EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2023
EMA/221123/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0125/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the last time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BMS	Bristol Myers Squibb
BOR	best overall response
BW	body weight
C	cycle
Cavg	time-averaged serum concentration
Cavg4	time-averaged serum concentration after 4 doses
Cavgss	time averaged steady state concentration
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL0	baseline clearance
CLSS	steady-state clearance
Cmax	maximum observed serum concentration
Cmax4	maximum concentration after 4 doses
Cmaxss	peak concentration at steady state
Cmin	observed predose trough serum concentration
Cmin4	trough concentration after 4 doses
Cminss	trough concentration at steady state
CNS	central nervous system
COG	Children’s Oncology Group
COVID-19	coronavirus disease 19
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CTEP	Clinical Trials Evaluation Program
CTLA-4	cytotoxic T lymphocyte antigen 4
CV	coefficient of variation

D	day
DBL	database lock
DFS	disease-free survival
DL	dose level
DLT	dose-limiting toxicity
DMFS	distant metastasis-free survival
dMMR	mismatch repair deficient
DMTR	Dutch Melanoma Treatment Registry
DOR	duration of response
EBE	empirical Bayes estimate
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eGFR	estimate glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
E-R	exposure-response
ESMO	European Society of Clinical Oncology
EU	European Union
FDA	Food and Drug Administration
FU	follow-up
Gr2+ / Gr3+	grade 2 or greater / grade 3 or greater
H&E	hematoxylin and eosin
HL	Hodgkin lymphoma
HR	hazard ratio
HRQoL	health related quality of life
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
IMAE	immune mediated adverse event
IND	investigational new drug
Ipi	ipilimumab
IRT	interactive response technology
IV	intravenous(ly)
KPS	Karnofsky performance scale
LBM	lean body mass
LDH	lactate dehydrogenase
LLN	lower limit of normal
LPFV	last patient first visit

mCRC	metastatic colorectal cancer
MIBG	meta-iodobenzylguanidine
max	maximum
MedDRA	medical dictionary for regulatory activities
min	minimum
mo	month
mono	monotherapy
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NA	not applicable
NAb	neutralizing antibodies
NCCN	National Cancer Comprehensive Cancer Network
NCI	National Cancer Institute
NED	no evidence of disease
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
Nivo	nivolumab
Nivo+ipi	nivolumab plus ipilimumab
NOS	not otherwise specified
NR	not reported
NSCLC	non-small cell lung cancer
OESI	other events of special interest
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PDCO	Paediatric Committee
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PNET	primitive neuroectodermal tumour
PPK	population pharmacokinetic
PR	partial response
PS	performance status
PSUR	periodic safety update report
PWR	paediatric written request

QxW	every x weeks
QLQ-C30	quality of life questionnaire - 30-item score
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	recurrence-free survival
RMS	rhabdomyosarcoma
RP2D	recommended Phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SD	standard deviation
SmPC	summary of product characteristics
Tmax	time of maximum observed serum concentration
TTR	time to response
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
UV	ultraviolet
VC	volume of distribution of the central compartment
vs	versus
WBC	white blood cell
WT	wild-type
yr	year

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 22 August 2022 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include adolescent patients aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) for Opdivo, based on results from a nonclinical biomarker study (Expression of PD-L1 (CD274), and characterization of tumor infiltrating immune cells in tumors of pediatric origin), also based on results from a Phase 1/2 clinical study (CA209070, A Phase 1/2 Study of Nivolumab (Ind# 124729) In Children, Adolescents, And Young Adults With Recurrent Or Refractory Solid Tumors As A Single Agent And In Combination With Ipilimumab) and a modelling and simulation study. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated.
The Package Leaflet is updated in accordance.
Version 30.0 of the RMP has also been submitted.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0432/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0432/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0432/2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	22 August 2022
Start of procedure:	17 September 2022
CHMP Rapporteur Assessment Report	1 December 2022
PRAC Rapporteur Assessment Report	22 November 2022
PRAC members comments	23 November 2022
Updated PRAC Rapporteur Assessment Report	25 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 December 2022
Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	5 April 2023
PRAC Rapporteur Assessment Report	31 March 2023
PRAC Outcome	13 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
Opinion	26 April 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The following indications for Opdivo are proposed to be expanded to include adolescent patients 12 years and older:

- OPDIVO as *monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.*
- OPDIVO as *monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.*

Epidemiology and risk factors, screening tools/prevention

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] In Europe, the age-adjusted incidence rates in 2020 were 20.0 per 100,000 persons for all ages (150,627 cases), 0.1 per 100,000 for ages < 15 years (169 cases), and 0.5 per 100,000 for ages < 20 years (805 cases).[4]

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 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.[5]

The genomic landscape of conventional melanoma in children is represented by many of the genomic alterations that are found in adults with melanoma.

Paediatric melanoma presents a clinical and histopathological challenge due to its rarity and atypical presentations. Melanomas affecting the pediatric age can be classified in 3 subtypes: Spitzoid melanoma, melanoma arising in congenital melanocytic nevi, and conventional (adult-type) melanoma. In patients 11 years and older, conventional melanoma is the prevailing subtype, which shares

[1] Brecht IB, De Paoli A, Bisogno G, et al. Pediatric patients with cutaneous melanoma: A European study. Pediatr Blood Cancer 2018;65(6):e26974.
[2] Jen M, Murphy M, Grant-Kels JM. Childhood melanoma. Clin Dermatol 2009;27:529-36.
[3] Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 2005;23:4735-41.
[4] European Cancer Information System (ECIS). Cancer burden statistics and trends across Europe. Access to: https://ecis.jrc.ec.europa.eu.
[5] Aldrink JH, Polites SF, Austin M. Pediatric melanoma - diagnosis, management, and anticipated outcomes. Surg Oncol Clin N Am 2021;30:373-88.

morphologic (superficial spreading and nodular) and molecular features with adult melanoma and is mainly located on the trunk.[6]

Common risk factors for melanoma in paediatric and adult patients are intermittent intense sun exposure, tendency to sunburn, tendency to freckle, fair skin, blue or green eyes, and blond or red hair. Genetic predisposing conditions for developing melanoma, specifically in the paediatric population, do more frequently manifest in early childhood than in adolescence.

The OS in pediatric and adolescent melanoma is similar to what is seen in adults.[7,8,9]

Clinical presentation, diagnosis and stage/prognosis

Primary tumor characteristics, such as the site of the primary tumor, stage at diagnosis, tumor thickness, or level of invasion were compared between pediatric and adult melanoma patients. The group of prepubescent patients appears to be in this context as a separate group with thicker tumor lesions, whereas primary tumor characteristics between adolescent and adult melanoma patients are comparable. Stage II and III melanoma in adults and adolescents can be considered as the same disease, sharing the same prognostic factors and the high risk of recurrence and death.[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 3-year OS of 100.0% for Stage I, 90.0% for Stage II, 92.1% for Stage III, and 57.1% for Stage IV tumors. Data from the 2004-2016 National Cancer Database collected from 1903 pediatric melanoma patients reported 5-year OS greater than 90.0% for Stage I-III tumors and of 34.4% for Stage IV tumors.[12]

Clinical studies in pediatric and adolescent melanoma patients as reported in the literature were analyzed to assess the response to intervention. Although the number of patients in these studies was small and the studies did not have a randomized design, treatment effects such as objective response or pharmacodynamic effects of immunotherapy appeared to be comparable to adult patients.[10,7,8,9]

Management

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

[6] Neves JM, Duarte B, Paiva Lopes MJ. Pediatric melanoma: epidemiology, pathogenesis, diagnosis and management. Revista SPDV 2020;78:107-14.
[7] Paradela S, Fonseca E, Pita-Fernandez S, et al. Prognostic factors for melanoma in children and adolescents: a clinicopathologic, single-center study of 137 patients. Cancer 2010;116(18):4334-44.
[8] Wong JR, Harris JK, Rodriguez-Galindo C, et al. Incidence of childhood and adolescent melanoma in the United States: 1973-2009. Pediatrics 2013;131:846-54.
[9] Brecht IB, Garbe C, Gefeller O, et al. 443 paediatric cases of malignant melanoma registered with the German Central Malignant Melanoma Registry between 1983 and 2011. Eur J Cancer 2015;51:861-8.
[10] Lange JR, Palis BE, Chang DC, et al. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. J Clin Oncol 2007;25:1363-8.
[11] Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(6):472-92.
[12] Yousif R, Boull C, Gerami P, Nardone B, Vivar KL, Liszewski W. THE demographics and trends in pediatric melanoma in the United States: An analysis of the National Cancer Database. Pediatr Dermatol 2021;38(5):1191-7.

guidelines for adult patients,[13,14,15] 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 in pediatric patients are comparable with adult patients. The mainstay of treatment of pediatric cutaneous melanoma is cure by surgical resection. 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.[5] Pediatric patients with Stages III and IV melanoma are considered for additional therapy. Prior to 2011, approved therapies were limited to dacarbazine chemotherapy and interleukine-2 immunotherapy as treatment of metastatic melanoma and interferon α-2b as adjuvant treatment. Since then, two distinct therapeutic classes have been developed with demonstrated efficacy in adult adjuvant and advanced settings: checkpoint inhibitors targeting the PD-1, LAG-3, and CTLA-4 coinhibitory receptor pathways and targeted therapies inhibiting tyrosine kinase signaling pathways (such as BRAF and MEK inhibitors).[16]

Treatment of Advanced (Unresectable or Metastatic) Melanoma

The checkpoint inhibitors, including ipilimumab, nivolumab, nivolumab in combination with relatlimab fixed dose combination, 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 as monotherapy (ipilimumab, nivolumab, and pembrolizumab) and the nivolumab plus ipilimumab combination were approved in adults in the US and EU. Nivolumab and relatlimab fixed-dose combination was approved in the US and received marketing authorization in the EU on September 2022. Three BRAF-MEK inhibitor combinations were approved in the 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.[13,15] 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.

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 again are based on extrapolation from adult data.[17] Adjuvant therapy for adult melanoma has changed dramatically in the past five years. Interferon α-2b remained the standard adjuvant therapy for high-risk melanoma until FDA approval of the CTLA-4 inhibitor ipilimumab in 2015. In adults, the adjuvant use of ipilimumab or PD-1 inhibitors (nivolumab and pembrolizumab) as well as the adjuvant use of BRAF and MEK inhibitors demonstrated efficacy in Phase 3 studies. The two checkpoint inhibitors, nivolumab and pembrolizumab, were approved in the US and EU for adults in the adjuvant setting. The combination of the BRAF (dabrafenib) and MEK (trametinib) inhibitors was approved in the US and EU for adult BRAF-mutant Stage III melanoma following complete resection.[13,15] The FDA and recently EMA approved the expanded indication of pembrolizumab for the adjuvant treatment of adults and adolescents 12 years and older with Stage

[13] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Melanoma: Cutaneous. Version 2.2022. Available from https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf.
[14] Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2019;80(1):208-50.
[15] Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U; ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1884-1901.
[16] Guo W, Wang H, Li C, et al. Signal pathways of melanoma and targeted therapy. Signal Transduction and Targeted Therapy 2021;6:424.
[17] Aldrink JH, Polites S, Lautz TB, et al. What's new in pediatric melanoma: An update from the APSA cancer committee. J Pediatr Surg 2020;55:1714-21.

IIB, IIC based on KEYNOTE-716 study[18] and Stage III melanoma based on KEYNOTE-054 study[19] following complete resection.

Approved Checkpoint Inhibitors for Paediatric Patients with Melanoma

Table 1 ***Approved Checkpoint Inhibitors for Paediatric Patients with Melanoma in EU and US***

Product Name	Date of approval		Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
	EMA[a]	FDA				
Ipilimumab (YERVOY)	2018	2017	Unresectable or metastatic melanoma in adult 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 2 studies (CA184070 [NCT01445379] and CA184178 [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 that 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)	2023	2022	US: Unresectable or metastatic melanoma in adult and pediatric patients 12 years and older EU: Unresectable or metastatic melanoma in adult and pediatric patients 12 years and older with tumor cell PD-L1 expression <1%	US: Pediatric patients 12 years of age or older who weigh at least 40 kg: 480 mg nivolumab and 160 mg relatlimab intravenously every 4 weeks. EU: This dose is established for adolescent patients weighing at least 30 kg.	Use of OPDUALAG in pediatric patients 12 years of age and older is supported by evidence from an adequate and well-controlled study in adults[20] and additional data analyses that suggest that nivolumab and relatlimab exposures in pediatric patients 12 years of age who weigh at least 40 kg for US and 30 kg for EU 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.[21,22]
Pembrolizumab (KEYTRUDA)	2022	Not approved	Unresectable or metastatic melanoma in adult and pediatric patients 12 years and older	2 mg/kg (up to 200 mg) intravenously every 3 weeks	In KEYNOTE-051,[23] 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%), leukopenia (30%), neutropenia (26%), and Grade 3 anemia (17%).	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.[24, 25]
	2022	2021	Adjuvant treatment of adult and pediatric patients 12 years and older with Stage IIB, IIC, or III melanoma following complete resection	2 mg/kg (up to 200 mg) intravenously every 3 weeks		

[18] Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected Stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. Lancet 2022;399(10336):1718-29.
[19] Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected Stage III melanoma. N Engl J Med 2018;378(19):1789-1801.
[20] Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 2022;386:24-34.
[21] OPDUALAG (nivolumab and relatlimab-rmbw) injection, for intravenous use. United States Prescribing Information. Bristol-Myers Squibb Company; May 2022.
[22] OPDUALAG (nivolumab and relatlimab-rmbw). Summary of Product Characteristics. Bristol-Myers Squibb Company; adopted by the CHMP on 21-Jul-2022 (EC Decision pending).
[23] Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:121-33.
[24] KEYTRUDA (pembrolizumab) injection, for intravenous use. United States Prescribing Information. Merck & Co, Inc.; May 2022.
[25] KEYTRUDA (pembrolizumab) injection. Summary of Product Characteristics. Merck & Co, Inc.; May 2022.

[a] EMA approval = European Commission (EC) decision in EU

Similarity of melanoma between adolescents and adults

The following discussion has been provided by the MAH:

Primary melanoma tumor characteristics are considered to be comparable between adolescent and adult melanoma patients, in contrast to the disease in prepubescent children. In an analysis of 1255 pediatric and young adults (age less than 20 years), the 10 to 19 year-old group had similar baseline characteristics compared with the group of 20 to 24 year-old young adults, while there were significant differences in baseline characteristics of young children (age less than 10 years) as compared with adolescents and young adults. Young children were more likely to be non-white and to have metastases, nodular or other histology, head, face, or neck primaries, thicker lesions, and history of cancer.[3]

Similarity of melanoma disease between adolescents and adults has been demonstrated by a comparable biology.[3]

Histology: The frequency of histological subtypes, such as lentigo malignant melanoma, superficial spreading melanoma, acral lentiginous melanoma, and nodular melanoma in tumors of adolescent melanoma patients is comparable to melanoma tumors in adult patients.

Clinical presentation: Primary tumor characteristics, such as the site of the primary tumor, stage at diagnosis, tumor thickness, or level of invasion were compared between pediatric and adult melanoma patients. The group of prepubescent patients appears to be in this context as a separate group with thicker tumor lesions, whereas primary tumor characteristics between adolescent and adult melanoma patients are comparable.[3] Stage II and III melanoma in adults and adolescents can be considered as the same disease, sharing the same prognostic factors and the high risk of recurrence and death.[26]

Risk factors: Common risk factors for melanoma in pediatric and adult patients are intermittent intense sun exposure, tendency to sunburn, tendency to freckle, fair skin, blue or green eyes, and blond or red hair. Genetic predisposing conditions for developing melanoma, specifically in the pediatric population, do more frequently manifest in early childhood than in adolescence.

Driver mutations: Among the pediatric melanomas, conventional melanoma, which predominantly occurs in adolescents, shares properties similar to adult melanomas, including mutation rates, high rate of single nucleotide variations that are characteristic of ultraviolet damage, and similar rate of activating BRAFV600 mutation, while the melanomas of childhood, especially in children < 10 years (melanomas arising in congenital melanocytic naevus and Spitzoid melanoma) share less genomic similarities with melanoma in adolescents and adults. [10,27,28]

Similarity of melanoma disease between adolescents and adults has also been shown by comparable outcomes:

[26] Lange JR, Palis BE, Chang DC, et al. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. J Clin Oncol 2007;25:1363-8.
[27] Newman S, Fan L, Pribnow A, et al. Clinical genome sequencing uncovers potentially targetable truncations and fusions of MAP3K8 in spitzoid and other melanomas. Nat Med 2019;25:597-602.
[28] Bahrami A, Barnhill RL. Pathology and genomics of pediatric melanoma: a critical reexamination and new insights. Pediatr Blood Cancer 2018;65:e26792.

- Survival: The OS in pediatric and adolescent melanoma is similar to what is seen in adults.[3,10,29,30,31]

- Response to intervention: Clinical studies in pediatric and adolescent melanoma patients as reported in the literature were analyzed to assess the response to intervention. Although the number of patients in these studies was small and the studies did not have a randomized design, treatment effects such as objective response or pharmacodynamic effects of immunotherapy appeared to be comparable to adult patients.[10,7,8,9]

- The few clinical studies with radiotherapy and chemotherapy in paediatric patients with melanoma showed a comparable safety profile to adult patients. Objective responses in individual patients were reported. However, the design of the reported studies and the small number of adolescent melanoma patients enrolled do not allow for a conclusive comparison of efficacy to adult studies.[32,33,34]

- Clinical studies with IFNα2b and high-dose IL-2 in paediatric patients showed the feasibility and overall comparable safety profile to adult patients. Pharmacodynamic effects of immunotherapy in children were reported to be comparable to adult patients.[35,36,37,38,39]

- The safety and effectiveness of the checkpoint inhibitor ipilimumab as a single agent have been established in adults and paediatric patients aged 12 years and older for the treatment of unresectable or metastatic melanoma.[40]

2.1.2. About the product

Nivolumab (Opdivo; BMS-936558, MDX-1106, ONO-4538) is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumours use PD-L1 expression as defence or escape mechanism against the host's antitumor T cell response; inhibiting PD-(L) 1 restores the function of these antitumor T cells which have become ineffective or suppressed. Therefore, the efficacy of PD-(L) 1 inhibition relies on a pre-existing immune response.

Nivolumab is approved in the US, EU, Japan, and several other countries as monotherapy and in combination with other agents for multiple tumour types.

[29] Paradela S, Fonseca E, Pita-Fernandez S, et al. Prognostic factors for melanoma in children and adolescents: a clinicopathologic, single-center study of 137 patients. Cancer 2010;116(18):4334-44.
[30] Wong JR, Harris JK, Rodriguez-Galindo C, et al. Incidence of childhood and adolescent melanoma in the United States: 1973-2009. Pediatrics 2013;131:846-54.
[31] Brecht IB, Garbe C, Gefeller O, et al. 443 paediatric cases of malignant melanoma registered with the German Central Malignant Melanoma Registry between 1983 and 2011. Eur J Cancer 2015;51:861-8.
[32] Pappo AS, Kaste SC, Rao BN, et al. Childhood melanoma. In: Balch CM, Houghton AN, Sober AJ, Soong SJ, eds. Cutaneous Melanoma. St Louis, MO, Quality Medical Publishing. 1998; 175-86.
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[34] Boddie AW, Cangir A. Adjuvant and neoadjuvant chemotherapy with dacarbazine in high-risk childhood melanoma. Cancer 1987;15;60:1720-3.
[35] Bernhardt MB, Hicks MJ, Pappo AS. Administration of high-dose interleukin-2 in a 2-year-old with metastatic melanoma. Pediatr Blood Cancer 2009;53:1346-8.
[36] Bauer M, Reaman GH, Hank JA, et al. A phase II trial of human recombinant interleukin-2 administered as a 4-day continuous infusion for children with refractory neuroblastoma, non- Hodgkin's lymphoma, sarcoma, renal cell carcinoma, and malignant melanoma. A Childrens Cancer Group study. Cancer 1995;15;75:2959-65.
[37] Navid F, Furman WL, Fleming M, et al. The feasibility of adjuvant interferon alpha-2b in children with high-risk melanoma. Cancer 2005;103:780-7.
[38] Ribeiro RC, Rill D, Roberson PK, et al. Continuous infusion of interleukin-2 in children with refractory malignancies. Cancer 1993;72:623-28.
[39] Shah NC, Gerstle JT, Stuart M, et al. Use of sentinel lymph node biopsy and high-dose interferon in paediatric patients with high-risk melanoma: the Hospital for Sick Children experience. J Pediatr Hematol Oncol 2006;28:496-500.
[40] Geoerger B, Bergeron C, Gore L, et al. Phase II study of ipilimumab in adolescents with unresectable Stage III or IV malignant melanoma. Eur J Cancer 2017;86:358-63.

Ipilimumab (Yervoy; BMS-734016, MDX-010, MDX-CTLA4) is a human CTLA-4-blocking antibody. Nivolumab and ipilimumab are both immune checkpoint inhibitors. Importantly, the recruitment of novel T cells to the tumour and the generation of memory T cells through CTLA-4 inhibition is independent of whether the tumour is expressing PD-L1 as a defence mechanism. Therefore, the combination of ipilimumab and nivolumab can potentially further reduce the tumour cells' escape mechanism against the host's anti-tumour T cell response. Ipilimumab in combination with nivolumab has demonstrated efficacy (which includes prolonged duration of response, among other efficacy outcomes) in various tumour types in multiple approved indications.

Nivolumab in combination with ipilimumab has been approved in the US, EU, Japan, and several other countries for multiple tumour types, including advanced melanoma, non-small cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, colorectal cancer, oesophageal squamous cell carcinoma, and hepatocellular carcinoma. In the EU, the approved dosing regimen for nivolumab in combination with ipilimumab for adults with advanced melanoma is nivolumab 1 mg/kg Q3W + ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab monotherapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical studies supporting the proposed melanoma indications and included in this application are summarized in section 2.3.1 below. The MAH did not seek scientific advice at the CHMP concerning the current procedure.

2.1.4. General comments on compliance with GCP

See section 2.3.1.

2.2. Non-clinical aspects

2.2.1. Introduction

The nonclinical pharmacology, pharmacokinetics and toxicology of nivolumab have been well characterized in a full non-clinical packaged included in the original marketing authorisation application (MAA) for Opdivo. In addition to studies performed in the initial MAA, the following non-clinical studies have been performed in support of this application for nivolumab:

A Non-clinical biomarker study in paediatric tumour tissue including:

- Quantification of PD-L1 expression on paediatric tumour cells
- Assessment the type and quantity of tumour infiltrating lymphocytes in at least 40 of the samples (CD3, CD4, CD8, PD-1, FOXp3, CD45RO).

All non-clinical studies in the agreed paediatric investigation plan P/0432/2020 were conducted.

2.2.2. Pharmacology

A total of 620 individual tumour samples were assessed for expression of PD-L1, including 91 samples for which whole sections were available, and 529 samples represented on 7 tumour microarrays. High rates of PD-L1+ staining at a > 1% threshold (≥1+ intensity, minimum 100 tumour cells evaluated)

were observed in samples from non-Hodgkin's lymphoma (8/10; 80%) and glioblastoma (7/20; 35%). Positive PD-L1 staining was also observed in 16/114 (14%) neuroblastoma samples (including both whole slide sections and TMA samples), ganglioneuroblastoma (2/18; 11%), ependymoma (2/40; 5%), and rhabdomyosarcoma (2/54; 4%). Other tumour types demonstrating positive PD-L1 expression in at least one sample included osteosarcoma (1/20; 5%), supratentorial primitive neuroectodermal tumour (1/5; 20%) and the single synovial sarcoma sample (1/1, 100%). No PD-L1 expression was observed in any of the medulloblastoma, ganglioneuroma or Ewing's sarcoma tumour samples examined.

Immune cells (lymphocytes or macrophages) were identified in most samples assessed (335/456; 73%). PD-L1+ staining on immune cells (qualitatively assessed) was identified in 71/335 (21%) tumour samples with tumour associated immune cells present.

Expression of CD3, CD4, CD8, CD45RO, PD-1 and FoxP3 cells was assessed in 60 total paediatric tumour samples, including osteosarcoma (n=20, whole slides) and a subset of tumours represented on the tumour microarrays (n=40). TMA samples were selected based on the observation of the presence of lymphocytes and/or macrophages or PD-L1 positivity. CD45RO+ cells (memory T cells) were the most ubiquitously present cells, seen in 49/60 (81%) tumours. CD8+ cells (cytotoxic T cells) were commonly observed as well (46/60; 77%). PD-1+ and FoxP3+ expression was seen in 28 (47%) and 25 (42%) tumours, respectively. CD4+ staining was only observed in 13 (22%) of tumours assessed.

2.2.3. Pharmacokinetics

No additional nonclinical PK studies have been submitted.

2.2.4. Toxicology

No additional nonclinical toxicity studies have been submitted.

2.2.5. Ecotoxicity/environmental risk assessment

Nivolumab is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), nivolumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not expect to pose a significant risk to the environment.

2.2.6. Discussion on non-clinical aspects

The data provided by the MAH show that prevalence of PD-L1+ staining on cell membranes of paediatric tumours varied by pathology. No PD-L1 expression was observed on any medulloblastoma, ganglioneuroma or Ewing's sarcoma tested; however, a high percentage of glioblastoma and non-Hodgkin's lymphoma samples showed positive PD-L1 expression. Other types of tumours expressed PD-L1 in a low number of samples. An integrated discussion of non-clinical data, clinical data and previous data of expression levels in adult tumours in order to discuss the clinical utility of PD-L1 expression has not been performed. This integrated discussion could be relevant for future paediatric indications, nevertheless the relevance of the data for the proposed indication is questionable since melanoma samples were not analysed in the study.

In a subset of tumours, expression of CD3, CD4, CD8, CD45RO, FoxP3, and PD-1 was assessed. CD45RO+ staining, a marker of T memory cells, was observed in nearly all tumours analysed, as was CD8+, a marker of cytotoxic T cells. CD3 and FoxP3, a general marker of T cells and a marker of regulatory T cells, respectively, were observed in approximately half of the tumours examined. CD4+ staining, a marker commonly associated with T helper cells, was observed only in a minority of tumours. A correlation between infiltrating cells and PD-L1 expression has not been established.

Assessment of paediatric data on non-clinical aspects

No separate juvenile toxicity studies were conducted by the MAH. The potential developmental effects of nivolumab were examined in the initial MAA, where an ePPND study that included assessments in infant monkeys up to 6-month-old, and a pivotal toxicity studies in cynomolgus monkeys as young as 2 years of age, which is approximately equivalent to a 6-year-old human, were provided. No developmental effects were observed in the pivotal intermittent-dose toxicity studies, and no developmental effects were observed in the surviving infants in the ePPND study. Thus, no specific toxicity findings relevant for the paediatric population were observed.

Animal toxicity studies have not revealed any relevant findings suggestive of a specific risk for use in the paediatric population, and updated information in the SmPC is not required.

2.2.7. Conclusion on the non-clinical aspects

A full nonclinical package was included in the original MAA. Except for the studies discussed above, no additional nonclinical data have been submitted. This is considered acceptable.

Nivolumab is a monoclonal antibody and is not expected to pose a significant risk to the environment, thus the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Study Population	Study Status, Type of Report
Pivotal Clinical Study - Multiple Tumor Types							
Safety Efficacy	Study identifier: CA209070/ ADVL1412 (NCT02304458) Report location: Interim CSR: Module 5.3.5.2	Safety, antitumor effects (ORR, TTR, DOR, OS), PK, immunogenicity	Phase 1/2, 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 [a]:** alternative dosing of nivo + ipi in rhabdomyosarcoma or Ewing sarcoma/peripheral PNET	**Parts A, B:** nivo 3 mg/kg IV Days 1,15 Q4W **Parts C, D:** nivo IV + ipi IV Day 1 Q3W Cycle 1-4 (induction), then nivo IV Days 1,15 Q4W (maintenance) (Cohort C Dose Level 1: nivo 1 mg/kg + ipi 1 mg/kg); (Cohort C Dose Level 2 and Cohort D: nivo 3 mg/kg + ipi 1 mg/kg) **Part E [a]:** nivo 1 mg/kg + ipi 3 mg/kg	**Parts A-D:** 126 **Part E [a]:** 8	Pediatric and young adult subjects with solid tumors (melanoma, neuroblastoma, Ewing sarcoma/ peripheral PNET, osteosarcoma, rhabdomyosarcoma, solid tumor NOS), and lymphoma (HL, non-HL)	**Study status:** Ongoing **Type of reports:** Interim CSR (includes Part A-D results)

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Study Population	Study Status, Type of Report
Supportive Clinical Studies - Treatment of Advanced (Unresectable or Metastatic) Melanoma							
Efficacy Safety	Study identifier: CA209067 (NCT01844505) Report location: Final CSR: Module 5.3.5.1 Addendum 03 to Final CSR: Module 5.3.5.1	To compare PFS and OS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma	Phase 3, randomized (1:1:1), double-blind study of nivolumab monotherapy, ipilimumab monotherapy, and nivolumab combined with ipilimumab	Randomized in 1:1:1 ratio to: **Arm A**: nivo 3 mg/kg IV Q2W **Arm B**: nivo 1 mg/kg IV combined with ipi 3 mg/kg IV Q3W for 4 doses then nivo 3 mg/kg IV Q2W **Arm C**: ipi 3 mg/kg IV Q3W for a total of 4 doses)	**Total subjects treated:** 937 **Arm A**: 313 **Arm B**: 313 **Arm C**: 311	Adult subjects with previously untreated, unresectable or metastatic melanoma (No subjects < 18 years treated)	**Study status:** Ongoing; subjects in follow-up **Type of reports:** Final CSR (includes final OS results) Addendum 03 to Final CSR (includes 5 years follow-up)

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Study Population	Study Status, Type of Report
Supportive Clinical Studies - Adjuvant Treatment of Melanoma							
Efficacy Safety	Study identifier: CA209915 (NCT03068455) Report location: Primary CSR: Module 5.3.5.1	To compare RFS with nivolumab + ipilimumab vs nivolumab in patients with tumor PD-L1 expression <1% and in the ITT population	Phase 3, randomized (1:1), double-blind study of nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks versus nivolumab monotherapy 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: nivo 3 mg/kg Q2W up to a max of 240 mg and ipi 1 mg/kg Q6W Nivo group: 6 mg/kg Q4W up to a max of 480 mg	**Total subjects treated:** 1833 Nivo + ipi group: 916 Nivo group: 917	Adult and adolescent (≥ 12 yrs) subjects with completely resected stage IIIb/c/d or stage IV NED melanoma (3 subjects < 18 yrs treated)	**Study status:** Complete **Type of reports:** Primary CSR
Efficacy Safety	Study identifier: CA209238 (NCT02388906) Report location: Interim CSR: Module 5.3.5.1 Final CSR: Module 5.3.5.1	To compare RFS with nivolumab vs ipilimumab	Phase 3, 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	**Total subjects treated:** 905 Nivo group: 452 Ipi group: 453	Adult and adolescent (≥ 15 yrs) subjects with completely resected Stage IIIb/c or Stage IV NED melanoma (No subjects < 18 years treated)	**Study status:** Ongoing; subjects in follow-up **Type of reports:** Interim CSR (includes primary RFS results) Final CSR (includes final OS results and updated RFS results at 4 years follow-up)

Abbreviations: COG: Children's Oncology Group, CSR: clinical study report, CTD: common technical document, DOR: duration of response, HL: Hodgkin lymphoma, ITT: intention-to-treat, IV: intravenous, ipi: ipilimumab, NED: no evidence of disease, nivo: nivolumab, NOS: other tumor type not included in the previous solid tumor categories, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, PK: pharmacokinetics, PNET: primitive neuroectodermal tumor, RFS: recurrence free survival, RP2D: recommended Phase 2 dose, TTR: time to response, QxW: every x weeks

[a] Data from Part E, not included in the CA209070 Interim CSR, are described in a progress report from Children's Oncology Group (Module 5.4 of dossier).

2.3.2. Pharmacokinetics

Pharmacokinetics in the target population

Pharmacometric analyses for nivolumab with or without ipilimumab in adolescent subjects with advanced melanoma (advMEL), nivolumab monotherapy for adjuvant treatment of melanoma (AdjMEL), and Exposure-Response (E-R) analysis have been conducted based on the data from 24 studies listed in the below tables.

Table 2 Studies Included in the Pharmacometric Analyses

	Nivo PPK (AdvMEL)	Ipi PPK (AdvMEL)	Nivo PPK (AdjMEL)	Nivo E-R
CA209001 (MDX1106-01) (Adults with solid tumors inc. MEL)	X		X	
CA209003 (MDX1106-03) (Adults with solid tumors inc. MEL)	X		X	X
CA209004 (Adults with advanced MEL)			X	X
CA209005 (ONO-4538-01) (Adults with MEL and NSCLC)	X		X	
CA209039 (Adults with R/R hematologic tumors)	X			
CA209066 (Adults with advanced MEL)	X		X	X
CA209067 (Adults with advanced MEL)	X	X	X	X
CA209069 (Adult advanced MEL)	X	X	X	X
CA209070 (ADVL1412) (Children, adolescents, and young adults with ST [inc. MEL] or cHL/NHL)	X	X	X	X
CA209143 (Adults with GBM)	X			
CA209205 (Adults with cHL)	X			
CA209238 (Adults with adjuvant MEL)			X	X
CA209498 (Adults with GBM)	X			
CA209511 (Adults with advanced MEL)			X	X
CA209744 (Children, adolescents and young adults with cHL)	X			
CA209908 (Pediatric and adult subjects with CNS tumors)	X	X		
CA209915 (Adults and adolescents with adjuvant MEL)			X	X
CA184004 (Adults with advanced MEL)		X		X
CA184007 (Adults with advanced MEL)		X		
CA184008 (Adults with advanced MEL)		X		X
CA184022 (Adults with advanced MEL)		X		X
CA184070 (Children, adolescents and young adults with refractory cancer)		X		X
CA184169 (Adults with advanced MEL)				X
CA184178 (Children and adolescents with advanced MEL)		X		X

Source: refer to Table 3.1-1 of the advPPK Report[1], Table 3.1-1 of the adjPPK Report[2], and Table 3.1-1 of the E-R Report[3].

Table 3 Description of Clinical Studies Included in the population pharmacokinetic (PPK) and E-R Analyses

Protocol #: Title ***Study Population***	**Treatment**	**Planned Sample Size[a]**	**Assessments**	**Analyses**
CA209001 (MDX1106-01) Phase 1, open-label, dose-escalation, safety and pharmacokinetic study of MDX-1106 in patients with selected refractory or relapsed malignancies *Multiple tumor types including melanoma, RCC, and NSCLC*	Single-dose Phase (Cycle 1): Nivo 0.3, 1, 3, or 10 mg/kg (60 min infusion) Re-treatment Phase (Cycle 2): Nivo 0.3, 1, 3, or 10 mg/kg (60 min infusion) on D1 and D29; eligible subjects were treated with the same dose level as in the single-dose phase and could receive additional re-treatment cycles	39	Single-dose Phase: Pre-dose, 30 mins into dosing, immediately post-infusion, and 30 mins, 1, 2, 4, 6, 8, 24, 48, and 72 hrs post-infusion end time; on D8, D15, D22, D29, D43, D57, D71, and D85 Re-treatment Phase: Pre-dose and peak on treatment D1 and D29; single samples on D8, D15, D36, D43, D57, D85, and D113	Nivo advanced MEL PPK Nivo adjMEL PPK
CA209003 (MDX1106-03) Phase 1, open-label, multicenter, multidose, dose-escalation study of BMS-936558 (MDX1106) in subjects with selected advanced or recurrent malignancies *Pathologically verified and advanced or recurrent and progressing colorectal adenocarcinoma, melanoma, NSCLC, metastatic castrate resistant prostate cancer, and RCC*	Nivo 0.1, 0.3, 1, 3, or 10 mg/kg depending upon tumor type (60 min infusion) Q2W for up to twelve 8-week cycles	450 (290 + 160 from amendment)	Pre-Amendment: C1: EOI and pre-infusion levels on infusion days: D1, D15, D29, and D43 and C2-C12: EOI and pre-infusion on D1 Follow-up visit 1 and visit 2: Single samples were collected Post-Amendment: Serial PK samples were collected from all subjects enrolled in 0.1, 0.3 and 1 mg/kg melanoma cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts. C1: D1 (after 60-min infusion, 4hr, 8hr), D2, D3, D5, D8, D15 (pre-infusion), C2: D1 (pre-infusion), C3: D1 (pre-infusion, after 60-min infusion), and D2, D3, D5, D8, D15(pre-infusion) Limited PK samples were collected from subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC. C1: D1 (pre-infusion and after 60-min infusion), D3, D8, D15(pre-infusion), C2D1 (pre-infusion), C3: D1 (pre-infusion, after 60-min infusion), and D3, D8, D15 (pre-infusion) Follow-up visit 1 to 6: Single samples were collected Each treatment cycle is comprised of 4 doses administered on D1, D15, D29, and D43 of the cycle	Nivo advanced MEL PPK (Only include subjects with MEL, NSCLC and RCC) Nivo adjMEL PPK E-R safety

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments	Analyses
CA209238 Phase 3, Randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence *Subjects with resected stage IIIb/c or stage IV Melanoma*	Nivo 3 mg/kg/dose IV Q2W or Ipi 10 mg/kg/dose IV Q3W x 4 doses, then 10 mg/kg/dose IV Q12W starting at week 2	906	Week 1 Day 1: pre-dose, EOI (1hr) Week 7 Day 1: pre-dose, EOI (1hr) Week 13, 23, 35: pre-dose First 2 Follow-up visits (approximately up to 100 days from the discontinuation of study drug) Survival Follow-up visits at 6 months and 1 year	Nivo adjMEL PPK E-R safety
CA209915 Phase 3, randomized study of adjuvant immunotherapy with nivolumab combined with ipilimumab versus nivolumab monotherapy after complete resection of stage IIIb/c/d or stage IV melanoma *Subjects with resected stage IIIb/c/d or stage IV Melanoma*	Arm A: Nivolumab 240 mg Q2W combined with Ipi 1 mg/kg Q6W Arm B: Nivolumab 480 mg Q4W Arm C: Ipilimumab 10 mg/kg Q3W	2000	Week 1 Day 1 predose, and troughs at week 5, 9, 15, 21, 37 and FU1, FU2	Nivo adjMEL PPK E-R safety
CA209067 Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. *Subjects with previously untreated, unresectable or metastatic melanoma*	A: Nivo 3 mg/kg IV Q2W B: Nivo 1 mg/kg IV combined with Ipi 3 mg/kg IV Q3W for 4 doses then Nivo 3 mg/kg IV Q2W C: Ipi 3 mg/kg IV Q3W for a total of 4 doses + Nivo-placebo on weeks 1, 3, 4 and 5 for cycles 1 and 2 then Q2W Nivo: 1 hr IV infusion Ipi: 90 min IV infusion	915	Pre-dose sample at Day1, Week 3 and 4 Cycle 1, Day 1 Cycle 2, Day 1 Cycle 3 and Cycle 4, and first 2 follow-up visits (approximately up to 100 days from the discontinuation study drug) End of infusion samples at Day 1 Cycle 1, 2 and 4.	Nivo advanced MEL PPK Ipi advanced MEL PPK Nivo adjMEL PPK E-R safety
CA209069 Phase 2, randomized, double blinded, study of nivolumab (BMS- 936558) in combination with Ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma *Subjects with previously untreated, unresectable or metastatic melanoma*	A: Part I: Nivo 1 mg/kg IV + Ipi 3 mg/kg IV Q3W for 4 doses; then Part II: Nivo 3 mg/kg IV Q2W B: Part I: Nivo-placebo + ipi 3 mg/kg IV Q3W for 4 doses; then Part II: Nivo-placebo Q2W Nivo: 1 hr IV infusion Ipi: 90 min IV infusion	150	Pre-dose sample at Day 1 Cycle 1 (Part I), Cycle 3 (Part I), Cycle 5 (Part II) and Cycle 11 (Part II) and first 2 follow-up visits (approximately up to 100 days from the discontinuation study drug)	Nivo advanced MEL PPK Ipi advanced MEL PPK Nivo adjMEL PPK E-R safety
CA209511 Phase 3b/4, randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in subjects with previously untreated, unresectable or metastatic melanoma *Subjects with previously untreated, unresectable or metastatic melanoma*	Part 1: Arm A: nivo 3 mg/kg + Ipi 1 mg/kg, Q3W for 4 doses Arm B: Nivo 1 mg/kg + Ipi 3 mg/kg, Q3W for 4 doses Arm C: 6=Nivo 6 mg/kg Q4W + Ipi 1mg/kg Q8W Part 2: Nivo 480 mg Q4W maintenance Nivo: 30 min IV infusion Ipi: 30 min IV infusion	346 Arm A= 180 Arm B= 178 Arm C= 27	Part 1: Predose, 30 min after EOI (Ipi), 90 min after EOI (Nivo) on Day 1 of each cycle Part 2: Predose and 30 min after EOI on Day 1 of Cycle 5. predose on Day 1 of Cycle 9, predose every 16 weeks after Cycle 9, and first 2 follow-up visits.	Nivo adjMEL PPK E-R safety
CA209004 Phase 1b, open-label, multicenter, multidose, dose-escalation study of MDX-1106 (BMS-936558) in combination with ipilimumab (BMS-734016) in subjects with unresectable stage III or stage IV malignant melanoma	**Cohort 1:** 0.3 mg/kg nivo Q3W for up to 8 doses + 3 mg/kg ipi Q3W for up to 4 doses **Cohort 2:** 1 mg/kg nivo Q3W for up to 8 doses + 3 mg/kg ipi Q3W for up to 4 doses **Cohort 2a:** 3 mg/kg nivo Q3W for up to 8 doses + 1 mg/kg ipi Q3W for up to 4 doses	127 (cohort 3, 8)	Blood samples were collected to estimate peak and trough levels of BMS-936558 (MDX-1106) and ipilimumab during the induction and maintenance periods and at follow-up Visit 2.	Nivo adjMEL PPK E-R safety

