
Diarrhoea	6 (18.2)	0	5 (25.0)	0	18 (28.1)	1 (1.6)	7 (21.2)	1 (3.0)	3 (18.8)	1 (6.3)	4 (30.8)	0
Blood and lymphatic system disorder	**24 (72.7)**	**9 (27.3)**	**16 (80.0)**	**8 (40.0)**	**52 (81.3)**	**24 (37.5)**	**27 (81.8)**	**10 (30.3)**	**12 (75.0)**	**5 (31.3)**	**7 (53.8)**	**1 (7.7)**
Anaemia	23 (69.7)	8 (24.2)	16 (80.0)	8 (40.0)	51 (79.7)	21 (32.8)	27 (81.8)	10 (30.3)	12 (75.0)	3 (18.8)	6 (46.2)	0
Respiratory, thoracic and mediastinal disorders	**25 (75.8)**	**8 (24.2)**	**12 (60.0)**	**5 (25.0)**	**49 (76.6)**	**15 (23.4)**	**21 (63.6)**	**7 (21.2)**	**11 (68.8)**	**3 (18.8)**	**11 (84.6)**	**2 (15.4)**

Table 27: Applicant - Any Adverse Events Summary (in ≥ 20% Subjects in Age < 18 Years Subgroup) by Worst CTC Grade by Age with 100 Days Safety Window - All Treated Subjects in CA209070 (Parts A-D)

	Age ≥ 12 years to < 18 years				Age < 18 years				Age ³ 18 years			
	Nivo		Nivo+Ipi		Nivo		Nivo+Ipi		Nivo		Nivo+Ipi	
SOC (%)	Total (N=33)		Solid (N=20)		Total (N=64)		Solid (N=33)		Total (N=16)		Solid (N=13)	
PT (%)	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4
Cough	12 (36.4)	0	8 (40.0)	0	28 (43.8)	0	14 (42.4)	0	7 (43.8)	0	7 (53.8)	1 (7.7)
Dyspnoea	11 (33.3)	2 (6.1)	5 (25.0)	3 (15.0)	16 (25.0)	5 (7.8)	7 (21.2)	4 (12.1)	4 (25.0)	1 (6.3)	3 (23.1)	1 (7.7)
Nasal congestion	7 (21.2)	0	3 (15.0)	0	13 (20.3)	0	4 (12.1)	0	5 (31.3)	0	4 (30.8)	0
Pleural effusion	7 (21.2)	3 (9.1)	7 (35.0)	3 (15.0)	10 (15.6)	5 (7.8)	11 (33.3)	5 (15.2)	1 (6.3)	0	1 (7.7)	0
Musculoskeletal and connective tissue disorders	**20 (60.6)**	**6 (18.2)**	**13 (65.0)**	**3 (15.0)**	**36 (56.3)**	**8 (12.5)**	**20 (60.6)**	**3 (9.1)**	**11 (68.8)**	**4 (25.0)**	**9 (69.2)**	**1 (7.7)**
Pain in extremity	9 (27.3)	1 (3.0)	7 (35.0)	3 (15.0)	20 (31.3)	2 (3.1)	9 (27.3)	3 (9.1)	4 (25.0)	1 (6.3)	4 (30.8)	0
Back pain	6 (18.2)	3 (9.1)	4 (20.0)	1 (5.0)	13 (20.3)	4 (6.3)	6 (18.2)	1 (3.0)	5 (31.3)	1 (6.3)	6 (46.2)	0
Nervous system disorders	**20 (60.6)**	**5 (15.2)**	**13 (65.0)**	**1 (5.0)**	**34 (53.1)**	**9 (14.1)**	**18 (54.5)**	**2 (6.1)**	**9 (56.3)**	**2 (12.5)**	**7 (53.8)**	**0**
Headache	12 (36.4)	0	10 (50.0)	0	20 (31.3)	0	12 (36.4)	0	6 (37.5)	0	6 (46.2)	0
Skin and subcutaneous tissue disorders	**17 (51.5)**	**1 (3.0)**	**10 (50.0)**	**1 (5.0)**	**33 (51.6)**	**4 (6.3)**	**17 (51.5)**	**2 (6.1)**	**10 (62.5)**	**0**	**5 (38.5)**	**0**
Rash maculo-papular	6 (18.2)	0	4 (20.0)	0	13 (20.3)	2 (3.1)	8 (24.2)	1 (3.0)	3 (18.8)	0	1 (7.7)	0
Pruritus	5 (15.2)	0	1 (5.0)	0	13 (20.3)	0	2 (6.1)	0	4 (25.0)	0	2 (15.4)	0
Cardiac disorders	**13 (39.4)**	**0**	**11 (55.0)**	**0**	**28 (43.8)**	**0**	**17 (51.5)**	**1 (3.0)**	**6 (37.5)**	**0**	**7 (53.8)**	**0**
Sinus tachycardia	12 (36.4)	0	9 (45.0)	0	27 (42.2)	0	15 (45.5)	0	5 (31.3)	0	7 (53.8)	0
Vascular disorders	**15 (45.5)**	**2 (6.1)**	**7 (35.0)**	**1 (5.0)**	**28 (43.8)**	**4 (6.3)**	**12 (36.4)**	**2 (6.1)**	**6 (37.5)**	**2 (12.5)**	**8 (61.5)**	**2 (15.4)**
Hypertension	8 (24.2)	0	6 (30.0)	1 (5.0)	15 (23.4)	1 (1.6)	9 (27.3)	2 (6.1)	4 (25.0)	1 (6.3)	6 (46.2)	2 (15.4)
Psychiatric disorders	**13 (39.4)**	**1 (3.0)**	**9 (45.0)**	**1 (5.0)**	**24 (37.5)**	**1 (1.6)**	**13 (39.4)**	**1 (3.0)**	**6 (37.5)**	**1 (6.3)**	**8 (61.5)**	**0**
Anxiety	9 (27.3)	1 (3.0)	5 (25.0)	1 (5.0)	15 (23.4)	1 (1.6)	8 (24.2)	1 (3.0)	2 (12.5)	0	5 (38.5)	0
Renal and urinary disorders	**14 (42.4)**	**2 (6.1)**	**6 (30.0)**	**0**	**25 (39.1)**	**7 (10.9)**	**11 (33.3)**	**1 (3.0)**	**6 (37.5)**	**1 (6.3)**	**8 (61.5)**	**1 (7.7)**
Hematuria	6 (18.2)	1 (3.0)	1 (5.0)	0	15 (23.4)	3 (4.7)	2 (6.1)	0	3 (18.8)	0	2 (15.4)	0
Proteinuria	7 (21.2)	0	5 (25.0)	0	11 (17.2)	0	8 (24.2)	0	4 (25.0)	0	5 (38.5)	0

Table 27: Applicant - Any Adverse Events Summary (in ≥ 20% Subjects in Age < 18 Years Subgroup) by Worst CTC Grade by Age with 100 Days Safety Window - All Treated Subjects in CA209070 (Parts A-D)

	Age ≥ 12 years to < 18 years				Age < 18 years				Age ³ 18 years			
	Nivo		Nivo+Ipi		Nivo		Nivo+Ipi		Nivo		Nivo+Ipi	
SOC (%)	Total (N=33)		Solid (N=20)		Total (N=64)		Solid (N=33)		Total (N=16)		Solid (N=13)	
PT (%)	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4	Any	G3-4
Endocrine disorders	**6 (18.2)**	**1 (3.0)**	**3 (15.0)**	**0**	**16 (25.0)**	**1 (1.6)**	**8 (24.2)**	**0**	**1 (6.3)**	**0**	**5 (38.5)**	**0**
Hypothyroidism	4 (12.1)	0	2 (10.0)	0	11 (17.2)	0	7 (21.2)	0	1 (6.3)	0	2 (15.4)	0

MedDRA Version: 23.0
CTC Version CTCAE V4 and V5
Includes events reported between first dose and 100 days after last dose of study therapy.
Preferred terms (PTs) were selected based on ≥ 20% subjects in any of the treatment groups for the age < 18 years subgroup
Source: CA209070 Interim CSR, Table S.6.1.5.4 (adae.xpt, adsl.xpt)

The Applicant's Position:
The overall safety profile of nivolumab and nivo+ipi was comparable between adolescent subjects (≥ 12 years to < 18 years) (N = 53) and adult subjects (≥ 18 years of age) (N = 29) (Table 27). No substantial differences in all causality AEs (all grades and Grade 3-4) were reported in subjects
≥ 18 years of age compared to all pediatric subjects (< 18 years) or adolescent subjects (≥ 12 years to < 18 years). Differences in AEs noted between the age groups were of limited interpretability because of small sample sizes in either treatment regimen.

The **only adolescent subject with melanoma** enrolled in CA209070 was a 15-year-old, Asian, female who received 2 doses (C1D1 and C1D15) of nivolumab 3 mg/kg. The subject had a Lansky performance status of 90, received prior lines of anticancer immunotherapies (including cellular therapy) and underwent surgery (3 resections). During treatment, the subject did not experience any DLTs. The subject experienced Grade 1 constipation and a Grade 2 allergic reaction. The subject discontinued treatment due to PD and died due to disease progression 137 days after receiving the last dose of nivolumab.

No meaningful differences in safety were noted for male subjects compared with female subjects. For subgroups based on race or ethnicity, most subjects were clustered in a single category (White or Not Hispanic/Not Latino), which limited the interpretability of potential differences.

The FDA's Assessment:
FDA agrees with the Applicant's position. Based on the overall small study size and small size of the demographic subgroups no conclusions can be made regarding an association between adverse events and demographic characteristics. Of the 126 patients treated in Study CA209070, there were 13 Black or African American patients (10.3%), 8 Asian patients (6.3%), 1 American Indian or Alaska native patient (0.8%),93 White patients (73.8%), 7 Unknown (5.6%) and 4 patients with race Not Reported (3.2%).

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Supportive studies CA209067, CA209915, and CA209238 provide data in adult subjects treated for advanced or adjuvant (resected) melanoma, and data in a limited number of adolescent subjects (CA209915).

CA209067 Safety Summary
Safety results provided below reflect the data presented in the current approved USPI:

- The median duration of exposure to nivolumab was 2.8 months (range: 1 day to 36.4 months) for the nivo+ipi arm and 6.6 months (range: 1 day to 36.0 months) for the nivolumab arm. In the nivo+ipi arm, 39% were exposed to nivolumab for ≥ 6 months and 30% exposed for > 1 year. In the nivolumab arm, 53% were exposed for ≥ 6 months and 40% for > 1 year.

- Serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the nivolumab and ipilimumab arm relative to the nivolumab arm.
- The most frequent (≥ 10%) serious adverse reactions in the nivo + ipi arm and the nivolumab arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). The most frequent adverse reactions leading to discontinuation of both drugs in the nivolumab and ipilimumab arm and of nivolumab in the nivolumab arm, respectively, were colitis (10% and 0.6%), diarrhea (8% and 2.2%), increased ALT (4.8% and 1.0%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%).
- The most common (≥ 20%) adverse reactions in the nivo + ipi arm were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases. The most common (≥ 20%) adverse reactions in the nivolumab arm were fatigue, rash, musculoskeletal pain, diarrhea, nausea, cough, pruritus, upper respiratory tract infection, decreased appetite, headache, constipation, arthralgia, and vomiting.
- The incidence of adverse reactions and laboratory abnormalities in this study are presented in Table 9 and Table 10, respectively, of the nivolumab USPI.[46]

Long-term results for CA209067 based on minimum follow-up of 48 months are described in the sBLA dossier; safety remained consistent over time. CA209067 is ongoing for further long term follow-up.

CA209915 Safety Summary

Overall Population: The safety profile of nivolumab and nivo+ipi were consistent with the established safety profiles of nivolumab and ipilimumab in other tumor types. No new safety concerns were identified.

As of DBL of 08-Sep-2020 (18-month FU), the frequencies of all causality SAEs (33.6% versus 20.2%), drug-related SAEs (21.6% versus 7.2%), AEs leading to discontinuation (33.8% versus 11.8%), drug-related AEs leading to discontinuation (31.6% versus 10.4%), and drug-related AEs (94.2% versus 85.9%) were greater in the nivo+ipi group compared to the nivolumab group.

A total of 99 (10.8%) and 101 (11.0%) deaths were reported in the nivolumab and nivo+ipi groups, respectively. Disease progression was the most common cause of death for all groups. Four drug-related deaths were reported in the nivo+ipi group (liver failure, myasthenia gravis, respiratory distress syndrome, and pneumonitis).

- <u>All-causality SAEs</u>: In the nivolumab group, the most frequently reported SAEs were basal cell carcinoma (2.4%) and squamous cell carcinoma (1.1%). In the nivo+ipi group, the most frequently reported SAEs were colitis (2.3%), and hypophysitis (2.0%).
- <u>Drug-related SAEs</u>: In the nivolumab group, the most frequently reported drug-related SAE was hypophysitis (0.7%). In the nivo+ipi group, the most frequently reported drug-related SAEs were colitis (2.3%) and hypophysitis (2.0%).
- <u>All-causality AEs leading to discontinuation</u>: In the nivolumab group, the most frequently reported AEs leading to discontinuation were colitis (0.9%) and diarrhea (0.8%). In the

nivo+ipi group, the most frequently reported AEs leading to discontinuation were colitis and diarrhea (2.6% each).

- All-causality AEs: In the nivolumab group, the most frequently reported AEs (≥ 20% of subjects) were fatigue (36.4%), diarrea (32.7%), pruritus (25.7%), and rash (25.2%). In the nivo+ipi group, the most frequently reported AEs (≥ 20% of subjects) were fatigue (37.0%), pruritus (36.7%), diarrhea (36.4%), headache (29.0%), and rash (27.9%).
- Drug-related AEs: In the nivolumab group, the most frequently reported drug-related AEs (≥ 20% of subjects) were fatigue (30.1%), pruritus (21.2%), rash (20.9%), and diarrhea (20.4%). In the nivo+ipi group, the most frequently reported drug-related AEs (≥ 20% of subjects) were pruritus (33.1%), fatigue (30.5%), diarrhea (27.1%), rash (24.2%), and hypothyroidism (22.1%).
- Laboratory Abnormalities: The majority of subjects in both treatment groups had normal (Grade 0) hematology values during the treatment reporting period. Abnormalities in hematology tests were primarily Grade 1 in both treatment groups. Grade 3 lymphocyte (absolute) abnormalities were reported in 1.6% of subjects in the nivo+ipi group. No other Grade 3-4 hematologic abnormalities were reported in ≥ 1% of subjects in either treatment group.

  The majority of subjects in both treatment groups had normal (Grade 0) hepatic values during the reporting period. Abnormalities in hepatic parameters (all increases) were primarily Grade 1 in both groups. In the nivo+ipi group, the only Grade 3-4 hepatic abnormality reported in ≥ 5% of subjects was increased ALT (6.3% Grade 3; 0.9% Grade 4). In the nivo group, there were no Grade 3-4 hepatic abnormalities reported in ≥ 5% of subjects.

  In both treatment groups, the majority of subjects had normal (Grade 0) creatinine values during the treatment reporting period, and the majority of reported abnormalities in creatinine were Grade 1 or 2.

  TSH increases (> ULN) from baseline (≤ ULN) were reported in 251/897 (28.6%) subjects in the nivo+ipi group and in 216/905 (23.9%) subjects in the nivo group. Decreases (< lower limit of normal [LLN]) from baseline (TSH ≥ LLN) were reported in 344/905 (39.1%) subjects in the nivo+ipi group and in 232/905 (25.6%) subjects in the nivo group.

  In both treatment groups, most subjects had normal (Grade 0) electrolyte levels during the treatment reporting period, and abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. Hyponatremia was the only Grade 3-4 electrolyte abnormality reported in≥ 2% of subjects, and this was seen only in the nivo+ipi group. Hyperglycemia during treatment was not reported in the nivo+ipi group. In the nivo group, 2 subjects experienced hyperglycemia, and both were of Grade 3.

  Hypoglycemia in both treatment groups were mainly Grade 2 in severity. Out of 8 subjects who had hypoglycemia, in the nivo+ipi group, Grade 3-4 hypoglycemia was reported in 2 subjects (1 Grade 3 and 1 Grade 4). In the nivo group, Grade 3 hypoglycemia occurred in 3 subjects and no Grade 4 hypoglycemia was reported.

Safety results for the nivo mono arm in CA209915 were consistent with results observed for nivo mono in Study CA209238.

Adolescent Subjects: Safety data for these 3 subjects are as follows:

- 15-year old White male who was randomized to nivolumab, reported few AEs and no SAEs. All reported AEs were Grade 1, and only 1 AE of nausea was considered related to study treatment.
- 16-year old White female who was randomized to nivolumab reported the following AEs that were assessed as being related to study treatment: anorexia, fatigue, low TSH, weight loss, alopecia, and lipase increased. Two AEs (wound infection and would dehiscence) were Grade 3. All other AEs were Grade 1 or 2. The subject reported no SAEs.
- 16-year old White male who was randomized to nivo+ipi, reported SAEs of Grade 3 thrombocytopenia on Day 364 and Grade 2 pneumocystis jirovecii pneumonia on Day 417, after the first dose of treatment. None of these SAEs was considered related to study treatment. This subject received 16 doses of nivolumab and 6 doses of ipilimumab. The subject died from disease progression 259 days after the last dose of treatment.

CA209238 Safety Summary

Safety results provided below reflect the data presented in the current approved USPI:

- The median duration of exposure was 11.5 months in nivolumab-treated patients. In this trial, 74% of patients received nivolumab for > 6 months.
- Serious adverse reactions occurred in 18% of nivolumab-treated patients. Study therapy was discontinued for adverse reactions in 9% of nivolumab-treated patients. Twenty-eight percent of nivolumab-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of nivolumab-treated patients.
- The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of nivolumab-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions (at least 20%) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).
- The incidence of adverse reactions and laboratory abnormalities in this study are presented in Table 11 and Table 12, respectively, of the nivolumab USPI.[46]

Long-term results for CA209238 based on minimum follow-up of 48 months are described in the sBLA dossier; safety remained consistent over time.

The FDA's Assessment:

[FDA agreed with the Applicant's summary of the safety results of the supportive trials. FDA notes there were only three adolescent patients enrolled to Study CA209915. The safety in the adult population in conjunction with the clinical pharmacology review of the population PK data and E-R safety data served as the basis to support the extension of the nivolumab and ipilimumab indications to a pediatric population.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

There were no findings related to human carcinogenicity.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Human Reproduction and Pregnancy

The Applicant's Position:

There is no new information.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

There is no new information.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is no new information.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Nivolumab

Based on pharmacovigilance activities conducted by BMS WorldWide Patient Safety, review of postmarketing safety data is consistent with, and confirms the nivolumab clinical trial safety data. The safety profile of nivolumab in the postmarketing setting remains favorable. Postmarketing data for nivolumab are subject to continued pharmacovigilance monitoring and are reported as per applicable post marketing safety reporting requirements, as well as periodically to global health authorities.

Ipilimumab

Based on pharmacovigilance activities conducted by BMS WorldWide Patient Safety, review of post-marketing safety data is consistent with, and confirms the ipilimumab clinical trial safety data. The benefit-risk profile of ipilimumab in the post-marketing setting remains positive for

the approved indications.

The FDA's Assessment:
FDA agrees with the Applicant's position. Postmarketing adverse event reporting updates for nivolumab and ipilimumab were submitted August 2022 for the time periods below. No new safety signals were identified during this postmarketing reporting period.

- Nivolumab PBRER #11 (04-Jul-2020 to 03-Jul-2021)
- Ipilimumab PBRER #12 (25-Mar-2021 to 24-Mar-2022)

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
The safety profile of nivolumab in the postmarketing setting remains favorable. The benefit-risk profile of ipilimumab in the post-marketing setting remains positive for the approved indications.

The FDA's Assessment:
The safety in the postmarketing setting is expected to be similar to that observed in the clinical trials that served as the basis for the approval of nivolumab and ipilimumab for the treatment of resectable, unresectable and metastatic melanoma.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
Safety data from pediatric and young adult subjects with R/R solid or hematologic tumors in Study CA209070 are consistent with the known safety profiles of nivo mono and nivo + ipi. Immune-related AEs, in adolescent subjects were manageable using treatment algorithms previously established for adult patients. No new safety signals were identified. No changes in risk minimization measures are warranted as per the new pivotal study data.

Advanced Melanoma (Nivolumab and Nivo+Ipi): The safety profiles of nivo mono and nivo+ipi (nivo 1 mg/kg + ipi 3 mg/kg) in advanced melanoma in adults are well characterized in CA209067. Additional safety data are available in the USPI for nivolumab for the approved indication of advanced melanoma in adults, as demonstrated by Studies CA209066 and CA209037. Safety data are available in the USPI for ipilimumab 3mg/kg as monotherapy for the approved indication of advanced melanoma in adolescents, as demonstrated by CA184070 and CA184178. Nivo mon and nivo+ipi (nivo 3mg/kg + ipi 1 mg/kg) was safe in adolescent patients across indications studied in CA209070. Despite limited clinical data, PK and exposure-response analyses support the safety of nivo 1 mg/kg + ipi 3 mg/kg in adolescent patients (Section 6).

Adjuvant Treatment of Melanoma (Nivolumab): The safety profile of nivo mono as adjuvant treatment of melanoma in adults is well characterized in CA209238. Safety results for the nivo mono arm in CA209915 were consistent with results observed for nivo mono in Study CA209238. Nivo monotherapy was safe in adolescent patients across indications studied in CA209070 and in the limited number of adolescent subjects studied in CA209915.

In summary, the totality of the safety data supports the use of nivo mono and nivo + ipi in adolescents ≥ 12 years as treatment for advanced melanoma and the use of nivo monotherapy in adolescents ≥ 12 years as treatment for adjuvant melanoma.

The FDA's Assessment:
The assessment of safety of nivolumab as a single agent and in combination with ipilimumab, and ipilimymab in combination with nivolumab was based primarily on data from previously conducted studies CA209067, CA209915 and CA209238 and from clinical pharmacology analyses (population PK data and E-R safety analysis) that support the recommended doses for the extension of the approved indications for the nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab adult melanoma indications to a pediatric population 12 years of age and older. The pediatric safety data submitted from the pivotal trial includes 126 pediatric patients that were treated with either nivolumab as a single agent (n=80) or nivolumab in combination with ipilimumab (n=46). Due to the limited median duration of treatment on this study (median duration of treatment was 0.84 months for nivolumab as a single agent and 0.72 months for nivolumab in combination with ipilimumab) conclusions could not be made regarding the pediatric safety profile of nivolumab and ipilimumab based on the results of these studies alone.

As the safety of nivolumab and ipilimumab has been previously reviewed and characterized in adult patients with resectable, unresectable and metastatic melanoma and also in other tumor types, FDA did not conduct an in depth analysis of the data from Studies CA209067, CA209915 or CA209238 during the review of this supplemental BLA. Safety results of Studies CA209067 and CA209238 served as the basis for prior approvals of nivolumab and ipilimumab and therefore have previously been reviewed in detail.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
Efficacy analyses for Study CA209070 were descriptive in nature and there was no demonstration of any clinically meaningful anti-tumor activity in the pediatric study. No statistical analyses were conducted by FDA.

8.4. Conclusions and Recommendations

The FDA's Assessment:
FDA concludes that the data submitted to support the extension of the nivolumab and ipilimumab adult indications to a pediatric population 12 year of age and older sufficiently support approval of the proposed doses. The safety and efficacy of nivolumab and ipilimumab has been well characterized in adult patients with resectable, unresectable, and metastatic melanoma. The population PK and E-R safety and efficacy analysis, and the known similarities between adolescent and adult melanoma further support the extension of the approved

melanoma indications. The review team recommends regular approval for nivolumab, as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab for the treatment of pediatric patients 12 years and older with unresectable or metastatic melanoma and for nivolumab as a single agent for the treatment of pediatric patients 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, in the adjuvant setting.]

X	X

Jamie Brewer, MD
Primary Clinical Reviewer and 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 Drug Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for these supplemental BLAs as no significant review issues were identified during the review.

10 Pediatrics

The Applicant's Position:

Development in pediatric populations for nivolumab and ipilimumab included submission of a proposed pediatric study report (PPSR), discussions with and feedback received from the FDA, followed by issuance of a Pediatric Written Request (PWR) by the FDA for both nivolumab and ipilimumab. As of 20-Jul-2017, the FDA determined that the PWR for ipilimumab was fulfilled.

The current nivolumab PWR, which includes Amendment 03, lists a request for non-clinical biomarker studies in pediatric tumor tissues, a clinical study (Study 1: ADVL1412/ CA209070), and pharmacokinetic analyses to establish pediatric dosing recommendations for nivolumab alone and in combination with ipilimumab in advanced melanoma.

Based on the similarity of melanoma between adolescents (≥ 12 to < 18 years) and adults, demonstrated by comparable general clinical characteristics, risk factors and maturation of immune system in adolescents, a similar exposure-response (E-R) relationship to treatment with nivolumab ± ipilimumab between adolescent and adult subjects with melanoma is expected. BMS developed a population pharmacokinetic (PPK) model using pooled data from CA209070 and other pediatric and adult studies to characterize pediatric PK in order to define recommended dosing regimens for nivolumab and nivolumab in combination with ipilimumab for the treatment of pediatric patients (12 years and older) with melanoma in support of efficacy extrapolation from adult to pediatric patients.

BMS requests the following:

- Determination of pediatric exclusivity for nivolumab, based on the results of the studies (non-clinical biomarker studies, CA209070, and pharmacokinetic analyses) conducted according to the nivolumab PWR. As part of the supplemental BLAs.
- Extension of the approved adult indications of nivolumab in advanced and adjuvant melanoma to include pediatric (12 years and older) patients, with a data package that includes the following clinical studies: CA209070, CA209915, CA209067, and CA209238.

The FDA's Assessment:
FDA Pediatric Exclusivity Review Board reviewed the Pediatric Exclusivity Determination

Request and determined that the Applicant had met the terms of the Written Request. Pediatric Exclusivity was granted to nivolumab (Refer to the Pediatric Determination Checklist) granted on February 2, 2023.

Refer to Section 6, Section 8 and Section 19.4 for a summary of the clinical data submitted to support the use of nivolumab as a single agent and in combination with ipilimumab, and ipilimumab in combination with nivolumab in pediatric patients 12 years and older with melanoma.

11 Labeling Recommendations

11.1. Labeling Recommendations for OPDIVO

Data:

Table 28: Applicant - Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations) - OPDIVO

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
1 . Indications and Usage	Adding pediatric patients 12 years and older to section 1.1 Unresectable or Metastatic Melanoma and to section 1.2 Adjuvant Treatment of Melanoma	Indication updated to include pediatric patients 12 years and older weighing ≥40 kg and <40 kg For consistency across oncology labels, Applicant was instructed to add approved age groups for other indications (e.g., RCC and HCC)
2. Dosage and Administration	Updated Table 1 (Opdivo montherapy) and Table 2 (Opdivo combination therapy with ipilimumab) with dose recommendation for pediatric patients 12 years and older weighing 40 kg or more and for pediatric patients 12 years and older weighing less than 40 kg for both indications unresectable or metastatic melanoma and Adjuvant Treatment of melanoma	Adult dosing recommendations added for pediatric patients 12 years and older weighing ≥40 kg Weight based dosing recommendations added for pediatric patients 12 years and older weight <40 kg
8.4 Pediatric use	Updated section with information on Checkmate-070 for pediatric population for indications unresectable or metastatic melanoma and Adjuvant Treatment of melanoma	Available data was added to describe the safety and effectiveness of OPDIVO in pediatric patients 12 years and older. The section was revised to be concise
12.3 Pharmacokinetics – Specific populations – Pediatric patients	Updated this section with Population PK information for pediatric patients compared to adults	Pediatric exposure data added.
Medication Guide	The OPDIVO Medication Guide was updated, in line with USPI, to include the following additional information in patient-friendly language: • Under "What is OPDIVO" - Addition of a "adults and children 12 years of age and older" for the melanoma indication.	Approved age groups added for all indications. Pediatric and contraception information edited for consistency with USPI.

The Applicant's Position:
The clinical data provided in this sBLA submission demonstrate the clinical benefit and safety of the use of nivo and nivo+ipi for the treatment of pediatric patients with unresectable or metastatic melanoma and the use of nivo for the adjuvant treatment of melanoma. Based on these data, Table 28 provides a high-level summary of the proposed changes to the labeling for OPDIVO (nivolumab).