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments	Analyses
Subjects with unresectable stage III or stage IV malignant melanoma	**Cohort 3**: 3 mg/kg nivo Q3W for up to 8 doses + 3 mg/kg ipi Q3W for up to 4 doses **Cohort 6**: 1 mg/kg nivo Q2W for up to 48 doses, following ipi monotherapy administered prior to enrollment on this study **Cohort 7**: 3 mg/kg nivo Q2W for up to 48 doses, following ipi monotherapy administered prior to enrollment on this study **Cohort 8**: 1 mg/kg nivo + 3 mg/kg of ipi, both Q3W for 4 doses, followed by 3 mg/kg nivo alone Q2W for up to 48 doses Nivo: 1 hr IV infusion Ipi: 90 min IV infusion			
CA209066 Phase 3, randomized, double-blind study of BMS-936558 (nivolumab) vs dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma *Subjects with previously untreated unresectable or metastatic melanoma*	Nivo 3 mg/kg Q2W, 60-minute IV infusion	206 (nivolumab treated)	Cycle 1: Day 1 predose and EOI (1 hr), Day 15 and Day 29 (Predose) Cycle 3: Day 15 predose and EOI (1hr) Cycle defined as 6 weeks.	Nivo advanced MEL PPK Nivo adjMEL PPK E-R safety
CA209005 (ONO-4538-01) Phase 1 single dose study to evaluate of safety, tolerability, and pharmacokinetics in subjects with progressive or recurrent solid tumors *Melanoma and NSCLC*	Nivo 1, 3, 10, and 20 mg/kg Q3W for 1st dose then Q2W (60 min infusion)	24 (up to 6 subjects at each dose level)	Single-dose phase: D1: 1 hour after the start and 2 and 8 hours after EOI, Pre-D2, pre-D3; pre-D4; D8, D15, and D22 or study discontinuation Multiple-dose phase: Before administration on D1; before administration and immediately after the end of administration on D15; and D29 or study discontinuation Extended-treatment phase: Before administration on D1; before administration on D15 and D29; before administration and immediately after the end of administration on D43 and D57	Nivo advanced MEL PPK Nivo adjMEL PPK
CA209205 Non-comparative, multi-cohort, single arm, open-label, Phase 2 study of nivolumab in classical Hodgkin Lymphoma (cHL) subjects *Adults with cHL*	Cohorts A, B, C: Nivolumab 3 mg/kg Q2W, 60 min IV infusion Cohort D: Nivolumab 240 mg Q2W, 60 min IV infusion	242	Pre-dose: Cycle 1, 3, 7, 13 Pre-dose day 1 of every 12th cycle 2 follow-up samples Each 14-day dosing period will constitute a cycle	Nivo advanced MEL PPK
CA209039 A Phase 1 dose escalation study to investigate the safety, pharmacokinetics, immunoregulatory activity, and preliminary antitumor activity of anti-programmed-death 1 (PD-1) antibody (nivolumab, BMS-936558) and the combinations of nivolumab and ipilimumab or nivolumab and lirilumab in subjects with relapsed or refractory hematologic malignancy *Adult subjects with relapsed or refractory hematologic malignancies*	1st Dose: Nivolumab 1 or 3 mg/kg, Q3W 60 min IV infusion Subsequent Doses: Nivolumab 1 or 3 mg/kg Q2W, 60 min IV infusion	23	Day 1: pre-dose, EOI (1hr), 3, 24-72, 168, 336 and 504 hr Pre-dose at Week 6 and week 20 Week 12: pre-dose and EOI (1hr) 2 follow-up samples	Nivo advanced MEL PPK
CA209143 A Randomized Phase 3 Open Label Study of Nivolumab versus Bevacizumab and	Dose: Nivo 3 mg/kg, 1h iv infusion Regimen: Every 2 weeks Nivo mono, nivo + RT (radiation therapy), and nivo + RT + TMZ (temozolomide)	Nivo mono: Cohort 1: 10 Cohort 2: 184,Cohort 1C & 1D :120	Predose at weeks 0, 3, 12, 28, and every 16 weeks afterwards until discontinuation; also, at follow-up visits 1 and 2.	Nivo advanced MEL PPK

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments	Analyses
Multiple Phase 1 Safety Cohorts of Nivolumab or Nivolumab in Combination with Ipilimumab Across Different Lines of Glioblastoma (GBM) *Adult subjects with GBM*		Nivo + RT + TMZ: (Cohort 1C) Nivo + RT: (Cohort 1D)		
CA209498 A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor O-6-methylguanine DNA methyltransferase) Glioblastoma *Adult subjects with GBM MGMT*	RT (radiation therapy) + Nivolumab 240 mg Q2W for 16 weeks followed by 480 mg Q4W	275 RT+Nivo	Pre-dose samples: Day1 at Week 1, 5, 13, 17, 21, 33	Nivo advanced MEL PPK
CA209908 Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies *Pediatric and adult subjects with high CNS malignancies*	A: Nivolumab 3 mg/kg Q2W B: Nivo 3 + Ipi 1 mg/kg Q3W X4 followed by nivo 3 mg/kg Q2W	160	Pre-dose and EOI: Cycle 1 and 4 Day 1 Pre-dose at Cycle 2, 5	Nivo advanced MEL PPK Ipi advanced MEL PPK
CA209744 Risk-based, response-adapted, Phase II open-label trial of nivolumab + brentuximab vedotin (N + Bv) for children, adolescents, and young adults with relapsed/refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by brentuximab vedotin+ bendamustine (Bv + B) for participants with a suboptimal response. *Pediatric, adolescent and young adult subjects with cHL*	Dose: Nivolumab 3 mg/kg Q3W (day 8 cycle 1; day 1 for others), 30 min IV infusion, 4 cycles; brentuximab vedotin, 1.8 mg/kg, 30 min IV infusion	80 Low risk relapse (R1 cohort) group: 40 patients Standard risk relapse (R2 cohort) group: 40 patients	Pre-dose: day 8 of Cycle 1 then on Day 1 of cycle 2, 3, 4 Follow up 2 - D100: Post last treatment	Nivo advanced MEL PPK
CA184004 Phase 2, randomized study in subjects with advanced Stage III or Stage IV melanoma *Subjects with advanced Stage III or Stage IV melanoma*	Subjects were administered a tetanus booster and influenza or pneumococcal vaccine within 10 days prior to receiving ipilimumab. Induction Period: Dose: 3 and 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	79	On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 3-7 (post-dose) after week 7 dose, Day 10-15 (post-dose) after week 7 dose and the pre-dose sample on Day 64.	Ipi advanced MEL PPK E-R safety
CA184007 A randomized, double-blind, placebo-controlled, Phase 2 study comparing the safety of ipilimumab administered with or without prophylactic oral budesonide (Entocort™ EC) in patients with unresectable stage III or IV malignant melanoma	Dose: 10 mg/kg ipilimumab (given with placebo or budesonide) Note: budesonide was administrated at 9 mg once daily until Week 12, tapered to 6 mg once daily until Week 14, and finally to 3 mg once daily until Week 16 Schedule: Q3W during induction period (Week 1, 4, 7 and 10), followed	110	Schedule A: On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 45-49, Day 52-57, and the pre-dose sample on Day 64. Schedule B: on day 1 and 43, pre-dose and after 90-minute infusion, 24, 72 hr post-infusion, day 8 (± 27 hours), day 15 (±48 hours); two additional pre-dose samples were taken on day 22 and day 64.	Ipi advanced MEL PPK

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments	Analyses
Subjects with a histologic or cytologic diagnosis of unresectable Stage III or IV malignant melanoma	by Q12W during maintenance period (starting on Week 24)			
CA184070 A Phase 1b study of ipilimumab (anti-CTLA-4) in children, adolescents, and young adults with treatment refractory cancer *Children, adolescents, and young adults (≥ 1 to ≤ 21 years) with treatment refractory cancer*	Ipilimumab 1, 3, 5, 10 mg/kg (90 min infusion) Q3W for 4 doses followed by maintenance Q12W	33	C1D1 (predose & EOI), C1D2, C1D4, C1D8, C1D15, C2D1 predose, C3D1 (predose & EOI), C3D2, C3D4, C3D8, C3D15, C4D1 predose, predose on D1 of each subsequent cycle	Ipi advanced MEL PPK E-R safety
CA184178 A Phase 2 study of Ipilimumab in children and adolescents (12-≤18 years) with previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma *Children and adolescents (≥ 12 to < 18 years) with unresectable malignant melanoma*	Ipilimumab 3, 10 mg/kg (90 min infusion) Q3W for 4 doses	12	Dose 1 Day 1 (predose & EOI), Dose 2 Day 22 predose, Dose 3 Day 43 (predose & EOI), Day 46-50, Day 53-58, Dose 4 Day 64 predose, Day 78 End of treatment.	Ipi advanced MEL PPK E-R safety
CA184022 Phase 2, randomized, double blinded, dose-ranging study in subjects with advanced Stage III or Stage IV melanoma who have received prior treatment with any regimen except a CD-137 agonist or a CTLA4 inhibitor or agonist. *Subjects with advanced Stage III or Stage IV melanoma, who were previously treated with any regimen except a CD-137 agonist or a CTLA4 inhibitor or agonist.*	Induction Period: Dose: 0.3, 3, 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	159	Induction Period: Dose: 0.3, 3, 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	Ipi advanced MEL PPK E-R safety
CA184169 A randomized double-blind phase 3 study of ipilimumab administered at 3 mg/kg vs at 10 mg/kg in subjects with previously treated or untreated unresectable or metastatic melanoma *Previously-treated or untreated unresectable Stage III or Stage IV melanoma (AJCC 2010) (regardless of BRaf mutation status or HLA type)*	Ipi 3 mg/kg or 10 mg/kg Q3W x 4 doses, then Q12W until 1 year after last induction dose.	700	Induction phase: Pre-infusion on Day 1, 22, 43, 64, 85, EOT, and then Q12W until 1 year after last induction dose. Re-induction phase: Same schedule as induction phase	E-R safety
CA184008 Open-label, single arm, Phase 2 study in subjects with previously treated, stage III or stage IV melanoma who have progressed during or after at least one prior therapy containing at least one of the following: IL-2, dacarbazine, paclitaxel, carboplatin, fotemustine, or temozolamide. *Subjects with previously treated unresectable Stage III or IV melanoma*	Induction Period: Dose: 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	148 (Schedule A: 144; Schedule B: 4)	Schedule A: On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 3-7 after week 7 dose, Day 10-15 after week 7 dose and the pre-dose sample on Day 64. Schedule B: on day 1 and 43, pre-dose and after 90-minute infusion, 24, 72 hr post-infusion, day 8 (± 27 hours), day 15 (±48 hours); two additional pre-dose samples were taken on day 22 and day 64.	Ipi advanced MEL PPK E-R safety
CA209070 (ADVL1412)	A/B: Nivo 3 mg/kg Q2W C:	A: 36 B: 170	Part A and B: Cycle 1 Day 1 (EOI), 2, 4, 8, 15 Cycle 2: 1 (EOI), 2, 4, 8	Nivo advanced MEL PPK

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments	Analyses
Phase 1/2 study of nivolumab in children and adolescents with recurrent or refractory solid tumors as a single agent and in combination with ipilimumab *Pediatric and young adult subjects with solid tumors or Hodgkin lymphoma/non-Hodgkin lymphoma (lymphoma subjects were not included in the PPK analyses)*	Dose level 1:Nivo 1 mg /kg + Ipi 1 mg/kg Q3W Dose level 2: Nivo 3 mg /kg + Ipi 1 mg/kg Q3W D: Nivo 3 mg /kg + Ipi 1 mg/kg Q3W	C: 36 D: 110	Cycle 4 Part C/D: pre-dose samples and EOI in day 1 of Cycle 1, 2, 3, 4	Ipi advanced MEL PPK Nivo adjMEL PPK E-R safety

[a] As per protocol

Source: refer to Table 3.1-1 of the advPPK Report, Table 3.1-1 of the adjPPK Report, and Table 3.1-1 of the E-R Report

PPK Analysis of Nivolumab for Adolescent Advanced Melanoma

The objectives of the PPK analysis for nivolumab relevant to adolescent advanced melanoma were as follows:

- To characterize the PK of nivolumab in paediatric subjects who received nivolumab alone or in combination with ipilimumab, including the effect of covariates on PK parameters.
- To provide recommendations of a nivolumab monotherapy dosing regimen and a nivolumab - ipilimumab combination dosing regimen for adolescent patients (from 12 to <18 years) with advanced melanoma, using model-based simulations.

The nivolumab PPK analysis for advanced melanoma includes data from 13 studies (among which 4 studies with nivo + ipi combination therapy [CA209067, CA209069, CA209070, CA209908]) that support the characterization of nivolumab PPK when administered as nivolumab monotherapy or nivolumab in combination with ipilimumab in adult and paediatric patients with advanced melanoma. Studies CA209070, CA209908, and CA209744 included paediatric patients with advanced solid tumours/ Hodgkin lymphoma (HL)/non-HL (NHL), central nervous system (CNS) tumours, and classical HL (cHL), respectively.

A total of 2325 subjects were included in the nivolumab PPK analysis dataset, including 2050 adult subjects and 275 paediatric subjects. The 2050 adult subjects included 993 subjects with advanced melanoma, 274 subjects with HL, 556 subjects with Glioblastoma (GBM), and 227 subjects with other tumours; the 275 paediatric subjects included 79 subjects with advanced solid tumours (only one subject with melanoma), 46 subjects with lymphoma (31 cHL, 6 HL, 9 NHL), and 150 subjects with CNS tumours.

Table 4 Subjects Included in the Nivolumab Population Pharmacokinetic Analysis by Study

	Number of Subjects			
Study	**Nivolumab Treated**	**PK Database[a]**	**Flagged**	**Included (% of subjects in PK Database)**
MDX1106-01 (CA209001)	39	39	0	39 (100)
MDX1106-03 (CA209003)	306	274	6	268 (97.8)
ONO-4538-01 (CA209005)	17	17	0	17 (100)
CA209039	23	23	0	23 (100)
CA209066	206	192	14	178 (92.7)
CA209067	626	627	6	621 (99)
CA209069	94	95	21	74 (77.9)
ADVL1412 (CA209070)[b]	126	125	3	122 (97.6)
CA209143	309	307	27	280 (91.2)
CA209205	242	242	9	233 (96.3)
CA209498	278	275	13	262 (95.3)
CA209744[b]	44	44	0	44 (100)
CA209908[b]	166	165	1	164 (99.4)
Total	2476	2425	100	2325 (95.9)

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1.1-1.rtf

[a] Samples in eToolbox or PAMS; all which are included in the analyses dataset with flag, as noted.

[b] Pediatric study. In CA209070, a total of 39 pediatric subjects with solid tumors of the 125 included in the PK database had intensive PK analyses (i.e., 5 PK time points after the first dose in Cycle 1)".

Table 5 Summary of the PK samples in the nivolumab PPK analysis dataset

Study	PK Database[a]	Day 1 Pre-Dose[b]	Missing Dose or Sample Information[c]	Below LLOQ	Duplicate Samples[d]	|CWRES|>6	Others[e]	Samples Included in Analysis N(%)[g]
MDX1106-01 (CA209001)	915	40	33	42	0	1	0	799 (91.3)
MDX1106-03 (CA209003)	3373	295	32	73	147	6	2	2818 (91.6)
ONO-4538-01 (CA209005)	285	17	0	0	0	0	0	268 (100.0)
CA209039	249	21	0	2	2	0	0	224 (98.2)
CA209066	872	166	26	15	0	1	0	664 (94.1)
CA209067	4803	602	13	186	6	7	6	3983 (94.8)
CA209069	295	86	7	36	0	0	1	165 (78.9)
ADVL1412 (CA209070)[f]	1029	120	16	4	105	1	0	783 (86.1)
CA209143	1046	273	4	5	0	0	1	763 (98.7)
CA209205	861	230	4	0	0	0	1	626 (99.2)
CA209498	1398	251	7	1	18	0	0	1121 (97.7)
CA209744[f]	198	40	0	6	0	0	0	152 (96.2)
CA209908[f]	924	158	11	10	6	0	1	738 (96.3)
Total	16248	2299	153	380	284	16	12	13104 (93.9)

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1.2-1.rtf

[a] Samples in eToolbox or PAMS; all which are included in the analyses dataset with flag, as noted.

[b] Day 1 Pre-dose samples are excluded from the calculation of the percentage of samples included in analysis.

[c] No dosing records, all PK samples flagged, missing sample date or time or concentration (but not below LLOQ), error in dosing date/time.

[d] Duplicate sample at same actual time after first dose.

[e] Others include samples flagged as crossover, error in dose amount and amount missing or equal to zero and sample conc > 2000ug/mL.

[f] Pediatric study

[g] The percentage is calculated as samples included in the analysis/(samples in PK database – day 1 pre-dose samples).

Table 6 Summary of Covariates in the Nivolumab Population Pharmacokinetic Analysis by Patient Population

Covariate	Adult MEL N=993	Adult HL N=274	Adult GBM N=556	Adult Others N=227	Pediatric ST N=79	Pediatric HL N=46	Pediatric CNST N=150	Total N=2325
Sex N (%)								
Male	637 (64.1)	161 (58.8)	374 (67.3)	148 (65.2)	47 (59.5)	27 (58.7)	83 (55.3)	1477 (63.5)
Female	356 (35.9)	113 (41.2)	182 (32.7)	79 (34.8)	32 (40.5)	19 (41.3)	67 (44.7)	848 (36.5)
Race N (%)								
White	969 (97.6)	237 (86.5)	487 (87.6)	190 (83.7)	58 (73.4)	38 (82.6)	120 (80.0)	2099 (90.3)
Black/African American	2 (0.2)	16 (5.8)	10 (1.8)	19 (8.4)	8 (10.1)	4 (8.7)	7 (4.7)	66 (2.8)
Asian	9 (0.9)	8 (2.9)	38 (6.8)	14 (6.2)	7 (8.9)	1 (2.2)	9 (6.0)	86 (3.7)
Other	13 (1.3)	13(4.7)	21(3.8))	4(1.8)	6 (7.6)	3 (6.5)	14 (9.3)	74 (3.2)
Baseline Performance Status N (%)								
0	726 (73.1)	150 (54.7)	136 (24.5)	61 (26.9)	21 (26.6)	26 (56.5)	55 (36.7)	1175 (50.5)
1	262 (26.4)	124 (45.3)	366 (65.8)	163 (71.8)	47 (59.5)	19 (41.3)	68 (45.3)	1049 (45.1)
2	5 (0.5)	0 (0)	54 (9.7)	3 (1.3)	11 (13.9)	1 (2.2)	26 (17.3)	100 (4.3)
3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (0.0)
Tumor Type N (%)								
MEL	993 (100.0)	0(0)	0 (0)	0 (0)	1 (1.3)	0(0)	0 (0)	994 (42.8)
HL	0 (0)	274 (100.0)	0 (0)	0 (0)	0 (0)	46 (100.0)	0 (0)	320 (13.8)
CNST	0 (0)	0 (0)	556 (100.0)	0 (0)	0 (0)	0 (0)	150 (100.0)	706 (30.4)
Others	0 (0)	0 (0)	0 (0)	227 (100.0)	78 (98.7)	0 (0)	0 (0)	305 (13.1)
Treatment N (%)								
Nivo Monotherapy	608 (61.2)	261 (95.3)	184 (33.1)	215 (94.7)	49 (62.0)	15 (32.6)	76 (50.7)	1408 (60.6)
Nivo + Ipi 1 mg/kg Q3W	0 (0)	0 (0)	6 (1.1)	12 (5.3)	30 (38.0)	0 (0)	74 (49.3)	122 (5.2)
Nivo + Ipi 3 mg/kg Q3W	385 (38.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	385 (16.6)
Nivo + Brentuximab vedotin	0 (0)	13 (4.7)	0 (0)	0 (0)	0 (0)	31 (67.4)	0 (0)	44 (1.9)
Nivo + Radiation	0 (0)	0 (0)	314 (56.5)	0 (0)	0 (0)	0 (0)	0 (0)	314 (13.5)
Nivo + Radiation + Temozolomide	0 (0)	0 (0)	52 (9.4)	0 (0)	0 (0)	0 (0)	0 (0)	52 (2.2)
Age (years)								
Mean (SD)	59.9 (13.4)	35.9 (12.8)	56.5 (12.5)	58.8 (15.6)	11.2 (4.46)	13.8 (3.46)	9.44 (4.69)	50.3 (20.6)
Median (Min, Max)	62 (18, 90)	33 (18, 72)	58 (18, 83)	62 (18, 85)	12 (1, 17)	15 (4, 17)	10 (1, 17)	55 (1, 90)
Baseline Body Weight (kg)								
Mean (SD)	82.3 (18.1)	76.6 (21.6)	79.3 (17.4)	79.7 (19.6)	44.1 (23.6)	59.7 (22.6)	37.7 (20.6)	76 (22.7)
Median (Min, Max)	80.6 (37.4, 160)	73.6 (40, 168)	78 (41.7, 167)	78.7 (32.8, 153)	43.2 (9.3, 99.6)	58.2 (13.6, 121)	33 (9.8, 90)	76.2(9.3, 168)
Baseline eGFR (ml/min/1.73m²)								
Mean (SD)	86.7 (18.1)	106 (23.3)	93.1 (15.1)	83.7 (25)	119 (28.1)	136 (26.8)	118 (27.7)	94.3 (23.5)
Median (Min, Max)	88.1 (35.5, 139)	108 (32.2, 155)	93.7 (41, 148)	85.6 (31.2, 172)	116 (43.5, 202)	142 (70.4, 185)	115 (70.8, 215)	93.1(31.2, 215)
Missing N (%)	4 (0.403)	0 (0)	1 (0.18)	2 (0.881)	0 (0)	0 (0)	5 (3.33)	12 (0.516)
Baseline Lactate Dehydrogenase (U/L)								
Mean (SD)	337 (336)	253 (141)	227 (98.5)	225 (147)	N/A	290 (113)	298 (169)	285 (254)
Median (Min, Max)	223 (98, 2980)	213 (94, 1029)	196 (58, 827)	185 (91, 1106)	N/A	256 (148, 558)	223 (144, 689)	210 (58, 2980)
Missing N (%)	16 (1.61)	5 (1.82)	25 (4.5)	26 (11.5)	79 (100)	16 (34.8)	126 (84)	293 (12.6)
Baseline Serum Albumin (g/dL)								
Mean (SD)	4.12 (0.55)	4.02 (0.56)	4.06 (0.419)	3.95 (0.447)	3.75 (0.946)	3.65 (0.636)	4.37 (0.381)	4.08 (0.5)
Median (Min, Max)	4.2 (2.2, 5.1)	4.1 (1.9, 5.2)	4.1 (3, 5.2)	4 (2.3, 4.9)	4 (2.3, 5)	3.65 (3.2, 4.1)	4.4 (3.3, 5.5)	4.1 (1.9, 5.5)

Missing N (%)	872 (87.8)	27 (9.85)	282 (50.7)	17 (7.49)	68 (86.1)	44 (95.7)	7 (4.67)	1317 (56.6)
Baseline Tumor Burden (cm)								
Mean (SD)	7.83 (6.47)	8.38 (5.74)	N/A	11.7 (7.94)	8.38 (6.43)	7.35 (6.43)	N/A	8.48 (6.86)
Median (Min, Max)	5.8 (1, 38.4)	7.1 (1.9, 17.6)	N/A	9.8 (1, 61.5)	5.9 (1, 26)	4 (0.82, 21.7)	N/A	6.7 (0.82, 61.5)
Missing N (%)	4 (0.403)	269 (98.2)	556 (100)	17 (7.49)	14 (17.7)	31 (67.4)	150 (100)	1041 (44.8)
Baseline Tumor Burden (cm^3)								
Mean (SD)	N/A	28.6 (29)	9.54 (8.52)	N/A	N/A	30.8 (29.3)	7.74 (7.11)	12.2 (15.2)
Median (Min, Max)	N/A	14.6 (4.86, 101)	6.89 (0, 52.8)	N/A	N/A	24 (1.5, 125)	5.64 (1, 36.5)	7.7 (0, 125)
Missing N (%)	993 (100)	239 (87.2)	244 (43.9)	227 (100)	79 (100)	15 (32.6)	75 (50)	1872 (80.5)
Baseline Lean Body Mass (kg)								
Mean (SD)	57.7 (10.8)	55.9 (11.5)	56.9 (10.3)	57.3 (11.1)	35.4 (16.1)	44.9 (14.3)	30.2 (14.8)	54.5 (13.8)
Median (Min, Max)	58.4 (31.7, 94.7)	54.1 (36.1, 96.5)	57.4 (34.9, 94.9)	57.8 (27.8, 91.2)	36.3 (7.81, 67.9)	45.2 (12.4, 80.4)	28 (8.68, 63)	55.8(7.81, 96.5)
Missing N (%)	25 (2.52)	1 (0.365)	5 (0.899)	16 (7.05)	0 (0)	0 (0)	4 (2.67)	51 (2.19)

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final
Program Source: Analysis-Directory/sas/Table3.3.1.5-1.sas
Source: analysis-directory/reports/Table3.3.1.5-1.rtf
Adult Others include NSCLC (N=139), CRC (N=18), RCC (N=35), Prostate Cancer (N=8), Ewing Sarcoma (N=11), Osteosarcoma (N=7), Rhabdomyosarcoma (N=2), Neuroblastoma (N=3), and other solid tumors (N=4).
Pediatric ST includes Rhabdomyosarcoma (N=17), Osteosarcoma (N=19), Ewing Sarcoma (N=10), Neuroblastoma (N=18), Melanoma (N=1), and other solid tumors (N=14).
Adult GBM includes glioblastoma (N=542), Diffuse Intrinsic Pontine Glioma (N=2), Diffuse Midline Glioma (N=1), Ependymoma (N=3), Glioma - High Grade (N=5), Medulloblastoma (N=2), and Pineoblastoma (N=1).

Pediatric CNST includes Anaplastic Pleomorphic Xanthoastrocytoma (N=1), Atypical Teratoid Rhabdoid Tumor (N=7), Choroid Plexus Carcinoma (4), Diffuse Intrinsic Pontine Glioma (N=34), Diffuse Midline Glioma (N=9), Embryonal Tumor with Multilayered Rosettes (N=1), Ependymoma (N=19), Glioma - High Grade (N=20), Malignant Germ Cell Tumor (N=2), Medulloblastoma (N=28), Pineoblastoma (N=3), and Others (N=22).
Adult HL: Adult lymphoma including Classical Hodgkin's lymphoma (N=269), non-Hodgkin's lymphoma (N=1), and Hodgkin's lymphoma (N=4)
Pediatric HL: Pediatric lymphoma including Classical Hodgkin's lymphoma (N=31), non-Hodgkin's lymphoma (N=9), and Hodgkin's lymphoma (N=6)

Erratum:

An error was identified in the derivation of baseline estimated glomerular filtration rate (eGFR) values in subjects younger than 19 years of age for which CKD-EPI equation was used instead of the more appropriate Schwartz equation.

The impact of the change in the calculated eGFR values on the nivolumab PPK model has been assessed by re-estimating the parameters of the nivolumab full model with the corrected eGFR. A comparison of the parameter estimates indicated minimal changes in the established PPK model and judged to have no meaningful impact on the paediatric simulation results and no change in the conclusions of the report. In addition, the changes in the calculated eGFR values did not have any impact on the ipilimumab PPK model, as eGFR was not a covariate in that model.

Table 7 Summary of Covariates in the Nivolumab Population Pharmacokinetic Analysis by Patient Population (revised from table 5)

Covariate	Adult MEL N=993	Adult HL N=274	Adult GBM N=556	Adult Others N=227	Pediatric ST N=79	Pediatric HL N=46	Pediatric CNST N=150	Total N=2325
Baseline eGFR (ml/min/1.73m^2)								
Mean (SD)	86.7 (**18.0**)	**105 (23)**	93.1 (15.1)	83.7 (25)	119 (28.1)	**118 (24.2)**	118 (27.7)	**93.8 (22.8)**
Median (Min, Max)	88.1 (35.5, 139)	**107 (32.2, 155)**	93.7 (41, 148)	85.6 (31.2, 172)	116 (43.5, 202)	**125 (70.4, 159)**	115 (70.8, 215)	**92.9 (31.2, 215)**
Missing N (%)	4 (0.403)	0 (0)	1 (0.18)	2 (0.881)	0 (0)	0 (0)	5 (3.33)	12 (0.516)

Analysis Directory:/global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo-update/
Program source: Analysis Directory/final/sas/Table3.3.1.5-1.sas
Source: Analysis Directory/final/reports/Table3.3.1.5-1.rtf
Note - revised numbers have been bolded

Model Development

The nivolumab PPK model was developed in 2 stages, as shown below:

1) Base Model: Re-estimate the parameters of a previously determined final model, including covariates retained in the previous final model, except the tumour type effect.

2) Full Model: Key known effects of covariates on nivolumab PK were included in the base model. The focus of the full model was to assess the effect of additional covariates (namely, patient population and combination therapy on nivolumab CL; patient population, combination therapy, and PS on EMAX).

Base Model

Base model development consisted of re-estimating parameters of the previously developed final model that had been developed to characterize PK in nivolumab in solid tumour subjects.

The base model was a 2-compartment, zero-order IV infusion PK model, with time-varying CL (sigmoidal-EMAX function); and a combined proportional and additive residual error model, with random effects on CL, Q, VC, VP, and EMAX; and the correlation of random effect between CL and VC. The variance of random effect was estimated jointly for the two CL parameters (CL, Q) and for the two volume parameters (VC, VP). The base model contained WTB, sex, race, baseline eGFR, and PS on CL, WTB and sex on VC, WTB on Q, and WTB on VP. CL and VC constrained to the same value as Q and VP.

The parameter estimates of the selected base model are provided below.

Table 8 Parameter Estimates of the Base 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	9.84	0.232 (2.36)	9.38 - 10.3
VC_{REF} [L]	θ_2	3.86	0.0365 (0.946)	3.79 - 3.93
Q_{REF} [mL/h]	θ_3	37.6	1.60 (4.25)	34.5 - 40.7
VP_{REF} [L]	θ_4	2.41	0.0833 (3.45)	2.25 - 2.57
CL_{WTB}	θ_7	0.860	0.0251 (2.92)	0.811 - 0.909
CL_{GFR}	θ_9	-0.127	0.0351 (27.7)	-0.196 - -0.0579
CL_{FEMALE}	θ_{12}	-0.0757	0.0200 (26.4)	-0.115 - -0.0365
CL_{PS}	θ_{13}	-0.0152	0.0190 (125)	-0.0525 - 0.0221
CL_{RAAA}	θ_{14}	-0.0117	0.0529 (454)	-0.115 - 0.0920
CL_{RAAS}	θ_{15}	-0.0245	0.0379 (154)	-0.0987 - 0.0497
VC_{WTB}	θ_{16}	0.878	0.0144 (1.63)	0.850 - 0.906
VC_{SEX}	θ_{17}	-0.0766	0.0168 (22.0)	-0.110 - -0.0436
$EMAX_{REF}$	θ_{18}	-0.403	0.0365 (9.06)	-0.475 - -0.332
$T50$ (h)	θ_{19}	2.11E+03	318 (15.1)	1.49E+03 - 2.73E+03
$HILL$	θ_{20}	2.07	0.292 (14.1)	1.50 - 2.64
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.159 (0.398)	0.00942 (5.94)	0.140 - 0.177
ZVC [-]	$\omega_{2,2}$	0.0828 (0.288)	0.00786 (9.49)	0.0674 - 0.0982
$ZEMAX$ [h]	$\omega_{4,4}$	0.113 (0.337)	0.0270 (23.8)	0.0605 - 0.166
$ZCL:ZVC$	$\omega_{1,2}$	0.0334 (0.292)	0.00400 (12.0)	0.0256 - 0.0413
Residual Error				
$PERR$ [-]	θ_6	0.200	0.00389 (1.95)	0.192 - 0.207
$RESERR$[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: Analysis-Directory/nm/base/reports/base_RTF.rtf

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject, 60-year old white male, weighing 75 kg, with a normal PS status (PS = 0). $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject. VC_{REF},

Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 75 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note 2: Eta shrinkage (%): ETA_CL: 9.73; ETA_VC: 28.1; ETA_EMAX: 44.4; EPS shrinkage (%): 15.6

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 intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*.

Full Model

The full model was developed from the base model, by incorporating additional covariates in the PK parameters, including assessment of age, combination therapy, and patient population (adult MEL as reference) on baseline CL, as well as PS, patient population, and combination therapy on EMAX.

Full model selection steps include:

Table 9 Selection of Nivolumab Population Pharmacokinetic Full Models

Model No.	Model Description (Covariate Effects)			Parameter Number	OFV	BIC	ΔBIC[a]
	Effect on Baseline CL	Effect on EMAX	Effect on VC				
Starting full1 model							
Full1	WTB, baseline eGFR, Sex, PS, Race, and patient population (HL, CNST, Others vs MEL), Combination (I1Q3, I3Q3, and BVCO)	Patient population (Adult MEL, Adult HL, Adult Others, and Pediatric CNST), Combination (nivo + ipi)	WTB, Sex	31	74339	74653	0
Investigate which body size parameters to be in the model (LBM or BSA vs WTB)							
Full3	Same as Full1 except LBM on CL	Same as Full1	LBM on VC	31	74286	74601	-53
Full3a	Same as Full1	Same as Full1	LBM on VC	31	74248	74563	-90
Full3b	Same as Full1 except LBM on CL	Same as Full1	Same as Full1	31	74388	74703	50
Full3c	Same as Full1 except BSA on CL	Same as Full1	BSA on VC	31	74289	74604	-50
Add age effect on CL and VC using different forms without tumor difference in age effect							
Full2	Same as Full3a except adding single numeric effect of age on CL	Same as Full1	Single numeric effect of age on VC	33	74138	74473	-180
Full2a	Same as Full3a except categorical effect (pediatric <12 years, adolescent 12-17 years vs adult) of age on CL	Same as Full1	Categorical effect (pediatric <12 years, adolescent 12-17 years vs adult) of age on VC	35	74137	74493	-160
Full2b	Same as Full3a except separate numeric effect (by pediatric <12 years, adolescent 12-17 years, and adult) of age on CL	Same as Full1	Separate numeric effect (by pediatric <12 years, adolescent 12-17 years, and adult) of age on VC	37	74228	74604	-49
Add categorical age effect on CL with tumor type difference, and categorical age effect on VC							
Full1a	Same as Full3a except pediatric (< 18 years) ST, HL, and CNST on CL	Same as Full1	Pediatric (<12 years) and adolescent (12-17 years) effect on VC	36	74134	74499	-154

Full1b	Same as Full3a except pediatric (<12 years) and adolescent (12-17 years) ST, HL, and CNST on CL	Same as Full1	Same as Full1a	39	74120	74517	-137
Full1c	**Same as Full1b except combining pediatric and adolescent effect for HL and CNST**	**Same as Full1**	**Same as Full1a**	**37**	**74122**	**74498**	**-156**

Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd.Rmd

Source: Analysis-Directory/R/export/model.bic.csv

Note 1: Model selected is shown in bold font.

Note 2: base model is not shown in this table and BIC value is 75468.

Abbreviations: BSA = baseline body surface area; CL = clearance; Emax = maximal change of CL with Time; LBM = lean body mass; VC = central volume; WTB = baseline body weight; eGFR = estimated glomerular filtration rate

[a] Difference between BIC of a model and BIC of the reference model (Full1)

The models full2 and full1c had the lowest BIC value in each category (above). Full2 model assumes the age effect on CL is the same across different tumour types. The parameter estimates of Full2 mode showed CL increased with age regardless of the tumour types. However, this assumption may not hold true as the paediatric HL and adult HL had similar CL as shown in figure 1. In addition, prior nivolumab PPK showed there was no age effect on CL in adult patient populations, and therefore it was not appropriate to apply a single age effect across adult and paediatric populations. Taking together, full1c model was selected as the full model for model application.

Parameter estimates for the full model are presented in **Table 9**, and the covariate effects are shown in **Figure 1**.

The value of CL for subject *i* in full model is given by:

$$CL_i(t) = CL0_{TV,i} \times e^{\left(\frac{EMAX_i * t^{HILL}}{TS0^{HILL} + t^{HILL}}\right)} \times e^{\eta_{CL,i}},$$

where

$$\begin{aligned} CL0_{TV,i} = {} & CL0_{REF} \times \left(\frac{WTB_i}{WTB_{REF}}\right)^{CL_{WTB}} \times \left(\frac{eGFR_i}{eGFR_{REF}}\right)^{CL_{eGFR}} \times e^{CL_{SEX}(\text{if female})} \times e^{CL_{PS}(\text{if PS>0})} \\ & \times e^{CL_{RAAA}(\text{if RACE is AA})} \times e^{CL_{RAAS}(\text{if RACE is Asian})} \times e^{CL_{HL}(\text{if POP is Adult HL})} \\ & \times e^{CL_{GBM}(\text{if POP is Adult GBM})} \\ & \times e^{CL_{OTH}(\text{if POP is Adult Others})} \times e^{CL_{PEDST}(\text{if POP Pediatric <12yrs ST})} \\ & \times e^{CL_{ADOST}(\text{if POP Adolescent 12-17yrs ST})} \times e^{CL_{PEDHL}(\text{if POP Pediatric <18yrs HL})} \\ & \times e^{CL_{PEDCNST}(\text{if POP Pediatric <18yrs CNST})} \times e^{CL_{1\,1Q3}(\text{if nivo + ipi 1 mg/kg Q3W})} \\ & \times e^{CL_{3\,3Q3}(\text{if nivo + ipi 3 mg/kg Q3W})} \times e^{CL_{BVCO}\left(e^{CL_{BVCO}}\right)(\text{if nivo + brentuximab vedotin})} \end{aligned}$$

And

$$\begin{aligned} EMAX_i = {} & EMAX_{REF} + EMAX_{PS}(\text{if PS} > 0) + EMAX_{HL}(\text{if POP is Adult HL}) \\ & + EMAX_{OTH}(\text{if POP is Adult Others}) \\ & + EMAX_{PEDCNST}(\text{if POP is Pediatric} < 18\text{yrs CNST}) \\ & + EMAX_{COMBO}(\text{if nivo + ipi combination}) + \eta_{\text{EMAX},i} \end{aligned}$$

The value of VC for subject *i* is given by:

$$\begin{aligned} VC_i = {} & VC_{REF} \times \left(\frac{LBM_i}{LBM_{REF}}\right)^{VC_{LBM}} \times e^{VC_{SEX}(\text{if female})} \\ & \times e^{VC_{ADO}(\text{if POP is 12-17 yrs})} \times e^{VC_{PED}(\text{if POP <12 yrs})} \times e^{\eta_{VC,i}} \end{aligned}$$

The values of Q and VP for subject *i* are given by:

$$Q_i = Q_{REF} \times \left(\frac{WTB_i}{WTB_{REF}}\right)^{Q_{WTB}} \times e^{\eta_{Q,i}}$$

$$VP_i = VP_{REF} \times \left(\frac{LBM_i}{LBM_{REF}}\right)^{VP_{LBM}} \times e^{\eta_{VP,i}}$$

In these equations, CL_{REF} is the typical value of CL at time 0 (CL0) at the reference values of baseline body weight (WTB) [75 kg], lean body mass (LBM) [55 kg], age (60 years), PS (PS = 0), baseline eGFR (90 mL/min/1.73 m2), sex (male), race (White), and patient population (adult MEL); is the typical value of VC at the reference values of LBM [55 kg], sex (male), and patient population (all adults); QREF and VPREF are typical values of Q and VP at the reference values of WTB and LBM, respectively; and EMAXREF represents the typical value of EMAX at the reference value of PS (PS = 0), patient population (adult MEL), and nivolumab monotherapy. T50 represents the time at which the change in CL is 50% of EMAX, and HILL represents the sigmoidicity of the relationship with time.

Table 10 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_{IIQ3}	θ_{28}	0.0976	0.0520 (53.3)	-0.00167 - 0.207
CL_{IBQ3}	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[/]	$\sigma_{1,1}$	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

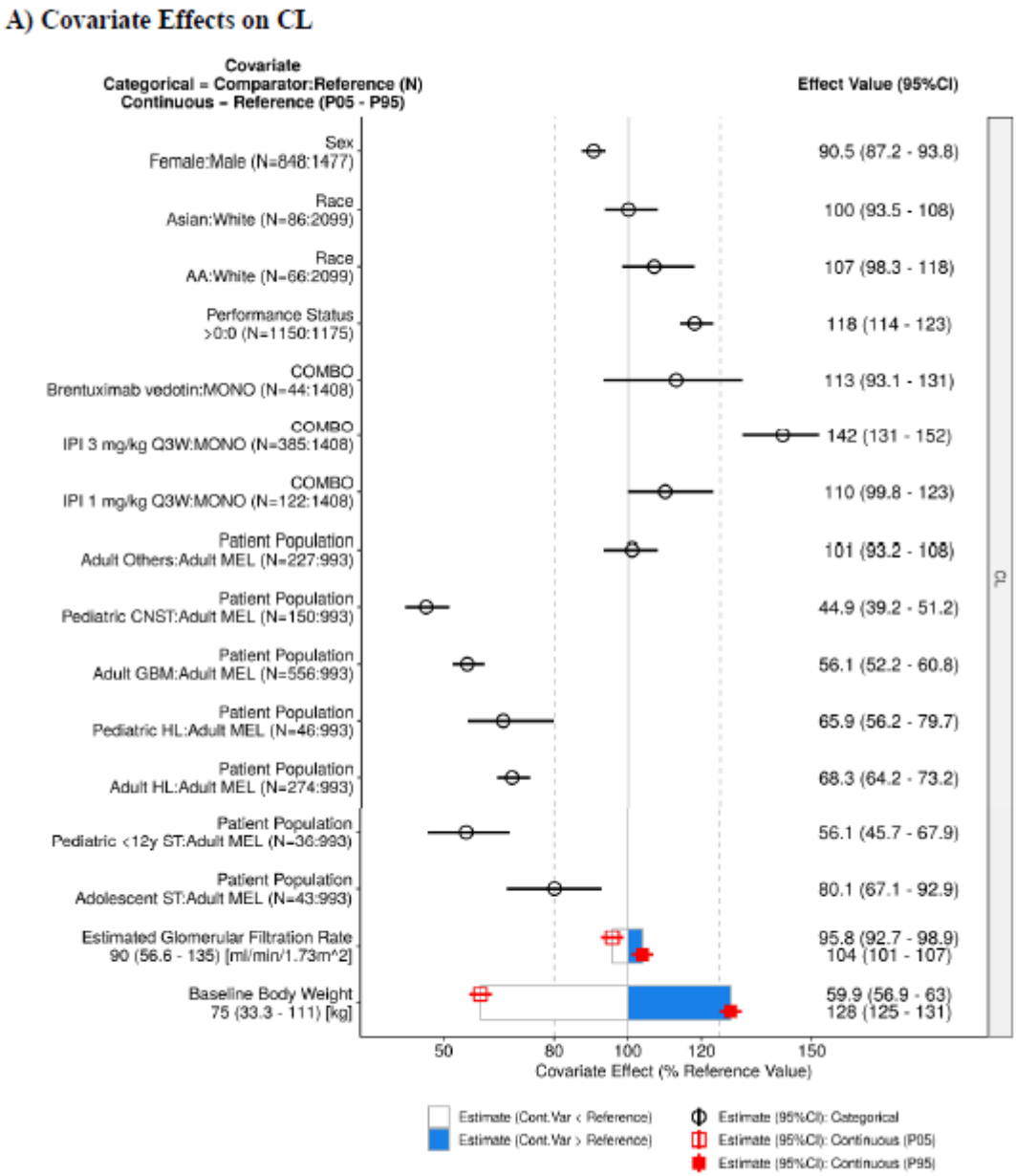
Source (for Estimate and Standard Error): Analysis-Directory/nm/full1c/reports/full1c_RTF0.rtf

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject with MEL, receiving nivolumab monotherapy, 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 nivolumab monotherapy 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.

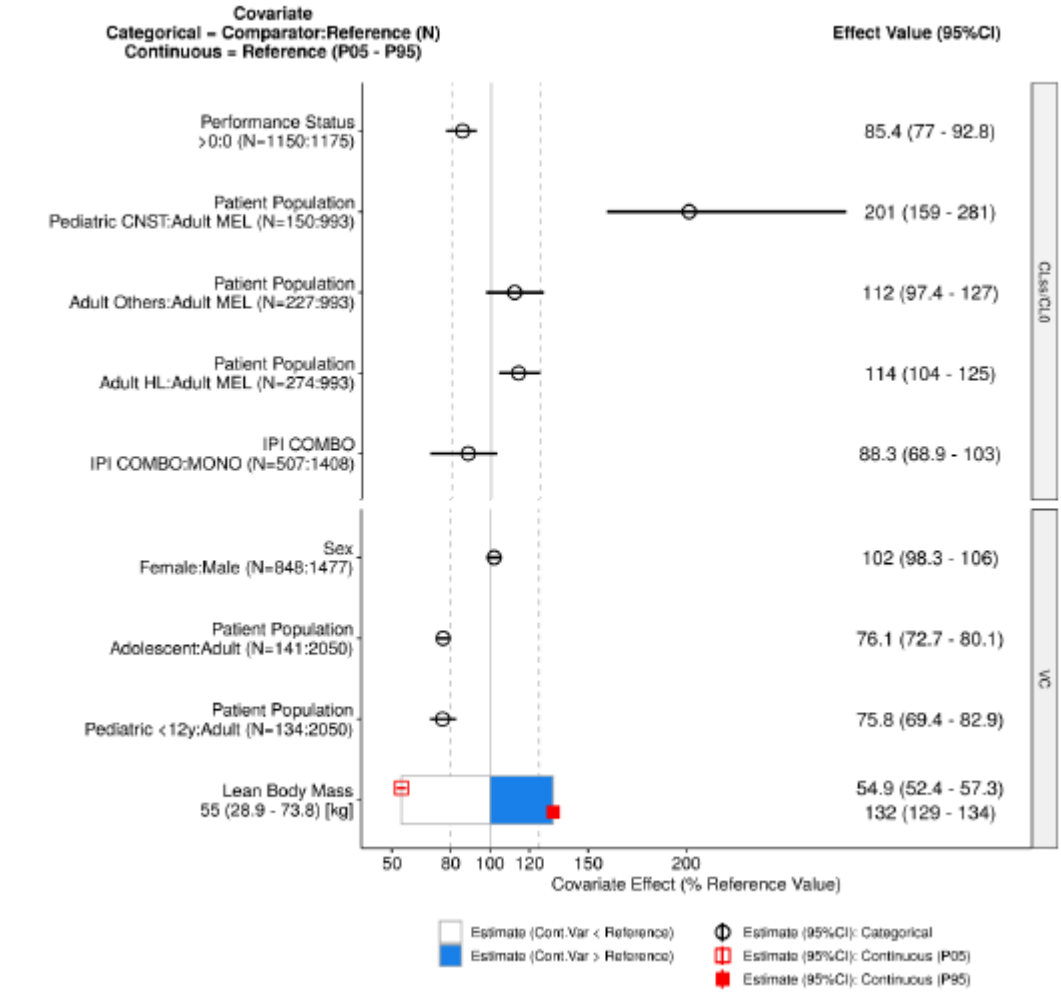
Note 2: Eta shrinkage (%): ETA_CL: 12.2; ETA_VC: 28.1; ETA_EMAX: 50.3; EPS shrinkage (%): 15.0.

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

Figure 1 Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters



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 nivolumab monotherapy, 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: $CLss/CL0 = e^{EMAX}$

Model Evaluation

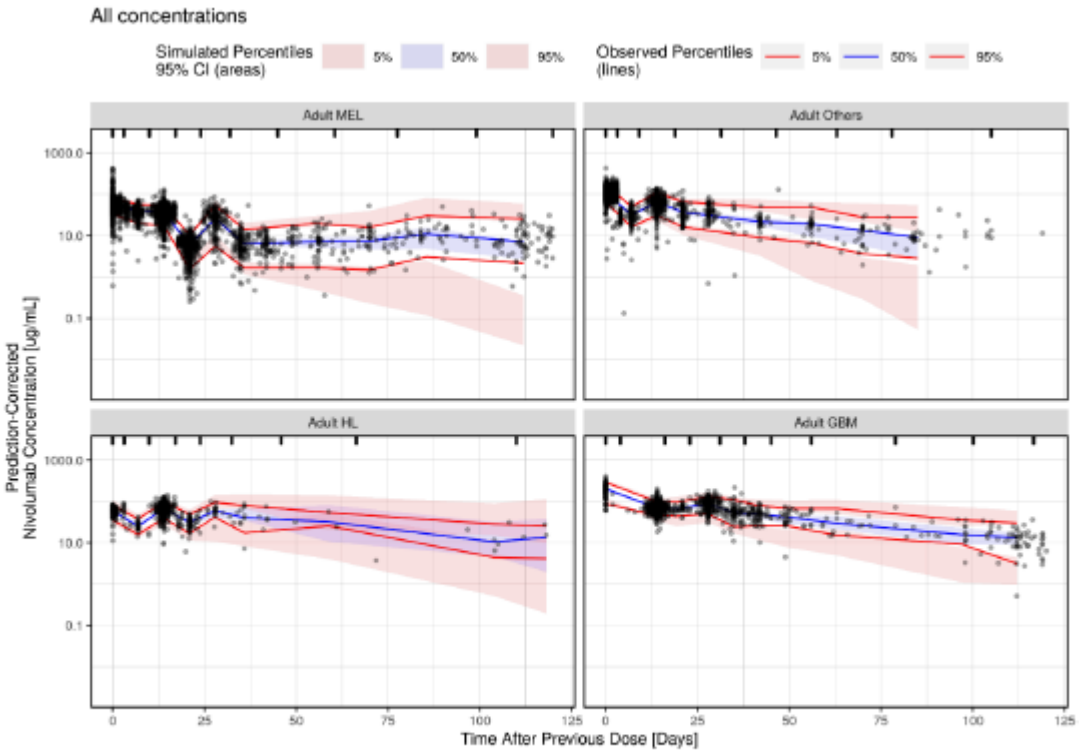
Prediction-Corrected visual predictive checks (VPCs)

Model evaluation was performed using a prediction-corrected visual predictive check (pcVPC) to provide a graphical assessment of the agreement between the time course of model predictions and observations.

The predictive performance of the nivolumab full model was evaluated using a VPC stratified by patient population. The pcVPC plots for adult MEL, adult HL, adult GBM, and adult others are shown in **Figure**

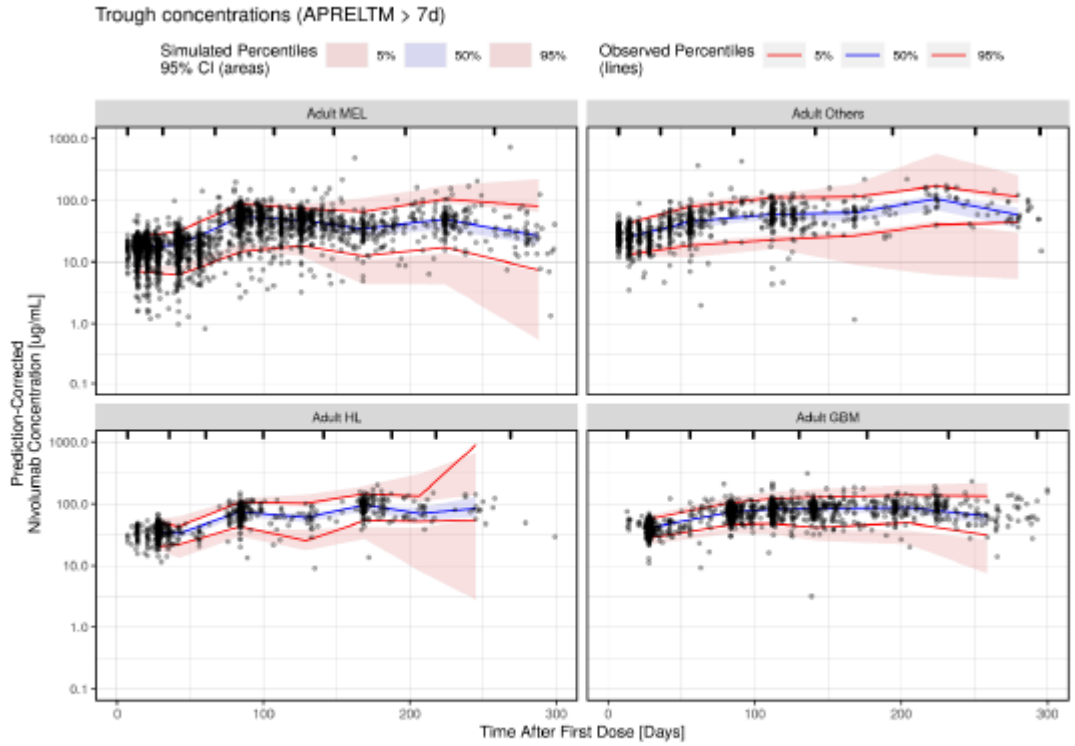
2 and **Figure 3**. The VPC plots for paediatric ST, paediatric HL, and paediatric CNST subjects are shown from **Figure 4** to **Figure 9**.

Figure 2 Prediction-Corrected Visual Predictive Check of Nivolumab Concentrations versus Actual Time after Previous Dose in Adult Patient Populations [Full Nivolumab Population Pharmacokinetic Model]



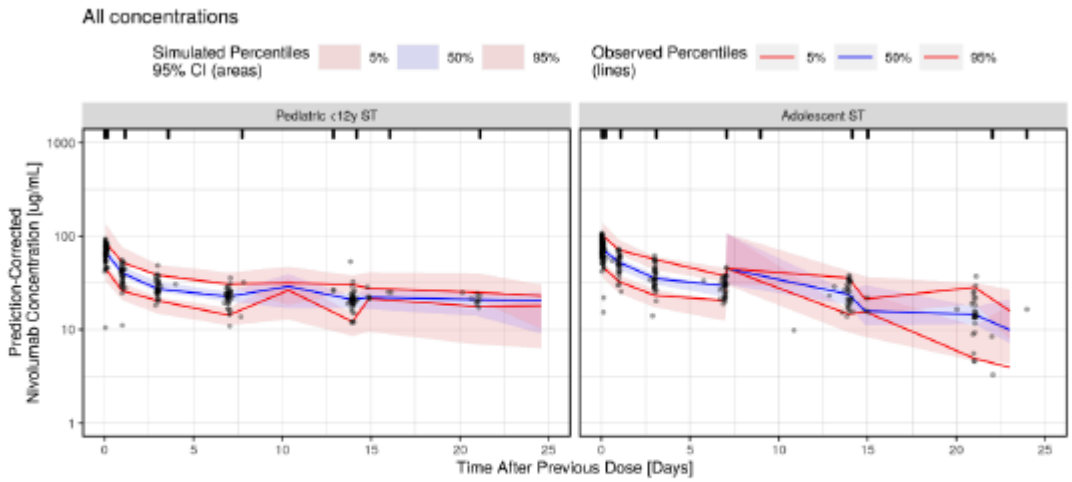
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-adult.png

Figure 3 Prediction-Corrected Visual Predictive Check of Trough Nivolumab Concentrations versus Actual Time after First Dose in Adult Patient Populations [Full Nivolumab Population Pharmacokinetic Model]



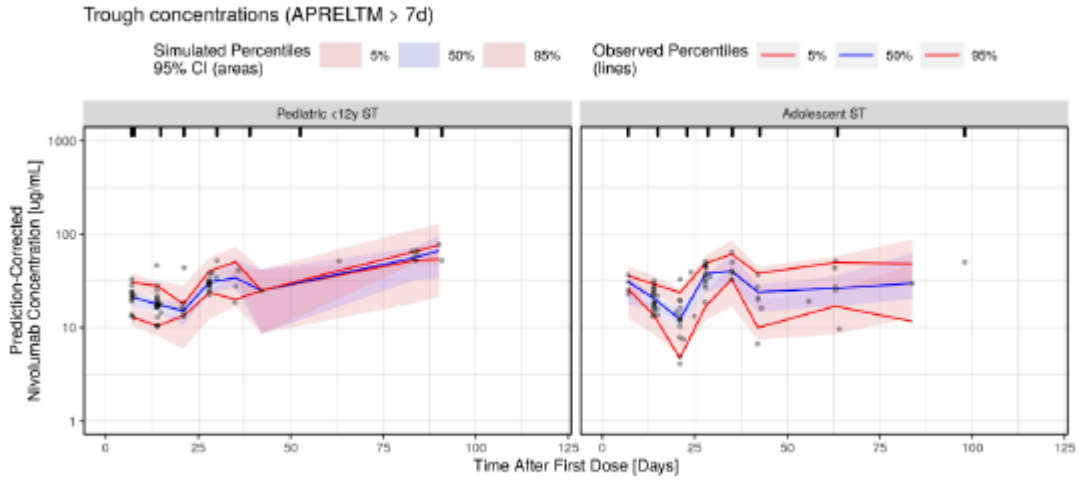
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-trough-adult.png

Figure 4 Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose in Paediatric Solid Tumour (ST) Subjects [Full Nivolumab Population Pharmacokinetic Model]



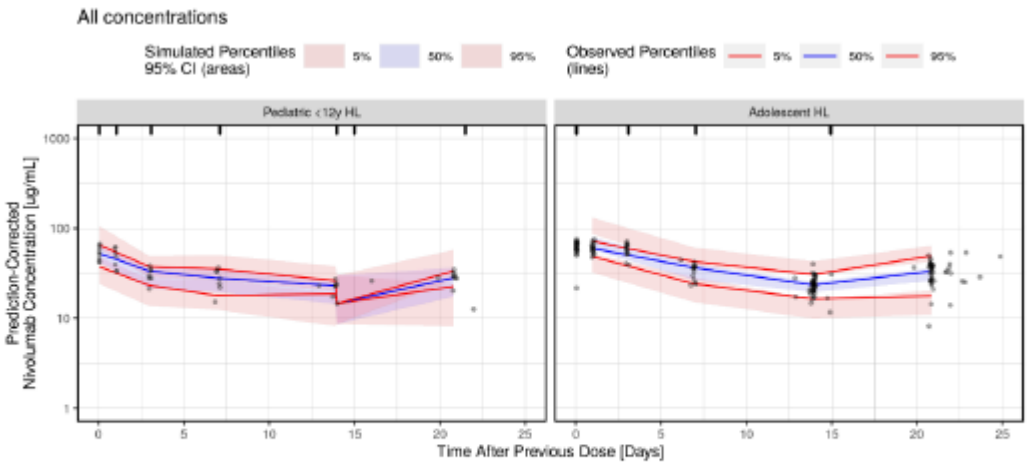
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-ped-st.png

Figure 5 Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose in Paediatric Solid Tumour (ST) Subjects [Full Nivolumab Population Pharmacokinetic Model]



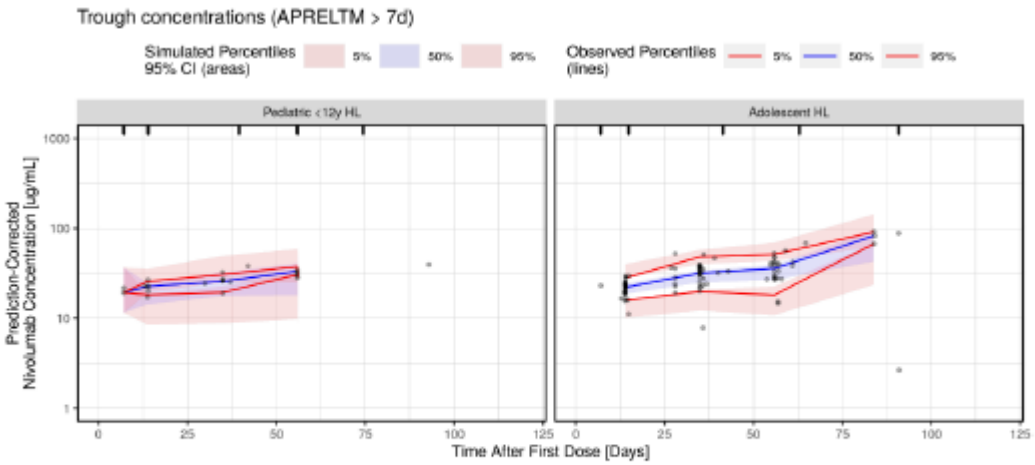
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-trough-ped-st.png

Figure 6 Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose in Paediatric Hodgkin Lymphoma (HL) Subjects [Full Nivolumab Population Pharmacokinetic Model]



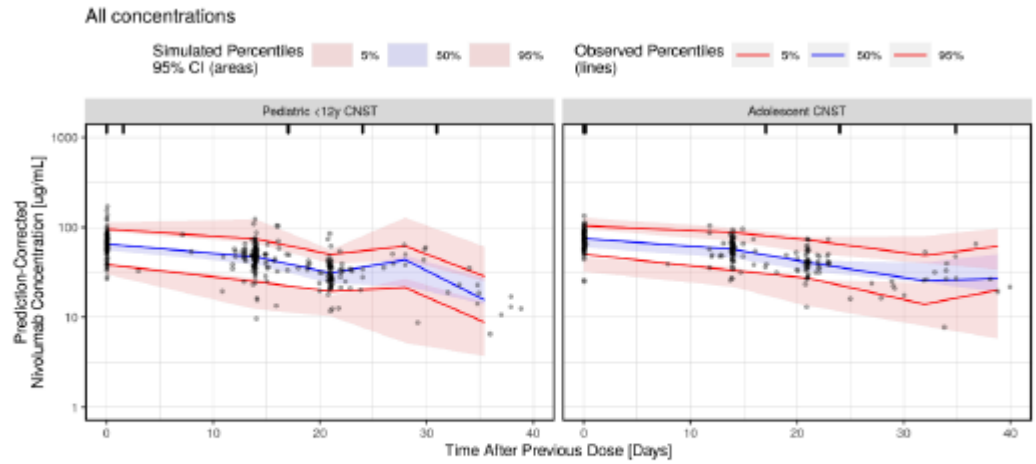
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-all-ped-hl.png

Figure 7 Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose in Paediatric Hodgkin Lymphoma (HL) Subjects [Full Nivolumab Population Pharmacokinetic Model]



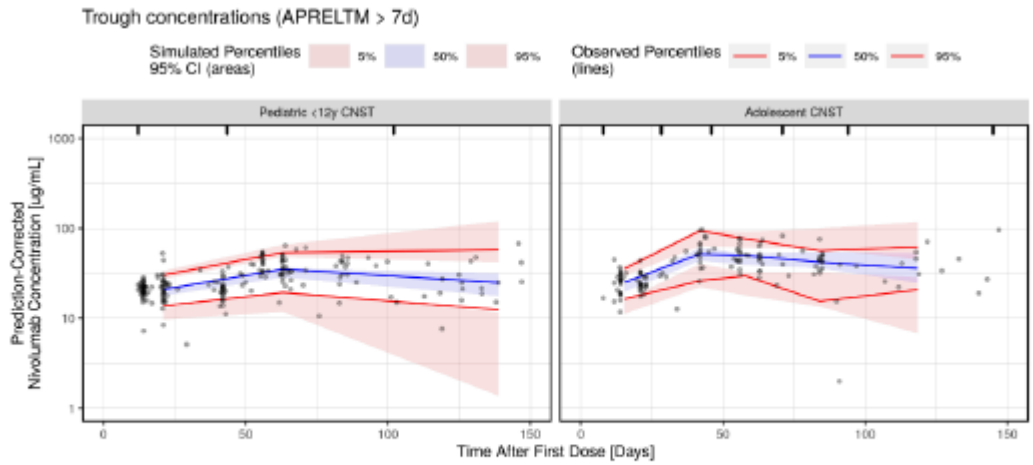
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/4-model-eval-app.Rmd
Source: Analysis-Directory/R/plots/full-vpc-trough-ped-hl.png

Figure 8 Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose in Paediatric CNS Tumour (CNST) Subjects [Full Nivolumab Population Pharmacokinetic Model]



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-cnst.png

Figure 9 Prediction-Corrected Visual Predictive Check of Trough Concentrations versus Actual Time after First Dose in Paediatric CNS Tumour (CNST) Subjects [Full Nivolumab Population Pharmacokinetic Model]



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-trough-ped-cnst.png

Assessment of Uncertainty in Paediatric PK Model Parameters

The uncertainty of CL and VC for a typical paediatric ST, paediatric HL, or paediatric CNST subject at 17, 12, 8, or 4 years old was assessed. The 95% CI of the CL and VC for a typical paediatric ST, HL, and CNST subject at 17, 12, 8 or 4 years old were all contained within the 80% - 120% of typical value.

Model Application

Comparison of PK Parameters Among Patient Populations

Nivolumab empirical Bayes estimates (EBE) PK parameters including baseline CL (CL0), steady state CL (CLss), and VC were obtained from the full model for each subject.

Table 11 Comparison of Nivolumab PK Parameters among Adult Melanoma (MEL), Adult Others, Adult Hodgkin Lymphoma (HL), and Adult Glioblastoma (GBM)

Parameters	Adult MEL Geo. Mean (%CV) (N = 608, G1)	Adult Others Geo. Mean (%CV) (N = 227, G2)	Adult HL Geo. Mean (%CV) (N = 274, G3)	Adult GBM Geo. Mean (%CV) (N = 556, G4)	% Diff GM (G2-G1)[a]	% Diff GM (G3-G1)[b]	% Diff GM (G4-G1)[c]
CL0 (mL/h)	10.1(45.7)	10.9(39.3)	6.99(39.3)	6.18(27.2)	7.92	-30.8	-38.8
CLss (mL/h)	7.21(91.6)	8.08(56.1)	5.55(54)	6.18(27.2)	12.1	-23	-14.3
VC (L)	4.01(28.3)	4.07(30.8)	4.02(22.1)	4.14(19.3)	1.5	0.249	3.24
VP (L)	2.82(21.4)	2.84(30)	2.76(20.6)	2.86(18.5)	0.709	-2.13	1.42
VSS (L)	6.9(22.7)	6.95(27.9)	6.79(21.3)	7(18.4)	0.725	-1.59	1.45
PEMAX (%)	71.4(30.2)	74.1(25.2)	79.4(17.3)	100(0)	3.78	11.2	40.1

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/export/param-stats-adult-with diff.csv
VSS was calculated using formula: VSS=VC+VP.
PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.
GM = geometric mean

[a] Percent difference in geometric mean (GM) of Adult Others (G2) relative to Adult MEL (G1).

[b] Percent difference in geometric mean (GM) of Adult HL (G3) relative to Adult MEL (G1).

[c] Percent difference in geometric mean (GM) of Adult GBM (G4) relative to Adult MEL (G1).

Table 12 Nivolumab PK Parameters in Paediatric Patient Populations

Parameters	<12 yrs ST Geo. Mean (%CV) (N = 36, G1)	12-17 yrs ST Geo. Mean (%CV) (N = 43, G2)	<12 yrs HL Geo. Mean (%CV) (N = 9, G3)	12-17 yrs HL Geo. Mean (%CV) (N = 37, G4)	<12 yrs CNST Geo. Mean (%CV) (N = 89, G3)	12-17 yrs CNST Geo. Mean (%CV) (N = 61, G4)
CL0 (mL/h)	3(41.4)	7.95(38.5)	3.84(39.8)	7.05(38.3)	2.29(38.8)	4.14(42.5)
CLss (mL/h)	1.91(39.1)	4.91(40.8)	2.74(35.4)	4.84(32.8)	2.92(38.2)	5.2(62.4)
VC (L)	1.24(39)	2.74(26.5)	1.39(35)	2.92(22)	1.13(41.8)	2.27(31)
VP (L)	1.05(41.1)	2.31(21.4)	1.21(33.8)	2.51(18.4)	1.04(40.2)	2.12(26.7)
VSS (L)	2.29(39.5)	5.06(22.7)	2.61(33.4)	5.43(19.7)	2.18(39)	4.41(27.1)
PEMAX (%)	63.8(9.33)	61.8(10.1)	71.4(9.42)	68.7(16.1)	128(24)	126(19.1)

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/export/param-stats-ped.csv
VSS was calculated using formula: VSS=VC+VP.
PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.

Simulation of Paediatric Exposures for **adolescents with solid tumours**

Nivolumab exposures were simulated using stochastic simulations for adolescents with solid tumours (≥ 12 to < 18 years) with selected dose regimen of nivolumab alone or in combination with ipilimumab to identify doses that produce similar nivolumab exposures to the adult MEL population with following approved dosing regimens.

1. Adult Approved Dosing Regimens Simulated:

Nivolumab: 240 mg Q2W or 480 mg Q4W

Nivolumab + Ipilimumab: 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered IV Q3W for the first 4 doses, followed by nivolumab 240 mg Q2W or 480 mg Q4W

2. Nivolumab Monotherapy Regimens Simulated in Adolescent Advanced Melanoma (with a * to indicate the adolescent recommended dose):

Flat Dosing

-240 mg Q2W (≥ 40 kg) or 3 mg/kg Q2W (< 40 kg)*

-480 mg Q4W (≥ 40 kg) or 6 mg/kg Q4W (< 40 kg)*

Body Weight Based Dosing

-3 mg/kg Q2W

-6 mg/kg Q4W

Body Weight Based Dosing with Dose Cap

-3 mg/kg (up to 240 mg) Q2W

-6 mg/kg (up to 480 mg) Q4W

3. Nivolumab in Combination with Ipilimumab Regimens Simulated in Adolescent Advanced Melanoma (with a * to indicate the adolescent recommended dose):

Body Weight Based Dosing:

-Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W, for 4 doses, then nivolumab 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W*

-Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W, for 4 doses, then nivolumab 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W*

Body Weight Based Dosing with Dose Cap:

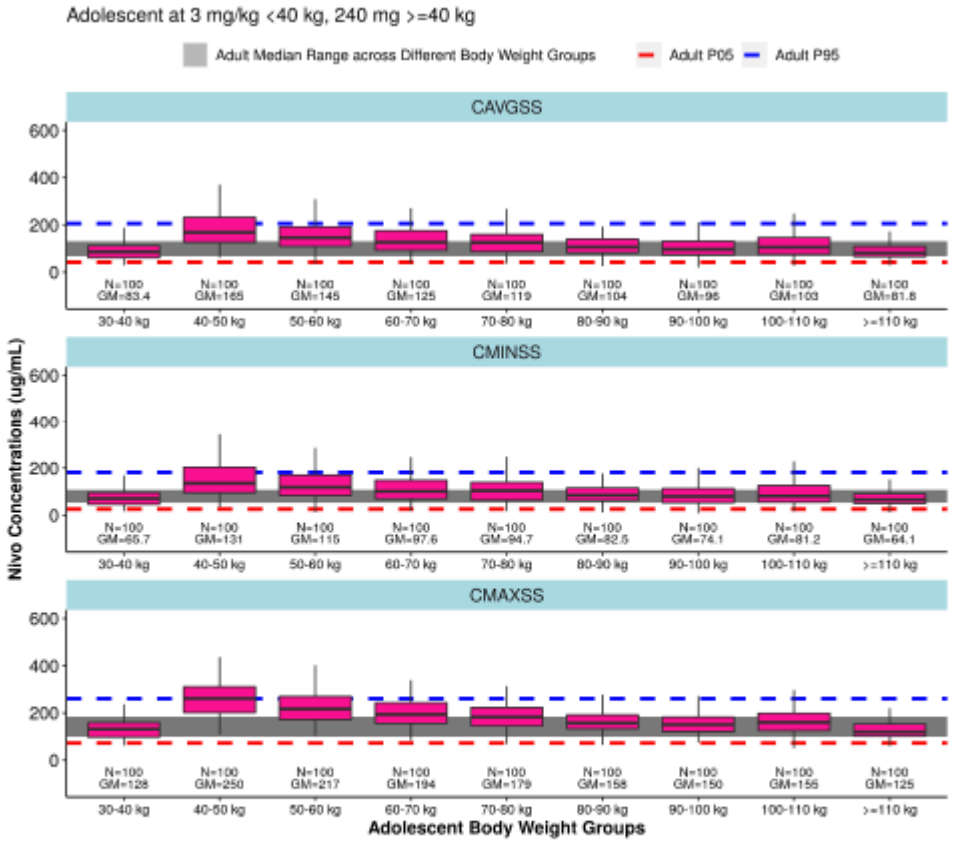
-Nivolumab 1 mg/kg (up to 80 mg) Q3W + Ipilimumab 3 mg/kg (up to 240 mg) Q3W, for 4 doses, then nivolumab 3 mg/kg up to a maximum of 240 mg Q2W

-Nivolumab 1 mg/kg (up to 80 mg) Q3W + Ipilimumab 3 mg/kg (up to 240 mg) Q3W, for 4 doses, then nivolumab 6 mg/kg up to a maximum of 480 mg Q4W

- **Monotherapy**

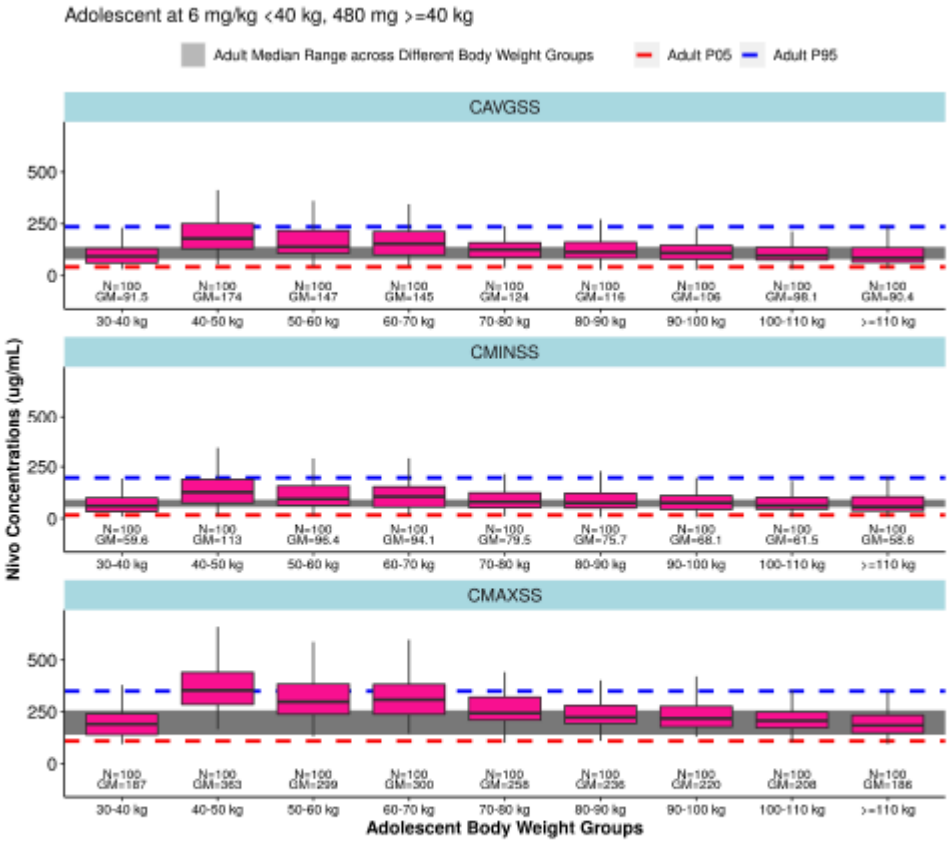
Flat Dosing

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



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/plots/expo-ped-sto-mel-mono-240.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

Figure 11 Predicted Nivolumab Exposures for Adolescents with Solid Tumours at 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W Nivolumab Monotherapy



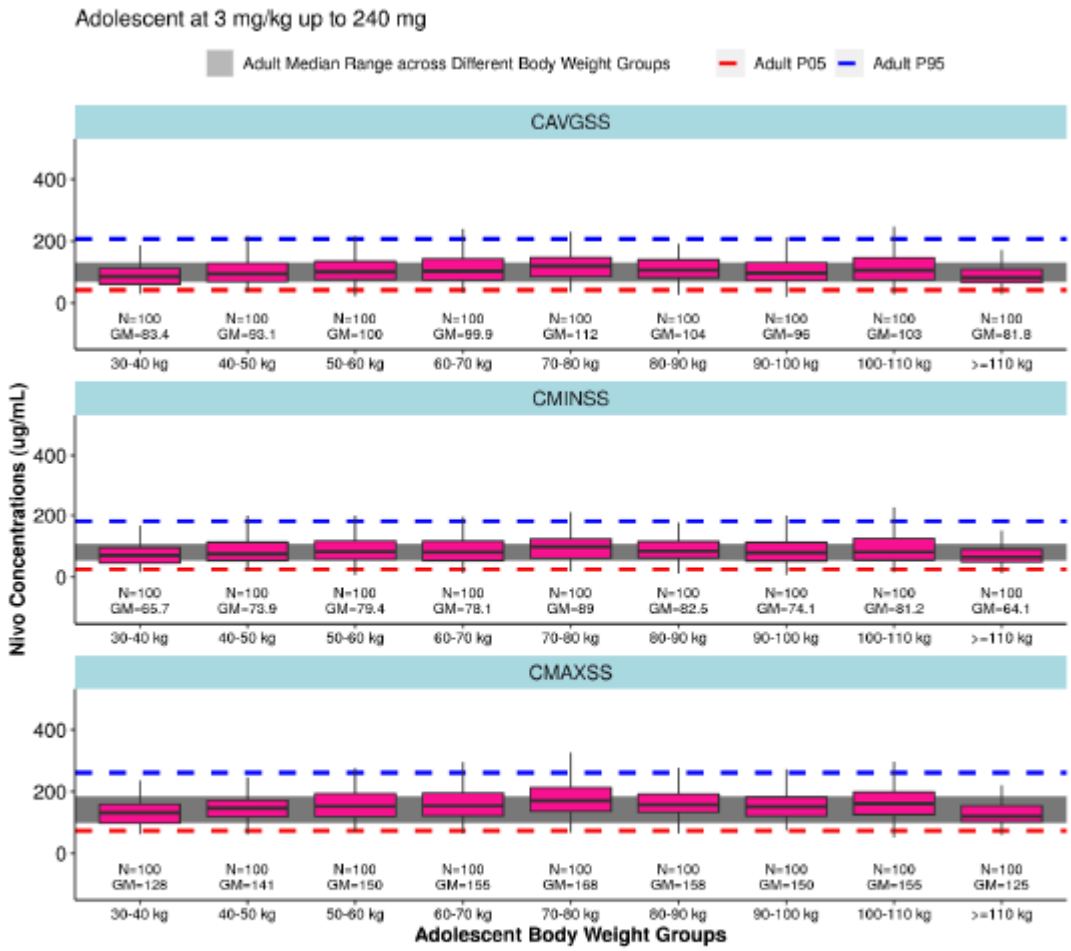
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/plots/expo-ped-sto-mel-mono-480.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

Body weight based dosing

Figure 12 Predicted Nivolumab Exposures for Adolescents with Solid Tumours at 3 mg/kg Q2W Nivolumab Monotherapy

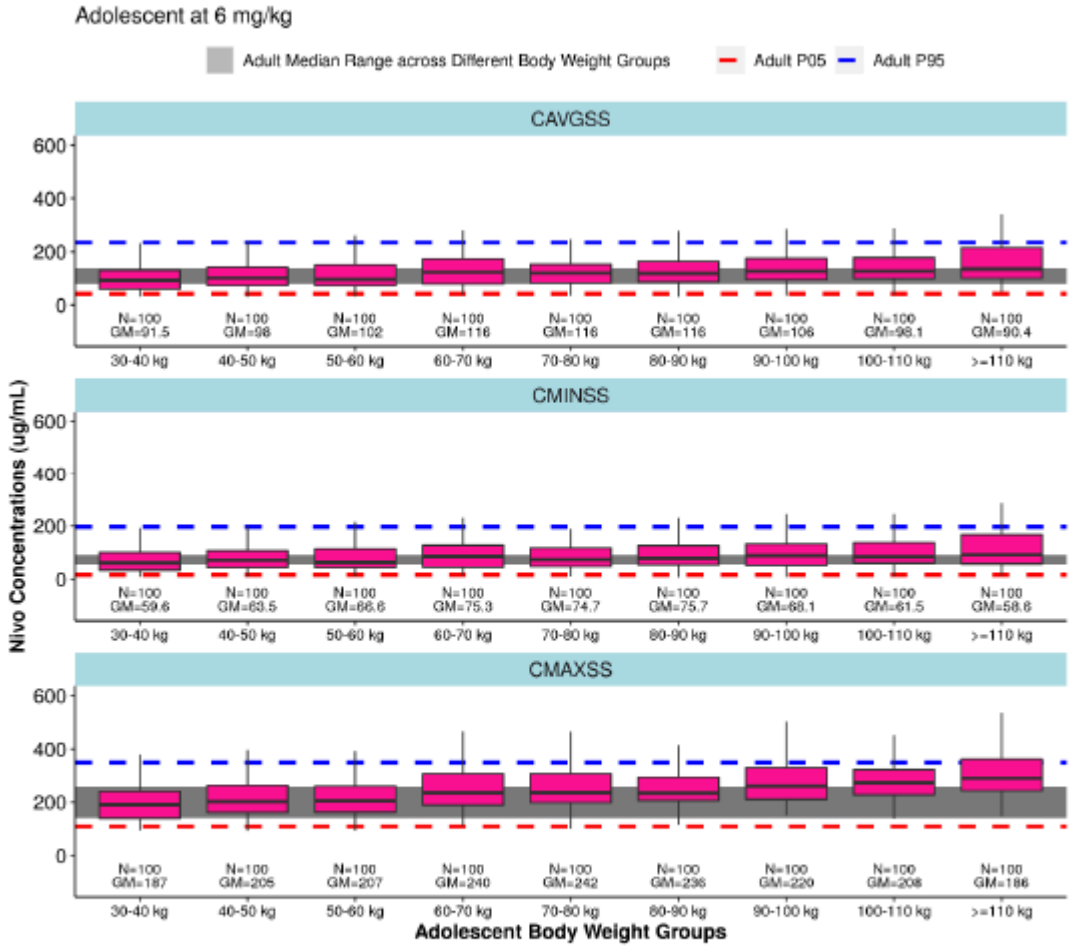
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/plots/expo-ped-sto-mel-mono-3mpk-all.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

Figure 13 Predicted Nivolumab Exposures for Adolescents with Solid Tumours at 3 mg/kg up to 240 mg Q2W Nivolumab Monotherapy



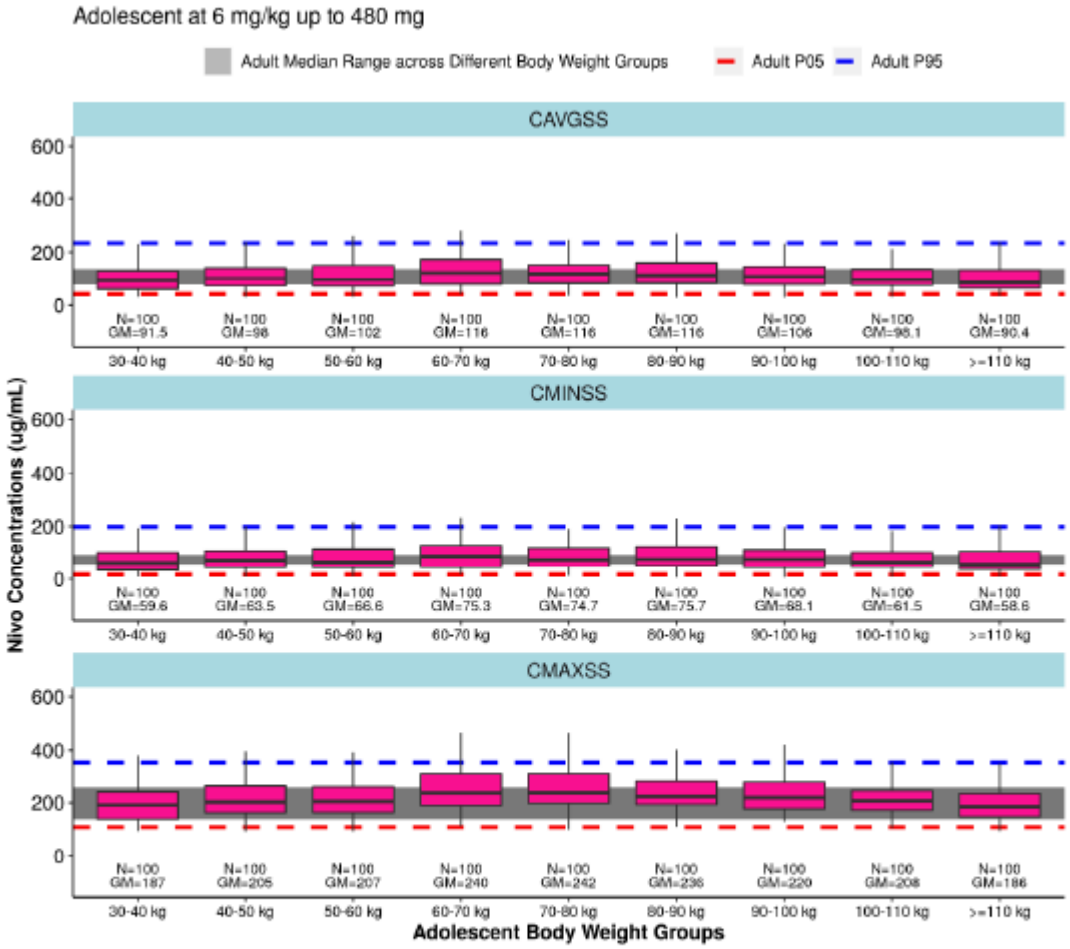
Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd
Source: Analysis-Directory/R/plots/expo-ped-sto-mel-mono-3mpk.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