The FDA's Assessment:
FDA agrees that Table 28 summarizes the Applicant's proposed changes to the prescribing information. See the final approved prescribing information for OPDIVO (nivolumab) accompanying the approval letter for more information.

11.2. Labeling Recommendations for YERVOY

Data:

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

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
1 . Indications and Usage	Adding pediatric patients 12 years and older to section 1.1 Unresectable or Metastatic Melanoma	Indication updated to include pediatric patients 12 years and older weighing ≥40 kg and <40 kg For consistency across oncology labels, Applicant was instructed to add approved age groups for other indications (e.g., RCC and HCC)
8.4 Pediatric use	Updated section with information on Checkmate-070 for pediatric population for indications unresectable or metastatic melanoma	Available data was added to describe the safety and effectiveness of OPDIVO in pediatric patients 12 years and older. The section was revised to be concise

12.3 Pharmacokinetics – Specific populations – Pediatric patients	Updated this section with Population PK information for pediatric patients compared to adults	Pediatric exposure data added.
Medication Guide	The Yervoy Medication Guide was updated, in line with USPI, to include the following additional information in patient-friendly language: • Under "What is Yervoy" - For the malanoma indication, the "adults and children 12 years of age and older" apply now to both Yervoy monotherapy as well as Yervoy in combination with nivolumab.	Approved age groups added for all indications. Pediatric and contraception information edited for consistency with USPI.

The Applicant's Position:

The clinical data provided in this sBLA submission demonstrate the clinical benefit and safety of the use of nivo+ipi for the treatment of pediatric patients with unresectable or metastatic melanoma. Based on these data, Table 29 provides a high-level summary of the proposed changes to the labeling for YERVOY (ipilimumab).

The FDA's Assessment:

FDA agrees that Table 29 summarizes the Applicant's proposed changes to the prescribing information. See the final approved prescribing information for YERVOY (ipilimumab) accompanying the approval letter for more information.

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 as as a single agent or in combination with ipilimumab or for ipilimumab in combination with nivolumab for the indicated population given the experience of the medical oncology community with these drug products and in managing immune-mediated adverse reactions. Recommendations for the safe and effective use of nivolumab and ipilimumab, including monitoring for immune-related adverse events, are provided in the US prescribing information as well as in the patient medication guide.

13 Postmarketing Requrements and Commitment

The FDA's Assessment:

No PMR/PMC 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.	__ Yes _X_ 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 __ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

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

19 Appendices

19.1. References

The Applicant's References:
References are provided in Section 19.6.

The FDA's References:

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.

Lange JR, Palis BE, Chang DC, et al. Melanoma in Children and Teenagers: An Analysis of Patients From the National Cancer Data Base. Journal of Clinical Oncology 2007 25:11, 1363-1368

SEER Cancer Stat Facts: Melanoma of the Skin. National Cancer Institute. Bethesda, Maryland, https://seer.cancer.gov/statfacts/html/melan.html

Hawryluk EB, Pappo AS, Marghoob AA, et al. Melanoma in Children. In: UpToDate, Corona R (Ed), UpToDate, Waltham, MA, 2022

19.2. Financial Disclosure

The Applicant's Position:
Due to NCI/CTEP (CA209070 study sponsor) policy precluding provision of Financial Disclosure Forms to pharmaceutical companies, BMS proposed that financial disclosure information for CA209070 shall be provided directly from NCI/CTEP to FDA upon request by the FDA. FDA

agreed with this proposal (IND 120909 Preliminary Meeting Comments; Reference ID: 5001702) and therefore, BMS is not providing financial disclosure information for CA209070 in this application.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Given the the limited duration of study treatment and the absence of clinically meaningful anti-tumor activity in the relapsed/refractory solid tumor population on study, the FDA has concluded that the Investigator's financial disclosures are unlikely to have biased the interpretation of the study results.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
The results of study report Expression of PD-L1, and Characterization of Tumor Infiltrating Immune Cells in Tumors of Pediatric Origin are submitted in Module 4.2.1.1. This nonclinical biomarker report is provided in this submission to fulfill the nivolumab PWR and PIP01, and no corresponding Module 2 non-clinical summaries are included in this application, as the pediatric non-clinical study results are out of the scope of the proposed extension of the approved adult indications of nivolumab as a single agent or in combination with ipilimumab for the treatment of melanoma to include pediatric (12 years and older) patients.

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

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
Sufficient PK data from adolescent (12 years and older) and adult patients were included in the popPK model for nivolumab and ipilimumab. The popPK model adequately described the PK profile for nivolumab and ipilimumab in adult and adolescent patients. PopPK results showed that the nivolumab exposure following the proposed dosing regimen in adolescent patients with adjuvant melanoma (Figure 9) or with metastatic melanoma who received nivolumab as a single agent(Figure 10) were comparable to adult exposure. In addition, the nivolumab and ipilimumab exposure after 4 cycles of the proposed dosing regimens in adolescent patients with metastatic melanoma who received the combination therapy (Figure 11 and Figure 12) were also comparable to the adult exposure.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

General Information - Advanced Melanoma (Adv PPK)		
Objectives of PPK Analysis		• To characterize the PK of nivolumab in pediatric subjects who received nivolumab alone or in combination with ipilimumab, including the effect of covariates on PK parameters. • To characterize the PK of ipilimumab in pediatric subjects who received combination treatment with nivolumab, including the effect of covariates on PK parameters. • To provide recommendations of a nivo mono dosing regimen and a nivolumab -ipilimumab combination dosing regimen for adolescent patients (from 12 to <18 years) with advanced melanoma, using model-based simulations.
Study Included		Nivolumab PPK: The nivolumab PPK analysis dataset included 13 clinical studies. These included 3 Phase 1/2 studies from which 275 children and adolescents with solid tumors, primary CNS malignancies, and lymphoma receiving nivo mono or combination therapy including with ipilimumab or brentuximab vedotin (CA209070/ADVL1412, CA209908 and CA209744) were included. Also included were ten Phase 1 to 3 studies in adults with advanced melanoma (CA209066, CA209067, CA209069), classical Hodgkin Lymphoma (cHL, CA209205,),Glioblastoma (CA209143, CA209498) and other solid tumors or lymphoma (CA209001, CA209003, CA209005/ONO-4538-01, CA209039). Ipilimumab PPK: The ipilimumab PPK analysis dataset included 10 clinical studies. These included 4 Phase 1/2 studies from which 138 children and adolescents with MEL, CNS malignancies and other solid tumors receiving ipi mono or in combination with nivolumab (CA184070, CA184178, CA209070/ADVL1412, CA209908) were included. Six Phase 1 to 3 studies in adults with advanced MEL (CA184004, CA184007, CA184008, CA184022, CA209067, CA209069) were also included in the PPK dataset.
Dose(s) Included		Nivo: 0.1, 0.3, 1, 3, 10, and 20 mg/kg Q2W, 1 and 3 mg/kg Q3W, 240 mg Q2W, 480 mg Q4W Ipi:0.3, 1, 3, 5, 10 mg/kg Q3W
Population Included		Nivo: Children and adolescents with solid tumors, primary CNS malignancies, and lymphoma. Adults with advanced melanoma, classical Hodgkin Lymphoma, Glioblastoma and other solid tumors or lymphoma Ipi: Children and adolescents with MEL, CNS, maglignance and other solid tumors; adults with advanced MEL
Population Characteristics	General	Nivo (adult MEL): • Median (range) age: 62 (18, 90) years • Median (range) baseline body weight: 80.6 (37.4, 160) kg • Sex, n (%): 637 (64.1) males, 356 (35.9) females

		• Race, n (%): White: 969 (97.6), Black/African American: 2 (0.2), Asian: 9 (0.9), Other: 13 (1.3) Ipi (adult MEL): • Median (range) age: 61 (18, 89) years • Median (range) baseline body weight: 80.4 (38.6, 160) kg • Sex, n (%): 808 (64.1) males, 452 (35.8) females • Race, n (%): White: 1231 (97.6), Black/African American: 3 (0.2), Asian: 13 (1), Other: 13 (1)
	Organ Impairment	Renal function was defined based on eGFR. Nivo: Median (range) eGFR: 93.1 (31.2, 215) mL/min/1.73 m^2 Ipi: Median (range) eGFR: 90.1 (21, 230) mL/min/1.73 m^2
	Pediatrics (if any)	Nivo: • Median (range) age: 12 (1, 17) years • Median (range) baseline body weight: 41.1 (9.3, 121) kg • Sex, n (%): 157 (57.1) males, 118 (42.9) females • Race, n (%): White: 216 (78.5), Black/African American: 19 (6.9), Asian: 17 (6.2), Other: 23 (8.4) Ipi: • Median (range) age: 12 (1, 17) years • Median (range) baseline body weight: 44.3 (10.2, 151) kg • Sex, n (%): 73(52.9) males, 65 (47.1) females • Race, n (%): White: 100 (72.5), Black/African American: 10 (7.2), Asian: 11 (8.0), Other: 17 (12.3)
No. of Patients, PK Samples, and BLQ		Nivo PPK: • Total population: 2325 subjects, 13104 samples (380 samples excluded as below LLOQ post dose) • Pediatric (< 18 yrs): 275 subjects Ipi PPK: • Total population: 1427 subjects, 6020 samples (155 samples excluded as below LLOQ post dose) • Pediatric (< 18 yrs): 138 subjects
Sampling Schedule	Rich Sampling	Nivolumab monotherapy: • Study CA209001 Predose, 30 minutes into dosing, immediately post-infusion, and 30 minutes, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h, 48 h, and 72 h post-infusion end time; on Days 8, 15, 22, 29, 43, 57, 71, and 85 • Study CA209003 Cycle 1: Day 1 (after 60-minute infusion, 4 h, and 8 h); Days 2, 3, 5, 8, and 15, Cycle 2: Day 1 (pre-infusion), Cycle 3: Day 1 (pre-infusion, after 60-minute infusion); Days 2, 3, 5, 8, and 15
	In ITT Population	Nivo pediatric study ADVL1412 (CA209070): Part A and B: Cycle 1 Day 1 (end of infusion), Days 2, 4, 8, 15, Cycle 2: Day 1 (end of infusion), Days 2, 4, 8. Cycle 4. Part C/D: pre-dose samples and end of infusion in day 1 of Cycle 1, 2, 3, 4 Ipi pediatric study CA184070: On Day 1 and Day 43: preinfusion and 1.5, 48, 96, 192, 216, 336, and 504 hours poststart of infusion. One additional sample was taken on Day 85.

Covariates Evaluated	Static	Nivolumab PPK Analysis: Age, sex, race, baseline body weight, lean body weight, ECOG performance status, patient population, combination therapy Ipi PPK Analysis: Age, baseline body weight, lean body weight, patient population, combination therapy	
	Time-varying	N/A	
Final Model		**Summary**	**Acceptability [FDA's comments]**
Software and Version		The PPK analysis was performed using the nonlinear mixed effects modeling (NONMEM 7.4) computer program, compiled using GNU Fortran 7.5.0, and all exploratory data analyses and presentations of data used R (version 4.0.2 or higher). The VPC, non-parametric bootstrap, and PPK model were executed through PsN 4.9.0.	Acceptable
Model Structure		Nivo: 2 compartment, zero-order IV infusion PK model with time-varying CL Ipi: 2 compartment, zero-order IV infusion PK model	Acceptable
Model Parameter Estimates		Nivo: Table 30 in Section 19.4.1.2 Ipi: Table 31 in Section 19.4.1.2	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		Nivolumab parameters were precisely estimated. Relatively high RSE (≥ 50%) for parameter estimates CL_{RAAA}, CL_{RAAS}, CL_{OTH}, CL_{I1Q3}, CL_{BVCO}, VC_{SEX} , $EMAX_{IPICO}$ and $EMAX_{OTH}$ were observed, which was due to the small magnitude of effects and consequently the uncertainties in the estimated effects are small despite the high RSE. Based on 1000 Bootstrap calculations, the effect of African American on CL, Asian effect on CL, Adult Others on CL, ipi combination effect (I1Q3), brentuximab combination effect on CL, Sex effect on VC, Ipi combination effect on EMAX and Adult others on Emax was 107% (95% CI, 98.3-118%), 100% (95%CI, 93.5-108%), 101% (95% CI, 93.2-108%), 110% (95% CI 99.8-123%), 113% (93.1-131%), 102% (98.3-106%), 88.3% (95% CI, 68.9-103%) and 112% (95% CI, 97.4-127%), respectively, indicating a small effect size. The shrinkage values: ETA (between subject variability) shrinkage (%): ETA_CL: 12.2; ETA_VC: 28.1; ETA_EMAX: 50.3; EPS shrinkage (%): 15. The relatively higher ETA-shrinkage for Emax is unlikely to	Acceptable

	impact individual exposures, since ETA shrinkage for CL and VC are relatively low, which are the primary parameters important for the Empiric Bayes Estimate-derived exposures. In the current PPK analysis, the Emax parameter is well estimated with a meaningful magnitude of decrease of -0.298 (RSE 11.9%, 95% CI -0.382 to -0.199). The ETA on Emax is also well estimated with a point estimate of 0.160 (RSE 27.2%, 95% CI: 0.0803 to 0.257). Ipilimumab parameters were precisely estimated except for CL_{N1} 1mg/kg Q3W and CL_{N3} 3mg/kg Q3W effect on CL. N1mg/kg Q3W has small magnitude of effects and consequently the uncertainties in the estimated effects are small despite the high RSE (104%, 95%CI 99.7-109%). Based on 1000 bootstrap, the N3 mg/kg Q3W effect is 137% (95% CI 96.2 - 196%) and is unlikely to have impact on other parameter estimates. The shrinkage values: ETA (between subject variability) shrinkage (%): ETA_CL: 10.7; ETA_VC: 22.2; EPS shrinkage (%): 16.7.	
BLQ for Parameter Accuracy	PK samples with below level of quantitation were excluded from the PPK analysis. Exclusion of below level of quantitation is not expected to impact PPK parameter estimates as only approximately < 3% of total PK concentrations had below level of quantitation.	Acceptable
GOF, VPC	Nivo: Figure 6 in Section 19.4.1.2 Ipi: Figure 7 in Section 19.4.1.2	Acceptable
Significant Covariates and Clinical Relevance	Nivo: Figure 1 in Section 6.3.1 Ipi: Figure 2 in Section 6.3.1	Acceptable
Analysis Based on Simulation (optional)	N/A	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	Updated this section with Population PK information for pediatric patients compared to adults	Acceptable

Table 30: Applicant - Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model

Parameter [Units][a,b]	Symbol	Estimate[c]	Standard Error, (RSE%)[d]	95% CI[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	9.66	0.264 (2.74)	8.98 - 10.3
VC_{REF} [L]	θ_2	4.01	0.0441 (1.10)	3.92 - 4.10
Q_{REF} [mL/h]	θ_3	35.9	1.71 (4.75)	32.8 - 39.4
VP_{REF} [L]	θ_4	2.77	0.0621 (2.24)	2.63 - 2.93
CL_{WTB}	θ_7	0.630	0.0328 (5.20)	0.570 - 0.694
CL_{GFR}	θ_9	0.0935	0.0378 (40.5)	0.0229 - 0.164
CL_{SEX}	θ_{12}	-0.0994	0.0183 (18.4)	-0.137 - -0.0644
CL_{PS}	θ_{13}	0.166	0.0206 (12.4)	0.128 - 0.208
CL_{RAAA}	θ_{14}	0.0689	0.0479 (69.5)	-0.0173 - 0.163
CL_{RAAS}	θ_{15}	0.00354	0.0372 (1.05E+03)	-0.0670 - 0.0762
VC_{LBM}	θ_{16}	0.932	0.0329 (3.53)	0.866 - 1.00
VC_{SEX}	θ_{17}	0.0195	0.0189 (97.1)	-0.0175 - 0.0597
$EMAX_{REF}$	θ_{18}	-0.298	0.0356 (11.9)	-0.382 - -0.199
T50 [h]	θ_{19}	2.67E+03	440 (16.5)	1.90E+03 - 3.72E+03
HILL	θ_{20}	2.32	0.375 (16.2)	1.73 - 3.86
CL_{HL}	θ_{22}	-0.381	0.0333 (8.73)	-0.444 - -0.313
CL_{GBM}	θ_{23}	-0.577	0.0332 (5.74)	-0.650 - -0.497
CL_{OTH}	θ_{24}	0.00671	0.0354 (528)	-0.0709 - 0.0787
CL_{PEDST}	θ_{25}	-0.578	0.0892 (15.4)	-0.783 - -0.388
CL_{PEDHL}	θ_{26}	-0.417	0.0802 (19.2)	-0.576 - -0.227
$CL_{PEDCNST}$	θ_{27}	-0.800	0.0661 (8.27)	-0.936 - -0.669
CL_{I1Q3}	θ_{28}	0.0976	0.0520 (53.3)	-0.00167 - 0.207
CL_{I3Q3}	θ_{29}	0.349	0.0336 (9.61)	0.269 - 0.421
CL_{BVCO}	θ_{31}	0.120	0.0819 (68.4)	-0.0718 - 0.272
$EMAX_{PS}$	θ_{34}	-0.157	0.0449 (28.5)	-0.262 - -0.0746
$EMAX_{IPICO}$	θ_{35}	-0.124	0.0784 (63.1)	-0.372 - 0.0257
$EMAX_{HL}$	θ_{36}	0.132	0.0467 (35.5)	0.0414 - 0.222
$EMAX_{OTH}$	θ_{37}	0.118	0.0684 (58.2)	-0.0268 - 0.242
$EMAX_{PEDCNST}$	θ_{40}	0.696	0.132 (19.0)	0.465 - 1.03
CL_{ADOST}	θ_{41}	-0.222	0.0830 (37.4)	-0.399 - -0.0735
VC_{PED}	θ_{42}	-0.277	0.0464 (16.7)	-0.366 - -0.187
VC_{ADO}	θ_{43}	-0.273	0.0254 (9.33)	-0.319 - -0.222
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.108 (0.329)	0.00600 (5.54)	0.0957 - 0.119
ZVC [-]	$\omega_{2,2}$	0.0751 (0.274)	0.00763 (10.2)	0.0603 - 0.0904
ZEMAX [h]	$\omega_{4,4}$	0.160 (0.400)	0.0434 (27.2)	0.0803 - 0.257
ZCL:*ZVC*	$\omega_{1,2}$	0.0220 (0.244)	0.00310 (14.1)	0.0162 - 0.0280
Residual Error				
PERR [-]	θ_6	0.199	0.00377 (1.90)	0.191 - 0.206
RESERR[f]	$\sigma_{1,1}$	1.00 (1.00)	NA	NA

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd
Source (for bootstrap 95% CI): Analysis-Directory/nm/full1c/reports/full1c_RTF.rtf
Source (for Estimate and Standard Error): Analysis-Directory/nm/full1c/reports/full1c_RTF0.rtf

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject with MEL, receiving nivo mono, 60-year old white male, weighing 75 kg with lean body mass of 55 kg, and with a normal PS status (PS = 0). $EMAX_{REF}$ is a

typical value of change in magnitude of CL in a reference adult MEL subject receiving nivo mono with PS = 0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 75 kg with lean body mass of 55 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note 2: Eta shrinkage (%): ETA_CL: 12.2; ETA_VC: 28.1; ETA_EMAX: 50.3; EPS shrinkage (%): 15.0.

Note 3: The condition number for the full model is 157.

Abbreviations: CI = confidence interval; HILL = coefficient for time-varying CL; Q = intercompartmental CL; RSE = relative standard error; T50 = time at which CL achieves half of the maximum value; VC = central volume; VP = peripheral volume.

[a] Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column.

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate).

[e] Confidence Interval values are taken from bootstrap calculations (966 successful out of a total of 1000).

Table 31: Applicant - Parameter Estimates of the Full Ipilimumab Population Pharmacokinetic Model

Parameter[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL_{REF} [mL/h]	θ_1	13.5	0.2.07 (1.53)	13.1 - 13.9
VC_{REF} [L]	θ_2	3.90	0.0307 (0.786)	3.84 - 3.96
Q_{REF} [mL/h]	θ_3	35.8	2.33 (6.51)	31.2 - 40.4
VP_{REF} [L]	θ_4	3.47	0.0817 (2.35)	3.31 - 3.63
CL_{LBM}	θ_7	0.789	0.0536 (6.79)	0.684 - 0.894
V_{LBM}	θ_8	0.874	0.0351 (4.01)	0.805 - 0.943
CL_{CNS}	θ_{10}	-0.661	0.236 (35.7)	-1.12 - -0.199
CL_{OTH}	θ_{11}	-0.698	0.277 (39.8)	-1.24 - -0.154
CL_{PEDOTH}	θ_{12}	-0.462	0.110 (23.7)	-0.677 - -0.248
$CL_{PEDCNST}$	θ_{13}	-0.668	0.191 (28.5)	-1.04 - -0.294
CL_{PEDMEL}	θ_{14}	-0.347	0.107 (30.8)	-0.557 - -0.138
CL_{N1} *1mg/kg Q3W*	θ_{15}	0.0417	0.0229 (54.9)	-0.00318 - 0.0866
CL_{N3} *3mg/kg Q3W*	θ_{16}	0.316	0.181 (57.3)	-0.0390 - 0.670
$V1_{PED}$	θ_{18}	-0.296	0.0552 (18.7)	-0.404 - -0.188
$V1_{ADO}$	θ_{19}	-0.217	0.0341 (15.8)	-0.283 - -0.150
Random Effects				
ZCL[-]	$\omega_{1,1}$	0.147 (0.383)	0.00853 (5.82)	0.130 - 0.163
ZVC [-]	$\omega_{2,2}$	0.0531 (0.230)	0.00720 (13.6)	0.0390 - 0.0672
ZCL[-]:ZVC	$\omega_{1,2}$	0.0258 (0.293)	0.00412 (15.9)	0.0178 - 0.0339
Residual Error				
PERR [-]	θ_5	0.185	0.00708 (3.83)	0.171 - 0.199
AERR [ug/mL]	θ_6	1.14	0.171 (15.0)	0.805 - 1.48

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-ipi/final/
Program Source: Analysis-Directory/R/scripts/2-model-dev-ipi.Rmd
Source (for bootstrap 95% CI): Analysis-Directory/nm/full1/reports/full1_RTF.rtf
Source (for Estimate and Standard Error): Analysis-Directory/nm/full1/reports/full1_RTF0.rtf

Note 1: CL_{REF} is the typical value of clearance in a reference subject with MEL, receiving ipi mono, 60-year old white male with lean body mass of 55 kg. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject with lean body mass of 55 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note 2: Eta shrinkage (%): ETA_CL: 10.7; ETA_VC: 22.2;; EPS shrinkage (%): 16.7.

Note 3: The condition number for the full model is 162.

Abbreviations: CI = confidence interval; Q = intercompartmental CL; RSE = relative standard error; VC = central volume; VP = peripheral volume.

a Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

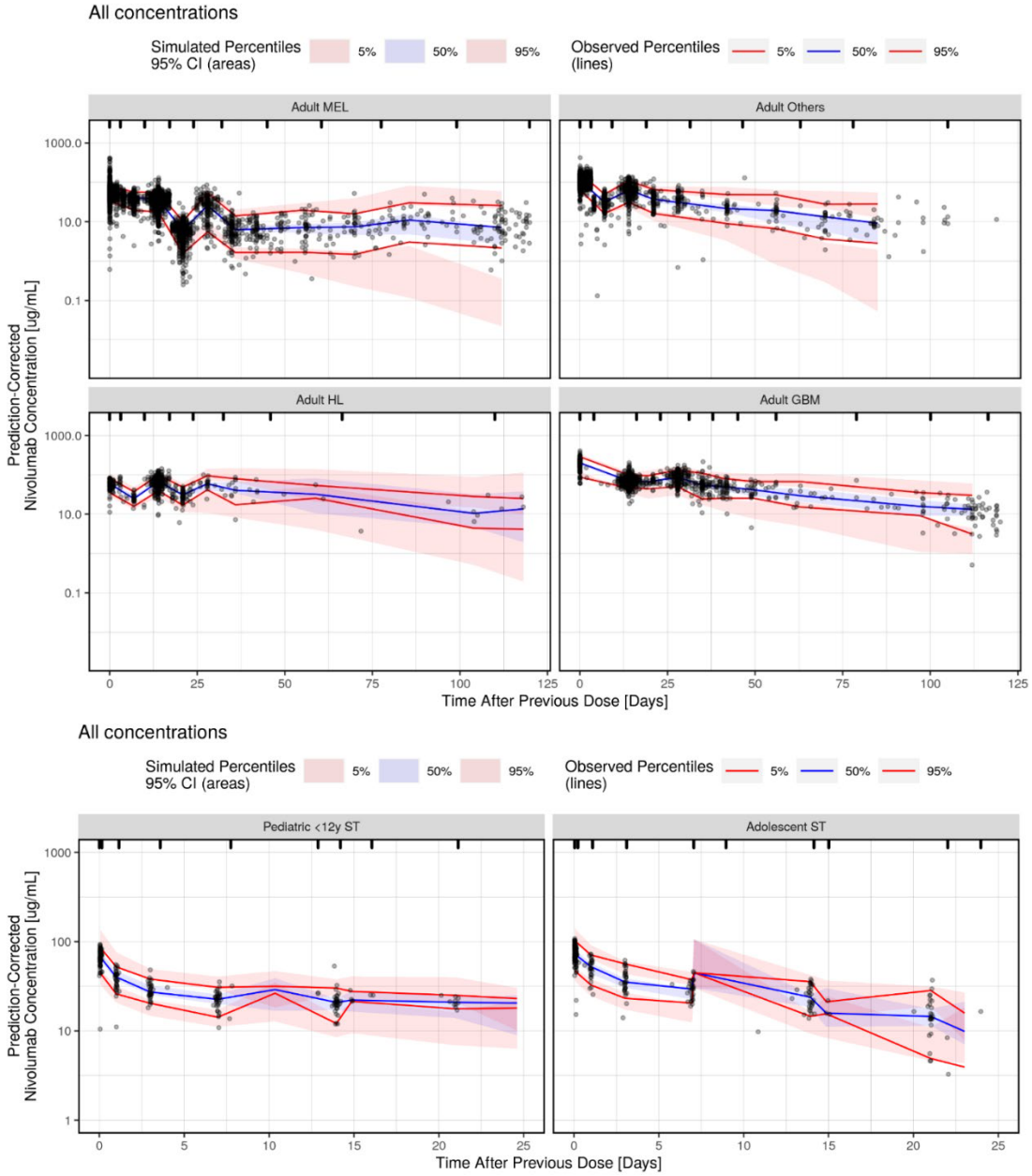
b Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

c Random Effects and Residual Error parameter estimates are shown as Variance (Standard Deviation) for diagonal elements (ωi,i or σi,i) and Covariance (Correlation) for off-diagonal elements (ωi,j or σi,j)

d RSE% is the relative standard error (Standard Error as a percentage of Estimate)

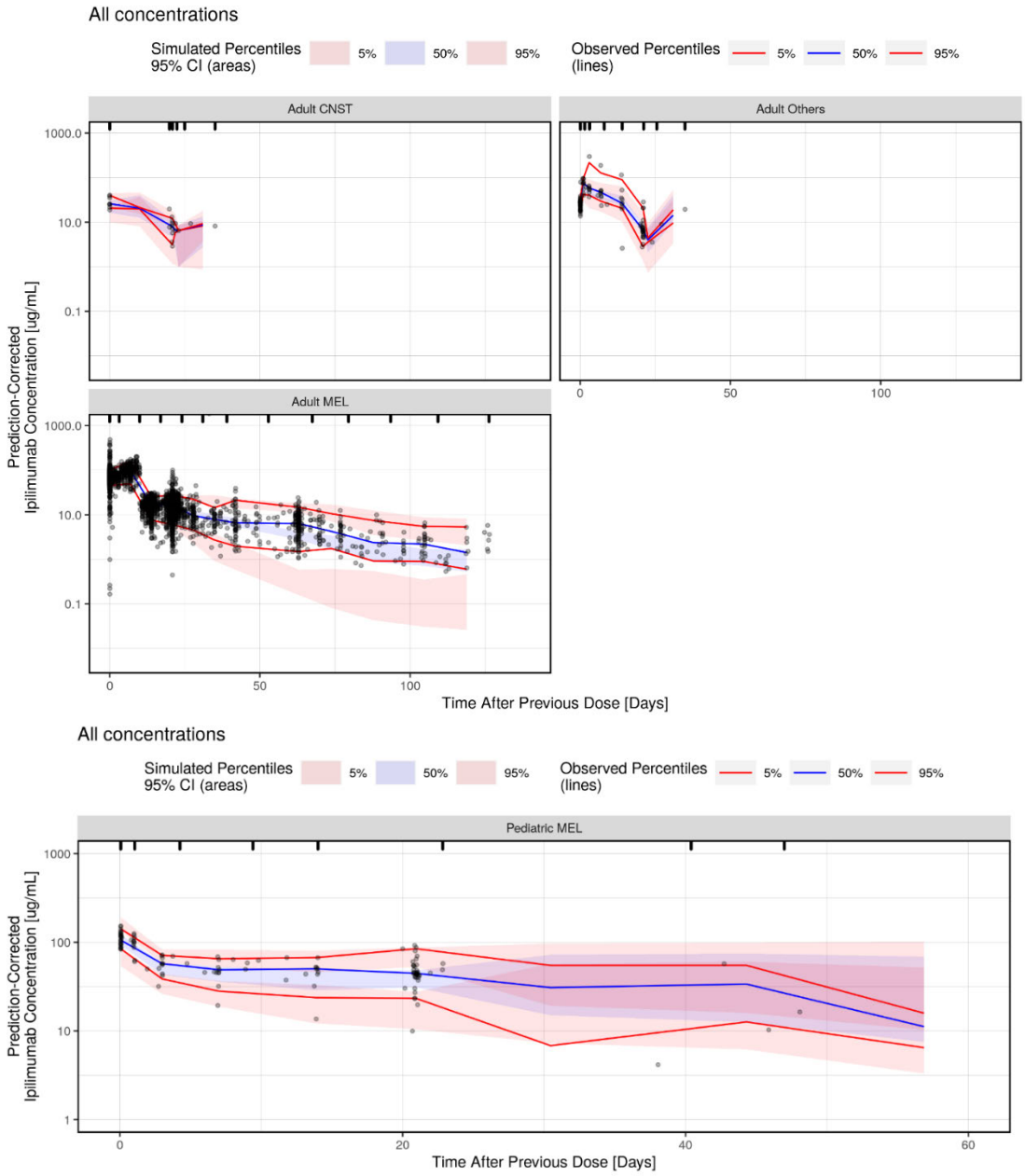
e Confidence Interval values are taken from bootstrap calculations (982 successful out of a total of 1000).