Figure 14 Predicted Nivolumab Exposures for Adolescents with Solid Tumours at 6 mg/kg Q4W Nivolumab Monotherapy



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/plots/expo-ped-sto-mel-mono-6mpk-all.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

Figure 15 Predicted Nivolumab Exposures for Adolescents with Solid Tumours at 6 mg/kg up to 480 mg Q4W Nivolumab Monotherapy



Analysis-Directory: /global/pkms/data/CA/209/mel-ped-pip01/prd/ppk-nivo/final/

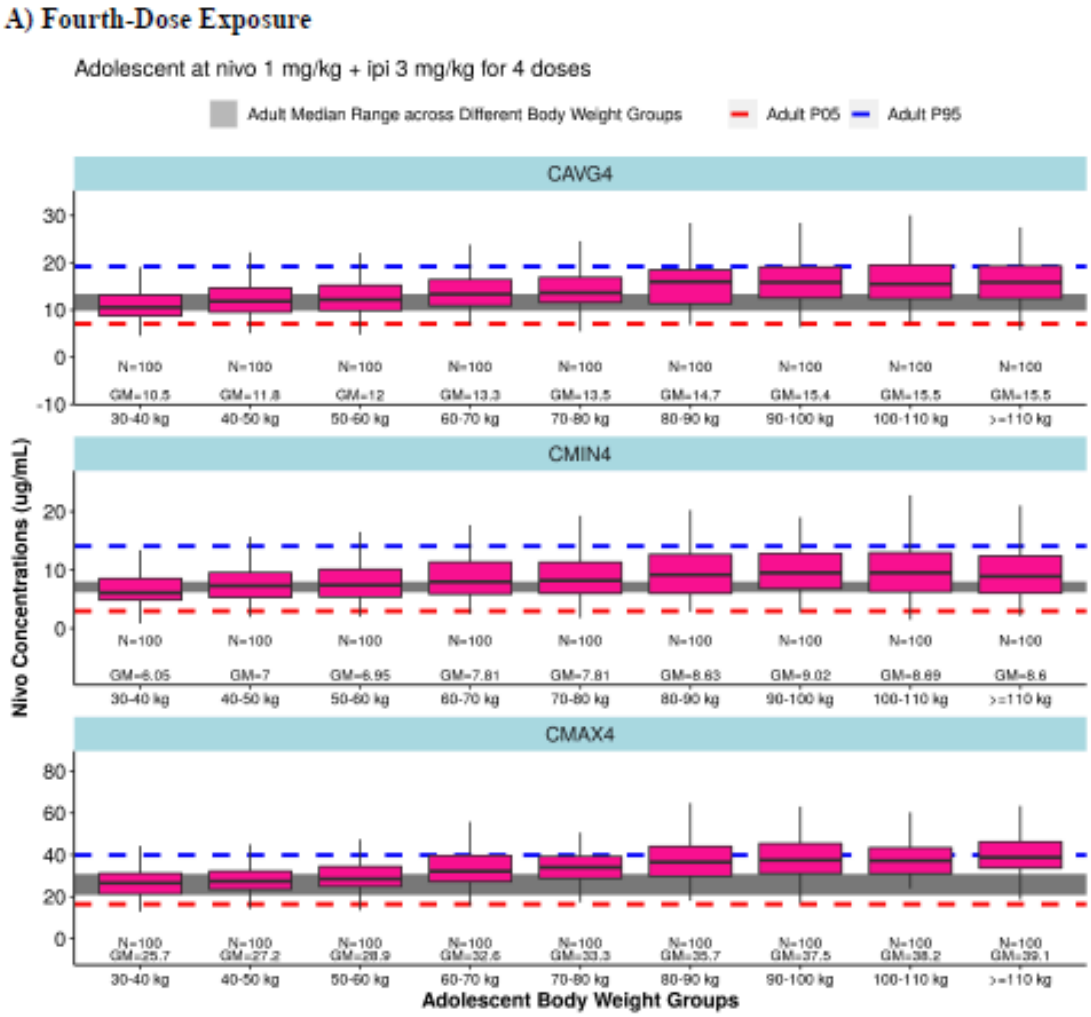
R-Program Source: Analysis-Directory/R/scripts/3-simulation.Rmd

Source: Analysis-Directory/R/plots/expo-ped-sto-mel-mono-6mpk.png

Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

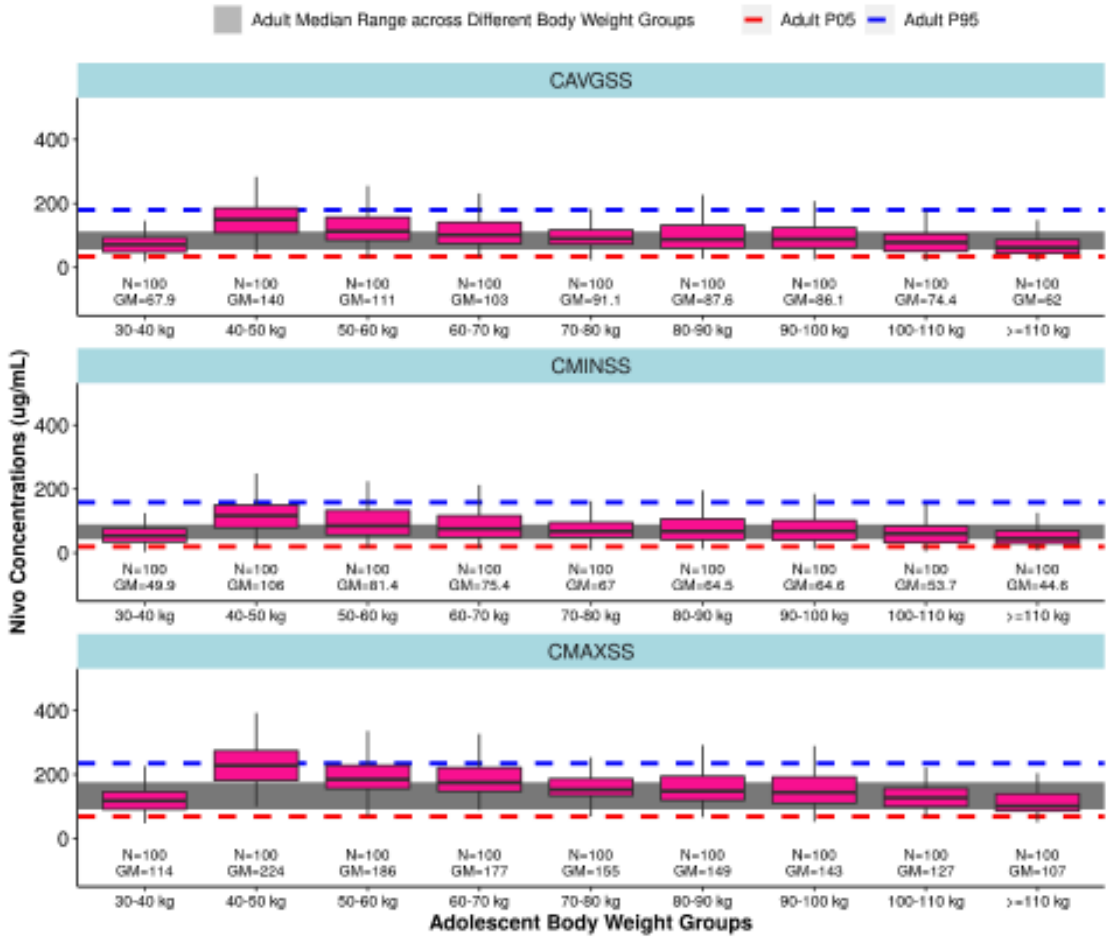
- **Combination therapy**

Figure 16 Predicted Nivolumab Exposures for Adolescents with Solid Tumours 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



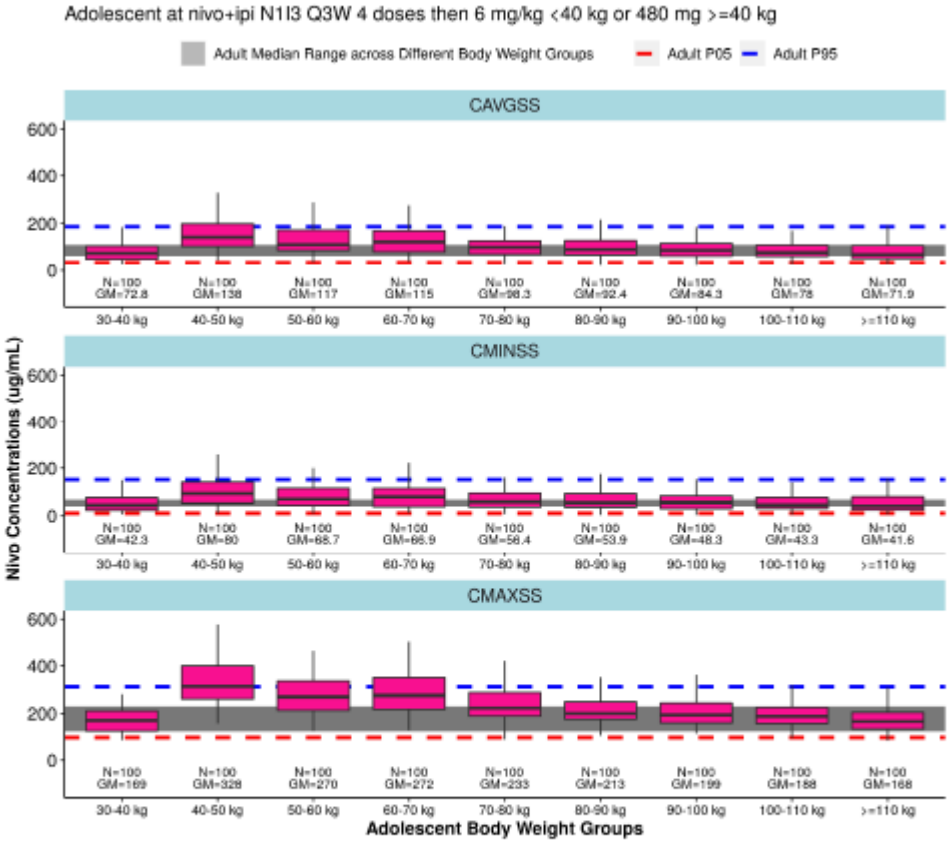
B) Steady-State Exposure

Adolescent at nivo+ipi N1I3 Q3W 4 doses then 3 mg/kg <40 kg or 240 mg >=40 kg



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/plots/expo4-ped-sto-mel-combo.png
Source: Analysis-Directory/R/plots/expo-ped-sto-mel-combo-240.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

Figure 17 Predicted Nivolumab Exposures for Adolescents with Solid Tumours 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



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/plots/expo-ped-sto-mel-combo-480.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Two dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. GM is geometric mean.

PPK Analysis of Nivolumab Monotherapy in Adolescent with Adjuvant Treatment of Melanoma

The objectives of the PPK analysis relevant to adolescent subjects undergoing adjuvant treatment of melanoma were as follows:

- 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 recommendations for nivolumab monotherapy dosing regimens for adolescent subjects (≥ 12 to < 18 years) in the adjuvant treatment of melanoma using model-based simulations.

The current nivolumab PPK analysis included data from 11 clinical studies, including adult data from study CA209238 (nivolumab monotherapy) and CA209915 (nivolumab + ipilimumab and nivolumab monotherapy) to characterize nivolumab PK in subjects with melanoma treated in the adjuvant setting, which included three adolescent subjects from Study CA209915. Adult PK in advanced melanoma and young paediatric (1 to < 12 years) and adolescent (≥ 12 to < 18 years) PK from Study CA209070 in solid tumours for nivolumab and nivolumab in combination with ipilimumab were also included.

A total of 3965 subjects were included in the PPK analysis dataset, including 3883 adult subjects and 82 paediatric subjects. The 3883 adult subjects included 1412 subjects with advanced melanoma,

2244 subjects with adjuvant treatment of melanoma, 227 subjects with other advanced solid tumours. The 82 paediatric subjects included 3 adolescents with adjuvant treatment of melanoma, 43 adolescents with advanced solid tumours, and 36 young paediatric (1 to < 12 years) subjects with advanced solid tumours.

Table 13 Subjects Included in the Nivolumab Population Pharmacokinetic Analysis Dataset by Study

	Number of Subjects			
Study	Nivolumab Treated	PK Database[a]	Flagged for Exclusion	Included (% of subjects in PK Database)
CA209001 (MDX1106-01)	39	39	0	39 (100)
CA209003 (MDX1106-03)	306	274	6	268 (97.8)
CA209004	127	64	0	64 (100)
CA209005 (ONO-4538-01)	17	17	0	17 (100)
CA209066	206	190	12	178 (93.7)
CA209067	626	625	4	621 (99.4)
CA209069	94	92	18	74 (80.4)
CA209070 (ADVL1412)[b]	126	105	3	102 (97.1)
CA209238	452	448	0	448 (100)
CA209511	358	355	0	355 (100)
CA209915	1833	1823	24	1799 (98.7)
Total	4184	4032	67	3965 (98.3)

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1.1-1.rtf

[a] Samples in eToolbox or PAMS; all which are included in the analyses dataset with flag, as noted.

[b] Subjects with lymphoma were not included in the analyses.

Table 14 provides a summary of the PK samples in the nivolumab PPK analysis dataset, with the percentage of samples included in the PPK analysis and the reason for exclusion of the remaining samples.

Table 14 Summary of Samples Included in the Nivolumab Population Pharmacokinetic Analysis

Study	PK Database[a]	Day 1 Pre-Dose[b]	Missing Dose or Sample Information[c]	Below LLOQ	Duplicate Samples[d]	|CWRES|>6	Others[e]	Samples Included in Analysis N(%)[g]
CA209001 (MDX1106-01)	915	40	33	42	0	1	0	799 (91.3)
CA209003 (MDX1106-03)	3373	295	32	73	147	6	2	2818 (91.6)
CA209004	828	68	2	43	16	6	0	693 (91.2)
CA209005 (ONO-4538-01)	285	17	0	0	0	0	0	268 (100.0)
CA209066	870	166	24	15	0	0	0	665 (94.5)
CA209067	4801	602	11	186	6	6	6	3984 (94.9)
CA209069	291	86	4	36	0	0	0	165 (80.5)
CA209070 (ADVL1412)[f]	806	101	7	3	79	1	0	615 (87.2)
CA209238	3754	436	20	62	0	5	1	3230 (97.3)
CA209511	2336	345	46	58	42	22	0	1823 (91.6)
CA209915	11343	1751	45	54	0	4	3	9486 (98.9)
Total	29602	3907	224	572	290	51	12	24546 (95.5)

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1.2-1.rtf

[a] Samples in eToolbox or PAMS; all which are included in the analyses dataset with flag, as noted.

[b] Day 1 Pre-dose samples are excluded from the calculation of the percentage of samples included in analysis.

[c] No dosing records, all PK samples flagged, missing sample date or time or concentration (but not below LLOQ), error in dosing date/time.

[d] Duplicate sample at same actual time after first dose.

[e] Others include samples with error in dose amount and amount missing or equal to zero and sample conc > 2000 ug/mL.

[f] Subjects with lymphoma were not included in the analyses.

[g] The percentage is calculated as samples included in the analysis/(samples in PK database – day 1 pre-dose samples).

Table 15 Summary of Covariates in the Nivolumab Population Pharmacokinetic Analysis Dataset by Subject Type

Covariate	Adult MEL N = 1412	Adult AdjMEL N = 2244	Adult Others N = 227	Adolescent ST N = 43	Adolescent AdjMEL N = 3	Young Pediatric ST N = 36	Total N = 3965
Sex, N (%)							
Male	870 (61.6)	1275 (56.8)	148 (65.2)	28 (66.7)	2 (66.7)	19 (52.8)	2342 (59.1)
Female	542 (38.4)	969 (43.2)	79 (34.8)	15 (34.9)	1 (33.3)	17 (47.2)	1623 (40.9)
Race, N (%)							
White	1368 (96.9)	2192 (97.7)	190 (83.7)	31 (72.1)	3 (100.0)	27 (75.0)	3811 (96.1)
Black/African American	4 (0.3)	5 (0.2)	19 (8.4)	4 (9.3)	0 (0)	4 (11.1)	36 (0.9)
Asian	11 (0.8)	32 (1.4)	14 (6.2)	4 (9.3)	0 (0)	3 (8.3)	64 (1.6)
Other	29 (2.1)	15 (0.7)	4 (1.8)	4 (9.3)	0 (0)	2 (5.6)	54 (1.4)
Baseline PS, N (%)							
0	1035 (73.3)	2070 (92.2)	61 (26.9)	10 (23.3)	3 (100)	11 (30.6)	3190 (80.5)
1	368 (26.1)	174 (7.8)	163 (71.8)	26 (60.5)	0 (0)	21 (58.3)	752 (19.0)
2	6 (0.4)	0 (0)	3 (1.3)	7 (16.3)	0 (0)	4 (11.1)	20 (0.5)
3	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.0)
Missing	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)
Tumor Type, N (%)							
Advanced MEL	1412 (100)	0 (0)	0 (0)	1 (2.3)	0(0)	0 (0)	1413 (35.6)
AdjMEL	0 (0)	2244 (100.0)	0 (0)	0 (0)	3 (100.0)	0 (0)	2247 (56.7)
Advanced ST	0 (0)	0 (0)	227 (100.0)	42 (97.7)	0 (0)	36 (100)	305 (7.7)
Treatment, N (%)							
Nivo Monotherapy	608 (43.1)	1350 (60.2)	215 (94.7)	23 (53.5)	2 (66.7)	26 (72.2)	2224 (56.1)
Nivo + Ipi 1 mg/kg Q3W	178 (12.6)	0 (0)	12 (5.3)	20 (46.5)	0 (0)	10 (27.8)	220 (5.5)
Nivo + Ipi 3 mg/kg Q3W	626 (44.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	626 (15.8)
Nivo + Ipi 1 mg/kg Q6W	0 (0)	894 (39.8)	0 (0)	0 (0)	1 (33.3)	0 (0)	895 (22.6)
Age (years)							
Mean (SD)	59 (13.5)	54.2 (13.9)	58.8 (15.6)	14.7 (1.71)	15.7 (0.577)	7 (2.69)	55.3 (15.3)
Median (Min, Max)	61 (18, 90)	55 (18, 89)	62 (18, 85)	15 (12, 17)	16 (15, 16)	8 (1, 11)	57 (1, 90)
Baseline Body Weight (kg)							
Mean (SD)	81.1 (18)	81.8 (18.3)	79.7 (19.6)	59.9 (16.7)	72.1 (19.8)	25.2 (15.2)	80.7 (19.1)
Median (Min, Max)	79.5 (37.4, 160)	80 (39, 183)	78.7 (32.8, 153)	58.2 (30.2, 99.4)	61.8 (59.6, 95)	23.3 (9.3, 99.6)	79.8 (9.3, 183)
Baseline eGFR (mL/min/1.73m^2)							
Mean (SD)	88.2 (18.1)	91.6 (17.3)	83.7 (25)	114 (27)	86.3 (9.48)	124 (28.7)	90.5 (18.9)
Median (Min, Max)	89.5 (35.5, 144)	92.4 (30.7, 139)	85.6 (31.2, 172)	114 (66.9, 179)	81.6 (80.1, 97.2)	122 (43.5, 202)	91.3 (30.7, 202)
Missing N (%)	5 (0.354)	6 (0.267)	2 (0.881)	N/A	N/A	N/A	13 (0.328)
Baseline LDH (U/L)							
Mean (SD)	343 (382)	210 (80.1)	225 (147)	N/A	142 (37.6)	N/A	260 (249)
Median (Min, Max)	222 (79, 5868)	186 (75, 954)	185 (91, 1106)	N/A	158 (99, 169)	N/A	195 (75, 5868)
Missing N (%)	18 (1.27)	26 (1.16)	26 (11.5)	43 (100)	N/A	36 (100)	149 (3.76)

Covariate	Adult MEL N = 1412	Adult AdjMEL N = 2244	Adult Others N = 227	Adolescent ST N = 43	Adolescent AdjMEL N = 3	Young Pediatric ST N = 36	Total N = 3965
Baseline Serum Albumin (g/dL)							
Mean (SD)	4.09 (0.542)	4.28 (0.388)	3.95 (0.447)	3.48 (1.42)	4.37 (0.764)	3.91 (0.715)	4.22 (0.43)
Median (Min, Max)	4.2 (2.1, 5.1)	4.3 (2.9, 6.2)	4 (2.3, 4.9)	3.3 (2.3, 5)	4.2 (3.7, 5.2)	4 (2.7, 4.7)	4.2 (2.1, 6.2)
Missing N (%)	1205 (85.3)	510 (22.7)	17 (7.49)	39 (90.7)	N/A	29 (80.6)	1800 (45.4)
Baseline Tumor Size (cm)							
Mean (SD)	7.37 (6.14)	N/A	11.7 (7.94)	8.87 (7.1)	N/A	7.77 (5.54)	7.94 (6.55)
Median (Min, Max)	5.4 (0.9, 38.4)	N/A	9.8 (1, 61.5)	5.55 (1, 26)	N/A	6.1 (1, 22)	6 (0.9, 61.5)
Missing N (%)	4 (0.283)	2244 (100)	17 (7.49)	7 (16.3)	3 (100)	7 (19.4)	2282 (57.6)
Baseline Lean Body Mass (kg)							
Mean (SD)	57 (10.8)	57.1 (10.8)	57.3 (11.1)	47.3 (9.37)	54.8 (14)	21.1 (9.5)	56.6 (11.4)
Median (Min, Max)	57.4 (31.7, 94.7)	57.2 (30.4, 105)	57.8 (27.8, 91.2)	47.1 (26.8, 67.9)	54.3 (41.1, 69.1)	20 (7.81, 62.1)	56.9 (7.81, 105)
Missing N (%)	38 (2.69)	43 (1.92)	16 (7.05)	0 (0)	0 (0)	0 (0)	97 (2.45)

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final

Program Source: Analysis-Directory/sas/Table3.3.1.5-1.sas

Source: analysis-directory/reports/Table3.3.1.5-1.rtf

Adult Others include NSCLC (N = 139), CRC (N = 18), RCC (N = 35), Prostate Cancer (N = 8), Ewing Sarcoma (N = 11), Osteosarcoma (N = 7), Rhabdomyosarcoma (N = 2), Neuroblastoma (N = 3), and other solid tumors (N = 4).

Young Pediatric (1 to < 12 years) ST includes Rhabdomyosarcoma (N = 11), Osteosarcoma (N = 1), Ewing Sarcoma (N = 3), Neuroblastoma (N = 15), and other solid tumors (N = 6).

Adolescent ST: Ewing Sarcoma (N = 7), Melanoma (N = 1), Neuroblastoma (N = 3), Osteosarcoma (N = 18), Rhabdomyosarcoma (N = 6), and other solid tumors (N = 8)

Model Development

The adolescent adjuvant treatment of melanoma PPK model development presented was based on the developed adolescent PPK full model in the advanced setting with additional data from subjects receiving adjuvant treatment of melanoma (including 3 adolescent subjects). The nivolumab PPK model was developed in 2 stages, as shown below:

1) Base Model: Re-estimated the base model parameters from the previously developed full model and applied the same time-varying CL for subjects receiving adjuvant treatment of melanoma. For the three adolescent adjuvant subjects, volume was set to be the same as adolescent solid tumour (ST) as no subject type effect on volume was detected in the previous study; clearance was treated the same as adult advanced melanoma.

2) Full Model: Time-varying CL was removed for all subjects receiving adjuvant treatment of melanoma based on the previous knowledge that CL is stationary for adult subjects with adjuvant treatment of melanoma. The focus of the full model was then to evaluate different grouping methods of the baseline clearance (CL0) and VC for the three adolescent adjuvant subjects.

Base Model

Base model development consisted of re-estimating parameters of the previously developed full model that had been developed to characterize nivolumab PK in adult, young paediatric (1 to < 12 years), and adolescent subjects.

The parameter estimates of the selected base model are provided in **Table 16**.

Table 16 Parameter Estimates of the Base 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	8.94	0.197 (2.2)	8.56 - 9.33
VC_{REF} [L]	θ_2	3.79	0.0415 (1.1)	3.71 - 3.87
Q_{REF} [mL/h]	θ_3	31.8	1.57 (4.92)	28.8 - 34.9
VP_{REF} [L]	θ_4	2.76	0.0498 (1.8)	2.66 - 2.86
CL_{WTB}	θ_7	0.665	0.03 (4.51)	0.606 - 0.723
CL_{GFR}	θ_9	0.15	0.0264 (17.6)	0.0982 - 0.202
CL_{FEMALE}	θ_{12}	-0.0972	0.0131 (13.4)	-0.123 - -0.0716
CL_PS_1	θ_{13}	0.208	0.0216 (10.4)	0.165 - 0.25
CL_{RAAA}	θ_{14}	0.148	0.0686 (46.5)	0.0131 - 0.282
CL_{RAAS}	θ_{15}	-0.0206	0.0419 (203)	-0.103 - 0.0615
$V1_{LBM}$	θ_{16}	0.951	0.0324 (3.4)	0.888 - 1.01
$V1_{FEMALE}$	θ_{17}	0.0525	0.0187 (35.7)	0.0158 - 0.0892
$EMAX_{REF}$	θ_{18}	-0.0772	0.0117 (15.1)	-0.1 - -0.0543
$T50$ [h]	θ_{19}	2130	161 (7.54)	1820 - 2450
$HILL$	θ_{20}	4.62	0.807 (17.5)	3.04 - 6.2
CL_{ADJMEL}	θ_{21}	-0.305	0.0198 (6.5)	-0.344 - -0.266
CL_{OTH}	θ_{22}	0.0251	0.0348 (139)	-0.0431 - 0.0933
CL_{ADOST}	θ_{23}	-0.189	0.0874 (46.3)	-0.36 - -0.0173
CL_{PEDST}	θ_{24}	-0.533	0.0883 (16.6)	-0.706 - -0.36
CL_{I1Q3}	θ_{25}	0.0683	0.0352 (51.5)	-0.000619 - 0.137
CL_{I3Q3}	θ_{26}	0.325	0.0255 (7.86)	0.275 - 0.375
$EMAX\_PS_1$	θ_{28}	-0.181	0.0261 (14.4)	-0.232 - -0.13
$EMAX_{IPICO}$	θ_{29}	-0.0606	0.0171 (28.2)	-0.094 - -0.0271
$V1_{PED}$	θ_{30}	-0.108	0.0473 (43.7)	-0.201 - -0.0156
$V1_{ADO}$	θ_{31}	-0.155	0.0375 (24.2)	-0.229 - -0.0817
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.0924 (0.304)	0.00434 (4.69)	0.0839 - 0.101
ZVC [-]	$\omega_{2,2}$	0.0939 (0.306)	0.0067 (7.14)	0.0807 - 0.107
$ZEMAX$ [h]	$\omega_{4,4}$	0.0362 (0.190)	0.00499 (13.8)	0.0264 - 0.046
$ZCL:ZVC$	$\omega_{1,2}$	0.0237 (0.254)	0.00234 (9.87)	0.0191 - 0.0282
Residual Error				
$PERR$ [-]	θ_6	0.206	0.00286 (1.39)	0.2 - 0.211
$RESERR^f$	$\sigma_{1,1}$	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/base/reports/base_RTF.rtf

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject with melanoma, receiving nivolumab monotherapy, 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 nivolumab monotherapy 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: 10.5; ETA_VC: 28.1; ETA_EMAX: 46.5; EPS shrinkage (%): 14.8.

Note 3: The condition number for the base model is 172

[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

Full Model

Full model development started with evaluating the stationary CL of subjects receiving adjuvant treatment of melanoma (Full1). The Full1 model improved the description of the data relative to the base model, in which adjuvant treatment of melanoma was treated as time-varying CL.

Further full model development focused on evaluating different grouping methods of the CL0 and volume of VC for the three adolescent adjuvant subjects. Six full models as described in the methods section and in **Table 17** were tested.

Table 17 Selection of Nivolumab Population Pharmacokinetic Full Models

Model No.	Model Description (Covariate Effects)			Parameter Number	OFV	BIC	ΔBIC[a]
	Effect on Baseline CL	Effect on EMAX	Effect on VC				
Full1	WTB, baseline eGFR, Sex, PS, Race, and subject type (Adult Others, Pediatric ST, Adult Adjuvant MEL, Adolescent ST), Combination (I1Q3, I3Q3), CL of Adolescent adjuvant MEL equal to adult adjuvant MEL	PS, Combination (ipi)	LBM, Sex, Subject type (Adolescent, Pediatric), VC of Adolescent Adjuvant MEL equal to adolescent ST	30	143808	144111	0
Full2	Same as Full1 except CL of Adolescent adjuvant MEL equal to adolescent ST	Same as Full1	Same as Full1	30	143813	144116	5
Full3	Same as Full1 except estimating unique CL0 of adolescent adjuvant MEL	Same as Full1	Same as Full1	31	143806	144119	8
Full4	Same as Full1 except estimating unique CL0 of adolescent adjuvant MEL	Same as Full1	Same as Full1except estimating unique VC of adolescent adjuvant MEL	32	143803	144127	15
Full5 (selected)	**Same as Full1 except CL of Adolescent adjuvant MEL parameterized to be equal to the multiplication of the effects of adult adjuvant MEL and adolescent ST**	**Same as Full1**	**Same as Full1**	**30**	**143806**	**144109**	**-2**
Full6	Same as Full1 except CL of Adolescent adjuvant MEL equal to the multiplication of the effects of adult adjuvant MEL and adolescent ST	Same as Full1	Same as Full1except estimating unique VC of adolescent adjuvant MEL	31	143804	144117	6

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
Program Source: Analysis-Directory/R/scripts/2-model-dev.Rmd
Source: Analysis-Directory/R/export/model.bic.csv
Note 1: Model selected is shown in bold font.
Note 2: Base model is not shown in this table and BIC value is 144793.
Note 3: Stationary CL for adolescent and adult adjuvant treatment of melanoma in Full model 1 through 6.
[a] Difference between BIC of a model and BIC of the reference model (Full1)

As described in the above section, full5 was selected as the full model for model application. The value of CL for subject *i* in full model is given by:

$$CL_i(t) = CL0_{TV,i} \times \exp\left(\frac{EMAX_i * t^{HILL}}{T50^{HILL} + t^{HILL}}\right) \times e^{\eta_{CL,i}},$$

where

$$CL0_{TV,i} = CL0_{REF} \times \left(\frac{WTB_i}{WTB_{REF}}\right)^{CL_{WTB}} \times \left(\frac{eGFR_i}{eGFR_{REF}}\right)^{CL_{eGFR}} \times e^{CL_{SEX}\,(\text{if female})} \times e^{CL_{PS}\,(\text{if PS}>0)}$$
$$\times e^{CL_{RAAA}\,(\text{if RACE is AA})} \times e^{CL_{RAAS}\,(\text{if RACE is Asian})}$$
$$\times e^{CL_{OTH}\,(\text{if POP is Adult Others})} \times e^{CL_{PEDST}\,(\text{if POP is Pediatric <12yrs ST})}$$
$$\times e^{CL_{ADOST}\,(\text{if POP is Adolescent 12-17yrs ST})} \times e^{CL_{ADJMEL}\,(\text{if POP is Adult adjuvant melanoma})}$$
$$\times e^{CL_{I1Q3}\,(\text{if nivo + ipi 1 mg/kg Q3W})} \times e^{CL_{I3Q3}\,(\text{if nivo + ipi 3 mg/kg Q3W})}$$

and the value of EMAX is given by:

for adult or adolescent adjuvant treatment of melanoma

$$EMAX_i = 0,$$

for other subject types

$$EMAX_i = EMAX_{REF} + EMAX_{PS}(\text{if PS} > 0) + EMAX_{COMBO}(\text{if nivo + ipi combination}) + \eta_{\text{EMAX},i}$$

The value of VC for subject *i* is given by:

$$VC_i = VC_{REF} \times \left(\frac{LBM_i}{LBM_{REF}}\right)^{VC_{LBM}} \times e^{VC_{\text{SEX}}\,(\text{if female})} \times e^{VC_{ADO}\,(\text{if POP is 12-17 yrs})} \times e^{VC_{PED}\,(\text{if POP <12 yrs})} \times e^{\eta_{VC,i}}$$

The values of Q and VP for subject *i* are given by:

$$Q_i = Q_{REF} \times \left(\frac{WTB_i}{WTB_{REF}}\right)^{Q_{WTB}} \times e^{\eta_{Q,i}}$$

$$VP_i = VP_{REF} \times \left(\frac{LBM_i}{LBM_{REF}}\right)^{VP_{LBM}} \times e^{\eta_{VP,i}}$$

In these equations, CL_{REF} is the typical value of CL at time 0 (CL0) at the reference values of WTB (75 kg), LBM (55 kg), age (60 years), PS (PS = 0), baseline eGFR (90 mL/min/1.73 m2), sex (male), race (White), and subject type (adult melanoma); VC_{REF} is the typical value of VC at the reference values of LBM (55 kg), sex (male), and subject type (all adults); Q_{REF} and VP_{REF} are typical values of Q and VP at the reference values of WTB and LBM, respectively; and $EMAX_{REF}$ represents the typical value of EMAX at the reference value of PS (PS = 0), subject type (adult melanoma), and nivolumab monotherapy. T50 represents the time at which the change in CL is 50% of EMAX, and *HILL* represents the sigmoidicity of the relationship with time.

Categorical age effect of adolescent (≥ 12 to < 18 years) and young paediatric (1 to < 12 years) subjects on CL and VC were separated because adolescent subjects were the subject type of interest for the paediatric dose simulation as specified previously,1 and there was a significant paediatric (all < 18 years) effect on CL and VC.

Parameter estimates for the full model are presented in **Table 18**, and the covariate effects are shown in **Figure 18**.

Table 18 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 nivolumab monotherapy, 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 nivolumab monotherapy 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 18 Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters

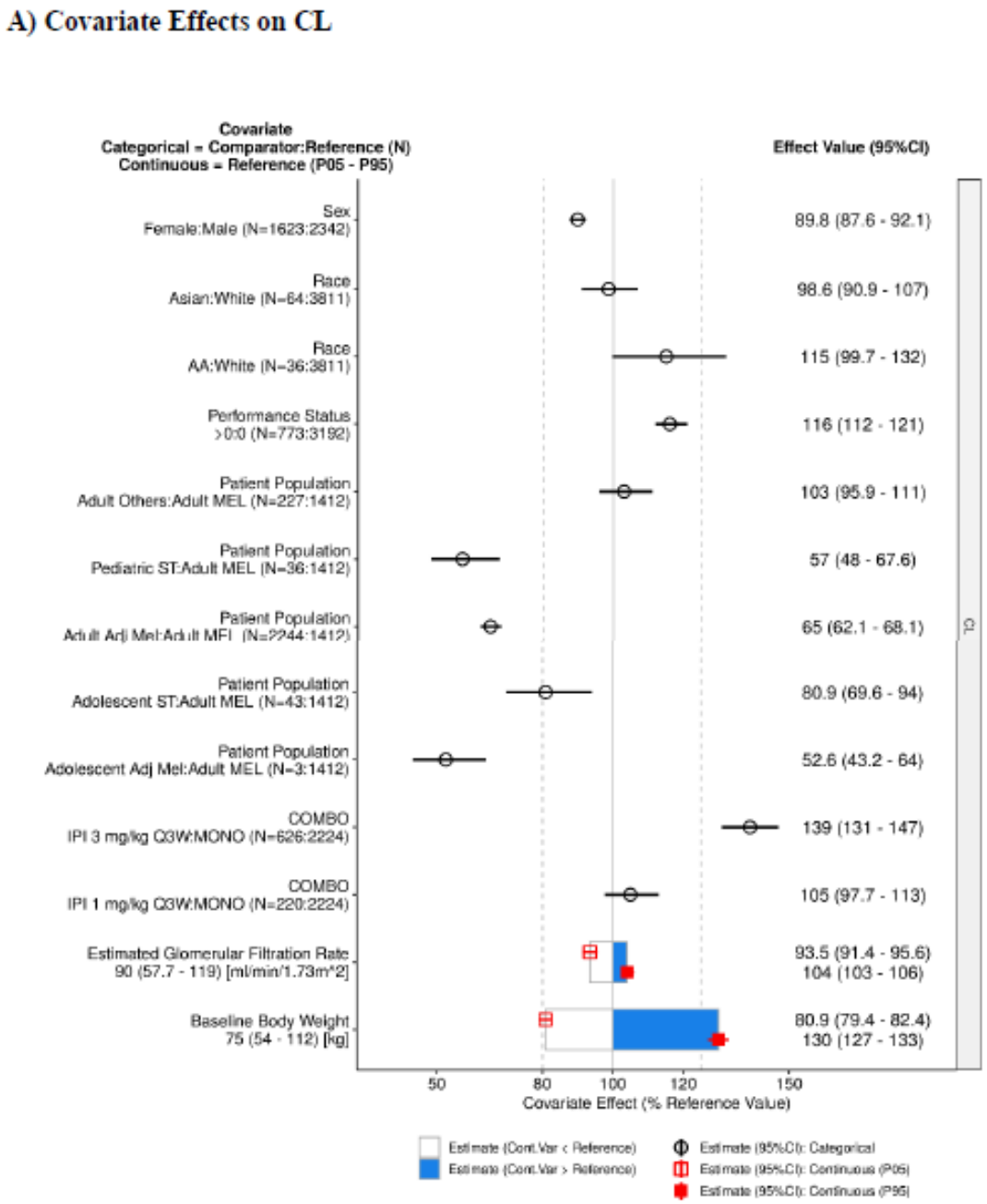
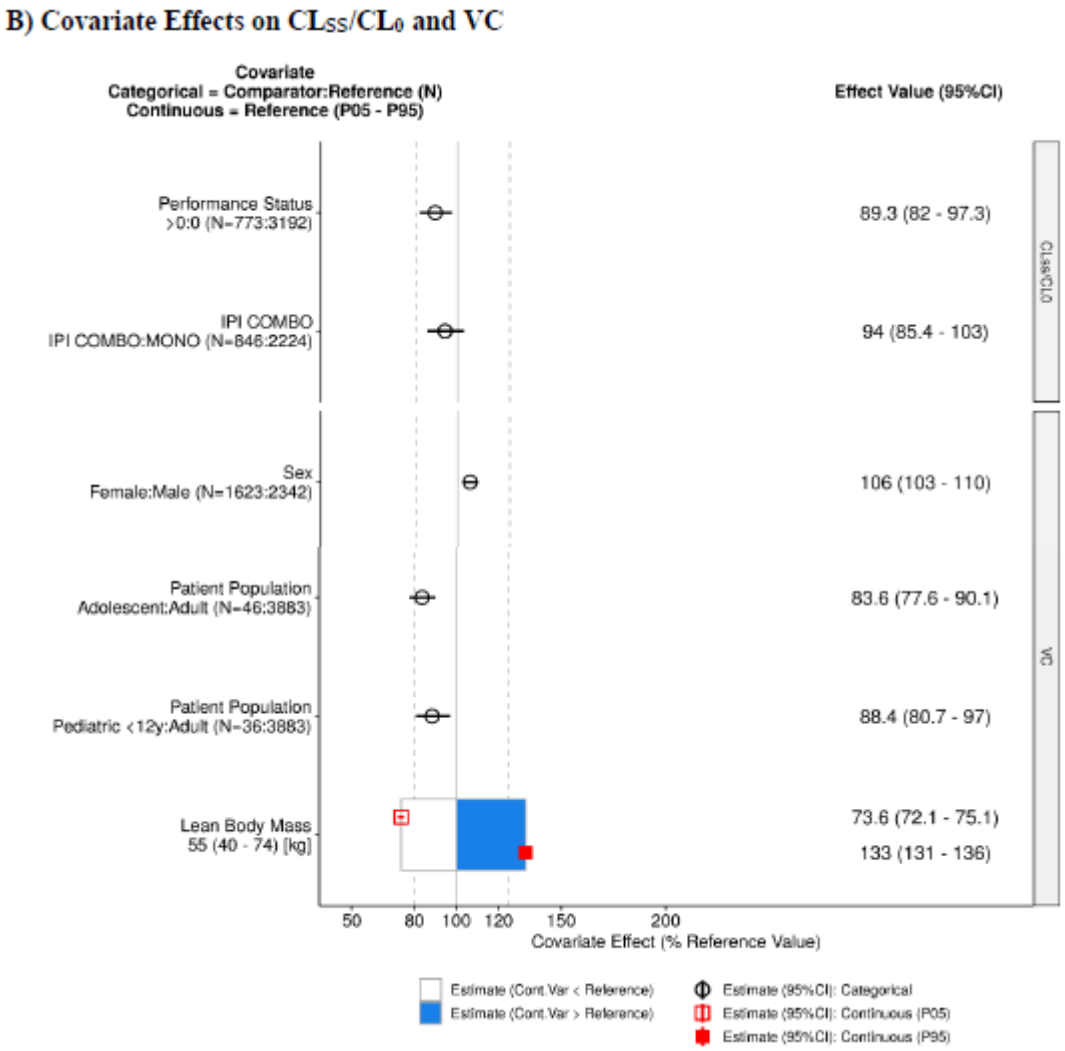


Figure 19 Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters



Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
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 nivolumab monotherapy, 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

Model Evaluation

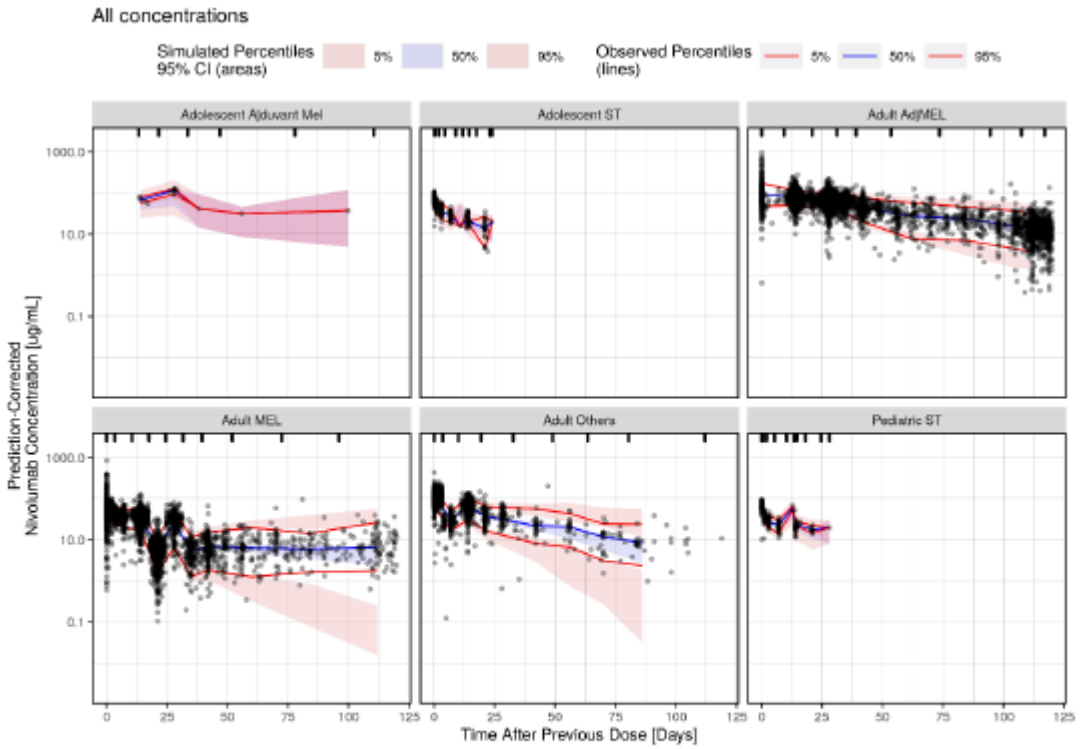
Prediction-Corrected VPCs

Model evaluation was performed using a prediction-corrected visual predictive check (pcVPC) to provide a graphical assessment of the agreement between the time course of model predictions and observations.