Figure 6: Applicant - Prediction-Corrected Visual Predictive Check of Nivolumab Concentrations versus Actual Time after Previous Dose, by Population [Full Nivolumab Population Pharmacokinetic Model]



Adult Subjects:
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-adult.png
Pediatric Solid Tumor (ST) Subjects:
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-ped-st.png

Figure 7: Applicant - Prediction-Corrected Visual Predictive Check of Ipilimumab Concentrations versus Actual Time after Previous Dose, by Population [Full Ipilimumab Population Pharmacokinetic Model]



Adult Subjects:
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-ipi/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app-ipi.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-adult.png
Pediatric Melanoma (MEL) Subjects:
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-ipi/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app-ipi.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-ped-mel.png

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

General Information - Adjuvant Melanoma (Adj PPK)		
Objectives of PPK Analysis		• To characterize the PK of nivolumab in adolescent subjects (≥ 12 to < 18 years) in the adjuvant treatment of melanoma, including the effect of covariates on PK parameters. • To provide dosing considerations for nivo mono dosing regimens for adolescent subjects (≥ 12 to < 18 years) in the adjuvant treatment of melanoma using model-based simulations.
Study Included		The nivolumab population PK (PPK) analysis dataset included 11 clinical studies. Studies CA209001, CA209003, CA209005, and CA209066 have been selected to provide intensive PK data of nivo mono in adult subjects with solid tumors including advanced melanoma over a wide dose range (0.3 to 10 mg/kg). Studies CA209004, CA209067, CA209069 and CA209511 provide PK of nivolumab ± ipilimumab in the advanced melanoma setting. Study CA209238 provides PK for adult and CA209915 provides PK of nivolumab in adult and adolescent (N = 3) subjects with adjuvant treatment of melanoma. Study CA209070 provides PK of nivolumab in young pediatric (1 to < 12 years) and adolescent subjects with solid tumors as monotherapy and in combination with ipilimumab.
Dose(s) Included		Nivo: 0.1, 0.3, 1, 3, 10, and 20 mg/kg Q2W, 1 and 3 mg/kg Q3W, 240 mg Q2W, 480 mg Q4W
Population Included		Children and adolescents with solid tumors, including advanced melanoma in the adjuvant setting. Adults with advanced melanoma and other solid tumors, and adults with adjuvant treatment of melanoma.
Population Characteristics	General	Adult adjuvant MEL: • Median (range) age: 55 (18, 89) years • Median (range) baseline body weight: 80 (39, 183) kg • Sex, n (%): 1275 (56.8) males, 969 (43.2) females • Race, n (%): White: 2192 (97.7), Black/African American: 5 (0.2), Asian: 32 (1.4), Other: 15 (0.7)
	Organ Impairment	Renal function was defined based on eGFR. Median (range) eGFR: 91.3 (30.7, 202) mL/min/1.73 m^2
	Pediatrics (if any)	• Median (range) age: 12 (1, 17) years • Median (range) baseline body weight: 44 (9.3, 99.6) kg • Sex, n (%): 49 (59.8) males, 33 (40.2) females • Race, n (%): White: 61 (74.4), Black/African American: 8 (9.8), Asian: 7 (8.5), Other: 6 (7.3)
No. of Patients, PK Samples, and BLQ		• Total population: 3965 subjects, 24546 samples (572 samples excluded as below LLOQ post dose) • Adolescents(≥ 12 to < 18 yrs): 46 subjects • Young Pediatric (< 12 yrs): 36 subjects
Sampling Schedule	Rich Sampling	Nivolumab monotherapy: • Study CA209001 Predose, 30 minutes into dosing, immediately post-infusion, and 30 minutes, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h, 48 h, and 72 h post-infusion end time; on Days 8, 15, 22, 29, 43, 57, 71, and 85

		Study CA209003 Cycle 1: Day 1 (after 60-minute infusion, 4 h, and 8 h); Days 2, 3, 5, 8, and 15, Cycle 2: Day 1 (pre-infusion), Cycle 3: Day 1 (pre-infusion, after 60-minute infusion); Days 2, 3, 5, 8, and 15
	In ITT Population	Nivo pediatric study ADVL1412 (CA209070) Part A and B: Cycle 1 Day 1 (end of infusion), Days 2, 4, 8, 15, Cycle 2: Day 1 (end of infusion), Days 2, 4, 8. Cycle 4 Part C/D: pre-dose samples and end of infusion in day 1 of Cycle 1, 2, 3, 4
Covariates Evaluated	Static	Nivolumab PPK Analysis: Age, sex, race, baseline body weight, lean body weight, ECOG performance status, patient population, combination therapy
	Time-varying	N/A

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	The PPK analysis was performed using the nonlinear mixed effects modeling (NONMEM 7.4) computer program, compiled using GNU Fortran 7.5.0, and all exploratory data analyses and presentations of data used R (version 4.0.2 or higher). The VPC, non-parametric bootstrap, and PPK model were executed through PsN 4.9.0.	Acceptable
Model Structure	Nivo: 2 compartment, zero-order IV infusion PK model with time-varying CL for tumor type other than adjuvant melanoma	Acceptable
Model Parameter Estimates	Nivo: Table 32in Section 19.4.1.2	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Nivolumab parameters were precisely estimated. Relatively high RSE for parameter estimates CLRAAA, CLRAAS, CLOTH, CLI1Q3 and EMAXIPICO were observed, which was due to the small magnitude of effects and consequently the uncertainties in the estimated effects are small despite the high RSE. The effect of African American on CL, Asian effect on CL, Adult Others on CL, ipi combination effect (I1Q3) and Ipi combination effect on EMAX was 115% (95% CI, 99.7-132%), 98.6% (95%CI, 90.9-107%), 103% (95% CI, 95.9-111%), 105% (95% CI 97.7-113%), 94% (85.4-103%), respectively, indicating a small effect size. The shrinkage values: ETA (between subject variability) shrinkage (%): ETA_CL: 8.5; ETA_VC: 26.5; ETA_EMAX: 59.6; EPS shrinkage (%): 14.6. The relatively higher ETA-shrinkage for Emax is unlikely to impact individual exposures, since ETA	Acceptable

	shrinkage for CL and VC are relatively low, which are the primary parameters important for the Empiric Bayes Estimate-derived exposures. In the current PPK analysis, The Emax parameter is well estimated with a meaningful magnitude of decrease of -241 (RSE 12%, 95% CI --0.184 to -0.298). The ETA on Emax is also well estimated with a point estimate of 0.185 (RSE 22.6%, 95% CI: 0.103 to 0.263).	
BLQ for Parameter Accuracy	PK samples with below level of quantitation were excluded from the PPK analysis. Exclusion of below level of quantitation is not expected to impact PPK parameter estimates as only approximately < 3% of total PK concentrations had below level of quantitation.	Acceptable
GOF, VPC	Figure 8 in Section 19.4.1.2	Acceptable
Significant Covariates and Clinical Relevance	Nivo: Figure 3 in Section 6.3.1	Acceptable
Analysis Based on Simulation (optional)	N/A	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	Updated this section with Population PK information for pediatric patients compared to adults	Acceptable

Table 32: Applicant - Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model

Parameter [Units][a,b]	Symbol	Estimate[c]	Standard Error, (RSE%)[d]	95% CI[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	9.57	0.221 (2.31)	9.14 - 10.0
VC_{REF} [L]	θ_2	3.84	0.0419 (1.09)	3.76 - 3.92
Q_{REF} [mL/h]	θ_3	33.5	2.15 (6.42)	29.3 - 37.8
VP_{REF} [L]	θ_4	2.84	0.0478 (1.69)	2.74 - 2.93
CL_{WTB}	θ_7	0.645	0.0291 (4.51)	0.588 - 0.702
CL_{GFR}	θ_9	0.152	0.0258 (17.0)	0.101 - 0.202
CL_{FEMALE}	θ_{12}	-0.107	0.0126 (11.7)	-0.132 - -0.0825
CL_PS_1	θ_{13}	0.150	0.0192 (12.8)	0.112 - 0.188
CL_{RAAA}	θ_{14}	0.136	0.0712 (52.3)	-0.00338 - 0.276
CL_{RAAS}	θ_{15}	-0.0137	0.0418 (305)	-0.0956 - 0.0682
$V1_{LBM}$	θ_{16}	0.962	0.0323 (3.36)	0.899 - 1.03
$V1_{FEMALE}$	θ_{17}	0.0626	0.0185 (29.6)	0.0262 - 0.0989
$EMAX_{REF}$	θ_{18}	-0.241	0.0291 (12.0)	-0.298 - -0.184
T50 [h]	θ_{19}	2.37E+03	219 (9.26)	1.94E+03 - 2.80E+03
HILL	θ_{20}	3.48	0.768 (22.1)	1.97 - 4.98
CL_{ADJMEL}	θ_{21}	-0.430	0.0233 (5.41)	-0.476 - -0.385
CL_{OTH}	θ_{22}	0.0300	0.0367 (122)	-0.0419 - 0.102
CL_{ADOST}	θ_{23}	-0.212	0.0766 (36.1)	-0.362 - -0.0618
CL_{PEDST}	θ_{24}	-0.562	0.0870 (15.5)	-0.733 - -0.392
CL_{I1Q3}	θ_{25}	0.0496	0.0371 (74.8)	-0.0231 - 0.122
CL_{I3Q3}	θ_{26}	0.329	0.0296 (8.99)	0.271 - 0.387
$EMAX\_PS_1$	θ_{28}	-0.113	0.0439 (38.8)	-0.199 - -0.0271
$EMAX_{IPICO}$	θ_{29}	-0.0618	0.0488 (79.0)	-0.157 - 0.0339
$V1_{PED}$	θ_{30}	-0.123	0.0470 (38.2)	-0.215 - -0.0308
$V1_{ADO}$	θ_{31}	-0.179	0.0383 (21.4)	-0.254 - -0.104
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.0927 (0.304)	0.00427 (4.60)	0.0843 - 0.101
ZVC [-]	$\omega_{2,2}$	0.0973 (0.312)	0.00614 (6.31)	0.0853 - 0.109
ZEMAX [h]	$\omega_{4,4}$	0.185 (0.430)	0.0418 (22.6)	0.103 - 0.267
ZCL:*ZVC*	$\omega_{1,2}$	0.0225 (0.237)	0.00237 (10.5)	0.0179 - 0.0272
Residual Error				
PERR [-]	θ_6	0.203	0.00272 (1.34)	0.198 - 0.208
RESERR[f]	$\sigma_{1,1}$	1.00 (1.00)	NA	NA

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd
Analysis-Directory/nm/full5/reports/full5_RTF.rtf

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject with melanoma, receiving nivo mono, 60-year old white male, weighing 75 kg with lean body mass of 55 kg, and with a normal PS status (PS = 0). $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference adult melanoma subject receiving nivo mono with PS = 0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 75 kg with lean body mass of 55 kg. These reference values represent the approximate median values in the PPK analysis dataset.
Note 2: Eta shrinkage (%): ETA_CL: 8.5; ETA_VC: 26.5; ETA_EMAX: 59.6; EPS shrinkage (%): 14.6.
Note 3: The condition number for the full model is 277.4

[a] Parameters with fixed values (not estimated) are denoted with a superscript *'f'* after the names, with the fixed value given in the Estimate column.