The predictive performance of the nivolumab full model was evaluated using a VPC stratified by subject type. The pcVPC plots for Adolescent adjuvant treatment of melanoma, Adolescent solid tumour, Adult

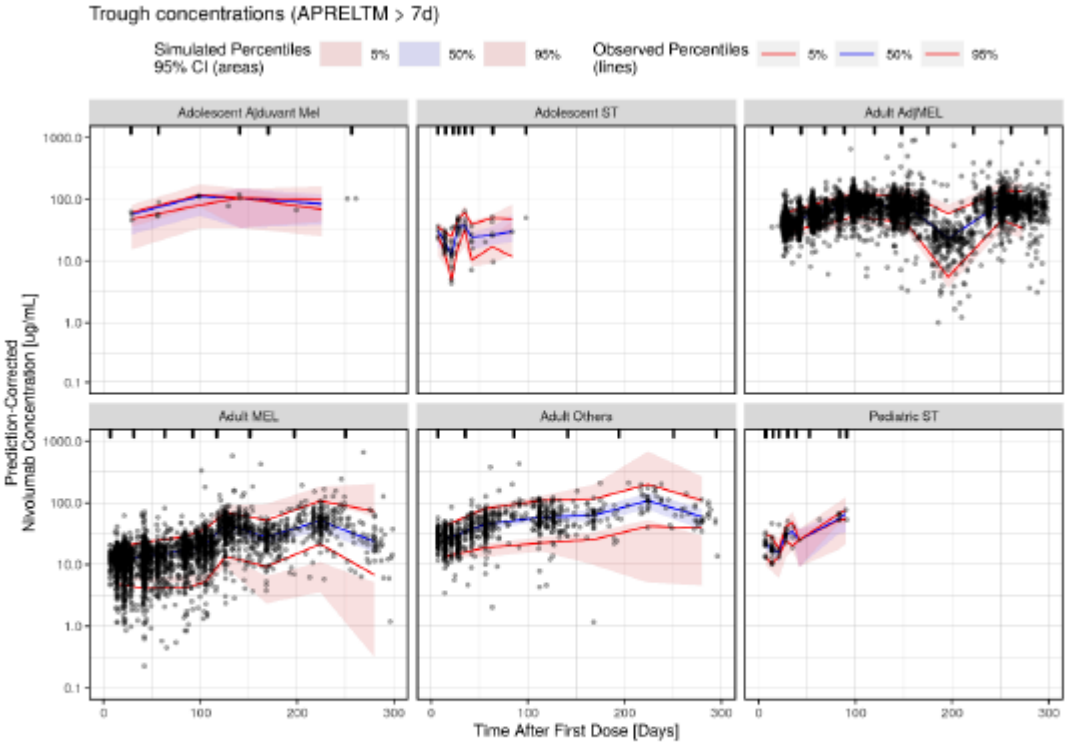
adjuvant treatment of melanoma, Adult melanoma, Adult Others, and Young Paediatric (1 to < 12 years) solid tumour are shown in **Figure 20** and **Figure 21**.

Figure 20 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

Figure 21 Prediction-Corrected Visual Predictive Check of Trough Nivolumab Concentrations versus Actual Time after First 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-trough.png

Model Application

Comparison of PK Parameters Among Patient Populations

Nivolumab PK parameters in adult, adolescent and young paediatric (1 to < 12 years) patient populations are summarized in below.

Comparison of Nivolumab PK Parameters Between Adult and Paediatric Patient Population

Table 19 Comparison of Nivolumab PK Parameters among Adult Advanced Melanoma (MEL), Adult Adjuvant Melanoma (AdjMEL), Adolescent Solid Tumour (ST), and Adolescent Adjuvant Melanoma (AdjMEL)

Parameters	Adult MEL Geo. Mean (%CV) (N = 1412, G1)	Adult AdjMEL Geo. Mean (%CV) (N = 2244, G2)	Adolescent ST Geo. Mean (%CV) (N = 43, G3)	Adolescent AdjMEL Geo. Mean (%CV) (N = 3, G4)	% Diff GM (G4-G2)[a]	% Diff GM (G3-G1)[b]	% Diff GM (G4-G3)[c]
CL0 (mL/h)	11.5(48.9)	6.27(30.8)	7.7(36.8)	4.21(38.3)	-32.9	-33	-45.3
CLss (mL/h)	8.48(69.6)	6.27(30.8)	5.36(39.1)	4.21(38.3)	-32.9	-36.8	-21.5
VC (L)	3.94(27.1)	3.98(25.3)	2.8(29.6)	2.69(34.1)	-32.4	-28.9	-3.93
VP (L)	2.77(23.4)	2.93(25.6)	2.36(23.3)	2.33(34.4)	-20.5	-14.8	-1.27
VSS (L)	6.77(22.6)	6.94(24)	5.18(24.5)	5.02(34.2)	-27.7	-23.5	-3.09
PEMAX (%)	73.6(34.5)	100(0)	69.7(6.83)	100(0)	0	-5.3	43.5

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/export/param-stats-with diff.csv
VSS was calculated using formula: VSS=VC+VP.
PEMAX was a percentage of maximal CL change from baseline and was calculated as (exp(EMAX))*100.
GM = geometric mean
a Percent difference in geometric mean (GM) of Adolescent Adj MEL (G4) relative to Adult Adj MEL (G2).
b Percent difference in geometric mean (GM) of Adolescent ST (G3) relative to Adult MEL (G1).
c Percent difference in geometric mean (GM) of Adolescent Adj MEL (G4) relative to Adolescent ST (G3).

Simulation of Paediatric Exposures for **adolescent subjects receiving adjuvant treatment of melanoma**

Nivolumab exposures were simulated using stochastic simulations for adolescent subjects (≥ 12 to < 18 years) receiving adjuvant treatment of melanoma with selected dose regimens of nivolumab alone to identify doses that produce similar nivolumab exposures to the adult adjuvant treatment of melanoma population with the approved dose regimens: 240 mg Q2W and 480 mg Q4W.

Nivolumab Monotherapy Regimens Simulated in Adolescent Adjuvant Treatment of Melanoma (with a * to indicate the adolescent recommended dose):

Flat Dosing

-240 mg Q2W (≥ 40 kg) or 3 mg/kg Q2W (< 40 kg)*

-480 mg Q4W (≥ 40 kg) or 6 mg/kg Q4W (< 40 kg)*

Body Weight Based Dosing

-3 mg/kg Q2W

-6 mg/kg Q4W

Body Weight Based Dosing with Dose Cap

-3 mg/kg (up to 240 mg) Q2W

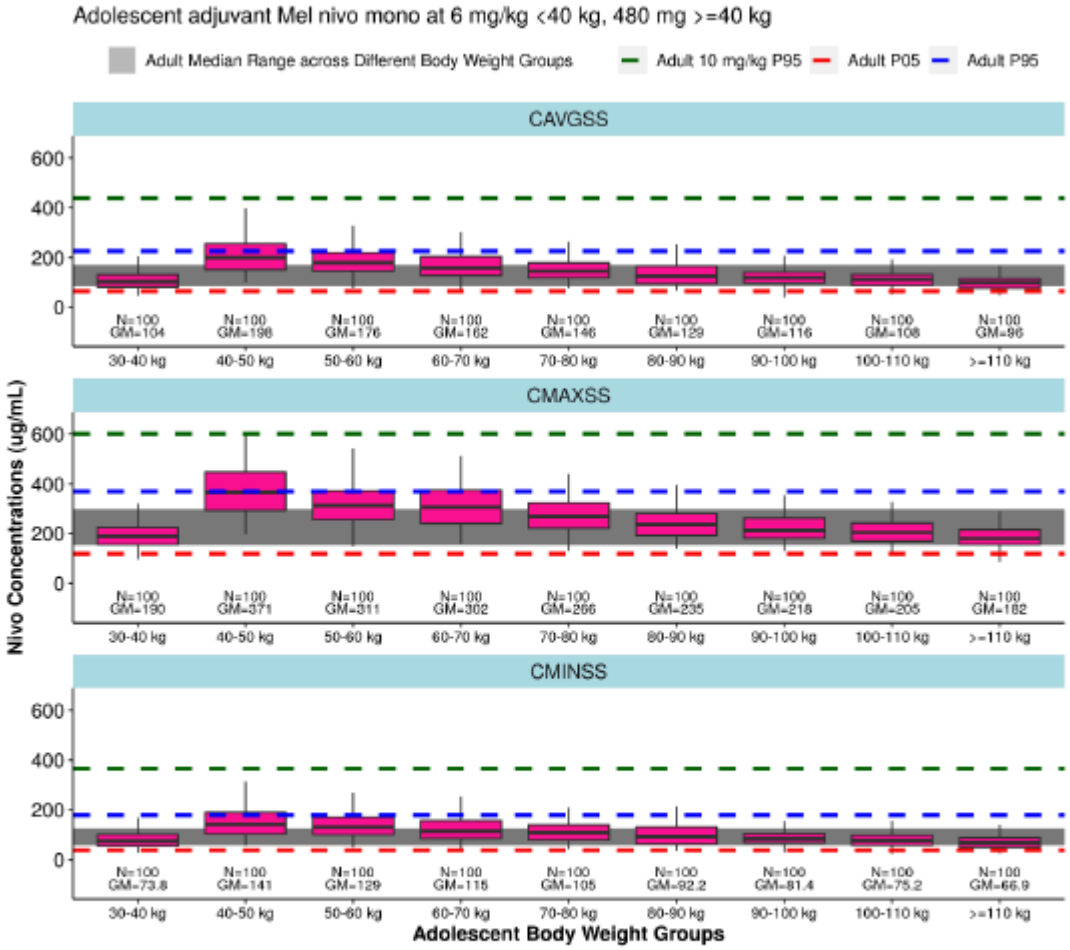
-6 mg/kg (up to 480 mg) Q4W

Flat Dosing

Figure 22 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W Nivolumab Monotherapy

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/plots/expo-adol-sto-adjmel-mono-240-03.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. The green dashed line represents the 95% percentile of the observed adult exposure upon 10 mg/kg Q2W dose. GM is geometric mean.

Figure 23 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W Nivolumab Monotherapy



Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/

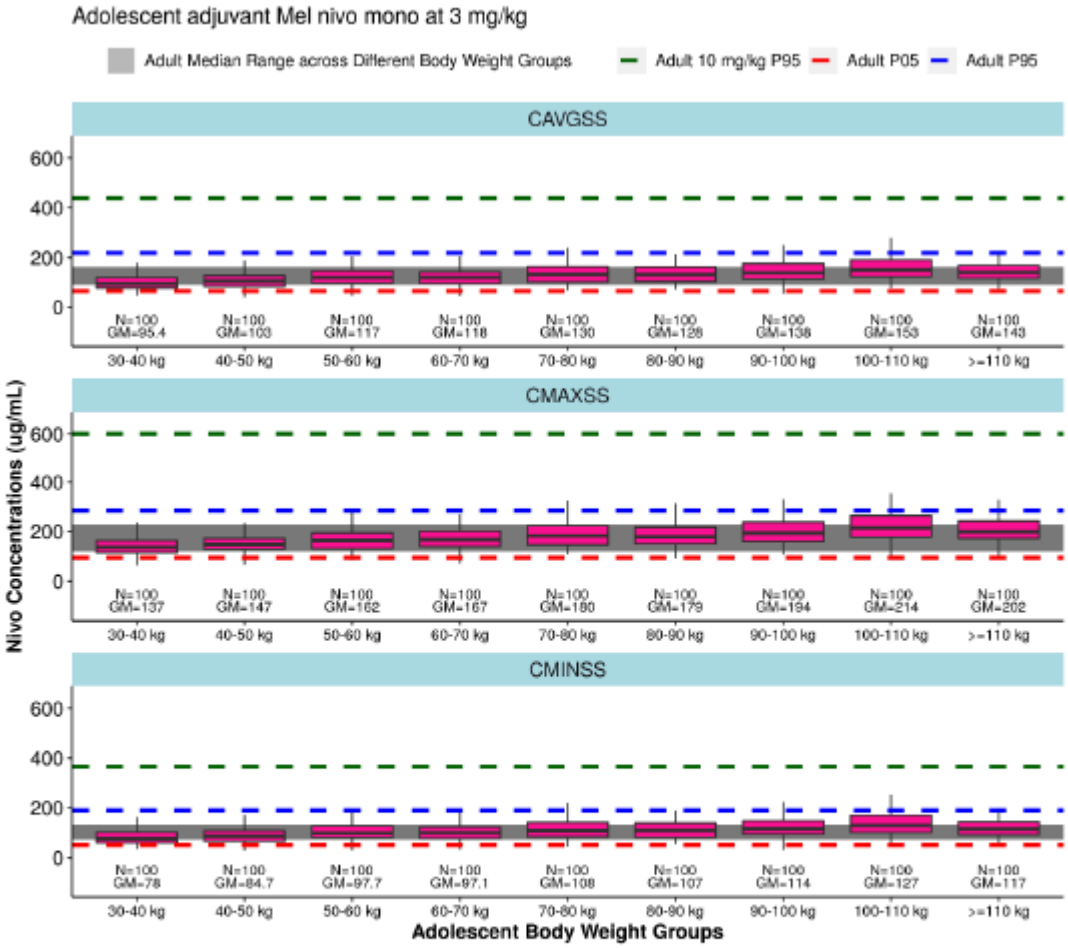
R-Program Source: Analysis-Directory/R/scripts/5-simulation-nivo.Rmd

Source: Analysis-Directory/R/plots/expo-adol-sto-adjmel-mono-480-06.png

Note: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. The green dashed line represents the 95% percentile of the observed adult exposure upon 10 mg/kg Q2W dose. GM is geometric mean.

Body Weight Based Dosing

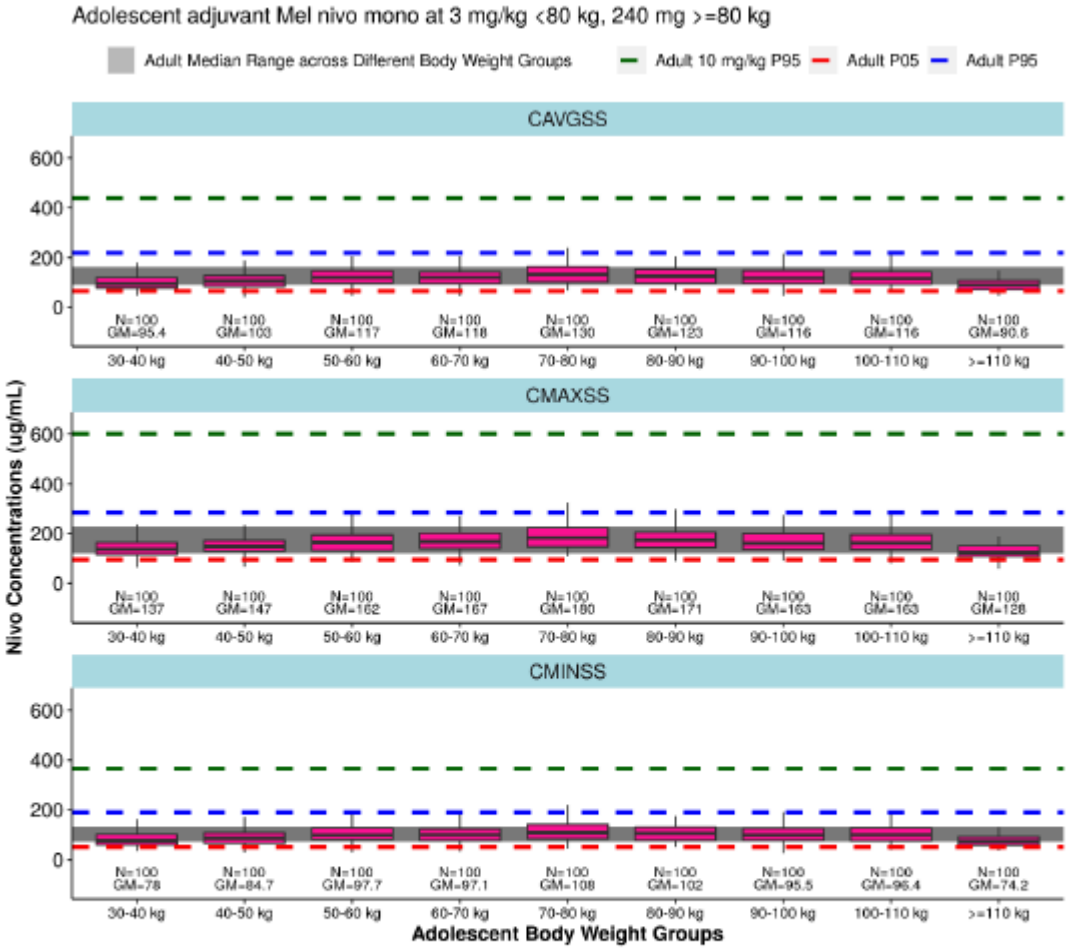
Figure 24 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 3 mg/kg Q2W Nivolumab Monotherapy



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/plots/expo-adol-sto-adjmel-mono-3mg.png
Note: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. The green dashed line represents the 95% percentile of the observed adult exposure upon 10 mg/kg Q2W dose. GM is geometric mean.

Figure 25 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 3 mg/kg up to 240 mg Q2W Nivolumab Monotherapy



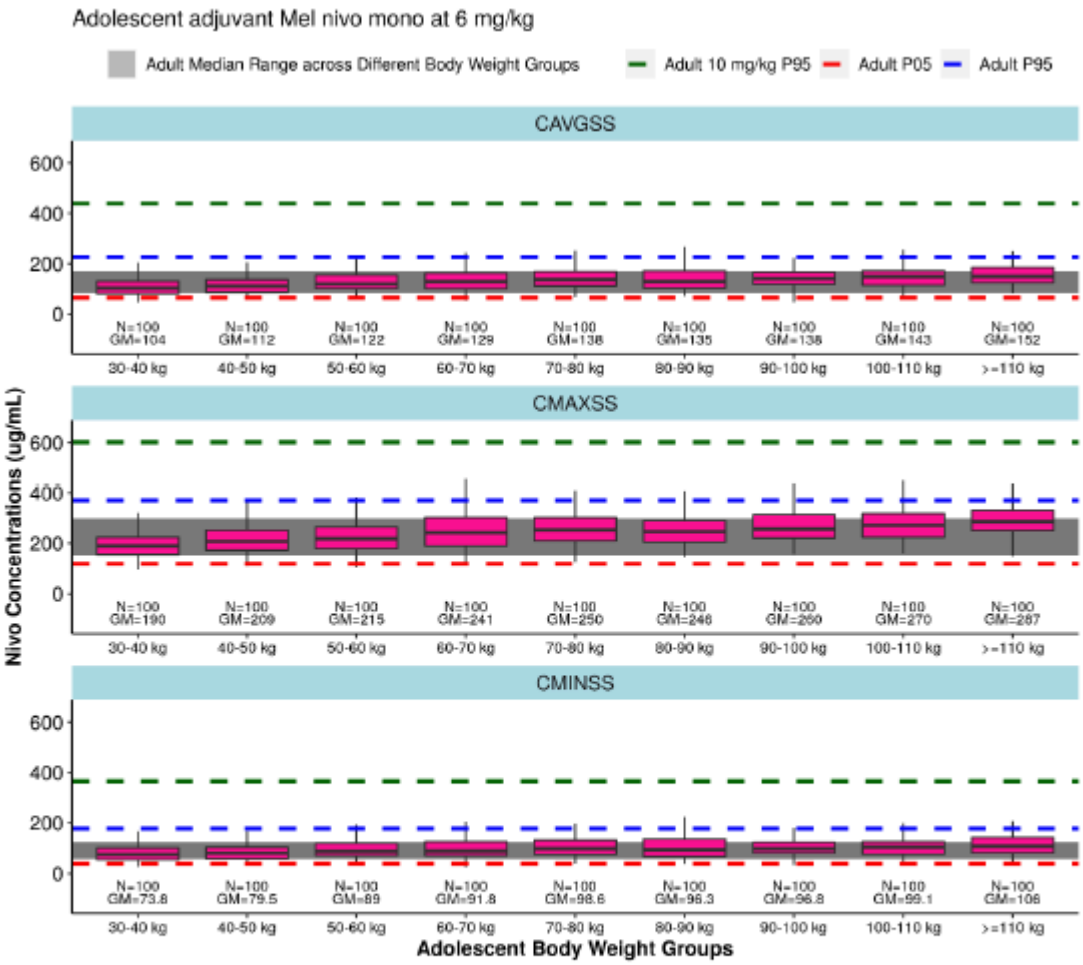
Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/

R-Program Source: Analysis-Directory/R/scripts/5-simulation-nivo.Rmd

Source: Analysis-Directory/R/plots/expo-adol-sto-adjmel-mono-240-cap.png

Note: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. The green dashed line represents the 95% percentile of the observed adult exposure upon 10 mg/kg Q2W dose. GM is geometric mean.

Figure 26 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 6 mg/kg Q4W Nivolumab Monotherapy



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/plots/expo-adol-sto-adjmel-mono-6mg.png

Note: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. The green dashed line represents the 95% percentile of the observed adult exposure upon 10 mg/kg Q2W dose. GM is geometric mean.

Figure 27 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 6 mg/kg up to 480 mg Q4W Nivolumab Monotherapy

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/plots/expo-adol-sto-adjmel-mono-480-cap.png

Note: Gray shaded area indicates the adult median exposure range across body weight groups. Red and Blue dashed lines indicate the adult exposure range of 5th percentile and 95th percentile. The green dashed line represents the 95% percentile of the observed adult exposure upon 10 mg/kg Q2W dose. GM is geometric mean.

Immunogenicity

Immunogenicity was evaluated from the detection of nivolumab and ipilimumab Anti-Drug Antibody (ADA) and characterization of neutralising antibody (NAb). 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 time points, 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 time point.

Other Positive: Not persistent but some ADA-positive samples with the last 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.

Table 20 Studies Evaluating Immunogenicity

Study	Population	Doses Administered	Drug Treatment Duration	No. of subjects (All Treated)	Immunogenicity Sampling Times
CA209070	Young pediatric, adolescent, and young adult subjects with solid tumors or Hodgkin lymphoma/non-Hodgkin lymphoma	**Part A/B:** Nivo 3 mg/kg Q2W **Part C:** **Dose level 1:** Nivo 1 mg /kg + Ipi 1 mg/kg Q3W for Cycles 1 to 4 followed by nivo 3 mg/kg Q2W for Cycles 5+ **Dose level 2:** Nivo 3 mg /kg + Ipi 1 mg/kg Q3W for Cycles 1 to 4 followed by nivo 3 mg/kg Q2W for Cycles 5+ **Part D:** Nivo 3 mg /kg + Ipi 1 mg/kg Q3W for Cycles 1 to 4 followed by nivo 3 mg/kg Q2W for Cycles 5+	Until progression or unacceptable toxicity	Nivo: N=80 Nivo + ipi: N=46	Parts A and B: prior to Day 1 nivolumab infusion in each cycle Parts C and D: prior to Day 1 nivolumab infusion in each cycle for ADA assessment of both nivolumab and ipilimumab

Source: CA209070 Interim CSR[4]

Table 21 Anti-Drug Antibody Assessments Summary by Treatment and Dose Level - All Immunogenicity Subjects from CA209070

	Nivo 3 mg/kg	Nivo + Ipi					
		Total		Nivo 1 mg/kg + Ipi 1 mg/kg		Nivo 3 mg/kg + Ipi 1 mg/kg	
Subject ADA Status (%)	Nivolumab ADA N = 51	Nivolumab ADA N = 35	Ipilimumab ADA N = 33	Nivolumab ADA N = 2	Ipilimumab ADA N = 2	Nivolumab ADA N = 33	Ipilimumab ADA N = 31
BASELINE ADA POSITIVE	3 (5.9)	2 (5.7)	1 (3.0)	0	0	2 (6.1)	1 (3.2)
ADA POSITIVE	1 (2.0)	1 (2.9)	0	1 (50.0)	0	0	0
PERSISTENT POSITIVE (PP)	0	0	0	0	0	0	0
NOT PP - LAST SAMPLE POSITIVE	1 (2.0)	1 (2.9)	0	1 (50.0)	0	0	0
OTHER POSITIVE	0	0	0	0	0	0	0
NEUTRALIZING POSITIVE	0	0	0	0	0	0	0
ADA NEGATIVE	50 (98.0)	34 (97.1)	33 (100.0)	1 (50.0)	2 (100.0)	33 (100.0)	31 (100.0)

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 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.
Post-baseline assessments are assessments reported after initiation of treatment.
Source: refer to Table 11.1.1-1 of the CA209070 CSR[4]

2.3.3. PK/PD modelling

The purpose of the Exposure-Response (E-R) analysis described in this report is to evaluate the potential impact of higher nivolumab exposures in adolescents with melanoma on safety when using the approved adult dosing regimens.

The E-R relationship for safety was characterized with respect to Grade 2+ immune mediated adverse event (Gr2+ IMAEs). The E-R relationship was characterized with data from nivolumab monotherapy, ipilimumab monotherapy, and nivolumab + ipilimumab combination therapy studies in adult, young paediatric (< 12 years) and adolescent (≥ 12 to < 18 years) subjects across solid tumours, including advanced melanoma and melanoma in the adjuvant setting.

The endpoint of time to Gr2+ IMAEs was selected to reflect AEs that are specific to cancer immunotherapy due to the increased activity of the immune system from the treatment.

Based on previous analyses, the endpoint of time to Gr2+ IMAEs was more sensitive to exposure changes and informed on more proximal mechanistic, immunomodulatory effects on safety, compared with Gr3+ AEs and Gr2+ TRAEs. Therefore, the Gr2+ IMAE endpoint was selected to characterize the combined paediatric and adult E-R of safety and to predict the impact on adolescent safety for different adolescent dosing regimens.

Time-varying daily Cavg (referred to hereafter as daily Cavg) of nivolumab and ipilimumab derived from the PPK analysis, was used as the measure of exposure.

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 nivolumab + ipilimumab. There were 42 young paediatric subjects (< 12 years) and 55 adolescent (≥ 12 to < 18 years) subjects included in the dataset.

The analysis population included data from all subjects for whom nivolumab and/or ipilimumab exposure measures determined by the PPK analysis were available. All adult and paediatric subjects who received ipilimumab 10 mg/kg Q3W in the advanced melanoma setting were excluded to focus on regimens relevant to the approved adult advanced melanoma regimens.

Adult subjects who received nivolumab 3 mg/kg and ipilimumab 1 mg/kg (N3I1) Q3W for 4 doses from Study CA209511 were also excluded due to the biased predictions for this adult dosing regimen during the initial model development. Exclusion of these regimens did not impact the ability to predict Gr2+IMAEs for the adolescent dosing regimens being considered in advanced and adjuvant treatment of melanoma.

Nivolumab and ipilimumab exposure measures for advanced melanoma in adults and adolescents were simulated using the EBEs of individual PK parameters based on a previous PPK analysis that characterized the PK of nivolumab monotherapy and combination with ipilimumab in adolescent subjects with advanced metastatic melanoma.

Nivolumab and ipilimumab exposure measures for Study CA209511 were obtained from a previous PPK analysis. Ipilimumab exposures measures for advanced melanoma from Study CA184169 were obtained from a previous PPK analysis.

Table 22 Subjects in the Exposure-Response of Gr2+ IMAEs Analysis Dataset

Treatment Group	Study	Subjects			
		Treated Subjects, N	Excluded Due to Missing Exposure, N (%)	Excluded Study/Treatment Group,[a] N (%)	Included in Analysis, N (%)
Nivolumab Monotherapy	CA209003	107	1 (0.9)	0 (0.0)	106 (99.1)
	CA209066	206	28 (13.6)	0 (0.0)	178 (86.4)
	CA209067	313	3 (1.0)	0 (0.0)	310 (99.0)
	CA209070	60	0 (0.0)	0 (0.0)	60 (100.0)

	CA209238	452	4 (0.9)	0 (0.0)	448 (99.1)
	CA209915	917	13 (1.4)	0 (0.0)	904 (98.6)
Ipilimumab Monotherapy	CA184004	82	1 (1.2)	42 (51.2)	39 (47.6)
	CA184008	155	0 (0.0)	155 (100.0)	0 (0.0)
	CA184022	214	21 (9.8)	71 (33.2)	122 (57.0)
	CA184070	33	1 (3.0)	13 (39.4)	19 (57.6)
	CA184169	726	18 (2.5)	364 (50.1)	344 (47.4)
	CA184178	12	0 (0.0)	8 (66.7)	4 (33.3)
	CA209067	311	0 (0.0)	0 (0.0)	311 (100.0)
Nivolumab + Ipilimumab Combination	CA209004	64	1 (1.6)	0 (0.0)	63 (98.4)
	CA209067	313	3 (1.0)	0 (0.0)	310 (99.0)
	CA209069	94	20 (21.3)	0 (0.0)	74 (78.7)
	CA209070	46	4 (8.7)	0 (0.0)	42 (91.3)
	CA209511	358	12 (3.4)	173 (48.3)	173 (48.3)
	CA209915[b]	916	916 (100.0)	0 (0.0)	0 (0.0)
Total		5379	1046 (19.4)	826 (15.4)	3507 (65.2)

[a] Adult and pediatric subjects who received ipilimumab 10 mg/kg Q3W for 4 doses and adults that received the combination regimen of nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W for 4 doses from Study CA209511 were excluded. All of Study CA184008 only contained subjects that received ipilimumab 10 mg/kg Q3W; therefore, the whole study was excluded.

[b] CA209915 for the combination was excluded due to the simulation of ipilimumab exposure from the PPK analysis not being available.

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final
Program Source: Analysis-Directory/sas/subj-er-safety.sas
Source: Analysis-Directory/reports/Table3.2.1.1-1.rtf

The following variables were included in the safety E-R analysis dataset:

- Exposure variables: daily Cavg
- Response variables: time to first occurrence of Gr2+ IMAEs
- Baseline demographic variables: age, sex, and race
- Baseline clinical laboratory variables: baseline LDH
- Baseline disease characteristics: PD-L1 expression, PS, tumour setting, line of therapy, and treatment
- Other: WTB

IMAEs are specific events (or groups of MedDRA preferred terms (PTs) describing specific events) that include diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrine disorders (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus).

The ipilimumab studies reported immune mediated adverse events (IRAEs), which are closely related to IMAEs. IRAEs were defined using a predefined list of MedDRA high level group terms, high-level terms, and PTs. Six subcategories of IRAEs were reported: gastrointestinal, liver, skin, endocrine, neurological, and other.

Model development

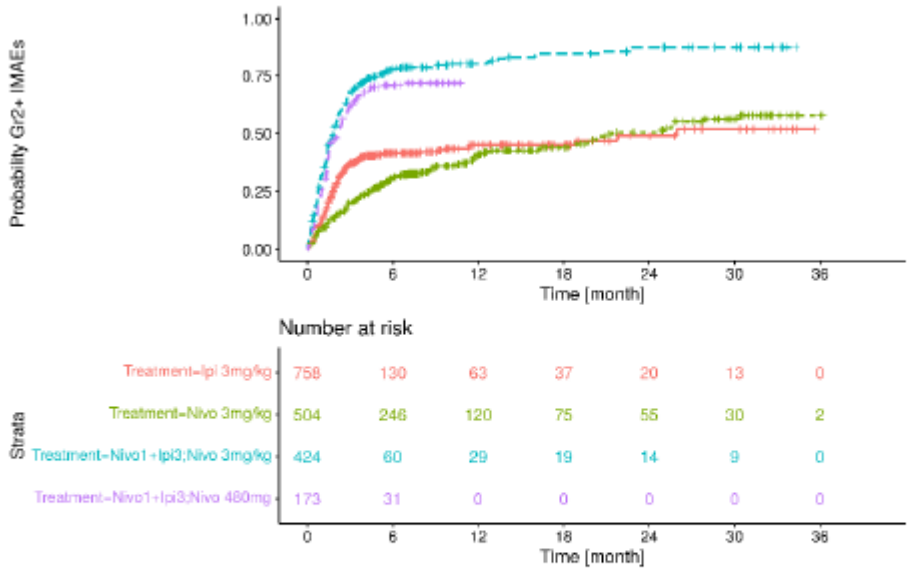
The relationship between nivolumab and/or ipilimumab exposure (daily Cavg) and time to first occurrence of Gr2+ IMAEs was characterized by a semi-parametric stratified Cox Proportional-Hazards (CPH) model.

Full Model

- Stratified (nivolumab, ipilimumab, and combination) and unstratified models were tested
- A stratified CPH model was used to account for different baseline hazard across treatment groups.
- Evaluated linear and log transformed nivolumab and ipilimumab exposure (daily Cavg) in the full model, which included pre-specified covariates; linear function for daily nivolumab and ipilimumab Cavg with interaction was included in the E-R model as evidenced by the lowest value in BIC.
- Assessed the impact of the following covariates on Gr2+ IMAEs:
  - Continuous covariates: age, body weight, and baseline LDH
  - Categorical covariates: PD-L1 status (5% cutoff), sex, PS, tumor setting, line of therapy, race
  - The interaction of the significant covariates with nivolumab and ipilimumab exposure

A treatment, stratified CPH model was evaluated using nivolumab monotherapy, ipilimumab monotherapy and nivolumab + ipilimumab combination and compared to an unstratified model. The treatment stratified model was suggested by the differences in the observed cumulative probability curves across these treatments (**Figure 28**) and the fact that all ipilimumab monotherapy studies may have a different baseline hazard given the use of a slightly different definition for immune mediated adverse events (IRAEs) as compared to the other treatments that used IMAE definitions.

Figure 28 Kaplan-Meier Plot of Gr2+ IMAEs by Selected Treatment Regimen in Adult Advanced Melanoma



Note: Nivo1+Ipi3;Nivo 480 mg (Nivo 1 mg/kg and Ipi 3mg/kg combination Q3W 4 doses, maintenance dose 480 mg Q4W); Nivo1Ipi3;Nivo 3 mg/kg (Nivo 1 mg/kg and Ipi 3 mg/kg combination Q3W 4 doses, maintenance dose 3 mg/kg Q2W)

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/KM-N1I3N3I3-Adultadvanced.png

The VPCs for the treatment stratified, full CPH model selected above indicated that the developed model was not able to characterize all the treatment groups included in the analysis dataset well (data

not shown). Particularly, the model underpredicted the Gr2+ IMAEs in the ipilimumab 10 mg/kg treatment group and overpredicted Gr2+ IMAEs in the adult combination dosing regimen of N3I1 when comparing to the observed data. Given the broad dose range in the pooled dataset and that the E-R relationship may not be the same across the groups, it was a challenge to develop a model that could characterize all the treatment groups. Therefore, the model was re-developed using a simplified dataset to focus on providing an adequate fit to the treatments of interest and providing adolescent predictions. Specifically, all adult and paediatric subjects that received ipilimumab 10 mg/kg Q3W and adult subjects that received N3I1 in Study CA209511 were excluded from model development. Paediatric subjects that received ipilimumab up to 5 mg/kg and paediatric subjects receiving the N3I1 regimen remained in the dataset.

The parameter estimates of the full E-R Gr2+ IMAEs model are presented in **Table 23**.

Table 23 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) [×ULN]	-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

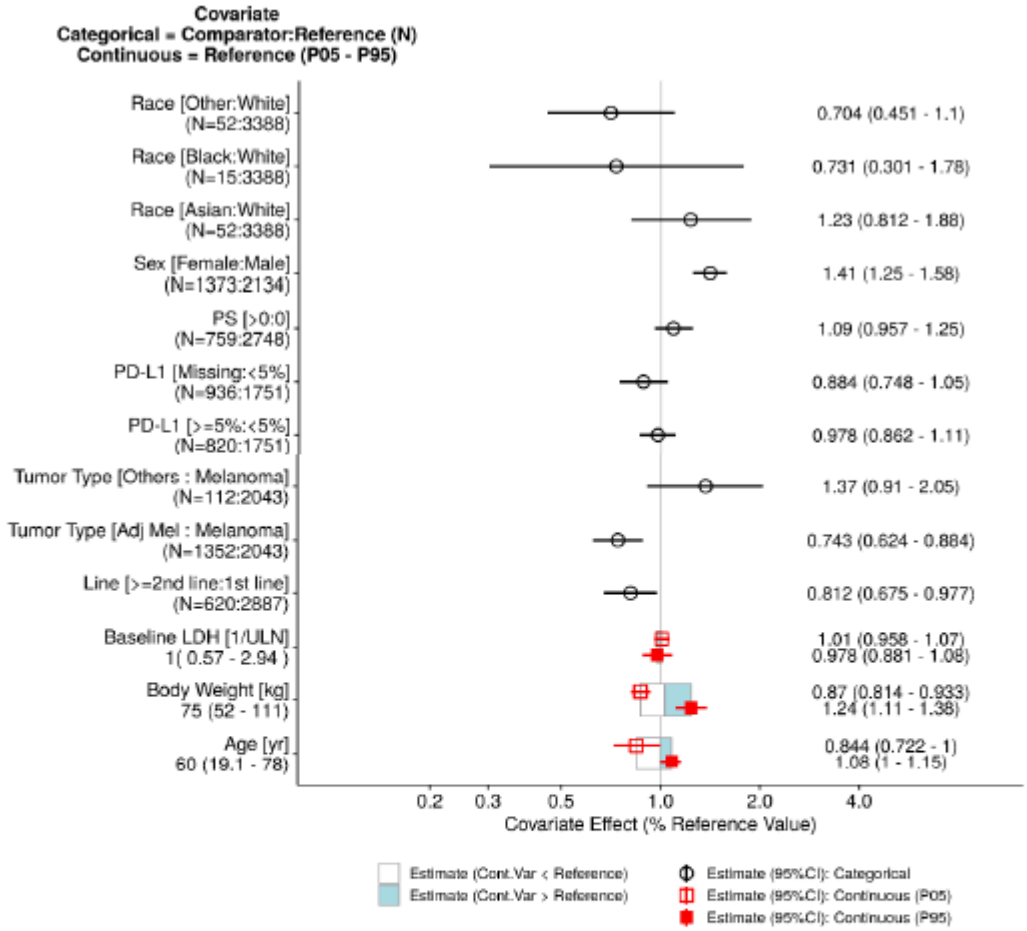
Source: Analysis-Directory/R/export/imae-param-cph-full.csv

The 95% CI for the estimated magnitude of effect of ipilimumab exposure on the risk of Gr2+ IMAEs did not include the null value, indicating it was statistically significant with a hazard increase per unit increase in exposure (HR 1.008 [95% CI 1.001, 1.014]) for ipilimumab after accounting for the potential effect of the other covariates as shown in Table 23. This indicated that higher ipilimumab exposure was associated with higher risk of Gr2+ IMAEs in contrast to nivolumab exposure, which had a model estimated coefficient that was slightly negative and not significant. The interaction between nivolumab and ipilimumab exposures in combination therapy was also statistically significant with a HR

of 0.9995 (95% CI 0.9991, 0.9998). This represents the synergistic interaction of exposure and treatment effects in addition to the exposure effects of nivolumab and ipilimumab alone.

Figure 29 is a graphical presentation of all the estimated effects of covariates that are constant over time in the full model, showing the HR of Gr2+ IMAEs across the predictor ranges.

Figure 29 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

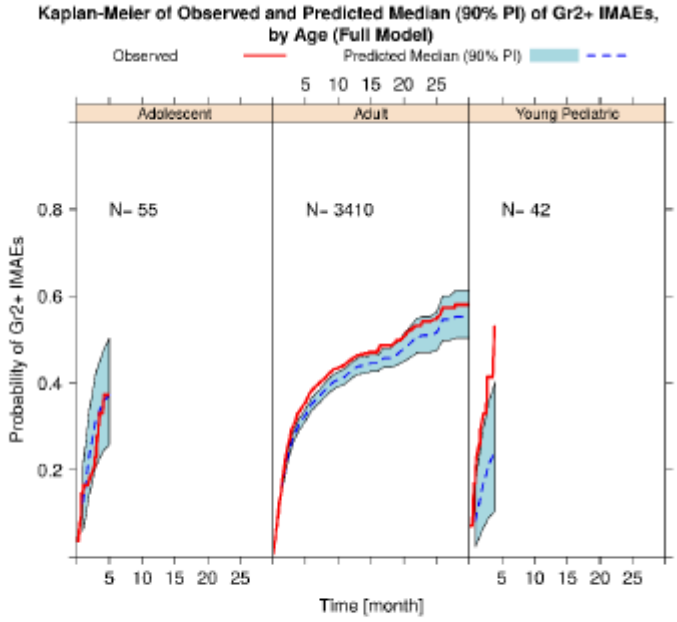
Model evaluation

Model performance for the E-R safety model was assessed by VPC comparing the cumulative probability of Gr2 +IMAEs with the corresponding model-predicted 90% PI of Gr2+ IMAEs.

The CPH model predictions were evaluated by comparing the model-predicted cumulative time to-event distributions of Gr2+ IMAEs with the corresponding distribution determined by nonparametric Kaplan-Meier (K-M) analysis. Data used in the model development were used as an internal validation dataset for K-M analysis.

VPCs of the cumulative probability of the first occurrence of a Gr2+ IMAE, stratified by adult, young paediatric (< 12 years), and adolescent (≥ 12 to < 18 years) subjects showed that the model-predicted cumulative probabilities were generally in good agreement with the model predictions in the analysis data set (Figure 30). There was a slight under-prediction of the young paediatric population.

Figure 30 Model Evaluation of the Exposure-Response of Gr2+ IMAEs by Age Group (Full Model)

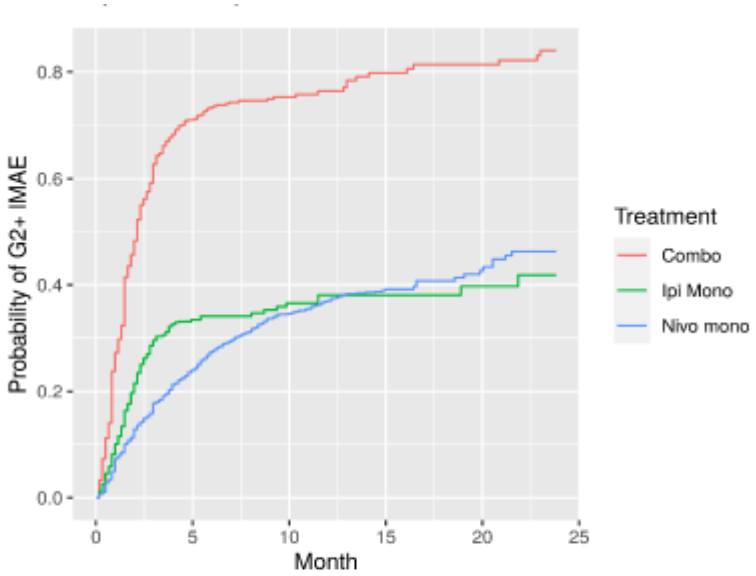


Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/
Program Source: Analysis-Directory/R/scripts/2-model-tv-imae-dev-final.Rmd
Source: Analysis-Directory/R/plots/AgeVPC.png

Model application

The cumulative rate of the risk of Gr2+ IMAEs was higher in the combination therapy group compared to the monotherapies and was higher in the ipilimumab monotherapy group compared to the nivolumab monotherapy group through the first 5 months (**Figure 31**).

Figure 31 Estimated Baseline Hazard of the Exposure-Response of Gr2+ IMAEs (Full Model)



Note: Baseline hazard was obtained by simulating a typical subject getting different treatments, where all the covariates of the typical subject were assigned to the reference value (Line of therapy = 1st line, Treatment setting = Advanced Melanoma, BLDHR = 1, PD-L1< 5%, PS = 0, AGE = 50y, BW = 75 kg, SEX = Male, RACE = White, Ipilimumab exposure = 0, Nivolumab exposure = 0)

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/er-safety/final/

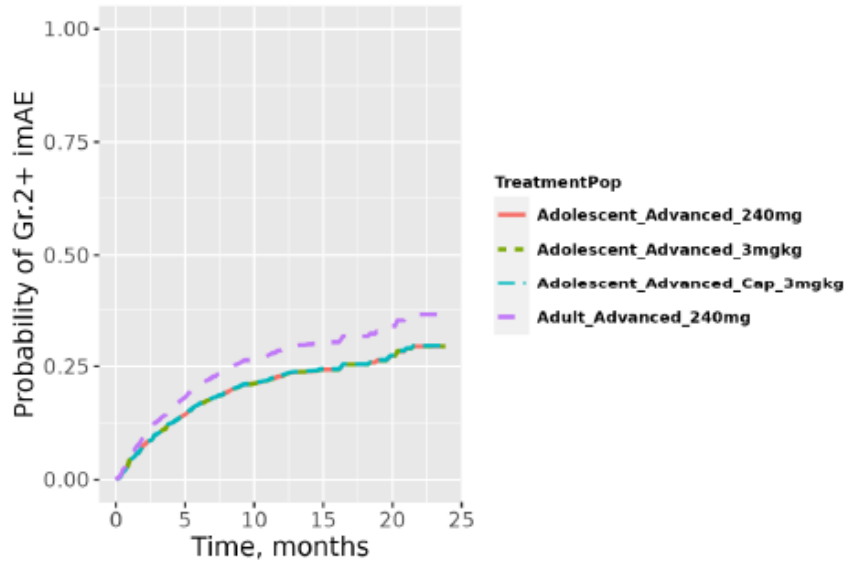
Program Source: Analysis-Directory/R/scripts/3-model-application-tv-imae.Rmd

Source: Analysis-Directory/R/plots/ full-imae-baselinehaz-sim.png

Nivolumab **Monotherapy in Advanced Melanoma**

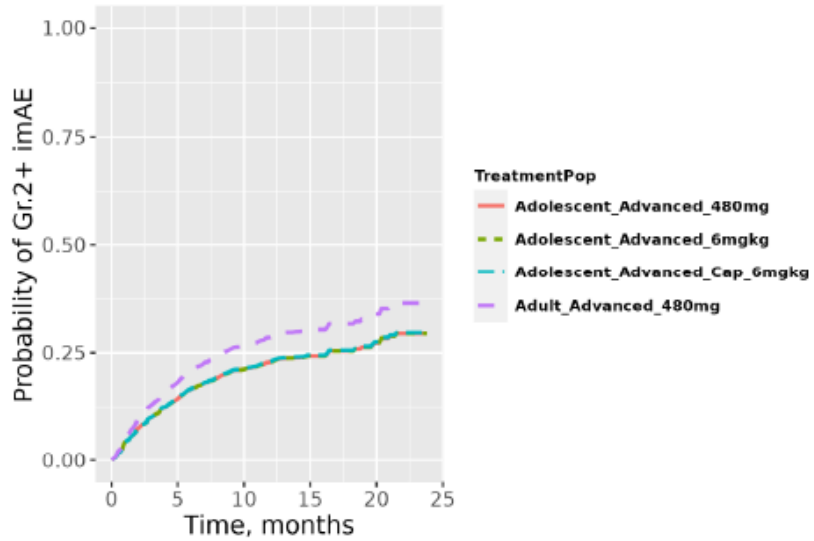
The results showed that predicted Gr2+ IMAEs for the adolescent subjects were similar across the evaluated dosing regimens, including Q2W (Figure 32) and Q4W (Figure 33) with and without cap.

Figure 32 Predicted Median Cumulative Probability of Gr2+ IMAEs using Predicted Time-Varying Daily Cavg for the Nivolumab Q2W Dosing Regimens in Adult and Adolescent Subjects with Advanced Melanoma



Note 1: Cap, dose cap of 240 mg applied to nivolumab.
Note 2: In the figure legend, Adolescent Advanced 240mg = Nivo 3 mg/kg Q2W (< 40 kg) or 240 mg (≥ 40 kg) Q2W
Note 3: Predictions are across the body weight range for adolescents (range: 29.3 kg to 154.8 kg) and adults (range: 40.3 kg to 159.9 kg)
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/N240-N3mgkg-adol-adv.png

Figure 33 Predicted Median Cumulative Probability of Gr2+ IMAEs using Predicted Time-Varying Daily Cavg for the Nivolumab Q4W Dosing Regimens in Adult and Adolescent Subjects with Advanced Melanoma



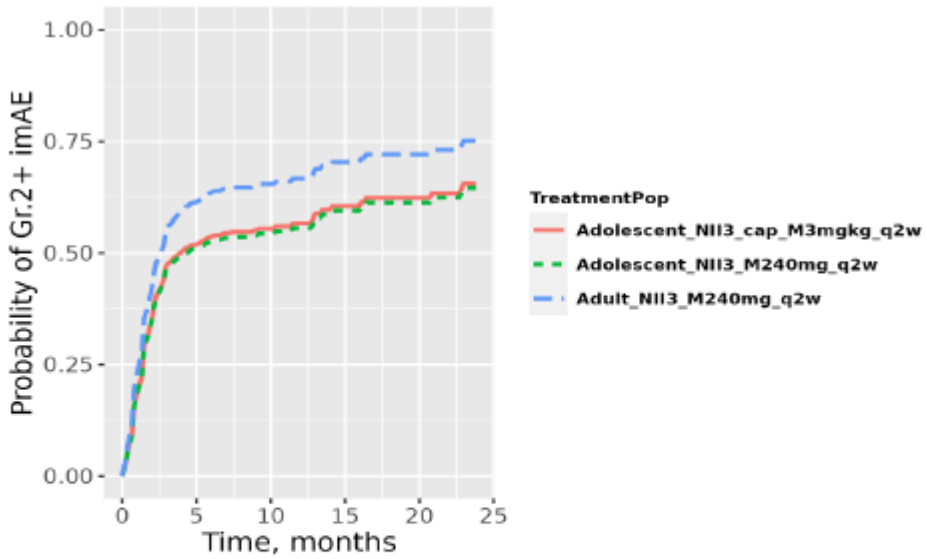
Note 1: Cap, dose cap of 480 mg applied to nivolumab.
Note 2: In the figure legend, Adolescent Advanced 480mg = Nivo 6 mg/kg Q4W (< 40 kg) or 480 mg (≥ 40 kg) Q4W
Note 3: Predictions are across the body weight range for adolescents (range: 29.3 kg to 154.8 kg) and adults (range: 40.3 kg to 159.9 kg)
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/N480-N6mgkg-adol-adv.png

The following different dosage regimens for advanced melanoma were simulated in adults and adolescents to compare the risk of Gr2+ IMAEs for nivolumab in combination with ipilimumab (with a * to indicate the adolescent recommended dose):

- Adult: Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 doses, then Nivo 240 mg Q2W or 480 mg Q4W
- Adolescent: 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 or 6 mg/kg Q4W (< 40 kg) or 480 mg (≥ 40 kg) Q4W*
- Adolescent with cap: Nivo 1 mg/kg (up to 80 mg) + Ipi 3 mg/kg (up to 240 mg) Q3W for 4 doses, then Nivo 3 mg/kg (up to 240 mg) Q2W or Nivo 6 mg/kg (up to 480 mg) Q4W

The results are presented in Figure 33 for the nivolumab + ipilimumab combination with nivolumab Q2W maintenance dosing and in Figure 34 for the nivolumab + ipilimumab combination with nivolumab Q4W maintenance dosing.

Figure 34 Predicted Median Cumulative Probability of Gr2+ IMAEs using Predicted Time Varying Daily Cavg for Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W, Followed by Nivolumab 240 mg Q2W in Adults and Adolescents with Advanced Melanoma



Note 1: N1I3, nivolumab 1 mg/kg Q3W+ ipilimumab 3 mg/kg Q3W for 4 doses; M= nivolumab maintenance dose; cap, dose cap of 80 mg applied to nivolumab and 240 mg applied to ipilimumab.

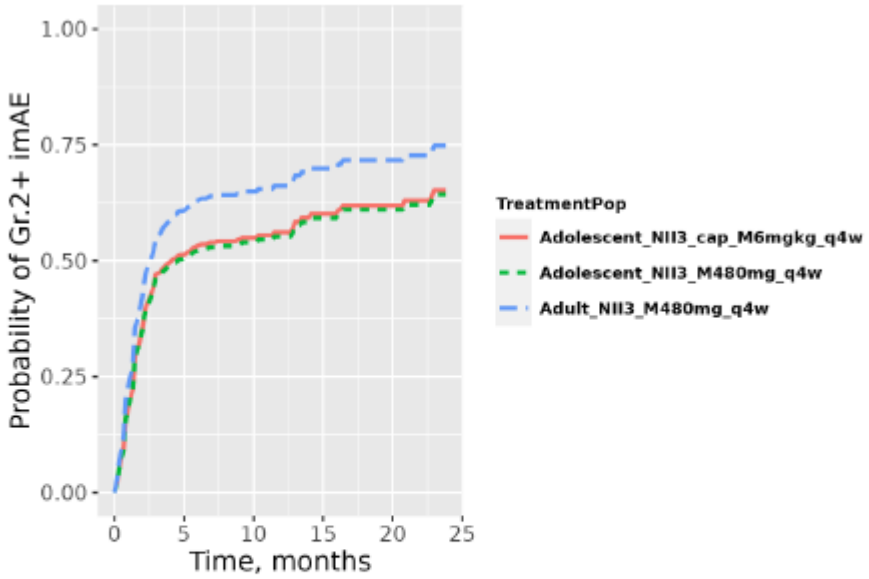
Note 2: Predictions are across the body weight range for adolescents (range: 29.3 kg to 154.8 kg) and adults (range: 40.3 kg to 159.9 kg)

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/ N1I3-N3I3-240-cap-nocap.png

Figure 35 Predicted Median Cumulative Probability of Gr2+ IMAEs using Predicted Time Varying Daily Cavg for Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W, Followed by Nivolumab 480 mg Q4W in Adults and Adolescents with Advanced Melanoma



Note 1: N1I3, nivolumab 1 mg/kg Q3W+ ipilimumab 3 mg/kg Q3W for 4 doses; M= maintenance dose; cap, dose cap of 80 mg applied to nivolumab and 240 mg applied to ipilimumab.
Note 2: Predictions are across the body weight range for adolescents (range: 29.3 kg to 154.8 kg) and adults (range: 40.3 kg to 159.9 kg)
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/N1I3-N3I3-480-cap-nocap.png

Nivolumab Monotherapy in the **Adjuvant Treatment of Melanoma**

Model-predicted cumulative probabilities of Gr2+ IMAEs were generated for adjuvant treatment of melanoma. The following different monotherapy regimens were simulated in adults and adolescents to compare the risk of Gr2+ IMAEs (with a * to indicate the adolescent recommended dose):

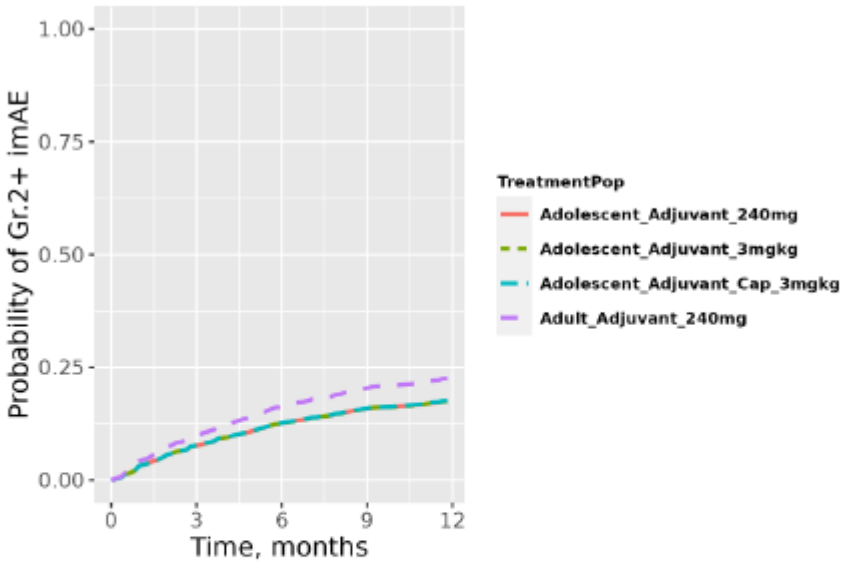
Q2W Regimen

- Adult: Nivo 240 mg Q2W
- Adolescent: Nivo 3 mg/kg Q2W (< 40 kg) or 240 mg (≥ 40 kg) Q2W*
- Adolescent: Nivo 3 mg/kg Q2W
- Adolescent with cap: Nivo 3 mg/kg (up to 240 mg) Q2W

Q4W Regimen

- Adult: Nivo 480 mg Q4W
- Adolescent: Nivo 6 mg/kg Q4W (< 40 kg) or 480 mg (≥ 40 kg) Q4W*
- Adolescent: Nivo 6 mg/kg Q4W
- Adolescent with cap: Nivo 6 mg/kg (up to 480 mg) Q4W

Figure 36 Predicted Median Cumulative Probability of Gr2+ IMAEs using Predicted Time-Varying Daily Cavg for the Nivo Q2W Dosing Regimens in Adult and Adolescent Subjects with Adjuvant Treatment of Melanoma



Note 1: Cap, dose cap of 240 mg applied to nivolumab.

Note 2: In the figure legend, Adolescent Adjuvant 240mg = Nivo 3 mg/kg Q2W (≤ 40 kg) or 240 mg (≥ 40 kg) Q2W

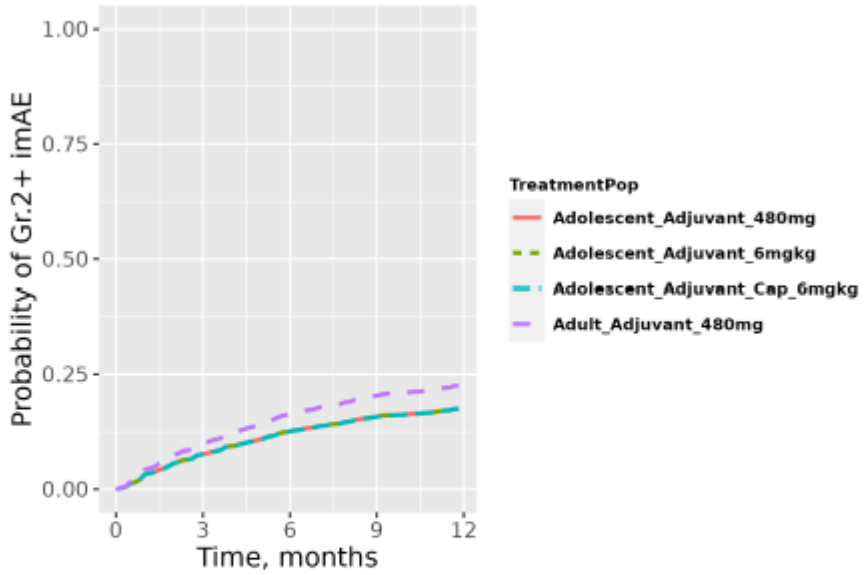
Note 3: Predictions are across the body weight range for adolescents (range: 29.3 kg to 154.8 kg) and adults (range: 40.3 kg to 159.9 kg)

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/ N240-N3mgkg-adol-adj.png

Figure 37 Predicted Median Cumulative Probability of Gr2+ IMAEs using Predicted Time-Varying Daily Cavg for the Nivo Q4W Dosing Regimens in Adult and Adolescent Subjects with Adjuvant Treatment of Melanoma



Note 1: Cap, dose cap of 480 mg applied to nivolumab.
Note 2: In the figure legend, Adolescent Adjuvant 480mg = Nivo 6 mg/kg Q4W (< 40 kg) or 480 mg (≥ 40 kg) Q4W
Note 3: Predictions are across the body weight range for adolescents (range: 29.3 kg to 154.8 kg) and adults (range: 40.3 kg to 159.9 kg)
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/ N480-N6mgkg-adol-adj.png

2.3.4. Discussion on clinical pharmacology

Population PK modelling and model-based simulation and exposure-safety analysis have been performed in order to recommend adolescent (from 12 to <18 years) dosing regimens for nivolumab as monotherapy and nivolumab in combination with ipilimumab in advanced melanoma, and for nivolumab as monotherapy in adjuvant treatment of melanoma.

PPK Analysis of Nivolumab for Adolescent Advanced Melanoma

The population PK analysis was based on a pooled dataset from 13 studies, which included data of nivolumab in combination with ipilimumab and data of nivolumab as monotherapy (Studies CA209067, CA209069, CA209070, CA209908, CA209001, CA209003, CA209066, CA209005, CA209205, CA209039, CA209143, CA209498, and CA209744). Studies CA209067, CA209069, CA209070 and CA209908 were with nivolumab in combination therapy. Studies CA209070, CA209908, and CA209744 included paediatric patients with advanced solid tumours/HL/non-HL, CNS tumours, and cHL, respectively. The dataset included 2050 adult subjects (993 with advanced melanoma) and 275 paediatric subjects (79 with advanced solid tumours and only one with melanoma).

PK samples of nivolumab below the lower limit of quantification (LLQ) were low (2.89 %) and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

The population PK model development of nivolumab included the re-use of the previously developed model to characterize the PK in nivolumab in subjects with solid tumours established as the new base model, with all the significant covariates previously identified excluding the tumour type effect.

Subsequently, additional covariates were tested in the PK parameters, including age, combination therapy, and patient population (adult MEL as reference) on baseline CL, as well as PS, patient population, and combination therapy on EMAX. In addition, body size parameters and age-related effects were tested on CL and VC.

Nivolumab PK was described using a linear, 2-compartment model with zero-order IV infusion, first-order elimination and time-varying CL.

Moderate inter-individual variability has been characterized on several PK parameters CL (33.77%), VC (27.92%) and Emax (41.65%). The full popPK model included 25 covariate effects. Eight of them (race Asian, race AA, combination IIQ3 and combination BVCO on CL, sex and other adult population on Vc and other adult population and ipilimumab combination on Emax) were non-significant based on the 95% CI, which included the null value (and those covariate effects were unreliable estimated based on the high RSE values). The MAH has explained the rationale for supporting the inclusion of these non-significant covariates in the final model. Although some of these parameters had high RSE values, this seems not to be relevant due to the small magnitude of the covariate effects on the overall exposure metrics. The MAH has developed a reduced model in order to confirm the impact of retaining these non-significant covariates. The results showed minimal impact on most of the PK parameters, although, for some of them larger differences were observed (CLpedhl (-23.4%), CLadost (-13.9%) and Emax (21.7%)). However, the overall impact in terms of Cavgss, Cminss and Cmaxss was negligible: Cavgss (4.3%), Cminss (6.3%) and Cmaxss (1.8%). Therefore, no clinically relevant changes in exposure are expected when the full or reduced models are used.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the main PK parameters (CL, VC and Emax). The impact of significant covariates on exposure metrics (Cmaxss, Cavgss, Cminss) was assessed using the full model by obtaining individual nivolumab exposures for subjects for whom EBE of PK parameters were available. Distributions of each exposure metric were presented. Similar exposure levels were observed across the different subgroups of body weight, baseline eGFR, sex, and baseline performance status. However, it should be highlighted that higher exposure (>20%) were observed in patients receiving the combination therapy at the proposed dosing regimen (3 mg/kg Q2W). Overall, no relevant covariate effect has been detected which could explain clinically relevant differences in exposure that would lead to a different dosing regimen proposal.

PPK Analysis of Nivolumab Monotherapy in Adolescent with Adjuvant Treatment of Melanoma

The population PK analysis was based on a pooled dataset from 11 studies, which included 4 Studies (CA209001, CA209003, CA209005, and CA209066) with intensive PK data of nivolumab monotherapy in adults, four studies (CA209004, CA209067, CA209069 and CA209511) with data of the combination in advance melanoma patients, Study CA209238 with data for adult with adjuvant treatment of melanoma and Study CA20991 with data for adult and adolescent (N=3) with adjuvant treatment of melanoma. The dataset included 3883 adult subjects (1412 with advanced melanoma, 2244 with adjuvant treatment of melanoma) and 82 paediatric subjects (3 adolescent with adjuvant treatment of melanoma).

PK samples of nivolumab below the lower limit of quantification (LLQ) were low (2.33%) and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

The population PK model development of nivolumab included the re-use of the previously developed adolescent PPK model in the advance setting as the new base model, and the same time-varying CL for subjects with adjuvant treatment of melanoma. Subsequently, time-varying CL was removed from all subjects receiving the adjuvant treatment.

Moderate inter-individual variability has been characterized on several PK parameters CL (31.16%), VC (31.96%) and Emax (45.96%). The full popPK model included 19 covariate effects. Five of them (race Asian, race AA and combination IIQ3 on CL, other adult population and ipilimumab combination on Emax) were non-significant based on the 95% CI, which included the null value (and those covariate effects were unreliable estimated based on the very high RSE values).

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the main PK parameters (CL, VC and Emax). The impact of significant covariates on exposure metrics (Cmaxss, Cavgss, Cminss) was assessed using the full model by obtaining individual nivolumab exposures for subjects for whom EBE of PK parameters were available. Based on the simulated exposure levels across the final covariates selected, no relevant differences in exposure were observed, except for the type of patient population when the proposed dosing regimen is selected (3 mg/kg Q2W).

Simulation of paediatric exposures

- **Nivolumab for Adolescent Advanced Melanoma**

Nivolumab exposures were simulated for adolescent with solid tumours (due to the lack of data of adolescents with melanoma) with nivolumab as monotherapy and nivolumab in combination with ipilimumab.

Simulations for the monotherapy treatments included (i) flat dosing regimen of 240 mg Q2W or 480 mg Q4W for adolescent patients >40 kg and a body weight regimen of 3 Q2W or 6 mg/kg Q4W in adolescent patients <40 kg, (ii) a body weight regimen of 3 Q2W or 6 mg/kg Q4W and (iii) a body weight regimen of 3 Q2W or 6 mg/kg Q4W up to 240 or 480 mg, respectively. The flat dosing regimen showed higher exposures in the 40 to 50 kg group compared to adults. Body weight 3 mg/kg (up to 240 mg) Q2W or high dose body weight regimen (6 mg/kg (up to 480 mg) Q4W) provided exposure levels of Cmin, Cavg and Cmax within the adult median range. Although the MAH has justified that the slight increase in exposure out of the 90% prediction interval of the adult population does not translate into higher safety events, it is highly uncertain whether a proper safety characterization in paediatric patients from 40 to 50 kg from an overall dataset of 83 paediatric patients (adolescent and young paediatrics) is adequately performed. Dose selection should be established based on achieving an exposure range within the adult range and only the body weight regimen of nivolumab with cap is able to achieve higher probability of exposure within the adult range compared to the other regimens. These results suggest that a body weight regimen with dose cap at 240 mg or 480 mg is more appropriate. The justification provided by the MAH regarding the use of a flat dosing regimen for nivolumab monotherapy in adolescents ≥40 kg relies mainly on assuming a similar exposure-safety relationship for adolescent patients as observed in adult patients, since the MAH confirmed that it was not possible to achieve similar exposure levels between the two population groups for the same dosage regimen. Therefore, the MAH extrapolated the exposure range from the maximum tolerable dose from adults to the paediatric population, which is questionable, since there is no experimental evidence to support it. In addition, based on the evidence provided, uncertainties remain regarding the similarity of the exposure-safety relationship between adult and paediatric patients. A body-weight regimen achieved comparable exposure levels across both populations (adult and paediatric), which would make it possible to comply with the main assumption for the selection of doses in the paediatric population (i.e. assumption that same exposure guarantees the same benefit-risk profile), given the lack of a solid exposure-efficacy or exposure-safety relationship. This said, since model predicted exposure in adolescent patients from 40 to 50 kg exceeded the exposure range observed in adults with the flat dosing regimen, but a comparable exposure was predicted in adolescent patients >50kg using flat dosing and body weight regimens, a body weight-based regimen for adolescent patients <50 kg was agreed while a flat dosing regimen is recommended for adolescent patients ≥50 kg.

Simulations for the combination treatments (Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W, for 4 doses, then nivolumab 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W or Nivolumab 1 mg/kg Q3W + Ipilimumab 3 mg/kg Q3W, for 4 doses, then nivolumab 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W) showed similar exposure levels at cycle 4 and at steady-state conditions. However, it is worth mentioning the higher Cmax,ss levels achieved at steady-state in adolescent patients from 40 to 50 kg.

Overall, the exposure predicted in adolescent receiving nivolumab in monotherapy or in combination treatment with ipilimumab across the body weight ranges evaluated showed a wider distribution compared to the adult population, which reinforces the need of a body weight dosing regimen in order to partially compensate the influence of body weight on the exposure.

- **Nivolumab for Adolescent subjects receiving adjuvant treatment of melanoma**

Nivolumab exposures were simulated for adolescent subjects receiving adjuvant treatment of melanoma with nivolumab as monotherapy.

Different posology (2QW and 4QW) was evaluated: (i) flat dosing regimen of 240 mg Q2W or 480 mg Q4W for adolescent patients >40 kg and a body weight regimen of 3 Q2W or 6 mg/kg Q4W in adolescent patients <40 kg, (ii) a body weight regimen of 3 Q2W or 6 mg/kg Q4W and (iii) a body weight regimen of 3 Q2W or 6 mg/kg Q4W up to 240 or 480 mg, respectively.

Simulations for the monotherapy treatments in adolescent subjects receiving adjuvant treatment of melanoma showed that low dose body weight regimen 3 mg/kg (up to 240 mg) Q2W) or high dose body weight regimen 6 mg/kg (up to 480 mg) Q4W) provided exposure levels of Cmin, Cavg and Cmax within the adult median range. On the other hand, flat dosing regimens of 240 mg Q2W or 480 mg Q4W reported >10% of patients for specific body weight ranges (40 to 50 kg) out of the adult exposure range. Although the MAH justified that the slight increase in exposure out of the 90% prediction interval of the adult population did not translate into higher safety events, it is highly uncertain whether a proper safety characterization in paediatric patients from 40 to 50 kg from an overall dataset of 83 paediatric patients (adolescent and young paediatrics) was adequately performed. Dose selection should be established based on achieving an exposure range within the adult range and only the body weight regimen of nivolumab with cap is able to achieve higher probability of exposure within the adult range compared to the other regimens. Therefore, a body weight regimen was considered for adolescent patients with melanoma in monotherapy. These results suggest that a body weight regimen with dose cap at 240 mg or 480 mg is more appropriate. The justification provided by the MAH regarding the use of a flat dosing regimen for nivolumab monotherapy in adolescents ≥40 kg relied mainly on assuming a similar exposure-safety relationship for adolescent patients as observed in adult patients, since the MAH confirms that it is not possible to achieve similar exposure levels between the two population groups for the same dosage regimen. Therefore, the MAH extrapolated the exposure range from the maximum tolerable dose from adults to the paediatric population, which is questionable, since there is no experimental evidence to support it. In addition, based on the evidence provided, uncertainties remain regarding the similarity of the exposure-safety relationship between adult and paediatric patients. A body-weight regimen achieves comparable exposure levels across both populations (adult and paediatric), which would make it possible to comply with the main assumption for the selection of doses in the paediatric population (i.e. assumption that same exposure guarantees the same benefit-risk profile), given the lack of a solid exposure-efficacy or exposure-safety relationship. This said, since model predicted exposure in adolescent patients from 40 to 50 kg exceeds the exposure range observed in adults with the flat dosing regimen, but a comparable exposure is predicted in adolescent patients >50kg using flat dosing and body weight regimens, a body weight-based regimen for adolescent patients <50 kg was agreed while a flat dosing regimen is recommended for adolescent patients ≥50 kg (see SmPC 4.2).

Immunogenicity

Immunogenicity was assessed in Study CA209070. Three out of 51 (5.9%) patients treated with nivolumab monotherapy tested positive for ADA at baseline and only one of them tested positive post baseline and it was not persistent positive. For the pool data of both combination treatment, 2 out of 35 (5.7%) tested positive at baseline for nivolumab ADA but it was not persistent positive and 1 out of 33 tested positive for ipilimumab (3.2%). Similar immunogenicity was observed in the different groups. The impact of immunogenicity after nivolumab monotherapy or combination treatment showed no relevant concerns.

Exposure-response

The MAH has justified the absence of an exposure-efficacy analysis in the target population. The limited paediatric melanoma patients in Study CA209070 and the higher exposure in adolescents hampers the development of an exposure-efficacy analysis in the target population. However, the lack of an exposure-efficacy relationships impedes to evaluate the assumption that similar exposure in adolescents compared to adults leads to similar efficacy profile.

The exposure-response safety analysis was performed with pool data from 15 studies which include data from nivolumab monotherapy, ipilimumab monotherapy and nivolumab in combination with ipilimumab in adult, young paediatric and adolescent subjects in treatment of solid tumours including treatment of advanced melanoma and adjuvant treatment of melanoma. 42 young paediatric subjects (< 12 years) and 55 adolescent (≥ 12 to < 18 years) were included.

Occurrence of Gr2+ IMAEs was used as safety outcome in the exposure safety analysis as this endpoint is more sensitive to change in exposure and is more related to nivolumab/ipilimumab immunomodulatory activity than Gr3+ AEs and Gr2+ TRAEs. 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 Cox Proportional-Hazards (CPH) model, which included the Cavg of ipilimumab. No statistically significant relationship was found for Cavg of nivolumab. Several additional covariates were included in the model, such as race, body weight, tumour type, sex, age, PD-L1 and line of treatment. Model evaluation suggests that a similar trend in the probability of Gr2+ IMAE in adolescents and adults was observed, although the curve for adolescents is terminated due to clinical trial design. For young paediatrics, the probability of Gr2+ IMAE seems to increase faster compared to adolescent or adults and the model clearly underpredicts the overall trend. This issue shows the lack of the CPH model to characterize the time-course of Gr2+ IMAE in young paediatric patients (<12 y), which would require to be further updated in case a dose justification was aimed in this subgroup of patients.

Different dosage regimens were simulated in adults and adolescents to compare the risk of Gr2+ IMAEs for nivolumab in combination with ipilimumab and for nivolumab as monotherapy. However, the lack of inclusion of nivolumab exposure to predict the safety outcome impedes to adjust any dose recommendation based on the different exposure levels of nivolumab across the different sub-groups of body weight in adolescent patients.

As mentioned above, for paediatric patients <12 years of age, an update of the model including additional data able to describe the plateau in the probability of safety events would be needed to fully characterize the CPH model before conducting any dose recommendation. Of note, only adolescents (≥12 years) are the target of the proposed extension of the indication.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab in adolescent patients with advanced melanoma or adolescent patients with adjuvant treatment for melanoma have been overall adequately characterized. For nivolumab monotherapy, the exposures of nivolumab in adolescents 12 years of age and older who weigh at least 50 kg are expected to be comparable to those in adult patients at the recommended dose of 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes. Body weight based dosing was agreed for adolescents 12 years of age and older who weigh less than 50 kg at 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes. For nivolumab in combination with ipilimumab, the exposures of nivolumab and ipilimumab in adolescents 12 years of age and older are expected to be comparable to those in adult patients at the recommended dose of 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes (see SmPC section 4.2 and 5.2).

2.4. Clinical efficacy

2.4.1. Main study

CA209070 (ADVL1412)

This is a multicentre, 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 paediatric patients (12 months to <18 years), and young adults (≤30 years) with recurrent or refractory solid and haematology (only lymphoma) tumours.

Methods

Pivotal study CA209070 (ADVL1412) is a Phase 1/2 open-label trial of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumours as a single agent and in combination with ipilimumab. This is an investigator sponsored research (ISR) study, designed, and conducted by the Children's Oncology Group (COG) and funded by Bristol Myers Squibb (BMS). This COG clinical study is included as one of the agreed measures in both approved Paediatric Investigation Plans (PIP) for nivolumab (procedures ref. EMEA-001407-PIP01-12-M03 and EMEA-001407-PIP02-15-M05) and other agreed to global paediatric plans.

The primary objectives of Study CA209070 are to determine safety and tolerability, antitumor effects, PK, and immunogenicity of nivolumab and nivo+ipi combination therapy.

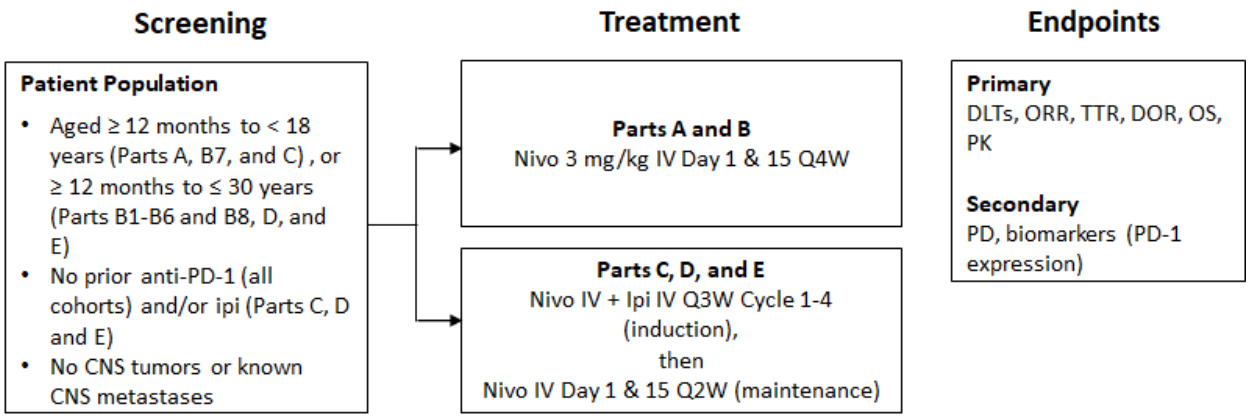
ADVL1412 evaluated the following:

- Part A: was a dose confirmation to establish the recommended phase 2 dose (RP2D) of nivolumab monotherapy in children and adolescents. The single-agent RP2D was determined to be nivolumab 3 mg/kg Q2W.
- Part B: was done to test the RP2D determined in part A, identify signals of activity, and generate further information regarding toxicity of the drug in the following disease specific cohorts: rhabdomyosarcoma, Ewing sarcoma/ peripheral primitive neuroectodermal tumour (PNET), osteosarcoma, neuroblastoma, Hodgkin lymphoma (HL), Non-Hodgkin lymphoma (NHL), and melanoma.

- Part C: was a dose confirmation to establish nivolumab and ipilimumab combination RP2D in children and adolescents. The RP2D of ipi+nivo was determined to be nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg Q3W.
- Part D: was performed to allow select disease cohorts in Part B (neuroblastoma, RMS, NHL, osteosarcoma, or Ewing sarcoma), which did not progress beyond the initial stage due to lack of objective responses to nivolumab monotherapy, to be further evaluated with a combination of nivolumab and ipilimumab using Part C RP2D.
- Part E: was done to evaluate alternative dosing of nivolumab and ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) compared to combination dosing achieved in Part C R2PD in rhabdomyosarcoma or Ewing sarcoma/peripheral PNET, the 2 tumour types where a response had been observed in Part D. 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.

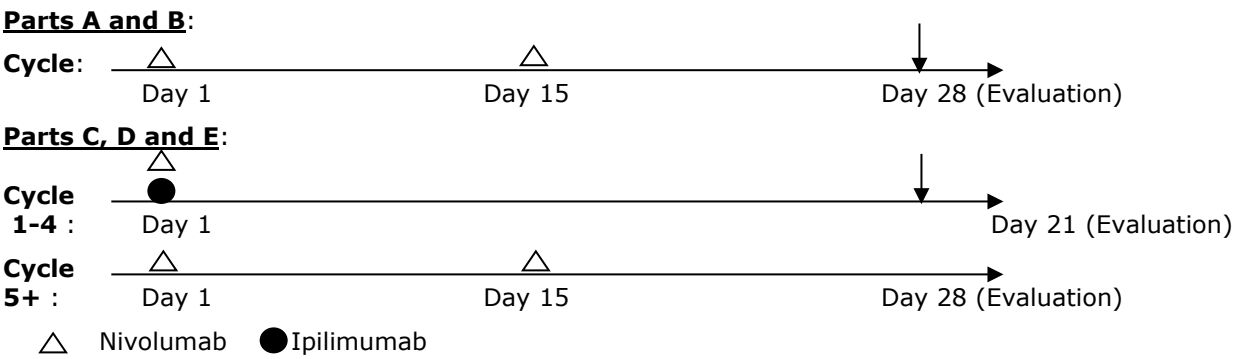
The study was initially planned with 3 parts (Part A, Part B, and Part C), and per Amendments 4 and 8B, Parts D and E were added later, respectively.

Figure 38 ***Study Design Schematic - CA209070***



Abbreviations: CNS = central nervous system; DLT = dose limiting toxicity; DOR = duration of response; ipi = ipilimumab; IV = intravenous; nivo = nivolumab; ORR = overall response rate; OS = overall survival; PD = pharmacodynamic; PD-1 = programmed death-1; PK = pharmacokinetic; QxW = every x weeks; TTR = time to response.