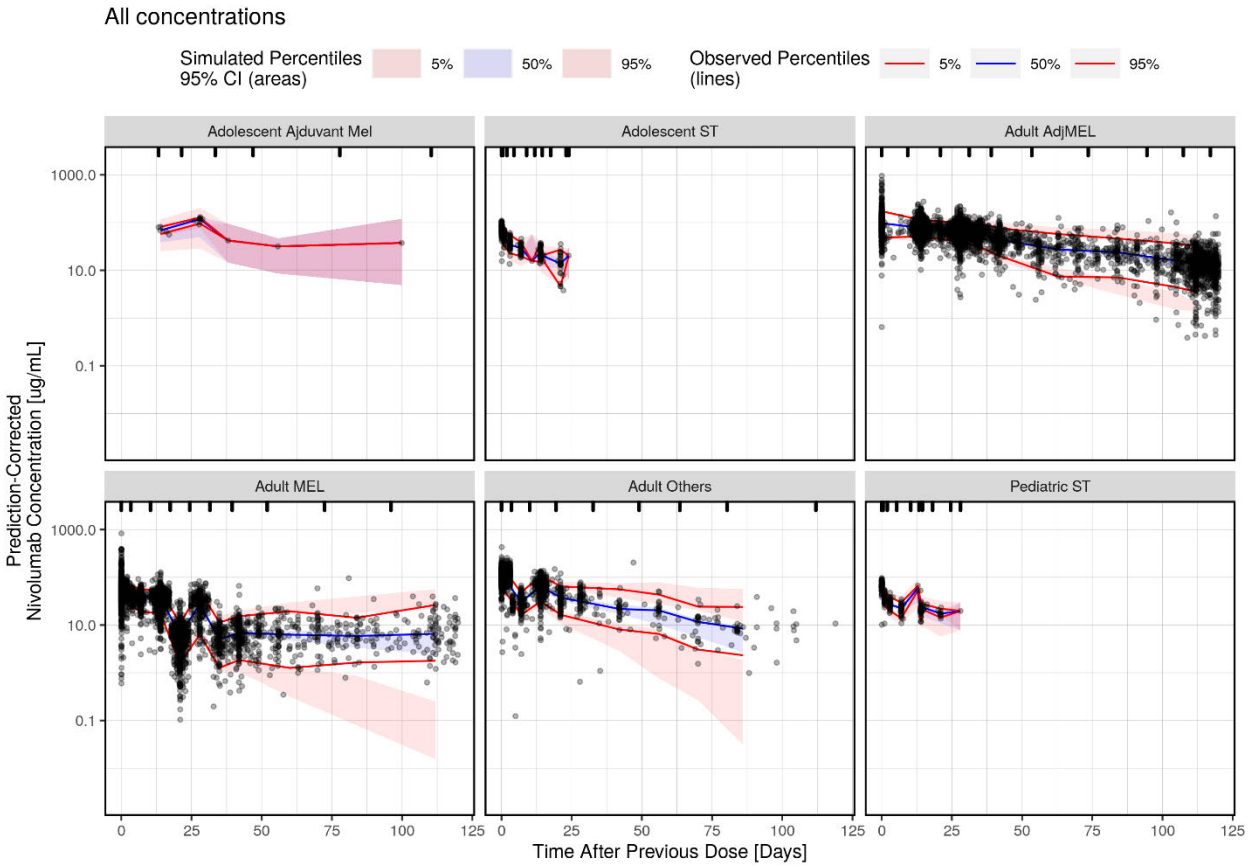
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate).

[e] Confidence intervals of Random Effects and Residual Error parameters are for Variance or Covariance

Figure 8: Applicant - Prediction-Corrected Visual Predictive Check of Nivolumab Concentrations versus Actual Time after Previous Dose, by Subject Types [Full Nivolumab Population Pharmacokinetic Model]



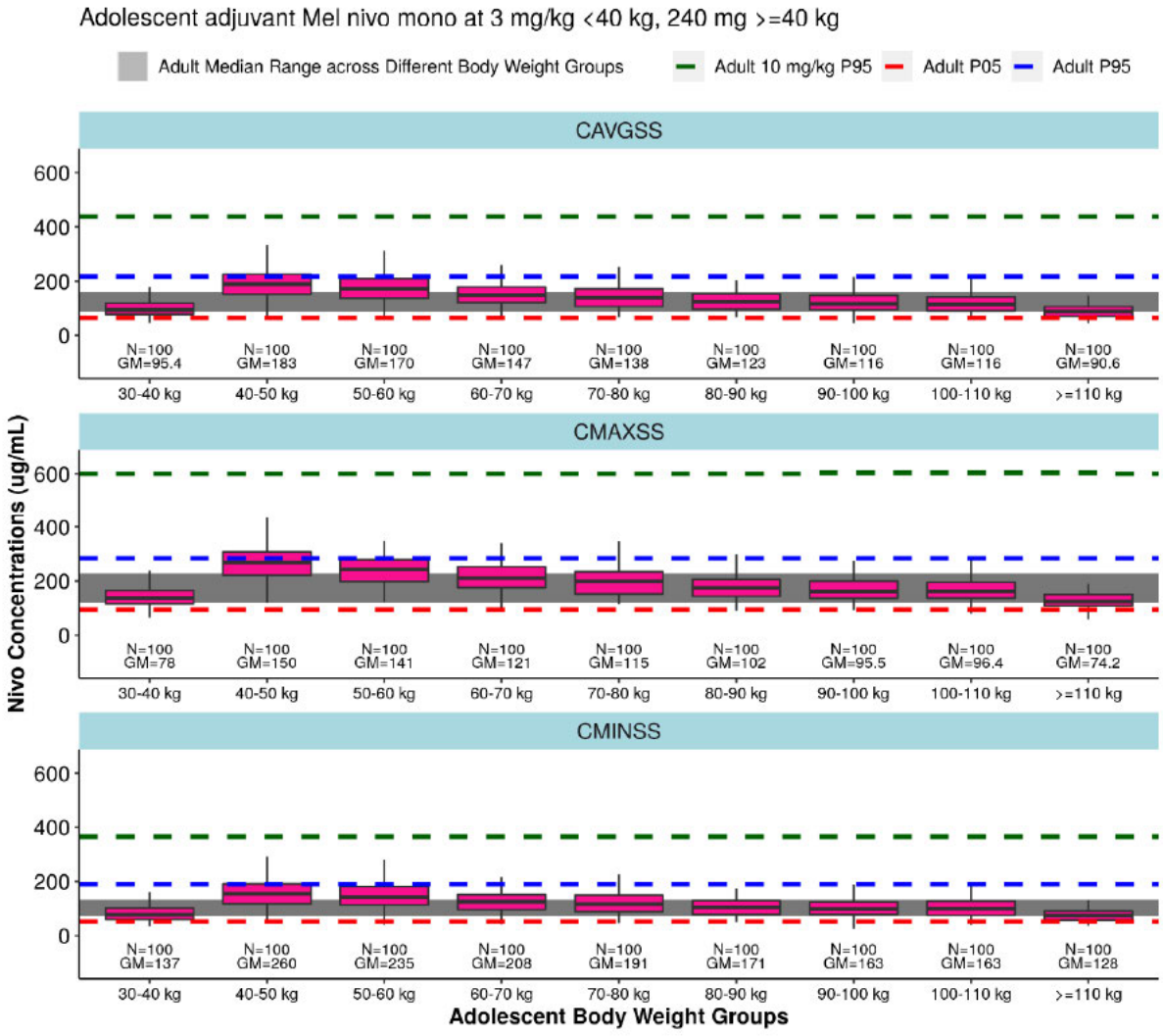
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all.png

The FDA's Assessment:

The results of the popPK analysis for nivolumab and ipilimumab in adult and adolescent (12 years and older) patients were checked by the reviewer. The results were generally acceptable due to the agreement of prediction and observation. PopPK results showed that the nivolumab exposure following the proposed dosing regimen in adolescents patients with adjuvant

melanoma (Figure 9) or in adolescent patients with metastatic melanoma who received nivolumab as monotherapy (Figure 10) were comparable to adult exposure. In addition, the nivolumab and ipilimumab exposure after 4 cycles of the proposed dosing regimens in adolescent patients with metastatic melanoma who received the combination therapy (Figure 11 and Figure 12) were also comparable to the adult exposure.

Figure 9: Predicted Nivolumab Exposures for Adolescent Adjuvant Treatment of Melanoma at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W Nivolumab Monotherapy

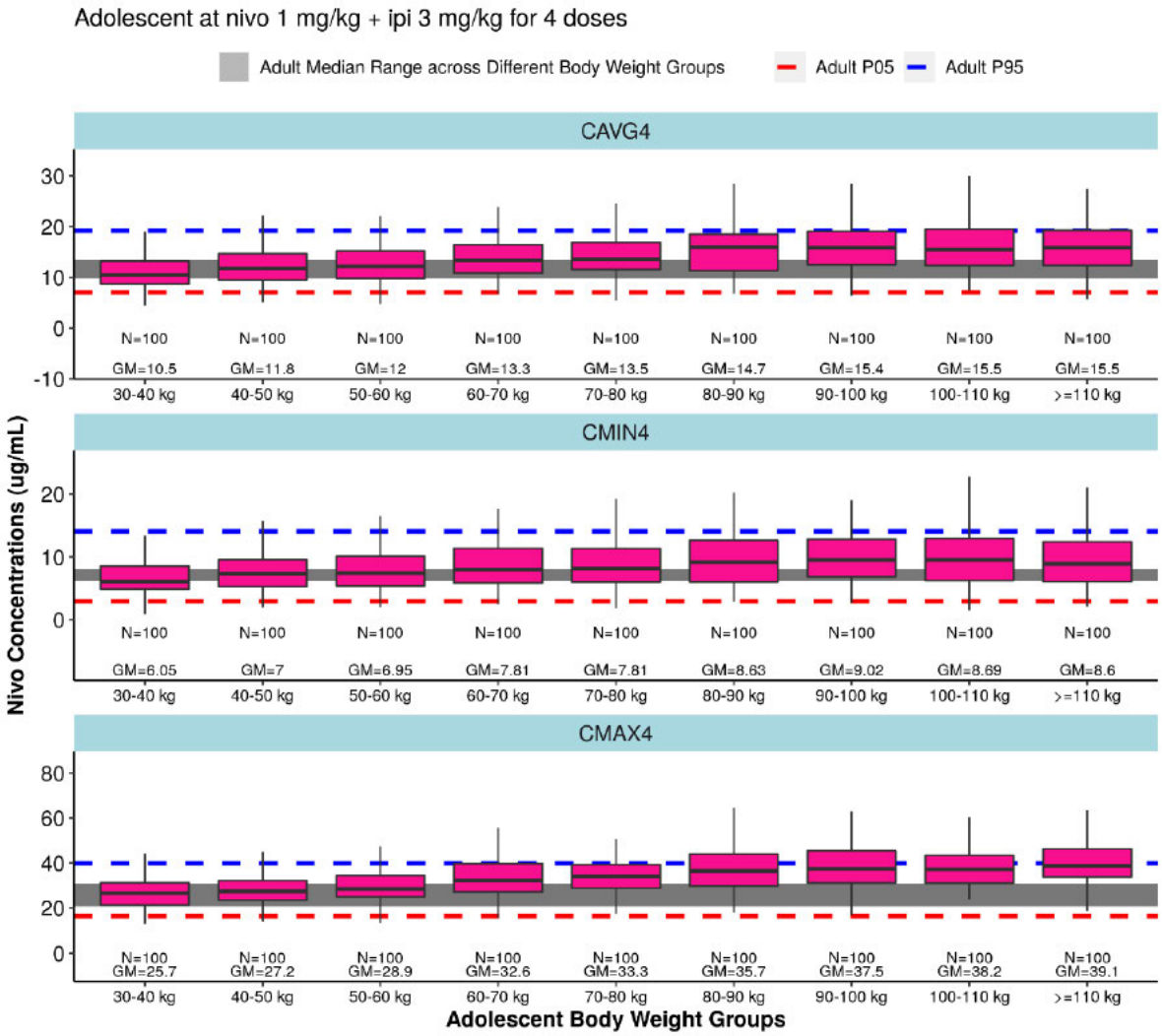


Source: Applicant's popPK report for adjuvant melanoma Figure 2, Page 8

Figure 10: Predicted Nivolumab Exposures for Adolescents with Solid Tumors at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W Nivolumab Monotherapy

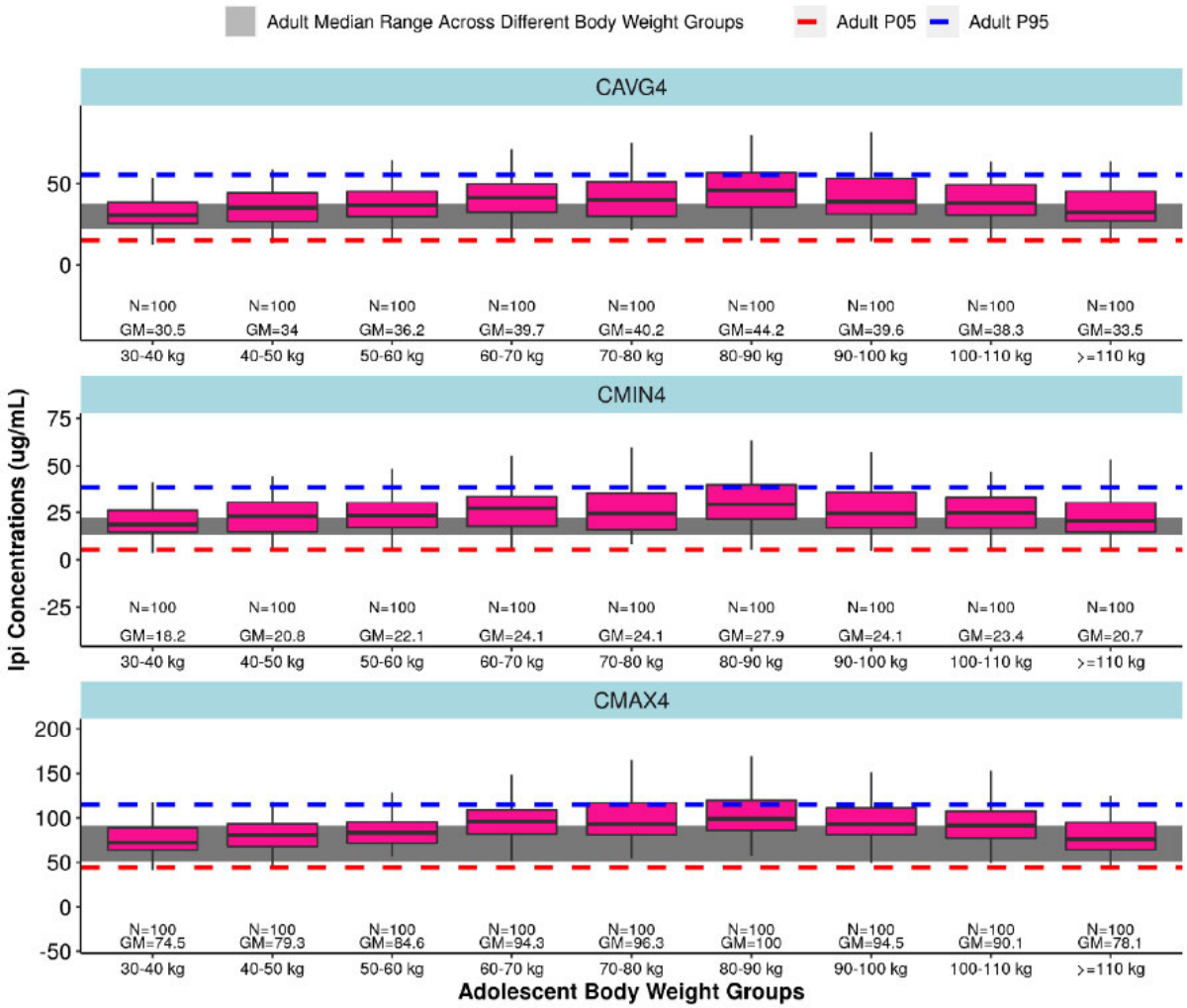
Source: Applicant's popPK report for metastatic melanoma Figure 2, Page 8