Figure 39 ***Study Dosing Schematic***



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).
Source: ADVL1412 Protocol Experimental Design Schema (Appendix 1.1)

Study participants

Key inclusion criteria

1. Age:
    - Parts A and C: Patients must be ≥12 months and < 18 years of age at the time of study enrolment.
    - Parts B1-B6, B8, D1-D6: Patients must be ≥12 months and ≤30 years of age at the time of study enrolment.
    - Part B7: Patients must be ≥12 months and < 18 years of age at the time of study enrolment.
2. Diagnosis: Patients must have had histologic verification of malignancy at original diagnosis or relapse.
    - Parts A and C: Patients with recurrent or refractory solid tumours, without Central Nervous System (CNS) tumours or known CNS metastases are eligible. Note: CNS imaging for patients without a known history of CNS disease was only required if clinically indicated.
    - Part B:
        - Part B1: Patients with relapsed or refractory neuroblastoma
        - Part B2: Patients with relapsed or refractory osteosarcoma
        - Part B3: Patients with relapsed or refractory rhabdomyosarcoma
        - Part B4: Patients with relapsed or refractory Ewing sarcoma or peripheral PNET
        - Part B5: Patients with relapsed or refractory HL
        - Part B6: Patients with relapsed or refractory NHL
        - Part B7: Patients with unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma
        - Part B8: Patients with relapsed or refractory neuroblastoma (MIBG evaluable disease without response evaluation criteria in solid tumours [RECIST] measurable lesion)

    Once the dose-escalation portion of Part A was completed, cohorts that were open concurrently for eligible patients (including Parts B and C and potential PK expansion cohorts) could be selected at the treating physician's discretion pending slot availability. In the event a disease cohort in Part B was completed after the initial stage of Simon's optimal two-stage design, for selected disease cohorts, a corresponding cohort in the same disease group for select disease types was opened in Part D

    - Part D:
        - Part D1: Patients with relapsed or refractory neuroblastoma
        - Part D2: Patients with relapsed or refractory osteosarcoma
        - Part D3: Patients with relapsed or refractory rhabdomyosarcoma
        - Part D4: Patients with relapsed or refractory Ewing sarcoma or peripheral PNET
        - Part D5: Patients with relapsed or refractory NHL

- Part D6: Patients with relapsed or refractory neuroblastoma (MIBG evaluable disease without RECIST measurable lesion)

3. Disease Status:

   - Parts A and C: Patients must have either measurable or evaluable disease.
   - Parts B and D: Patients must have measurable disease Parts B1-B6, and D1-D5. Melanoma patients in Part B7 must have either measurable or evaluable disease. Neuroblastoma patients in Parts B8 and D6 must have to be evaluable for MIBG response without evidence of RECIST measurable lesions.

4. Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

5. Performance Level: Karnofsky ≥50% for patients >16 years of age and Lansky ≥60 for patients ≤16 years of age.

6. Prior Therapy

   Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet different minimum duration from prior anti-cancer directed therapy prior to enrolment (details can be found in the protocol). If after the required timeframe, the defined eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

7. Organ Function Requirements

   - Adequate bone marrow function defined as:
     - For patients with solid tumours without known bone marrow involvement:
       - Peripheral absolute neutrophil count (ANC) ≥750/mm^3.
       - Platelet count ≥75,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrolment).
     - Patients with known bone marrow metastatic disease will be eligible for study provided they meet the established blood counts. These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients with a solid tumour must be evaluable for hematologic toxicity, for Parts A and C. If dose-limiting hematologic toxicity is observed on either Part A or C, all subsequent patients enrolled must be evaluable for hematologic toxicity on that Part.
   - Adequate renal function defined as:
     - Creatinine clearance or radioisotope GFR ≥70 ml/min/1.73 m^2 or
     - A serum creatinine based on age/gender
   - Adequate liver function defined as:
     - Bilirubin (sum of conjugated + unconjugated) ≤1.5 x upper limit of normal (ULN) for age
     - SGPT (ALT) ≤135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
   - Adequate pulmonary function: no evidence of dyspnoea at rest, no exercise intolerance due to pulmonary insufficiency, and a pulse oximetry >92% while breathing room air.
   - Adequate pancreatic function defined as: Serum lipase ≤ULN at baseline.

Key exclusion criteria

1. Pregnant or breast-feeding women were not to be entered on this study due to risks of foetal and teratogenic adverse events as there was yet no available information regarding human foetal or teratogenic toxicities. Pregnancy tests were to be obtained in girls who were post-menarchal. Women of childbearing potential (WOCBP) receiving nivolumab were to be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who were sexually active with WOCBP were to be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.
2. Concomitant Medications
    - Corticosteroids: Patients requiring daily systemic corticosteroids were not eligible. Patients must not have received systemic corticosteroids within 7 days prior to enrolment. If used to modify immune adverse events related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid. Note: Use of topical or inhaled corticosteroids did not render a patient ineligible.
    - Investigational Drugs: Patients who were currently receiving another investigational drug were not eligible.
    - Anti-cancer Agents: Patients who were currently receiving other anti-cancer agents were not eligible.
3. Patients with CNS tumours or known CNS metastases were excluded from this trial due to concerns regarding pseudo-progression in the CNS. Patients with a history of CNS metastases that were previously treated may have enrolled if sequential imaging showed no evidence for active disease. Patients with extra axial disease [e.g. skull (bone) metastasis that did not invade the dura] may have enrolled if there was no evidence for CNS oedema associated with the lesion.
4. Patients who had received prior anti-PD1 directed therapy (monoclonal antibody [mAb] or small molecule) were not eligible.
5. Parts C and D: Patients who had received prior ipilimumab were not eligible.

Treatments

Table 24: Treatments Administered

Study Part	Cohort ID/Cohort	Dose	Outcome
Part A	A/ Solid tumours, excluding brain and CNS tumours	To determine RP2D, nivolumab of 3 mg/kg every 2 weeks (Q2W) intravenous (IV).[a] A cycle was considered 28 days. If Dose Level 1 was not tolerable, then the 3 mg/kg dose could be deescalated to 1 mg/kg and a similar cohort of patients could be evaluated for tolerability at this dose	The RP2D for Part B was determined as nivolumab 3 mg/kg Q2W.[41]

[41] Kara Davis EF, et al: ADVL1412: Initial results of a phase I/II study of nivolumab and ipilimumab in pediatric patients with relapsed/refractory solid tumors—A COG study. Journal of Clinical Oncology 35, 2017

Table 24: Treatments Administered

Study Part	Cohort ID/Cohort	Dose	Outcome
Part B	B1/Relapsed or refractory neuroblastoma B2/Relapsed or refractory osteosarcoma B3/ Relapsed or refractory rhabdomyosarcoma B4/ Relapsed or refractory Ewing sarcoma or Peripheral PNET B5/ Relapsed or refractory Hodgkin Lymphoma B6/ Relapsed or refractory non-Hodgkin Lymphoma B7/ Unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma B8/ Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)	Nivolumab 3 mg/kg Q2W IV[a]	
Part C[b,c]	C1/ Solid tumours, excluding brain and CNS tumours	To identify the RP2D of the combination of nivolumab and ipilimumab, the following dose levels are administered **Dose Level 1**: Nivolumab 1 mg/kg + ipilimumab 1 mg/kg every 3 weeks (Q3W) IV for cycles 1 to 4 followed by nivolumab 3mg/kg Q2W IV for cycles 5+ until progression If no dose limiting toxicities (DLTs) were observed, the dose was to be escalated to level 2	The R2PD for Part D was determined to be nivolumab 3 mg/kg and ipilimumab 1 mg/kg for cycles 1 to 4 followed by nivolumab 3mg/kg for cycles 5+.
	C2/ Solid tumours, excluding brain and CNS tumours	**Dose Level 2**: Nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W IV for cycles 1 to 4 and nivolumab 3mg/kg Q2W IV for cycles 5+ until progression	
Part D[b,c]	D1/ Relapsed or refractory neuroblastoma[d] D2/ Relapsed or refractory osteosarcoma	Nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W for cycles 1 to 4 followed by nivolumab 3mg/kg Q2W for cycles 5+ until progression	

Table 24: Treatments Administered

Study Part	Cohort ID/Cohort	Dose	Outcome
	D3/ Relapsed or refractory rhabdomyosarcoma		
	D4/ Relapsed or refractory Ewing Sarcoma or Peripheral PNET		
	D5/ Relapsed or refractory non-Hodgkin lymphoma[d]		
	D6/ Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)[d]		

[a] Nivolumab was administered over a 60 min infusion.

[b] For Parts C and D, the cycle length is 21 days for the first 4 cycles, followed by 28 days for subsequent cycles 5+

[c] Infusion of ipilimumab (over 90 minutes) was to be initiated no sooner than 30 minutes after completion of the nivolumab infusion (over 60 minutes).

[d] No subjects were enrolled in Parts D1, D5, and D6.

Abbreviations: CNS = Central Nervous System, DLT = dose-limiting toxicities, IV = intravenous, MIBG = metaiodobenzylguanidine, PNET = primitive neuroectodermal tumour, Q2W = every 2 weeks, Q3W = every 3 weeks RECIST = response evaluation criteria in solid tumours, RP2D = recommended phase 2 dose.

Source: Section 5.1 of the protocol (Appendix 1.1)

No dose modifications were allowed for dose-limiting hematological toxicity (dose escalation or de-escalation to be guided by toxicity in Part A and C, respectively). For any dose-limiting non-hematological toxicity, dose modifications were allowed.

The study was designed to determine the safety and tolerability, assess antitumor effects, to determine whether the systemic nivolumab exposure in children was similar to the systemic exposure in adults and evaluate the PK of nivolumab alone and in combination with ipilimumab.

To determine RP2D for nivolumab monotherapy in children (Part A), a starting dose of nivolumab 3 mg/kg IV Q2W (hereafter referred to as nivolumab monotherapy) was infused and de-escalation to nivolumab 1 mg/kg IV Q2W was planned if the dose level was not tolerated. For the nivo + ipi combination, a starting dose of nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W (hereafter referred to as nivo 1 + ipi 1) was planned, and if <2 DLTs in a cohort of 6 patients were observed, the dose was escalated to nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (hereafter referred as nivo 3 + ipi 1).

Objectives

Primary objectives

- Determine the tolerability and define and describe the toxicities of nivolumab administered as a single agent in children with relapsed or refractory solid tumours at the adult recommended dose of 3 mg/kg.
- Determine the maximum tolerated dose (MTD) and/or RP2D and define and describe the toxicities of nivolumab plus ipilimumab administered to children with relapsed or refractory solid tumours.

- Assess antitumor effects of nivolumab across selected childhood solid tumours in seven expansion cohorts (Parts B1-B6, B8); neuroblastoma (2 cohorts: measurable disease; metaiodobenzylguanidine [MIBG] positive only non-measurable disease), osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, HL, and NHL. A non-statistical access cohort (without minimum or maximum accrual limits) for the rare diagnosis of melanoma (Part B7) was to remain open to enrolment until Parts B1-B6, B8 are complete 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 tumours (Part D).
- Characterize the pharmacokinetics of nivolumab alone and in combination with ipilimumab, including area under the concentration-time curve (AUC), maximum observed serum concentration (Cmax), and observed predose trough serum concentration (Cmin), using intensive sampling.
- Assess immunogenicity of nivolumab alone and in combination with ipilimumab by measuring anti-drug antibody (ADA) levels.

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.
- Explore whether correlations exist between PD-L1 expression on tumour and antitumor effects of nivolumab (alone and in combination with ipilimumab) in paediatric solid tumours.

Other objectives

Table 25 **Objectives Not Presented in the CSR and Justification**

Objective	Justification
Primary Objective	
Assess antitumor effects of nivolumab in combination with ipilimumab across selected childhood solid tumours in Part E.	Part E results will be reported after data becomes available to BMS in a separate report
Determine if systemic nivolumab exposure in children is similar to the systemic exposure in adults following a 3 mg/kg dose.	Comparisons with adults will be part of the integrated population PK report. Historical comparisons to adult PK data are presented in this report (Section 2.3).
Secondary Objectives	
To conduct exploratory studies of potential tumour associated biomarkers of response in tumour tissue (at least five out of the following markers: NRAS, BRAF, MEK, KIT, PDGF, TP53, RB1 and BRCA1, Akt phosphorylation, IL-17 or PD-L1).	Biomarker analysis for this study was based on archival tissue. Due to limited sample availability, only PD-L1 was tested
Explore presence of tumour infiltrating lymphocytes and their association with antitumor effects of nivolumab (alone and in combination with ipilimumab).	Per Amendment 8B, tumour infiltrating lymphocytes, cytokine levels in serum samples, and tumour mutational burden (TMB) analysis were added to the study design when Part E was added to the study protocol. Therefore, these secondary objectives are not in scope for Parts A to D and will not be reported in this CSR.
Conduct exploratory studies of the effect of nivolumab (alone or in combination with ipilimumab) on cytokine levels in serum samples.	
For Part E, determine tumour mutational burden of diagnostic specimens using Foundation One CDx testing to explore	

Table 25 **Objectives Not Presented in the CSR and Justification**

Objective	Justification
immune-related gene expression or mutation and its association with antitumor response to nivolumab in combination with ipilimumab.	

Source: Section 1.0 of the Protocol (Appendix 1.1)

Outcomes/endpoints

Table 26 ***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 tumours 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 analysed.
Determine the MTD and/or RP2D and define and describe the toxicities of nivolumab plus ipilimumab administered to children with R/R solid tumours.	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 protocol section 5.4.
Assess antitumor effects of nivolumab across selected childhood solid tumours 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 rare diagnosis of melanoma (Part B7) remained open to enrolment 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.	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. **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 tumour 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 tumour assessment. DOR was evaluated for responders only. When confirmation of response was required, the first date when initial response was observed was used.
Assess antitumor effects of nivolumab in combination with ipilimumab across selected childhood solid tumours in two dose combinations (Part D).		

Objective	Endpoint	Endpoint Description
		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 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 tumour and antitumor effects of nivolumab (alone and in combination with ipilimumab) in paediatric solid tumours.	PD-L1 status	PD-L1 expression was defined as the percent of tumour cell membrane staining in a minimum of 100 evaluable tumour 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 tumour 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 tumour biopsy specimen was sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation.

Objective	Endpoint	Endpoint Description
		Subjects with missing PD-L1 expression were subjects with no tumour 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.
Source: CA209070 Interim Clinical Study Report, Table 3.5.1-1.

Sample size

Overall, a maximum of 375 subjects were planned to be treated (Table 27). 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 be enrolled into stage 1. If at least 1 response was observed among 10 evaluable subjects, then stage 2 was to be opened for enrolment of 10 additional subjects.

Table 27 **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)

Source: Statistical Analysis Plan Table 5-1.

Determination of Recommended Phase 2 Dose for Nivolumab as a Single Agent

The primary objective of Part A was the determination of MTD/RP2D of single-agent nivolumab (Part A). A minimum of 4 subjects (2 by dose level) were to be enrolled in Part A, with a maximum possible enrolment of 36 subjects. A maximum of 36 subjects could occur in the unlikely scenario if each dose level is expanded to 12 subjects, and if a 20% unevaluable rate occurs.

Part A evaluated a single dose level (3 mg/kg). If 1 or fewer of 6 evaluable patients experienced DLT and at least 5/6 of patients achieved a Cmin of at least 10 mcg/ml, the 3 mg/kg dose level was considered to be the RP2D. If < 5 of 6 patients achieved a Cmin of at least 10 mcg/ml, a protocol amendment could be considered to test a higher dose level in Part A. Cmin levels > 30 mcg/ml could not, in and of itself result in a change in protocol design, unless excess toxicity was observed.

If 2 or more of the 6 patients experienced DLT at the 3 mg/kg dose level, then the MTD was exceeded and the 1 mg/kg dose level was to be evaluated. If 1 or fewer of 6 patients experienced DLT at the 1 mg/kg dose level and at least 5/6 of patients achieved a Cmin of at least 10 mcg/ml, then this dose level was to be the RP2D. Once the RP2D for nivolumab as a single agent was determined, Part B and Part C could open simultaneously.

Phase 2 Evaluation of Nivolumab as a Single Agent at RP2D

The primary objective of Part B was to identify histologic subtypes where there is a signal for anti-tumour 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. A minimum of 10 and maximum of 22 evaluable subjects per disease group were to be enrolled in Parts B1-B6 and B8. The following Simon's

optimal two stage design was used for Parts B1-B6, B8 (Table 28). The best response of disease to nivolumab was examined separately for each of the tumour strata.

Table 28 **Simons Optimal Two-stage Design**

	Cumulative number of responses	Decision
Stage 1: Enter 10 patients	0	Terminate the stratum: agent ineffective
	1 or more	Inconclusive result, continue stratum (proceed to stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the stratum: agent ineffective
	3 or more	Terminate the stratum: agent effective

Source: Section 11.4 of the Protocol (Appendix 1.1)

In the event that a cohort in a given disease group in Part B was completed after Stage 1 because no responses were observed, a cohort in the same disease group could open to up to 10 evaluable patients in Part D, at the RP2D of nivolumab in combination with ipilimumab as determined in Part C.

Nivolumab was not considered of sufficient interest for further evaluation in a disease category if the true response rate was 5% and of sufficient activity if the true response rate was 25%. If nivolumab had a true response rate of 5%, the rule described above could identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial would have an expected sample size of 14 with 60% probability of early termination. If nivolumab had a true response rate of 25%, the rule described above would identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

If cycle 1 DLT occurs in ≥33% of evaluable patients in a cohort of Part B with at least 3 evaluable patients, the maximum tolerated dose would have been exceeded in this tumour type and the cohort was to be closed to further enrolment.

Given the activity seen in adult patients with melanoma, an additional non-statistical cohort for patients with unresectable, metastatic, relapsed, or refractory melanoma was opened to accrual as Part B7 to preliminarily define the antitumor effects of nivolumab within the confines of a phase 1/2 study. Part B7 could remain open to enrolment until Parts B1-B6, B8 and Parts D1-D6 were completed. If at any time after enrolment of 3 subjects, cycle 1 DLT occurs in ≥33% in the melanoma cohort (Part B7), enrolment to that cohort was to be closed. A minimum of 0 evaluable subjects and a maximum of 16 subjects were anticipated to enroll in this disease group assuming the maximum study duration of 4 years.

<u>Dose Escalation and Determination of Recommended Phase 2 Dose for Nivolumab plus Ipilimumab (Part C)</u>

The primary objective of Part C was determination of MTD/Recommended RP2D of the combination nivolumab plus ipilimumab. A minimum of 2 patients were to be enrolled in Part C, with a maximum possible enrolment of 36 subjects similar to Part A.

A rolling six phase 1 trial design was used for the conduct of Part C of this study. Two to 6 patients could be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who had experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual was to be suspended when a cohort of six had enrolled or when the study endpoints were met.

Phase 2 Evaluation of Nivolumab (3 mg/kg) in Combination with Ipilimumab (1 mg/kg) (Part D)

The primary objective of Part D was to evaluate the dose of nivolumab in combination with ipilimumab determined in Part C in selected disease cohorts (neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma, osteosarcoma, or Ewing sarcoma) using the same Simon's optimal two-stage design9 as in Part B only if there was insufficient activity in the initial stage of the Simon's optimal two-stage design in Part B. A minimum of 10 and maximum of 22 evaluable subjects per disease group were to be enrolled in Parts D1-D6. Note that per amendment 4, no subjects were enrolled in D1, D5, and D6 Cohorts.

The best response of disease to nivolumab in combination with ipilimumab was to be examined separately for each of the tumour strata. Nivolumab in combination with ipilimumab was not considered of sufficient interest for further evaluation in a disease category if the true response rate was 5% and of sufficient activity if the true response rate was 25%. Design had the same operating characteristics as described for Part B.

If cycle 1 DLT occurred in ≥33% of evaluable patients in a cohort of Part D with at least 3 evaluable patients, the maximum tolerated dose would be exceeded in this tumour type and the cohort was to be closed to further enrolment. Up to 6 additional subjects with relapsed/refractory solid tumours without restrictions on hematology evaluability could be enrolled at the RP2D determined in Part A and Part C to acquire PK data in a representative number of young subjects (min 6 subjects <12 years of age) at the MTD/RP2D in each Part.

Randomisation

This is not a randomized trial.

Blinding (masking)

This was an open-label study.

Statistical methods

The SAP version 1.0 (dated 30-Apr-2021) has been provided.

Unless otherwise noted, all analyses were performed on all treated subjects per treatment group and cohort (A, B1 to B8, C1, C2, D2 to D4) and also nivolumab monotherapy (A+B, pooled) and nivolumab combined with ipilimumab (C+D) overall, and split by solid tumours and hematologic malignancies (HL and NHL). Analysis by disease indication was also to be performed, pooling subjects with same disease diagnosis from Parts A and B (nivolumab mono), and from Parts C and D (nivolumab + ipilimumab combination). Indications consisted of HL, NHL, neuroblastoma, Ewing Sarcoma, osteosarcoma, rhabdomyosarcoma, melanoma, and solid Tumour NOS (other tumour types not included in the previous solid tumour categories). Some analyses were also performed by age category.

Efficacy endpoints

Unless stated otherwise, analyses in this section were tabulated for all evaluable treated subjects and performed on the following groups:

- Nivolumab monotherapy and nivolumab combined with ipilimumab
- Nivolumab monotherapy and nivolumab combined with ipilimumab, per disease indication, total solid tumours and total hematologic malignancies.

ORR

Efficacy analyses based on tumour response were conducted using all response evaluable subject population. Tumour response was evaluated using RECIST except for subjects with neuroblastoma and MIBG only disease, Neuroblastoma and MIBG only disease were measured radiographically and other validated standard response criteria, respectively.

Estimates of objective response rate are presented along with their two-sided 95% CI by Clopper and Pearson.

OS

Overall Survival analysis was conducted using subjects treated with nivolumab monotherapy and using subjects treated with nivolumab+ipilimumab therapy, overall and by disease diagnosis. OS was estimated using the Kaplan-Meier (KM) technique. The two-sided 95% CI for median OS was computed via the log-log transformation method. OS rates at fixed time points (e.g. 3 months, depending on the minimum follow-up) were presented along with their associated 95% CIs. These estimates were derived from the KM estimate and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

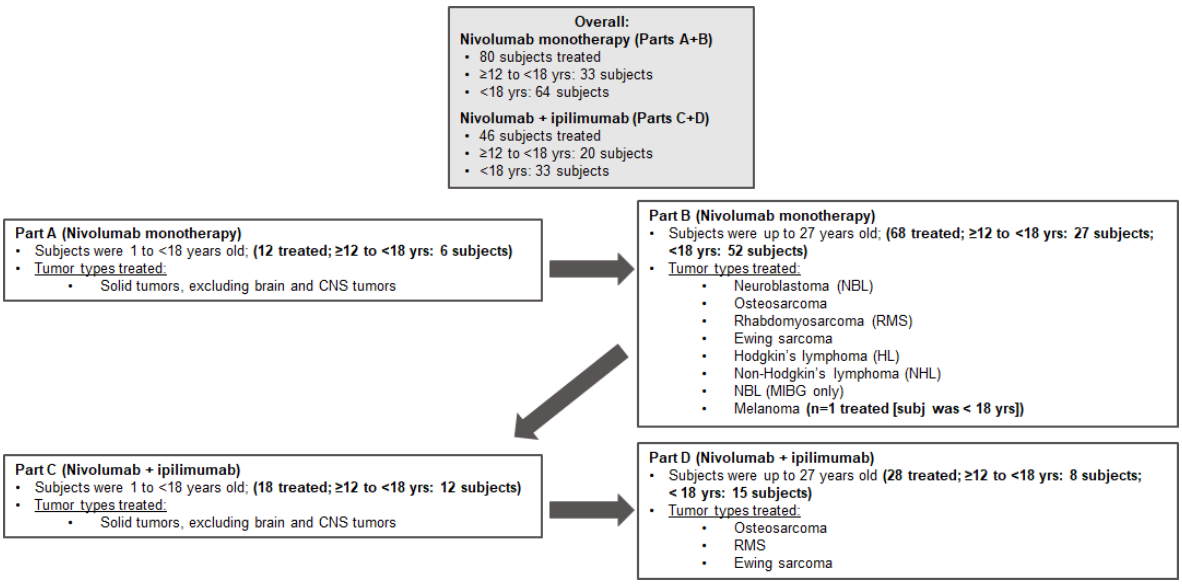
The status (on- vs off- study) of subjects who were censored in the OS KM analysis were tabulated.

Results

Participant flow

Overall, 132 subjects were enrolled 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 nivolumab monotherapy (N=80; 12 subjects in Part A and 68 subjects in Part B) or ipi+nivo (N=46; 18 subjects in Part C and 28 subjects in Part D) in 23 sites in the US, and 1 site in Canada. Overall, the 97 (77.0%) subjects who were less than 18 years of age were treated with nivolumab monotherapy (N=64: 12 subjects in Part A and 52 subjects in Part B), or ipi+nivo (N=33; 18 subjects in Part C and 15 subjects in Part D).

Figure 40 ***Summary of Study CA209070 – Parts A-D***



Source: refer to Table S.5.4B.1 of the CA209070 Interim CSR

Recruitment

The enrolment period was approximately 40 months (Mar-2015 to Jul-2018) for the nivo group and approximately 30 months (Aug-2015 to Feb-2018) for the nivo + ipi group.

For Parts A and B, the FPFV occurred on 03-Apr-2015, and LPFV occurred on 31-Jul-2018, this data includes up to the clinical cut-off date of 30-Sep-2019, the minimum follow-up (time from LPFV date to data cut-off date) was >24.0 months for all cohorts except for Cohort B6, where 2 subjects had <24 month of follow-up (1 subject died before the clinical data cut-off for Part A and B, and the other subject was off-study [withdrew consent], with a minimum follow-up of 16.1 and 14.0 months, respectively], which resulted in an overall minimum follow-up of 14.0 months for all subjects treated with nivo (N=80).

Similarly, for Parts C and D, the FPFV occurred on 13-Aug-2015, and LPFV occurred on 20-Feb-2018, this data includes up to the clinical cut-off date of 30-Jun-2020 providing 28.3 months of minimum follow-up time for all subjects treated with nivo + ipi. The median follow-up (time from clinical cut-off date to each subject first dosing date) for all subjects treated with nivo or nivo + ipi is 44.0 months.

As of 30-Jun-2020 data cut-off date, 8 subjects were enrolled in Part E of the study and data are reported in the Children's Oncology Group progress report dated July 2020.

Nivolumab monotherapy (Combined Cohorts of Parts A and B)

At the time of the database lock (DBL), only one (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 greater than 12 weeks after start of protocol therapy (13.8%), see Table 29.

Nivolumab + Ipilimumab (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 greater than 12 weeks after start of protocol therapy (17.4%), see Table 29.

Table 29 ***End of Treatment Period Subject Status Summary- Pooled Analysis: Solid vs. Haematology vs. Total for Each Treatment - All Treated Subjects in CA209070 - Parts A-D***

Status (%)	Nivo			Nivo + Ipi
	Solid N = 60	Hemato N = 20	Total N = 80	Solid N = 46
ONGOING TREATMENT	0	1 (5.0)	1 (1.3)	0
COMPLETED TREATMENT	0	0	0	0
DISCONTINUED TREATMENT	60 (100.0)	19 (95.0)	79 (98.8)	46 (100.0)
REASON FOR DISCONTINUED TREATMENT				
REFUSAL OF FURTHER PROTOCOL THERAPY BY PATIENT/PARENT/GUARDIAN	5 (8.3)	2 (10.0)	7 (8.8)	1 (2.2)
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE OF GREATER THAN 40% INCREASE FROM BASELINE TARGET LESIONS SELECTED ACCORDING TO RECIST CRITERIA	32 (53.3)	3 (15.0)	35 (43.8)	30 (65.2)
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE GREATER THAN 12 WEEKS AFTER START OF PROTOCOL THERAPY	7 (11.7)	4 (20.0)	11 (13.8)	8 (17.4)
PHYSICIAN DETERMINES IT IS NOT IN THE PATIENT'S BEST INTEREST	10 (16.7)	5 (25.0)	15 (18.8)	3 (6.5)
ADVERSE EVENTS REQUIRING REMOVAL FROM PROTOCOL THERAPY	3 (5.0)	4 (20.0)	7 (8.8)	3 (6.5)
DEATH	3 (5.0)	1 (5.0)	4 (5.0)	1 (2.2)
CONTINUING IN THE STUDY	12 (20.0)	14 (70.0)	26 (32.5)	5 (10.9)
NOT CONTINUING IN THE STUDY	48 (80.0)	6 (30.0)	54 (67.5)	41 (89.1)
REASON FOR NOT CONTINUING IN THE STUDY				
WITHDRAWAL OF CONSENT FOR ANY FURTHER REQUIRED OBSERVATIONS OR DATA SUBMISSION	4 (6.7)	2 (10.0)	6 (7.5)	2 (4.3)
LOST TO FOLLOW-UP	2 (3.3)	0	2 (2.5)	4 (8.7)
ENROLLMENT ONTO ANOTHER COG THERAPEUTIC (ANTI-CANCER) STUDY	8 (13.3)	0	8 (10.0)	8 (17.4)
DEATH	34 (56.7)	4 (20.0)	38 (47.5)	27 (58.7)

Percentages based on subjects entering period.
Source: Table S.2.7.2

Table 30 ***End of Treatment Period Subject Status Summary Pooled Analysis: Solid vs. Haematology vs. Total for Each Treatment - All Treated Subjects < 18 Years of Age in CA209070 - Parts A-D***

Status (%)	Nivo			Nivo + Ipi
	Solid N = 49	Hemato N = 15	Total N = 64	Solid N = 33
ONGOING TREATMENT	0	0	0	0
COMPLETED TREATMENT	0	0	0	0
DISCONTINUED TREATMENT	49 (100.0)	15 (100.0)	64 (100.0)	33 (100.0)
REASON FOR DISCONTINUED TREATMENT				
REFUSAL OF FURTHER PROTOCOL THERAPY BY PATIENT/PARENT/GUARDIAN	4 (8.2)	2 (13.3)	6 (9.4)	0
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE OF GREATER THAN 40% INCREASE FROM BASELINE TARGET LESIONS SELECTED ACCORDING TO RECIST CRITERIA	26 (53.1)	2 (13.3)	28 (43.8)	23 (69.7)
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE GREATER THAN 12 WEEKS AFTER START OF PROTOCOL THERAPY	6 (12.2)	3 (20.0)	9 (14.1)	6 (18.2)
PHYSICIAN DETERMINES IT IS NOT IN THE PATIENT'S BEST INTEREST	8 (16.3)	4 (26.7)	12 (18.8)	3 (9.1)
ADVERSE EVENTS REQUIRING REMOVAL FROM PROTOCOL THERAPY	3 (6.1)	3 (20.0)	6 (9.4)	0
DEATH	2 (4.1)	1 (6.7)	3 (4.7)	1 (3.0)
CONTINUING IN THE STUDY	11 (22.4)	10 (66.7)	21 (32.8)	2 (6.1)
NOT CONTINUING IN THE STUDY	38 (77.6)	5 (33.3)	43 (67.2)	31 (93.9)
REASON FOR NOT CONTINUING IN THE STUDY				
WITHDRAWAL OF CONSENT FOR ANY FURTHER REQUIRED OBSERVATIONS OR DATA SUBMISSION	4 (8.2)	1 (6.7)	5 (7.8)	2 (6.1)
LOST TO FOLLOW-UP	2 (4.1)	0	2 (3.1)	4 (12.1)
ENROLLMENT ONTO ANOTHER COG THERAPEUTIC (ANTI-CANCER) STUDY	6 (12.2)	0	6 (9.4)	6 (18.2)
DEATH	26 (53.1)	4 (26.7)	30 (46.9)	19 (57.6)

Percentages based on subjects entering period.
Program Source: /opt/zfs002/prd/bms255736/stats/primary/prog/tables/rt-ds-off-ped-gr2.sas

Conduct of the study

Protocol Amendments

The original protocol for this study was dated 16-Jan-2015 and there were a total of 12 global amendments. Key study changes are summarized below (Table 31).

Table 31 ***: 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	To add guidelines for management of pleural effusion as well as to add an additional cohort to Part B for enrolment 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	02-Mar-2016	The protocol was revised in response to the updated request for rapid amendment (RRA) from Primary Investigator dated 01-Mar-2016. Additional administrative edits have been made for clarity within the protocol.
Amendment	07-Jul-201	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 paediatric solid tumours. 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 (1 mg/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 enrolment 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 nivolumab and ipilimumab. The comprehensive adverse events and potential risks (CAEPR) list for 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	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 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.

Table 31 ***: Summary of Key Changes to CA209070 Protocol***

Document	Amendment Date	Summary of Key Changes
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 Primary Investigator, dated 20-Dec-2018 that includes administrative changes to reflect the transition from Children's Oncology Group Chair (COGC) to Paediatric 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 tumour (PNET).
Amendment 9	23-May-2019	Amendment in response to a RRA from Primary Investigator, 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-201[illegible]	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 Paediatric 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 Clinical Study Report, Table 4.1-1.

Important Protocol Deviations

Important or key Protocol Deviations (IPDs), previously known as Significant Protocol Deviations, are a subset of protocol deviations derived from COG audit deficiencies report that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Table 32 **CA209070/ ADVL1412 Summary of Important Protocol Deviations - All Enrolled Subjects**

Protocol Deviation Classification	Total
Adverse Event Deficiency Review Details	4
Adverse Events Details	4

Table 32 **CA209070/ ADVL1412 Summary of Important Protocol Deviations - All Enrolled Subjects**

Protocol Deviation Classification	Total
General Data Management Quality Deficiency Review Details	27
General Data Management Quality Details	21
Informed Consent Deficiency Review Details	4
Informed Consent Details	4
Treatment Deficiency Review Details	15
Treatment Details	11
Not Categorized	1
TOTAL	**91**

Source: Appendix 2.3

Relevant Protocol Deviations

Relevant Protocol Deviations (RPDs) are IPDs that could affect the interpretability of key study results, are programmable deviations from clinical database and are protocol-specific.

No relevant protocol deviations were reported in this study.

Regarding GCP, no significant deviations impacting the study or serious breaches were reported.

Baseline data

Demographics

Among the treated population, 97 subjects were paediatric 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 haematological tumour, 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 (Table 33).

Nivolumab monotherapy

In combined cohorts of Parts A and B, subjects treated with nivo mono:

- The median age was 13.5 years (range: 1 - 27 years). 64 (80.0%) subjects were < 18 years old and 16 (20.0%) subjects were ≥18 years old. Also, for Part A (used for DLT cycle analysis), all subjects are paediatric subjects only. Paediatric population (< 18 years old) size is described below by Cohort.
    - In Part A, 12 subjects (100.0%)
    - In Part B1 (Neuroblastoma/ N =10), 8 subjects (80.0%)
    - In Part B2 (Osteosarcoma/ N =10), 8 subjects (80.0%)
    - In Part B3 (Rhabdomyosarcoma/ N =10 subjects), 10 subjects (100.0%)
    - In Part B4 (Ewing sarcoma/ Peripheral PNET/ N =10): 4 subjects (40%)
    - In Part B5 (Hodgkin lymphoma/ N =10), 6 subjects (60.0%)
    - In Part B6 (Non-Hodgkin Lymphoma/ N =10), 9 subjects (90%)

- In Part B7 (Melanoma/ N =1), 1 subject (100%)
- In Part B8 (Neuroblastoma, MIBG/ N =7), 6 subjects (85.7%)

- The majority of subjects were White (75.0%), Not Hispanic or Latino (85.0%), and male (61.3%)
- All subjects (100.0%) were from the US.

Nivolumab + Ipilimumab

In combined cohorts of Parts C and D, subjects treated with nivo + ipi:

- The median age was 15.0 years (range: 4 - 27 years). 33 (71.7%) subjects were <18 years old and 13 (28.3%) subjects were ≥18 years old. Also, for Part C1 and C2 (used for DLT cycle analysis), all subjects are paediatric subjects only. Paediatric population size is described below by Cohort.
  - In Part C1 (N=6), 6 subjects (100.0%)
  - In Part C2 (N=12), 12 subjects (100.0%)
  - In Part D2 (Osteosarcoma/ N=10), 5 subjects (50.0%)
  - In Part D3 (Rhabdomyosarcoma/ N=10), 7 subjects (70.0%)
  - In Part D4 (Ewing sarcoma/ Peripheral PNET/ N=8), 3 subjects (37.5%)
- The majority of subjects were White (71.7%), Not Hispanic or Latino (78.3%), and male (65.2%)
- All subjects except 1 (97.8%) were from the US.

Table 33 ***Demographic Characteristics Summary by Treatment – All Treated Subjects***

	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
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)

Source: Table S.3.2.1.3

Baseline Disease Characteristics

Nivolumab Monotherapy

In combined cohorts of Parts A and B, subjects treated with nivo mono (Table 34):

- Most of the subjects had Karnofsky Performance Status (KPS)/ Lansky Performance Status (LPS) of 90 (41.3%) followed by 100 (28.8%), and 80 (18.8%).
- Disease diagnosis at baseline was as follows: Neuroblastoma (25.0%), osteosarcoma (16.3%), rhabdomyosarcoma and Ewing sarcoma/ PNET (13.8% each), and HL and Non-Hodgkin lymphoma (12.5% each).
- Number of subjects with PD-L1 quantifiable baseline expression were 63 (78.8%) subjects (Table 34). Subjects with baseline PD-L1 ≥1% by disease indication and treatment were as follows:
    - HL (N =9), 9 subjects (100.0%)
    - NHL (N =8), 6 subjects (75.0%)
    - Neuroblastoma (N =14), 1 subject (7.1%)
    - Ewing sarcoma or Peripheral PNET (N =10), 1 subject (10.0%)
    - Osteosarcoma (N =9), 2 subjects (22.2%)

- Rhabdomyosarcoma (N =9), 1 subject (11.1%)
- Melanoma (N =1), none, only 1 subject with PD-L1 expression missing at baseline
- Solid tumour NOS (N =4), 2 subjects (50.0%)

Nivolumab + Ipilimumab

In combined cohorts of Parts C and D, subjects treated with nivo+ipi:

- Most of the subjects had Karnofsky Performance Status (KPS)/ Lansky Performance Status (LPS) of 90 (41.3%) followed by 100 (26.1%), and 80 (23.9%).
- Disease diagnosis at baseline was as follows: Neuroblastoma (2.2%), osteosarcoma (28.3%), rhabdomyosarcoma and Ewing sarcoma/ PNET (21.7% each).
- Number of subjects with PD-L1 quantifiable baseline expression were 39 (84.8%) subjects (Table 34). Subjects with baseline PD-L1 ≥1% by disease indication and treatment were as follows:
    - Neuroblastoma (N = 1), none, only 1 subject, who is with baseline PD-L1 expression <1%
    - Ewing sarcoma or Peripheral PNET (N =8), 2 subjects (25.0%)
    - Osteosarcoma (N = 10), none, all 10 subjects are with baseline PD-L1 expression <1%
    - Rhabdomyosarcoma (N = 9), 1 subject (11.1%)
    - Solid tumour NOS (N = 11), 4 subjects (36.4%)

Table 34 ***Baseline Disease Characteristics by Treatment – All Treated Subjects***

	Number of Subjects (%)	
	Nivo N = 80	Nivo + Ipi N = 46
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)
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)

	Number of Subjects (%)	
	Nivo N = 80	Nivo + Ipi N = 46
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)

Source: Table S.3.2.7.3

Table 35 ***Frequency of PD-L1 Tumour Cell Expression Status by Treatment – All Treated Subjects***

Population PD-L1 Expression Category	Nivo N = 80	Nivo + Ipi N = 46
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	15 (18.8)	5 (10.9)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	63 (78.8)	39 (84.8)
PD-L1 EXPRESSION (%)		
MEAN	20.5	3.8
MEDIAN	0.0	0.0
MIN , MAX	0 , 100	0 , 100
STANDARD DEVIATION	38.0	16.4
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	22/ 63 (34.9)	7/ 39 (17.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	41/ 63 (65.1)	32/ 39 (82.1)
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	2 (2.5)	2 (4.3)

Source: Table S.10.2.2

Regarding previous treatments, all subjects treated with nivo and nivo+ipi received one or more than one type of prior systemic therapy (Table 36):

Table 36 ***Prior Cancer Therapy Summary by Treatment – All Treated Subjects***

	Number of Subjects (%)	
	Nivo N = 80	Nivo + Ipi N = 46
SUBJECTS WITH PRIOR CANCER THERAPY	80 (100.0)	46 (100.0)
TYPE OF PRIOR CANCER THERAPY RECEIVED (A)		
ANTIBODIES	19 (23.8)	6 (13.0)
ANTI-PD1 DIRECTED THERAPY	0	0
ANTI-RETROVIRAL THERAPY	0	0
ANTISENSE	0	0
BONE MARROW TRANSPLANT	6 (7.5)	2 (4.3)
CHEMOTHERAPY (MULTIPLE AGENTS SYSTEMIC, NON-CYTOTOXIC, NOS, SINGLE AGENT SYSTEMIC)	79 (98.8)	46 (100.0)
CELLULAR THERAPY	0	0
CYTOTOXIC OR MYELOSUPPRESSIVE CHEMOTHERAPY	79 (98.8)	46 (100.0)
NON-MYELOSUPPRESSIVE ANTI-CANCER AGENTS	15 (18.8)	17 (37.0)
DRUG AND/OR IMMUNOTHERAPY	21 (26.3)	6 (13.0)
GENE TRANSFER	0	0
HEMATOPOIETIC STEM CELL TRANSPLANTATION	12 (15.0)	4 (8.7)
HEMATOPOIETIC GROWTH FACTORS	67 (83.8)	42 (91.3)
HORMONAL THERAPY	0	1 (2.2)
IMAGE DIRECTED LOCAL THERAPY	0	0
INTERLEUKINS, INTERFERONS AND CYTOKINES	4 (5.0)	1 (2.2)
ONCOLYTIC VIROTHERAPY	0	0
NOS THERAPY	20 (25.0)	7 (15.2)
RADIATION THERAPY	52 (65.0)	31 (67.4)
RADIOPHARMACEUTICAL THERAPY	0	0
STEM CELL INFUSION WITH OR WITHOUT TBI	8 (10.0)	3 (6.5)
SURGERY	37 (46.3)	32 (69.6)
VACCINE	1 (1.3)	0

(A) Some subjects may have been treated with more than 1 type of therapy.
Source: Table S.3.3.5.3

Numbers analysed

The enrolled population (N=132 subjects) consisted of all subjects who signed an informed consent form (ICF). The treated population consisted of 126 subjects (80 treated with nivo mono and 46 with nivo+ipi). A description of the other analysis populations is provided in Table 37.

Table 37 ***Analysis Population in this CSR***

Population	**Nivolumab Monotherapy**			**Nivolumab + Ipilimumab**
	Solid	Hematology	Total	Solid
Enrolled: All subjects who signed the informed consent form and obtained a subject number.			85	47
Treated: All subjects who received at least one dose of any study treatment.	60	20	80	46
Response Evaluable: Treated subjects who have at least one post-baseline overall response assessment.	58	17	75	43
Immunogenicity: All treated subjects with study medication who have baseline and at least one post baseline immunogenicity assessment.	38	13	51	35
Nivolumab	38	13	51	35
Ipilimumab	NA	NA	NA	33

Source: Table S.3.2.2.1 (all enrolled subjects), Table S.3.2.7.2 (all treated subjects), Table S.5.5.1.1 (response-evaluable subjects), Table S.7.10.2.1 (immunogenicity subjects with solid tumours), Table S.7.10.2.2 (immunogenicity subjects with hematological tumours), Table S.7.10.2.3 (all immunogenicity subjects), and Table 9.2.1.1.2 (PK evaluable subjects, nivo hemato tumours).