Figure 11: Predicted Nivolumab Exposures for Adolescents with Solid Tumors at Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 Doses then Nivo 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W



Source: Applicant's popPK report for metastatic melanoma Figure 5, Page 11

Figure 12: Predicted Ipilimumab Exposures for Adolescents with MEL at Nivo 1 mg/kg (up to 80 mg) + Ipi 3 mg/kg (up to 240 mg) Q3W for 4 Doses



Source: Applicant's popPK report for metastatic melanoma Figure 11, Page 21

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (safety) Executive Summary

The FDA's Assessment:

The E-R safety analysis was performed with data from 3507 subjects with unresectable or metastatic melanoma and completely resected melanoma treated in the adjuvant setting from various studies. Forty-two patients <12 years and 55 patients 12 to <18 years were included in the analysis. E-R safety for Grade 2+ IMAEs was relatively flat with minimal change in predicted Gr2+ IMAEs across the nivolumab and ipilimumab exposure (Cavgs) range. Model predicted Gr2+ IMAEs for adolescents receiving nivolumab 3 mg/kg Q2W or 6mg/kg Q4W (<40 kg), 240 mg Q2W or 480 mg Q4W (≥40 kg) monotherapy are comparable to that for adults using the

approved Q2W or Q4W dosing regimen. Similarly, model-predicted Gr2+ IMAEs for adolescents receiving nivolumab 1 mg/kg and ipilimumab 3 mg/kg (N1I3) combination therapy followed by either nivolumab Q2W or Q4W maintenance are comparable to that for adults using the approved N1I3 dosing regimen followed by nivolumab maintenance. However, due to small number of pediatric patients included in the ER analysis, the applicability of identified ER relationship in adolescents (12 to < 18 years) should be interpreted with caution.

19.4.2.2. ER (safety) Assessment Summary

The Applicant's Position:

General Information Pooled E-R Safety Analysis		
Goal of ER analysis		To characterize the relationship between nivolumab and/or ipilimumab exposure and safety in adult and pediatric subjects as measured by time to Grade 2 or greater immune-mediated adverse events (Gr2+ IMAEs) in advanced melanoma and the adjuvant treatment of melanoma. To compare predicted safety between potential adolescent dosing regimens and approved adult dosing regimens in melanoma (nivolumab +/- ipilimumab for advanced melanoma and nivo mono for the adjuvant treatment of melanoma).
Study Included		CA209003, CA209066 and CA209067 were selected to provide safety data of nivo mono in subjects with advanced solid tumors including melanoma. Studies CA184004, CA184008, CA184022, and CA184169 provide safety data of ipi mono in adults. Studies CA184070 and CA184178 provide safety data of ipi mono in young pediatric and adolescent subjects. Studies CA209004, CA209067, CA209069, CA209915, and CA209511 provide safety data of nivolumab and ipilimumab combination therapy. Studies CA209238 and CA209915 provide safety data of nivolumab in adult and adolescent subjects (N=3) for the adjuvant treatment of melanoma. Study CA209070 provides safety data of nivolumab in young pediatric, adolescent, and young adult subjects, both as monotherapy and in combination with ipilimumab.
Population Included		The E-R safety analysis was performed with data from 3507 subjects with advanced or adjuvant treatment of melanoma from various studies that were treated with nivolumab (nivo), ipilimumab (ipi), or nivo + ipi. There were 42 young pediatric subjects (< 12 years) and 55 adolescent (≥ 12 to < 18 years) subjects included in the dataset.
Endpoint		Time to first occurence of Gr2+ IMAEs
No. of Patients (total, and with individual PK)		• Total population: 5379 total, 4333 with available PK from nivo or ipi mono studies and nivolumab/ipilimumab combination studies, and 3507 included from applicable arms. • Adolescents (≥ 12 to < 18 yrs): 55 subjects • Young Pediatric (< 12 yrs): 42 subjects
Population Characteristics	General	Adult Age [median (range)]: 59 (18, 90) years Baseline body weight [median (range)]: 80 (32.8, 183) kg

		Sex [n (%)]: males 2082 (61.1), females 1327 (38.9), missing 1 (0)
	Organ impairment	N/A
	Pediatrics (if any)	<12 Years Age [median (range)]: 7 (1, 11) years Baseline body weight [median (range)]: 20.5 (9.3, 99.6) kg Sex [n (%)]: males 20 (47.6), females 22 (52.4) ≥12 - <18 Years Age [median (range)]: 15 (12, 17) years Baseline body weight [median (range)]: 58.2 (28.1, 99.4) kg Sex [n (%)]: males 31 (56.4), females 24 (43.6)
	Geriatrics (if any)	N/A
Dose(s) Included		Nivo: 0.1, 0.3, 1, 3, 10 mg/kg Q2W, 1 and 3 mg/kg Q3W, 480 Q4W Ipi:0.3, 1, 3, 5 mg/kg Q3W
Exposure Metrics Explored (range)		Daily Cavg
Covariates Evaluated		Age, baseline body weight, baseline LDH, sex, line of therapy, tumor setting (treatment setting), race, performance status, PD-L1, combination effect (nivo mono, ipi mono vs nivo+ipi combination)

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	The relationship between nivolumab and/or ipilimumab exposure (daily Cavg) and time to first occurrence of Gr2+ IMAEs was characterized by a semi-parametric stratified CPH model and included assessments of the modulatory effect of covariates on the E-R relationships.	Acceptable
Model Parameter Estimates	Table 33 in Section 19.4.2.4	Acceptable
Model Evaluation	Figure 9 in Section 19.4.2.4	Acceptable
Covariates and Clinical Relevance	Figure 4 in Section 6.3.1	Acceptable
Simulation for Specific Population	Advanced Mel (Nivo): Table 6 and Table 7 in Section 6.2.1 Advanced Mel (Nivo + Ipi): Table 10 and Table 11 in Section 6.2.1 Adjuvant Mel (Nivo): Table 14 and Table 15 in Section 6.2.1	Acceptable
Visualization of E-R relationships	Nivo: Figure 10 in Section 19.4.2.4 Nivo + Ipi: Figure 11 in Section 19.4.2.4	Acceptable
Overall Clinical Relevance for ER	The risk of Gr2+ IMAEs is significantly associated with ipilimumab exposure and interaction between nivolumab and ipilimumab exposure. In addition, the combination therapy leads to a higher baseline probability of Gr2+ IMAEs, resulting in a higher risk in combination therapy compared to either monotherapy. The magnitude of the ipilimumab	In general acceptable. However, only 42 patients<12 years and 55 patients 12 to <18 years were included in the ER analysis for safety. The applicability of identified ER

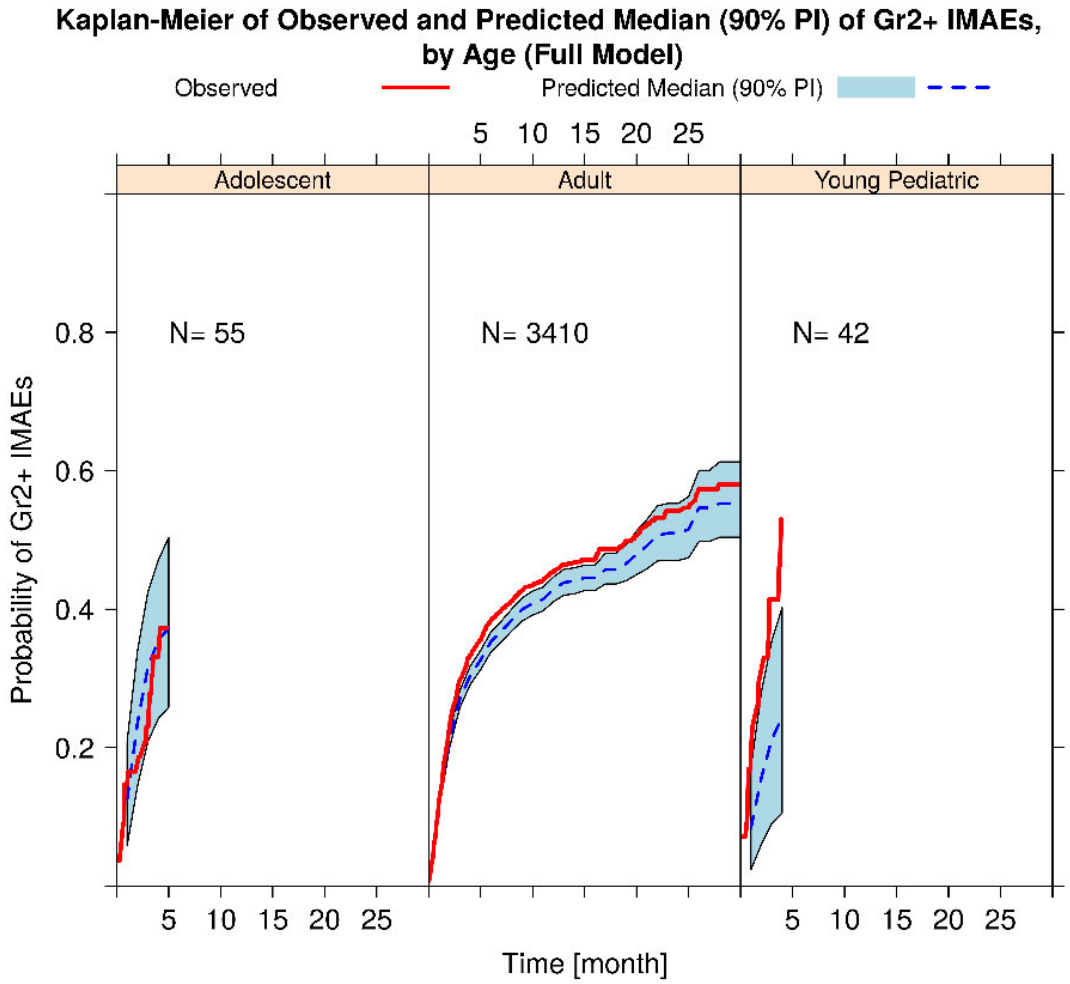
	exposure-response and interaction of ipilimumab and nivolumab exposure on the risk of Gr2+ IMAEs for the N1I3 Q3W combination is predicted to be minimal; The range of predicted Gr2+ IMAEs is narrow at Week 12 with a median (P05, P95) of 0.526 (0.490, 0.558) across the range of nivolumab and ipilimumab daily Cavgs for this combination regimen. The predicted probability of Gr2+ IMAEs are higher in subjects who are femaile, with older age, higher body weight, and who received treatment as first line therapy.	relationship in adolescents (12 to <18 years) should be interpreted with caution.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	N/A	NA

Table 33: Applicant - Parameter Estimates of the Exposure-Response of Gr2+ IMAEs (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Nivo daily Cavg [µg/mL]	-0.0004655	0.0009231	198.3	0.9995 (0.9977, 1.001)
Ipi daily Cavg [µg/mL]	0.007693	0.003228	41.96	1.008 (1.001, 1.014)
Age [yr]	0.00414	0.001987	47.99	1.004 (1, 1.008)
Body Weight [kg]	0.006033	0.00156	25.85	1.006 (1.003, 1.009)
Line of therapy [≥2L:1L]	-0.2079	0.09439	45.41	0.8123 (0.6751, 0.9774)
Treatment Setting [Adj Mel: Mel]	-0.2972	0.0889	29.91	0.7429 (0.6241, 0.8843)
Treatment Setting [Others: Mel]	0.3119	0.207	66.36	1.366 (0.9105, 2.05)
PD-L1 Status [≥5%:< 5%]	-0.02175	0.06456	296.8	0.9785 (0.8622, 1.11)
PD-L1 Status [missing:< 5%]	-0.1229	0.08553	69.62	0.8844 (0.7479, 1.046)
Performance Score [≥1:0]	0.0877	0.06695	76.35	1.092 (0.9574, 1.245)
Sex [Female:Male]	0.3423	0.05882	17.18	1.408 (1.255, 1.58)
Race [Asian:White]	0.2104	0.2139	101.7	1.234 (0.8115, 1.877)
Race [Black/African American:White]	-0.3134	0.4529	144.5	0.7309 (0.3008, 1.776)
Race [Others/unknown:White]	-0.3504	0.2276	64.97	0.7044 (0.4509, 1.101)
Log(LDH) [xULN]	-0.0209	0.04906	234.8	0.9793 (0.8895, 1.078)
Cavg Nivo:Cavg Ipi	-0.000549	0.000159	28.97	0.9995 (0.9991, 0.9998)

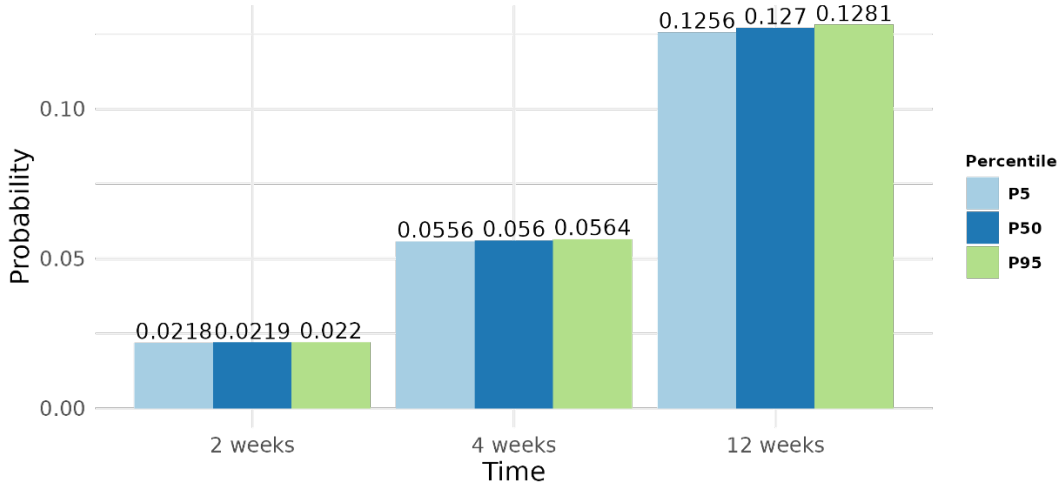
a Continuous predictors are indicated by [unit], and categorical predictors by [comparator:reference].
b RSE: Relative Standard Error = (100* SE/|Estimate|).
c Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group.
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/2-model-tv-imae-dev-final.Rmd
Source: Analysis-Directory/R/export/imae-param-cph-full.csv

Figure 13: Applicant - Model Evaluation of the Exposure-Response of Gr2+ IMAEs by Age Group (Full Model)



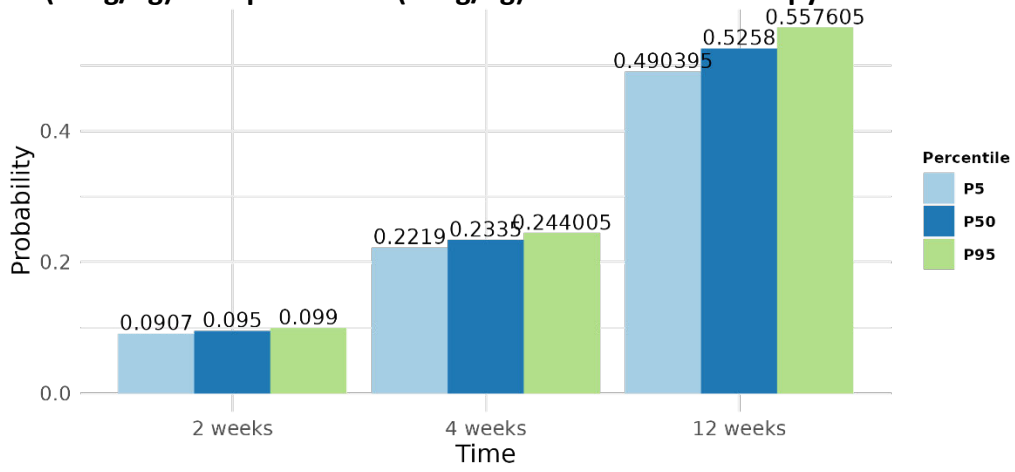
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/2-model-tv-imae-dev-final.Rmd
Source: Analysis-Directory/R/plots/AgeVPC.png

Figure 14: Applicant - Predicted Cumulative Probabilities (90% PI) of Gr2+ IMAEs for Nivolumab Monotherapy (3mg/kg) at Selected Timepoints



Note: The P5 and P95 of probability is constructed by the simulated probability of 800 subjects, where all covariates except exposure were assigned to the reference value (Line of therapy = ≥ 2nd, Treatment setting = Advanced Melanoma, BLDHR = 10, PD-L1 = < 5%, PS = 0, AGE = 50y, BW = 50 kg, SEX = Female, RACE = White, Ipilimumab exposure = 0). Time: the time after the first dose
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/ 3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/plots/ expeffect_N3.png

Figure 15: Applicant - Predicted Cumulative Probabilities (90% PI) of Gr2+ IMAEs for Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg) Combination Therapy at Selected Timepoints



Note: The P5 and P95 of probability is constructed by the simulated probability of 800 subjects, where all covariates except exposure were assigned to the reference value (Line of therapy = ≥2nd, Treatment setting = Advanced Melanoma, BLDHR = 10, PD-L1 = < 5%, PS = 0, AGE = 50y, BW = 50 kg, SEX = Female, RACE = White). Time: the time after the first dose
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/ 3-model-application-tv-imae.Rmd
Source: Analysis-Directory/R/plots/ expeffect_N1I3.png

The FDA's Assessment:
The E-R safety analysis was performed with data from 3507 patients with unresectable or metastatic melanoma and completely resected melanoma treated in the adjuvant setting from various studies. Forty-two patients <12 years and 55 patients 12 to <18 years were included in the analysis. E-R safety for Grade 2+ IMAEs was relatively flat with minimal change in predicted Gr2+ IMAEs across the nivolumab and ipilimumab exposure (Cavgs) range. Model predicted Gr2+ IMAEs for adolescents (12 to <18 years) receiving nivolumab 3 mg/kg Q2W or 6mg/kg Q4W (<40 kg), 240 mg Q2W or 480 mg Q4W (≥40 kg) monotherapy are comparable to that for adults using the approved Q2W or Q4W dosing regimen. Similarly, model-predicted Gr2+ IMAEs for adolescents receiving N1I3 combination therapy followed by either nivolumab Q2W or Q4W maintenance are comparable to that for adults using the approved N1I3 dosing regimen followed by nivolumab maintenance. However, due to small number of pediatric patients included in the ER analysis, the applicability of identified ER relationship in adolescents should be interpreted with caution.

19.4.2.3. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:
The dosing recommedations for adolescents for nivo mono in the advanced and adjuvant melanoma setting and for nivolumab in combination with ipilimumab in advanced melanoma (Table 3) are based on the totality of the data demonstrating a comparable benefit:risk assessment for adolescents versus adults. This included an understanding of adolescent and adult PK, adolescent and adult safety, adult efficacy, and results from a comphrensive, pooled E-R safety (Gr2+ IMAEs) analysis across adult and pediatric studies.

The E R relationship for safety was characterized with respect to Gr2+ IMAEs. The E-R relationship was characterized with data from nivo mono, ipi mono, and nivo + ipi combination therapy studies in adult, young pediatric (< 12 years) and adolescent (≥ 12 to < 18 years) subjects across solid tumors, including advanced melanoma and melanoma in the adjuvant setting.

For both adolescent and adult subjects, nivolumab in combination with ipilimumab leads to a higher baseline probability of Gr2+ IMAEs compared to either monotherapy. A relatively flat E-R relationship is observed for nivolumab exposure (time-varying daily Cavg) and Gr2+ IMAEs. Ipilimumab exposure and interaction between nivolumab and ipilimumab exposure are stronger predictors of Gr2+ IMAEs than nivolumab exposure.

The E-R for safety was characterized with respect to time to first occurrence of Gr2+ IMAEs. This endpoint was selected to reflect AEs that are specific to cancer immunotherapy due to the increased activity of the immune system from the treatment and is more sensitive to drug exposure than other safety endpoints previously evaluated.[47]

When the same baseline hazards of Gr2+ IMAEs were used for different treatment groups, it did not provide an adequate description of the data. In addition, model development showed that using a stratified baseline hazard significantly improved the model by decreasing the BIC value (stratified models BIC values [range: 19451.34 to 19460.42]; unstratified models BIC values [range: 22324.11 to 22534.66]); therefore, a strata function was included in the model. The strata allowed for isolating the monotherapy effects from the combination effects and for evaluating the nivolumab and ipilimumab exposure interaction specifically for the combination strata. Combination therapy contributes to a higher baseline probability of Gr2+ IMAEs compared to monotherapy. Ipi mono contributes to a higher baseline probability of Gr2+ IMAEs compared to nivo mono in the first 5 months.

The risk of Gr2+ IMAEs is best described by a linear functional form of nivolumab and ipilimumab daily Cavg with interaction. The estimated magnitude of effect for ipilimumab exposure and the interaction between nivolumab and ipilimumab exposure on the risk of Gr2+ IMAEs is significant with a hazard increase per unit increase in exposure (95% CI did not include the null value; HR 1.008 [1.001, 1.014]) for ipilimumab and 0.9995 [0.9991, 0.9998] for interaction) after accounting for the potential effect of the other covariates. This indicates that higher ipilimumab exposure is associated with higher risk of Gr2+ IMAEs. The estimated magnitude effect of nivolumab exposure on the risk of Gr2+ IMAEs is not a significant predictor (95% CI included the null value; HR 0.9995 [0.9977, 1.001]). To better understand the magnitude of the significant ipilimumab exposure measure and nivolumab:ipilimumab interaction effects on exposure for the combination, the daily Cavg effects on Gr2+ IMAEs for nivo mono and for nivolumab in combination with ipilimumab were simulated. Even though ipilimumab daily Cavg and the interaction with nivolumab daily Cavg is a significant predictor of Gr2+ IMAEs for the combination, the E-R remained relative flat across the predicted Gr2+ IMAE median (0.526), 5th (0.490) and 95th (0.558) percentiles at 12 weeks using the range of nivolumab and ipilimumab daily Cavgs predicted across the population.

<u>The effect of covariates on Gr2+ IMAEs</u>

Risk of Gr2+ IMAEs is 41% higher in female subjects than male subjects and 19% higher in subjects who received first line therapy than those that were previously treated. Older and higher body weight subjects are associated with higher risk of Gr2+ IMAEs (HR 1.24 for 95th percentile BW vs median BW; HR 1.08 for 95th percentile age vs median age). Age has a marginal effect on Gr2+ IMAEs, as the lower bound of 95% CI of age effect covers 1. The dataset includes a much larger number of adult subjects compared to adolescent and young pediatric subjects; therefore, 5th percentile of age in the dataset as shown in the covariate effect plot is 19.1 years. For an adolescent with median age at 15 years old, the HR is calculated to be 0.830 compared to an adult at median age of 60 years old. Subjects who received adjuvant treatment of melanoma have 26% lower risk of Gr2+ IMAEs compared to subjects with advanced melanoma. Other covariates including race, baseline LDH, PD-L1, and PS are not significant predictors. The lack of interactions between the significant covariates in the model and exposure suggest these covariates do not alter the exposure-dependence to response, and

conclusions about covariate effects apply across the entire pooled dataset for adult, adolescent, and young pediatric subjects.

Model-predicted Gr2+ IMAEs for adolescents receiving N1I3 combination therapy followed by nivolumab maintenance with or without dose cap are similar and are less than adults receiving N1I3 followed by nivolumab maintenance for advanced melanoma.

The lack of an increase in predicted Gr2+ IMAEs in going from adolescent dosing with and without a nivolumab and ipilimumab dose cap for the nivo + ipi (N1I3) combination with nivolumab Q2W maintenance dosing and for the nivo + ipi combination with nivolumab Q4W maintenance dosing, supports a lack of significant exposure-driven overlapping Gr2+ IMAE toxicities for the combination. Higher body weight and older age appear to be stronger predictors of Gr2+ IMAEs than exposures, resulting in higher Gr2+ IMAEs in adults than adolescents with and without a dose cap. The results from the E-R safety predictions showing lower median and overlapping Gr2+ IMAEs for adolescent versus adults for the N1I3 melanoma combination regimen expand the safety understanding for this regimen beyond that evaluated in Study CA209070 Part E, where a total of only 8 subjects (3 adolescent subjects) were enrolled.

Model-predicted Gr2+ IMAEs for adolescents receiving nivol mono flat dosing (240 mg Q2W or 480 mg Q4W) or body weight-based dosing with or without dose cap are similar and are less than adults receiving flat dose for advanced melanoma and adjuvant treatment of melanoma.

The model-predicted mean cumulative probabilities of Gr2+ IMAEs between Adolescent: Nivo 3 mg/kg Q2W (< 40 kg) or 240 mg (≥ 40 kg) Q2W, Adolescent: Nivo 3 mg/kg Q2W, and Adolescent with cap: Nivo 3 mg/kg (up to 240 mg) Q2W are identical and are each lower than Adult: Nivo 240 mg Q2W. The model-predicted mean cumulative probabilities of Gr2+ IMAEs between Adolescent: Nivo 6 mg/kg Q4W (< 40 kg) or 480 mg (≥ 40 kg) Q4W, Adolescent: Nivo 6 mg/kg Q4W and Adolescent with cap: Nivo 6 mg/kg (up to 480 mg) Q4W are identical and are each lower than Adult: Nivo 480 mg Q4W.

The FDA's Assessment:

E-R relationship for Gr2+ IMAEs was relatively flat with minimal change in predicted Gr2+ IMAEs across the nivolumab and ipilimumab exposure (Cavgs) range. Model predicted Gr2+ IMAEs for pediatric patients (12 years and older) receiving nivolumab 3 mg/kg Q2W or 6mg/kg Q4W (<40 kg), 240 mg Q2W or 480 mg Q4W (≥40 kg) monotherapy are comparable to that for adults using the approved Q2W or Q4W dosing regimen. Similarly, model-predicted Gr2+ IMAEs for adolescents receiving N1I3 combination therapy followed by either nivolumab Q2W or Q4W maintenance are comparable to that for adults using the approved N1I3 dosing regimen followed by nivolumab maintenance. However, due to small number of pediatric patients included in the ER analysis, the applicability of identified ER relationship in adolescents should be interpreted with caution.

19.5. Additional Safety Analyses Conducted by FDA

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

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BMS
sBLA 125554/117, 118, 119 and sBLA 125377/129
SIGNATURE PAGE

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Clinical Pharmacology Reviewer	Hairat Sabit	Division of Clinical Pharmacology II	Sections: 6 and 19.4	**Select one:** X Authored ___Approved
	Signature: Hairat Sabit -S Digitally signed by Hairat Sabit -S Date: 2023.02.08 15:39:08 -05'00'			
Clinical Pharmacology Team Lead	Jason Moore	Division of Clinical Pharmacology II	Sections: 6 and 19.4	**Select one:** X Authored ___X Approved
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Deputy Director	Stacy Shord	Division of Clinical Pharmacology II	Sections: 6 and 19.4	**Select one:** Authored __X Approved
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Associate Director for labeling	Doris Auth	Oncology Cancer for Excellence	Sections:	Authored Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2023.02.08 22:39:42 -05'00'			
Clinical Reviewer and Cross-Disciplinary Team Leader (CDTL)	Jamie Brewer	Division of Oncology 3	Sections: All	**Select one:** X Authored X Approved
	Signature: SEE SIGNATURE IN DARRTS			
Deputy Director	Lola Fashoyin-Aje	Division of Oncology 3	Sections: All	**Select one:** X Approved
	Signature: SEE SIGNATURE IN DARRTS			

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sBLA 125554/117, 118, 119 and sBLA 125377/129
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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
02/15/2023 03:33:30 PM

STEVEN J LEMERY on behalf of IBILOLA A FASHOYIN-AJE
02/15/2023 03:59:51 PM