Outcomes and estimation

The co-primary objectives for this study include antitumor effects of nivo monotherapy and nivo + ipi combination therapy efficacy assessments. The endpoints for efficacy assessments of antitumor effects include ORR, TTR, DOR, and OS. Other co-primary objectives include DLTs assessment, overall safety, pharmacokinetic, and immunogenicity assessments.

Efficacy analyses were descriptive in nature. The minimum follow-up (time from LPFV date to data cut-off date) was >24.0 months for all subjects treated with nivo mono in cohorts 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 are summarized by tumour type for nivolumab monotherapy (pooled solid tumour and haematological tumour) and for nivo + ipi (solid tumour) in Table 38.

For nivolumab monotherapy, no objective response was observed for the solid tumour cohorts (based on 58 response evaluable subjects including melanoma) (ORR 0% [95% CI: 0.0, 6.2]) while ORR was 23.5% (95% CI: 6.8, 49.9) for haematological tumour cohort (N=17 response evaluable subjects). Among the 4 responders (all paediatric subjects), 1 complete response (CR) in HL and 3 partial responses (PR) (2 with HL, 1 with NHL) were observed with nivolumab monotherapy for subjects with haematological tumours. Most response evaluable subjects treated with nivo monotherapy had either stable disease (SD, 28.0%) or progressive disease (PD, 58.7%). The median OS was 7.00 (95% CI: 5.98, 14.06) months for solid tumours (N=60 treated subjects), and not reached for haematological tumours (N=20 treated subjects). Overall, the median OS was 11.07 (95% CI: 6.37, 27.63) months for nivo monotherapy (table 38).

For nivo+ipi treatment (solid tumour only based on 43 response evaluable subjects), the ORR was 4.7% (95%CI: 0.6, 15.8). Two PRs were observed with nivo +ipi for solid tumours (1 paediatric subject with Ewing sarcoma/peripheral PNET and 1 adult subject with rhabdomyosarcoma. The majority of the subjects with nivo + ipi treatment had PD (74.4%). The median OS was 8.87 (95% CI: 5.75, 18.50) months for subjects treated with nivo + ipi (table 38).

Table 38 ***Efficacy Summary – Nivolumab Monotherapy and Nivolumab + Ipilimumab Treated Subjects in CA209070 – Parts A-D***

Efficacy Parameter	**Minimum follow-up: > 24 months[e] DBL: 30-Sep-2019**			**Minimum follow-up: 28.3 months DBL: 30-Jun-2020**
	Nivolumab			**Nivo + Ipi**
	Solid Tumour N = 60	**Haematology Tumour N =20**	**Total N =80**	**Solid Tumour N = 46**
ORR and BOR[a, b]				
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 (%)[c]	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				

Table 38 ***Efficacy Summary – Nivolumab Monotherapy and Nivolumab + Ipilimumab Treated Subjects in CA209070 – Parts A-D***

Efficacy Parameter	Minimum follow-up: > 24 months[e] DBL: 30-Sep-2019			Minimum follow-up: 28.3 months DBL: 30-Jun-2020
	Nivolumab			Nivo + Ipi
	Solid Tumour N = 60	Haematology Tumour N =20	Total N =80	Solid Tumour N = 46
# Events/#Subjects (%)	34/60 (56.7)	4/20 (20.0)	38/80 (47.5)	27/46 (58.7)
Median OS (Months) (95% CI)[d]	7.00 (5.98, 14.06)	N.A.	11.07 (6.37, 27.63)	8.87 (5.75, 18.50)
OS rate (95% CI),[d] %				
6-month	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	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	N.A	N.A.	N.A.	16.0 (4.3, 34.4)

[a] Of note, in the CA209070 Interim CSR Sections 7.1 and 7.2.1 texts, two 18-year-old subjects were inadvertently described as a paediatric subjects instead of adult. This affects 1 subject with PR in the nivo arm (with hematology tumour [HL]) and 1 subject with with PR in the nivo+ipi arm (solid tumour [Ewing sarcoma/peripheral PNET]). These 2 subjects were ≥18 years (adult) rather than the paediatric subjects (as noted in the Interim CSR Section 7.1 and 7.2.1). See Table S.5.5.2.1 in the Interim CSR; Table S. 11.1.1 and Table S.11.2.1 (ORR in paediatric subjects) in Appendix 2 of the SCE; (ORR, by age groups) for accurate information on responders in both the nivo and nivo+ipi arms.

[b] 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.

[c] 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).

[d] Based on Kaplan-Meier estimates

[d] except for Part B6, where 2 subjects had < 24 months of minimum follow-up

Source: Table 7.1-1 of the CA209070 Interim CSR

Objective Response Rate (ORR)

ORR and BOR results by pooled solid tumour vs haematology tumour vs total for all response evaluable population are presented in table 39 and results are described above. For nivo treated subjects with solid tumour, no objective response was observed; whereas for subjects with haematological tumour, 1 paediatric subject (with Hodgkin lymphoma) had CR and 3 paediatric subjects (2 with Hodgkin lymphoma, 1 with non-Hodgkin lymphoma) had PR with an ORR of 23.5% (95% CI: 6.8, 49.9). For subjects with nivo + ipi treatment, there were 2 responders with PR (1 paediatric subject with Ewing sarcoma/peripheral PNET and 1 adult subject with rhabdomyosarcoma), with an ORR of 4.7% (95% CI: 0.6, 15.8).

None of the B and D cohorts were expanded to stage 2 of the planned Simon's two stage design.

Results are also available by tumour type for all response evaluable population in table 39.

Table 39 ***Best Overall Response and Objective Response Rate Pooled Analysis: By Disease Indication and Treatment – All Response Evaluable Subjects***

	Total N	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)	Unable to Determine (UTD)	Objective Response Rate (1)	Clopper and Pearson 95% CI
HODGKIN LYMPHOMA								
NIVOLUMAB	10	1 (10.0)	2 (20.0)	5 (50.0)	2 (20.0)	0	3/10 (30.0%)	6.7, 65.2
NON-HODGKIN LYMPHOMA								
NIVOLUMAB	7	0	1 (14.3)	1 (14.3)	4 (57.1)	1 (14.3)	1/7 (14.3%)	0.4, 57.9
NEUROBLASTOMA								
NIVOLUMAB	20	0	0	9 (45.0)	11 (55.0)	0	0/20	0.0, 16.8
NIVOLUMAB + IPILIMUMAB	1	0	0	0	1 (100.0)	0	0/1	0.0, 97.5
EWING SARCOMA OR PERIPHERAL PNET								
NIVOLUMAB	10	0	0	1 (10.0)	8 (80.0)	1 (10.0)	0/10	0.0, 30.8
NIVOLUMAB + IPILIMUMAB	9	0	1 (11.1)	0	8 (88.9)	0	1/9 (11.1%)	0.3, 48.2
OSTEOSARCOMA								
NIVOLUMAB	12	0	0	2 (16.7)	7 (58.3)	3 (25.0)	0/12	0.0, 26.5
NIVOLUMAB + IPILIMUMAB	12	0	0	1 (8.3)	9 (75.0)	2 (16.7)	0/12	0.0, 26.5
RHABDOMYOSARCOMA								
NIVOLUMAB	11	0	0	2 (18.2)	8 (72.7)	1 (9.1)	0/11	0.0, 28.5
NIVOLUMAB + IPILIMUMAB	9	0	1 (11.1)	2 (22.2)	6 (66.7)	0	1/9 (11.1%)	0.3, 48.2
MELANOMA								
NIVOLUMAB	1	0	0	0	1 (100.0)	0	0/1	0.0, 97.5
SOLID TUMOR, NOS								
NIVOLUMAB	4	0	0	1 (25.0)	3 (75.0)	0	0/4	0.0, 60.2
NIVOLUMAB + IPILIMUMAB	12	0	0	4 (33.3)	8 (66.7)	0	0/12	0.0, 26.5

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.
(1) CR + PR
Source: Table S.5.5.1.2

Overall Survival (OS)

OS results by pooled solid tumour vs haematological tumour vs total for all treated subjects are presented in Table 40. Overall, 38 (47.5%) subjects had died with nivolumab treatment and 27 (58.7%) subjects had died with nivo + ipi treatment (table 40).

The Kaplan-Meier plot of OS by solid tumour or haematological tumour for nivo treated subjects and solid tumour for nivo+ipi treated subjects are presented in Figure 41. The median OS was 7.00 (95% CI: 5.98, 14.06) months for nivo treated subjects with solid tumour, and 8.87 (95% CI: 5.75, 18.50) months for nivo + ipi treated subjects with solid tumour. The median OS had not been reached for nivo treated subjects with haematological tumour.

Table 40 ***Overall Survival Rates - Pooled Analysis: Solid vs. Haematology vs. Total for Each Treatment - All Treated Subjects***

	Nivo[a]			Nivo + Ipi
OS Rate (95% CI)	Solid N = 60	Hemato N = 20	Total N = 80	Solid N = 46
3-MONTH	79.1 (66.2, 87.6)	83.6 (57.3, 94.4)	80.2 (69.3, 87.6)	85.7 (70.9, 93.3)
6-MONTH	62.5 (47.8, 74.2)	78.0 (51.5, 91.1)	66.6 (54.3, 76.4)	64.6 (46.3, 78.0)
9-MONTH	39.7 (25.2, 53.8)	78.0 (51.5, 91.1)	50.6 (37.6, 62.2)	46.7 (28.6, 62.9)
12-MONTH	36.4 (22.0, 50.9)	78.0 (51.5, 91.1)	48.1 (35.0, 60.1)	42.8 (25.0, 59.4)
15-MONTH	N.A.	N.A.	N.A.	37.4 (19.8, 55.1)
18-MONTH	N.A.	N.A.	N.A.	32.1 (15.1, 50.4)
21-MONTH	N.A.	N.A.	N.A.	21.4 (7.4, 40.1)
24-MONTH	N.A.	N.A.	N.A.	16.0 (4.3, 34.4)
27-MONTH	N.A.	N.A.	N.A.	16.0 (4.3, 34.4)

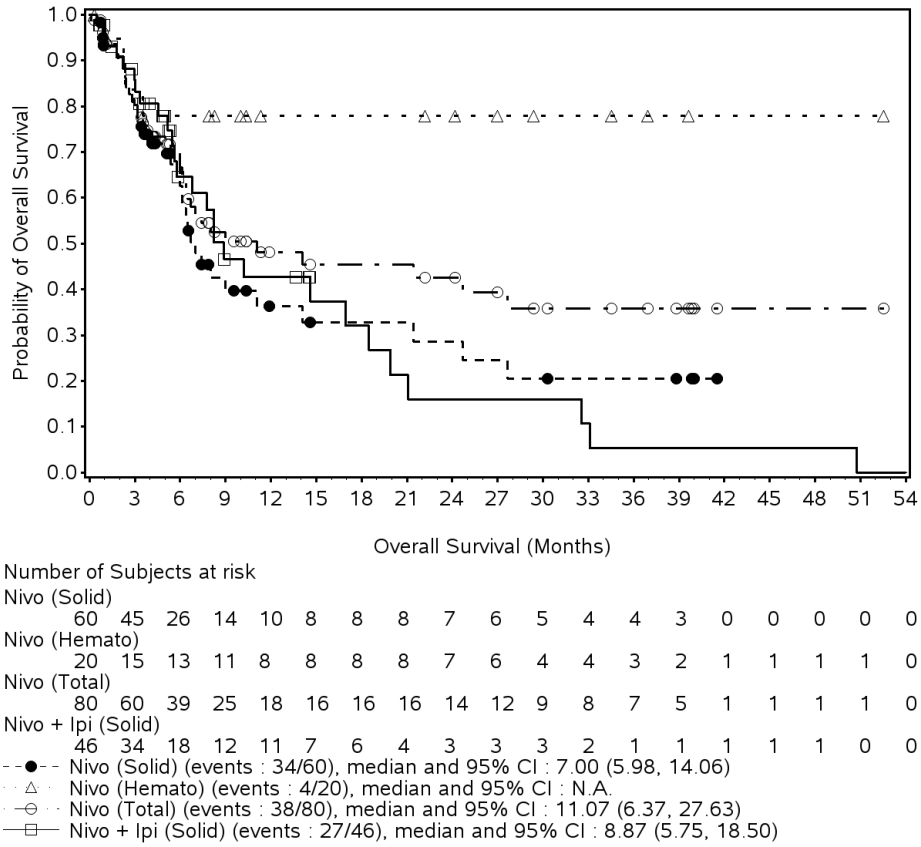
a The minimum follow-up (time from LPFV date to data cut-off date) was > 24.0 months for all subjects treated with nivo mono in cohorts A and B except Cohort B6

Based on Kaplan-Meier Estimates

N.A: Not Available: minimum follow up not reached.

Source: Table S.5.23.1

Figure 41 ***Kaplan-Meier Plot of Overall Survival - Pooled Analysis: Solid vs. Hemato vs. Total for Each Treatment - All Treated Subjects***



The status of censored subjects for OS overall by treatment, and by solid tumour or haematological tumour is presented in Table 41. For nivo treatment, 42/80 (52.5%) subjects were censored for OS at DBL. Of the censored subjects, only 1 subject with haematological tumour was still on-treatment, 25 (31.3%) subjects were in follow-up, and 16 (20.0%) subjects were off study. 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.

Table 41 ***Status of Censored Subjects, OS Primary Analysis - Pooled Analysis: Solid vs. Haematology vs. Total for Each Treatment - All Treated Subjects***

	Nivo			Nivo + Ipi
	Solid N = 60	Hemato N = 20	Total N = 80	Solid N = 46
NUMBER OF DEATHS (%)	34 (56.7)	4 (20.0)	38 (47.5)	27 (58.7)
NUMBER OF SUBJECTS CENSORED (%)	26 (43.3)	16 (80.0)	42 (52.5)	19 (41.3)
STATUS OF CENSORED SUBJECTS (%)				
STILL ON-TREATMENT	0	1 (5.0)	1 (1.3)	0
IN FOLLOW-UP	12 (20.0)	13 (65.0)	25 (31.3)	5 (10.9)
OFF STUDY	14 (23.3)	2 (10.0)	16 (20.0)	14 (30.4)
WITHDRAWAL OF CONSENT FOR ANY FURTHER REQUIRED OBSERVATIONS OR DATA SUBMISSION	4 (6.7)	2 (10.0)	6 (7.5)	2 (4.3)
LOST TO FOLLOW-UP	2 (3.3)	0	2 (2.5)	4 (8.7)
ENROLLMENT ONTO ANOTHER COG THERAPEUTIC (ANTI-CANCER) STUDY	8 (13.3)	0	8 (10.0)	8 (17.4)

Source: Table S.5.37.1

Secondary Efficacy Endpoints

PD-L1 expression was defined as the percent of tumour cells membrane staining in a minimum of 100 evaluable tumour cells per validated Dako PD-L1 IHC assay. Analyses for tumour cell PD-L1 expression were based on baseline PD-L1 ≥1% or <1%. 63/80 (78.8%) subjects with nivo treatment, and 39/46 (84.8%) subjects with nivo + ipi treatment had quantifiable PD-L1 expression at baseline. 41 of 63 subjects (65.1%) with nivo treatment and 32 of 39 subjects (82.1%) with nivo + ipi treatment had baseline PD-L1 <1%. For subjects with haematological tumours, within the HL cohort, all 10 subjects had quantifiable PD-L1 at baseline, among them 9 (90.0%) subjects had PD-L1 ≥1%. In the NHL cohort, 8 out of 10 subjects had quantifiable PD-L1 at baseline, among them 6 (75.0%) subjects had PD-L1 ≥1%. For subjects with solid tumours (neuroblastoma, Ewing sarcoma/ peripheral PNET, osteosarcoma, rhabdomyosarcoma, melanoma, solid tumour NOS), the majority of the subjects had PD-L1 <1%.

Nivolumab Monotherapy

Of the 80 subjects treated with nivolumab monotherapy, 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 (Table 42). Three paediatric subjects (2 with HL, 1 with NHL) in the PD-L1 ≥1% subgroup had PR, and 1 paediatric 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 (Table 42). One paediatric 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.

Table 42 ***Best Overall Response and Objective Response Rate by PD-L1 Tumour Cells Expression at Baseline by Treatment - All Treated Subjects in CA209070 – Parts A-D***

Baseline PD-L1 Status	Nivo N = 80	Nivo + Ipi N = 46
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	22 (27.5)	7 (15.2)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	0/22	0/ 7
PARTIAL RESPONSE (PR)	3/22 (13.6)	1/ 7 (14.3)
STABLE DISEASE (SD)	8/22 (36.4)	3/ 7 (42.9)
PROGRESSIVE DISEASE (PD)	9/22 (40.9)	3/ 7 (42.9)
UNABLE TO DETERMINE (UTD)	2/22 (9.1)	0/ 7
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	41 (51.3)	32 (69.6)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	0/41	0/32
PARTIAL RESPONSE (PR)	0/41	1/32 (3.1)
STABLE DISEASE (SD)	9/41 (22.0)	4/32 (12.5)
PROGRESSIVE DISEASE (PD)	25/41 (61.0)	24/32 (75.0)
UNABLE TO DETERMINE (UTD)	7/41 (17.1)	3/32 (9.4)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE	17 (21.3)	7 (15.2)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	1/17 (5.9)	0/ 7
PARTIAL RESPONSE (PR)	0/17	0/ 7
STABLE DISEASE (SD)	4/17 (23.5)	0/ 7
PROGRESSIVE DISEASE (PD)	10/17 (58.8)	5/ 7 (71.4)
UNABLE TO DETERMINE (UTD)	2/17 (11.8)	2/ 7 (28.6)

Source: Table 7.3-2 of the CA0209070 Interim CSR

Ancillary analyses

Age Subgroups including Adolescent Population

Nivolumab

No major differences in OS and ORR were observed among the age subgroups (≥12 to <18 years, <18 years, and ≥18 years).

In subjects ≥12 to <18 years, responses were observed in 2 subjects with haematological tumours including 1 complete response in HL and 1 partial response in NHL (ORR 6.5% [95% CI: 0.8, 21.4]), while no responses were observed in subjects with solid tumours. Nine (29.0%) subjects ≥12 to <18 years (5 subjects with solid tumours and 4 with haematology tumours) showed SD as the BOR (Table 43).

Among 2 responders ≥12 to <18 years with haematology tumours, TTR was 2.7 months for HL subject with CR and 8.6 months for NHL subject with PR. DOR was 1.0 month for HL subject with CR and 2.7 months for NHL subject with PR; DOR was censored on the date of their last evaluable tumour assessment for subject with PR.

In subjects ≥12 to <18 years, the 12-month OS rate was 46.6% (95% CI: 26.2%, 64.7%) and 24 month OS was not reached (Table 44).

Nivo+Ipi

In subjects ≥12 to < 18 years, no responses (CR or PR) were observed with nivo+ipi in subjects with the non-lymphoma, solid tumours; SD was observed in 4 (21.1%) subjects (Table 43). In subjects ≥12 to <18 years, the 12-month OS rate was 45.5% (95% CI: 17.5%, 70.1%) and 24 month OS was 30.3% (95% CI: 6.1%, 60.1%) (Table 44).

Table 43 **ORR and BOR by Age Subgroups - Nivolumab and Nivolumab + Ipilimumab - All Treated Response Evaluable Subjects in CA209070 - Parts A-D**

	Minimum follow-up: > 24 months DBL: 30-Sep-2019			**Minimum follow-up: 28.3 months DBL: 30-Jun-2020**		
	Nivolumab			**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: refer to Table S.5.5.2.1 of the CA209070 Interim CSR

Table 44 **OS by Age Subgroups - Nivolumab and Nivolumab + Ipilimumab - All Treated Subjects in CA209070 - Parts A-D**

	Minimum follow-up: > 24 months DBL: 30-Sep-2019			Minimum follow-up: 28.3 months DBL: 30-Jun-2020		
	Nivolumab			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: Table S.8.1.2 and Table S.9.1.2 in Appendix 2

Figure 42 ***Kaplan-Meier Plot of OS – Pooled Analysis: Solid vs. Hemato vs. Total for Each Treatment by Age group – All Treated Subjects in CA209070. Age group: ≥1 - <18 years***

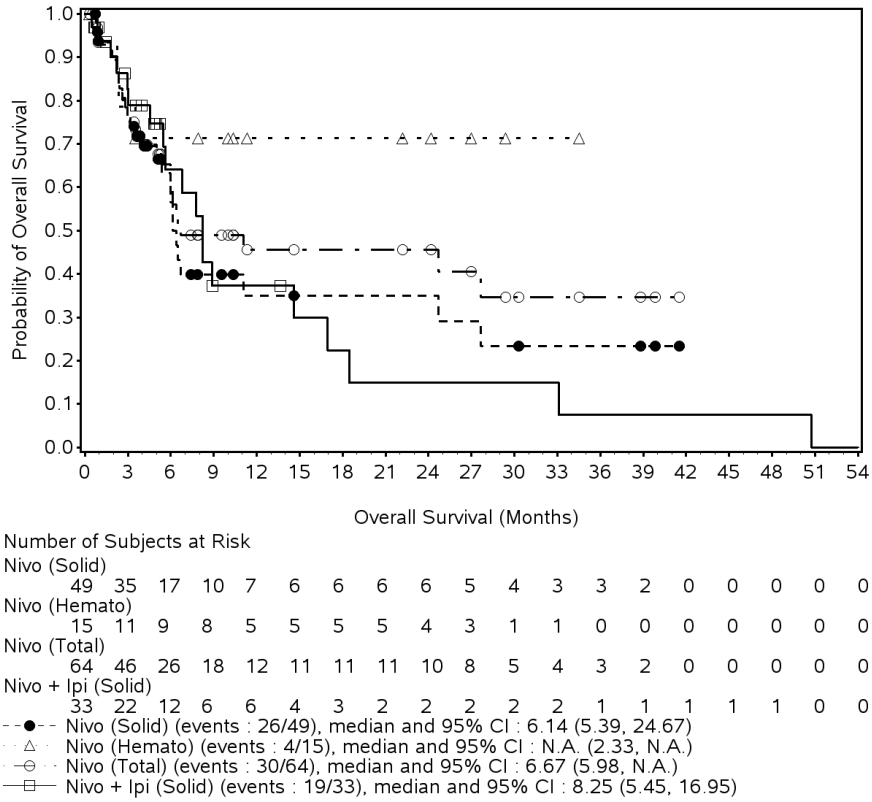
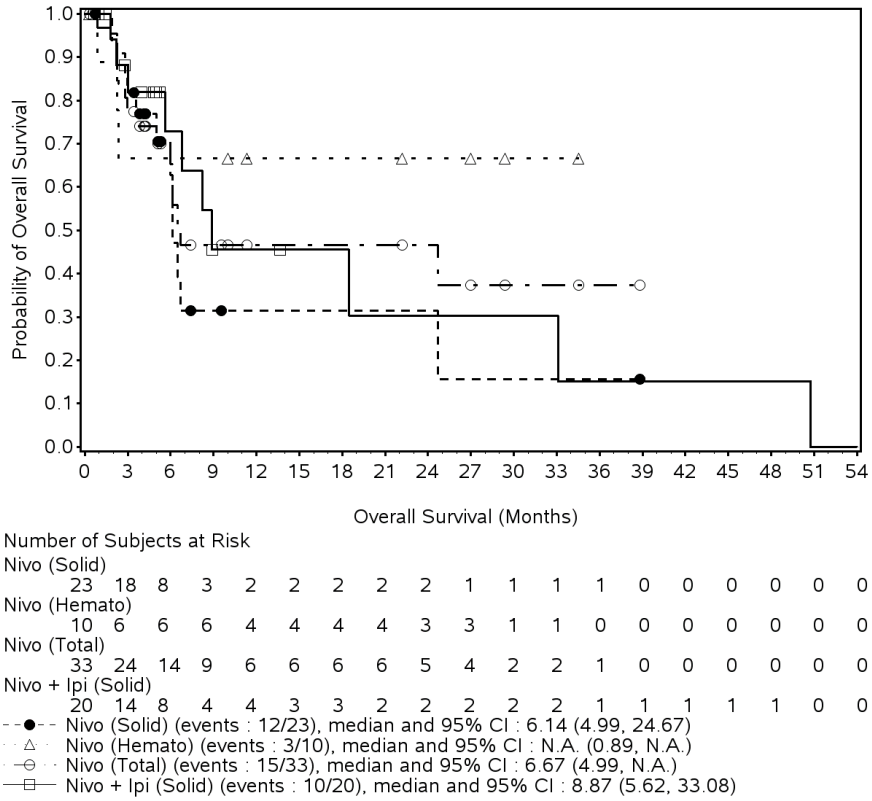


Figure 43 ***Kaplan-Meier Plot of OS – Pooled Analysis: Solid vs. Hemato vs. Total for Each Treatment by Age group – All Treated Subjects in CA209070. Age group: ≥12 - <18 years***



Adolescent (n=1) Subject with Melanoma in Study CA209070

There was one adolescent (15-year-old) subject with advanced melanoma in Part B who received nivolumab 3 mg/kg. This Asian, female subject had a Lansky performance status of 90, received prior lines of anticancer therapies (non-myelosuppressive chemotherapy and immunotherapies [interferon alpha and dendritic cells combined with cytokine-induced killer cells) 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.

Summary of main study(ies)

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 45 Summary of Efficacy for trial CA209070

Title: A phase 1/2 study of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumours as a single agent and in combination with ipilimumab	
Study identifier	CA209070, ADVL1412

<table>
<tr><td>Design</td><td colspan="3">Study CA209070 is a dose-confirmation and dose-expansion study of nivolumab with or without ipilimumab in paediatric and young adult (≤30 years) subjects with recurrent or refractory solid tumours including lymphoma. This COG clinical study is included as one of the agreed measures in both approved PIPs for nivolumab (procedures ref. EMEA-001407-PIP01-12-M03 and EMEA-001407-PIP02-15-M05).
The study consisted of 5 parts:
• Part A: nivo 3 mg/kg Q2W in advanced solid tumours; subjects 1 - <18 years.
• Part B: nivo 3 mg/kg Q2W in NBL, osteosarcoma, Ewing sarcoma, HL, NHL, MEL, NBL (MIGB only), RMS; subjects 1 – 30 years old.
• Part C: nivo+ipi dose escalation (2 dose levels) in advanced solid tumours; subjects 1 - <18 years.
1. Nivo 1 mg/kg + ipi 1 mg/kg Q3W x 4 cycles followed by nivo 3 mg/kg Q2W cycles 5+ until progression
2. Nivo 3 mg/kg + ipi 1 mg/kg Q3W x 4 cycles followed by nivo 3 mg/kg Q2W cycles 5+ until progression
• Part D: Nivo 3 mg/kg + ipi 1 mg/kg Q3W x 4 cycles followed by nivo 3 mg/kg Q2W for cycles 5+ until progression in NBL, osteosarcoma, RMS, Ewing sarcoma, NHL, NBL (MIBG only); subjects 1-30 yrs
• Part E: Nivo 1 mg/kg + ipi 3 mg/kg Q3W x 4 cycles followed by nivo 3 mg/kg Q2W cycles 5+ until progression in rhabdomyosarcoma, Ewing sarcoma; subjects 1-30 yrs old</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:
Nivo (Parts A and B):

Nivo+ipi (Parts C and D):</td><td>
FPFV: 03-Apr-2015; LPFV: 31-Jul-2018; DBL: 30-Sept-2019
FPFV: 13-Aug-2015; LPFV: 20-Feb-2018; DBL: 30-Jun-2020</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Nivolumab 3 mg/kg alone or in combination with ipilimumab 1 mg/kg is safe and tolerable and have antitumor activity in paediatric subjects with relapsed or refractory solid tumours with adequate exposure to nivolumab.</td></tr>
<tr><td>Treatments groups</td><td colspan="2">Nivolumab</td><td>N=80 (for treatment, see above)</td></tr>
<tr><td></td><td colspan="2">Nivolumab + Ipilimumab</td><td>N=46 (for treatment, see above)</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>ORR</td><td>Number of responders divided by the sum of the number of responders and non-responders, multiplied by 100.</td></tr>
<tr><td></td><td>Other endpoint</td><td>TTR</td><td>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).</td></tr>
<tr><td></td><td>Primary endpoint</td><td>DOR</td><td>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 tumour progression or death due to any cause, whichever occurs first.</td></tr>
<tr><td></td><td>Other endpoint</td><td>OS</td><td>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").</td></tr>
<tr><td>Database lock</td><td colspan="3">Interim CSR based on the DBLs of 30-Sep-2019 (Parts A and B) and 30-Jun-2020 (Parts C and D) summarizes results for Parts A-D.</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis: DBL for Parts A-B (nivolumab monotherapy) 30-Sep-2019. DBL for Parts C-D (nivolumab + ipilimumab) 30-Jun-2020</td></tr>
</table>

Analysis population and time point description	Across all cohorts in Parts A to D, a total of 132 subjects were enrolled and 126 treated: 80 subjects treated with nivolumab (Parts A and B) and 46 treated with nivo+ipi (Parts C and D)		
Descriptive statistics and estimate variability	Treatment group	Nivolumab monotherapy N=80	Nivolumab + Ipilimumab N=46
	Number of subjects	75 (response evaluable)	43 (response evaluable)
	ORR (%)	4/75	2/43 (4.7)
	(95% CI)	(1.5, 13.1)	(0.6, 15.8)
	Median OS (months)	11.07	8.87
	(95% CI)	(6.37, 27.63)	(5.75, 18.50)
Notes	Efficacy of Nivolumab and Nivolumab + Ipilimumab in All Treated Subjects in Study CA209070 Parts A-D		

Supportive studies

Study CA209067: A Phase 3, Randomized, Double-blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma

Study CA209067 provides data for nivolumab monotherapy and nivo+ipi in subjects ≥18 years in the approved advanced melanoma indication in adult patients.

Demographics and Baseline Disease Characteristics

No subjects aged <18 years were enrolled in CA209067. Demographic and baseline disease characteristics for all randomized subjects based on the 17-Feb-2015 DBL (final PFS analysis, interim CSR) were generally balanced across the 3 treatment arms.

Table 46 **Key Demographic and Baseline Characteristics - All Randomized Subjects CA209067**

	Nivo N = 316	**Nivo+ipi N =314**	**Ipi N =315**	**Total N =945**
Age, median (range), yrs	60.0 (25 , 90)	61.0 (18 , 88)	62.0 (18 , 89)	61.0 (18 , 90)
Male (n, %)	202 (63.9)	206 (65.6)	202 (64.1)	610 (64.6)
White (n, %)	308 (97.5)	310 (98.7)	303 (96.2)	921 (97.5)
ECOG PS, n (%)				
0	238 (75.3)	230 (73.2)	224 (71.1)	692 (73.2)
1	77 (24.4)	83 (26.4)	91 (28.9)	251 (26.6)
2	1 (0.3)	0	0	1 (0.1)
not reported	0	1 (0.3)	0	1 (0.1)
PD-L1 status (IVRS)				
positive	143 (45.3)	144 (45.9)	144 (45.7)	431 (45.6)
negative/indeterminate	173 (54.7)	170 (54.1)	171 (54.3)	514 (54.4)
M stage at study entry (CRF)				
M0/M1A/M1B	131 (41.5)	129 (41.1)	126 (40.0)	386 (40.8)
M1C	185 (58.5)	185 (58.9)	189 (60.0)	559 (59.2)
AJCC stage at study entry				

Table 46 **Key Demographic and Baseline Characteristics - All Randomized Subjects CA209067**

	Nivo N = 316	Nivo+ipi N =314	Ipi N =315	Total N =945
Stage III	25 (7.9)	17 (5.4)	22 (7.0)	64 (6.8)
Stage IV	291 (92.1)	297 (94.6)	293 (93.0)	881 (93.2)
Baseline LDH				
≤ ULN	196 (62.0)	199 (63.4)	194 (61.6)	589 (62.3)
> ULN	112 (35.4)	114 (36.3)	115 (36.5)	341 (36.1)
History of brain metastasis	8 (2.5)	11 (3.5)	15 (4.8)	34 (3.6)
BRAF status (IVRS)				
mutant	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
wildtype	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)

Source: refer to Table 5.3.1-1, Table 5.3.2-1, Table 5.3.3-1, and Table S.3.2 of the CA209067 Interim CSR

Efficacy

At the pre-specified final OS analysis (28 months minimum follow-up for OS and ORR; 18 minimum months follow-up for PFS), both nivolumab and nivo+ipi demonstrated statistically significant improvements in OS and PFS as well as in ORR compared to ipilimumab alone in adult subjects with advanced melanoma (Table 47). Of note, CA209067 was not designed to assess whether adding ipilimumab to nivolumab improves PFS or OS compared to nivolumab as a single agent, although exploratory analyses were provided.

Table 47 **Efficacy Summary - All Randomized Subjects - CA209067**

Efficacy Parameter	Minimum follow-up for OS and ORR: 28 months Minimum follow-up for PFS: 18 months DBL: 13-Sep-2016		
	Nivo N = 316	Nivo+ipi N = 314	Ipi N = 315
Co-primary endpoints			
OS			
Events, n (%)	142 (44.9)	128 (40.8)	197 (62.5)
HR (98% CI)[a]	N vs I 0.63 (0.48, 0.81)	N+I vs I 0.55 (0.42, 0.72)	
p-value[b]	<0.0001	<0.0001	
mOS (95% CI), months[c]	NA (29.08, NA)	NA	19.98 (17.08, 24.61)
OS rate, (95% CI)			
24 months	0.59 (0.53, 0.64)	0.64 (0.59, 0.69)	0.45 (0.39, 0.50)
PFS			
Events, n (%)	195 (61.7)	169 (53.8)	253 (80.3)
HR (95% CI)[a]	N vs I 0.54 (0.45, 0.66)	N+I vs I 0.42 (0.34, 0.51)	
mPFS (95% CI), months[d]	6.87 (4.34, 9.46)	11.73 (8.90, 21.88)	2.86 (2.79, 3.15)
PFS rate, (95% CI) %			
24 months	0.37 (0.31, 0.43)	0.43 (0.37, 0.48)	0.12 (0.09, 0.17)

Table 47 **Efficacy Summary - All Randomized Subjects - CA209067**

Efficacy Parameter	Minimum follow-up for OS and ORR: 28 months Minimum follow-up for PFS: 18 months DBL: 13-Sep-2016		
	Nivo **N = 316**	**Nivo+ipi** **N = 314**	**Ipi** **N = 315**
Secondary Endpoints			
CR rate[e]	47 (14.9%)	54 (17.2%)	14 (4.4%)
ORR[f]			
N responders (%)	141 (44.6%)	185 (58.9%)	60 (19.0%)
95% CI	39.1, 50.3	53.3, 64.4	14.9, 23.8
Difference of ORRs (95% CI)[g]	N vs I 25.7% (18.9, 32.5)	N+I vs I 39.7% (32.89, 46.5)	
Exploratory Endpoints			
Randomized Subjects with a Response	**Nivo** **N = 141**	**Nivo+Ipi** **N = 185**	**Ipi** **N = 60**
Time to Objective Response			
Median (Min, Max), months	2.79 (2.3, 32.9)	2.76 (1.1, 28.8)	2.79 (2.5, 17.3)
Duration of Objective Response			
Ongoing responder (as of the last available tumour assessment), n/N (%)	94/141 (66.7)	124/185 (67.0)	30/60 (50.0)
Median (95% CI), months[h]	31.11 (31.11, NA)	NA	18.20 (8.34, NA)
Min, Max[i]	0.0, 32.3	0.0, 33.3	0.0, 31.5

[a] Stratified Cox proportional hazard model.

[b] Log-rank Test stratified by PD-L1 status, BRAF status, and M stage at screening as entered into the IVRS.

[c] Kaplan-Meier estimate. NA - not available/not estimable

[d] Kaplan-Meier estimate.

[e] Per RECIST 1.1.

[f] Confidence interval based on the Clopper and Pearson method.

[g] The estimate of the difference in ORR and corresponding 95% CI is based on Cochran-Mantel-Haenszel method of weighting, adjusting for PD-L1 status, BRAF status and M-stage at screening as entered into the IVRS.

[h] Median computed using Kaplan-Meier product-limit method.

[i] Censored observation.

Source: refer to Table 7.1-1 of the CA209067 Final CSR

Efficacy results with longer follow-up (minimum follow-up for OS of 48 months and 60 months) remained consistent with the results of the final OS analysis at a minimum follow-up of 28 months (Table 48). Recently, updated results with extended follow-up (at least 7.5 years, DBL of 12-Nov-2021) have been provided and efficacy data concurred with the previous results.

Table 48 **Efficacy Summary - Long-Term Follow-up - All Randomized Subjects - CA209067**

Efficacy Parameter	48 Months Follow-up for OS DBL: 10-May-2018			60 Months Follow-up for OS DBL: 02-Jul-2019		
	Nivo N = 316	**Nivo+ipi N = 314**	**Ipi N = 315**	**Nivo N = 316**	**Nivo+ipi N = 314**	**Ipi N = 315**
Co-primary endpoints						
OS						
Events, n (%)	168 (53.2)	147 (46.8)	218 (69.2)	176 (55.7)	152 (48.4)	230 (73.0)
HR (95% CI)[a]	N vs I 0.65 (0.53, 0.79)	N+I vs I 0.54 (0.44, 0.67)		N vs I 0.63 (0.52, 0.76)	N+I vs I 0.52 (0.42, 0.64)	
mOS (95% CI), months[b]	36.93 (28.25, NA)	NA (38.18, NA)	19.94 (16.85, 24.61)	36.93 (28.25, 58.71)	NA (38.18, NA)	19.94 (16.85, 24.61)
OS rate, (95% CI)						
48 months	0.46 (0.41, 0.52)	0.53 (0.47, 0.58)	0.30 (0.25, 0.35)	0.47 (0.41, 0.52)	0.53 (0.47, 0.58)	0.30 (0.25, 0.35)
60 months	-	-	-	0.44 (0.39, 0.50)	0.52 (0.46, 0.57)	0.26 (0.22, 0.31)
PFS						
Events, n (%)	201 (63.6)	182 (58.0)	258 (81.9)	203 (64.2)	182 (58.0)	261 (82.9)
HR (95% CI)[a]	N vs I 0.53 (0.44, 0.64)	N+I vs I 0.42 (0.35, 0.51)		N vs I 0.53 (0.44, 0.64)	N+I vs I 0.42 (0.35, 0.51)	
mPFS (95% CI), months[c]	6.93 (5.13, 10.18)	11.50 (8.74, 19.32)	2.86 (2.79, 3.15)	6.93 (5.13, 10.18)	11.50 (8.74, 19.32)	2.86 (2.79, 3.15)
PFS rate, (95% CI) %						
48 months	0.31 (0.25, 0.36)	0.37 (0.31, 0.42)	0.09 (0.06, 0.13)	0.30 (0.25, 0.36)	0.37 (0.31, 0.42)	0.09 (0.06, 0.13)
60 months				0.29 (0.24, 0.35)	0.36 (0.31, 0.42)	0.08 (0.05, 0.12)
Secondary endpoints						
CR Rate[d]	56 (17.7%)	67 (21.3%)	16 (5.1%)	60 (19.0%)	69 (22.0%)	18 (5.7%)
ORR[e]						
N responders (%)	141 (44.6%)	183 (58.3%)	60 (19.0%)	141 (44.6%)	183 (58.3%)	60 (19.0%)
95% CI	39.1, 50.3	52.6, 63.8	14.9, 23.8	39.1, 50.3	52.6, 63.8	14.9, 23.8
Difference of ORRs (95% CI)[f]	N vs I 25.6% (18.8, 32.5)	N+I vs I 39.0% (32.2, 45.9)		N vs I 25.6% (18.8, 32.5)	N+I vs I 39.0% (32.2, 45.9)	
Exploratory endpoints						

Table 48 **Efficacy Summary - Long-Term Follow-up - All Randomized Subjects - CA209067**

Efficacy Parameter	48 Months Follow-up for OS DBL: 10-May-2018			60 Months Follow-up for OS DBL: 02-Jul-2019		
	Nivo N = 316	Nivo+ipi N = 314	Ipi N = 315	Nivo N = 316	Nivo+ipi N = 314	Ipi N = 315
Randomized Subjects with a Response	**Nivo N = 141**	**Nivo+Ipi N = 183**	**Ipi N = 60**	**Nivo N = 141**	**Nivo+Ipi N = 183**	**Ipi N = 60**
Time to Objective Response						
Median (Min, Max), months	2.79 (2.3, 42.9)	2.76 (1.1, 48.6)	2.86 (2.5, 49.7)	2.79 (2.3, 42.9)	2.76 (1.1, 27.8)	2.86 (2.5, 49.7)
Duration of Objective Response						
Ongoing responder (as of the last available tumour assessment), n/N (%)	88/141 (62.4)	112/183 (61.2)	26/60 (43.3)	86/141 (61.0)	113/183 (61.7)	24/60 (40.0)
Median (95% CI), months[g]	NA (45.70, NA)	50.07 (44.02, NA)	14.39 (8.34, NA)	NA (50.43, NA)	NA	14.39 (8.34, 53.65)
Min, Max[h]	0.0, 50.8	0.0, 53.5	0.0, 50.5	0.0, 63.3	0.0, 65.2	0.0, 61.9

[a] Stratified Cox proportional hazard model.

[b] Kaplan-Meier estimate. NA - not available/not estimable

[c] Kaplan-Meier estimate.

[d] Per RECIST 1.1.

[e] Confidence interval based on the Clopper and Pearson method.

[f] The estimate of the difference in ORR and corresponding 95% CI is based on Cochran-Mantel-Haenszel method of weighting, adjusting for PD-L1 status, BRAF status and M-stage at screening as entered into the IVRS.

[g] Median computed using Kaplan-Meier product-limit method.

[h] Censored observation.

Source: refer to Table 3.1-1 of the of the Addendum 02 to the CA209067 Final CSR (48-month follow-up) and Table 4.1-1 of the Addendum 03 to the CA209067 Final CSR (60-month follow-up)

Study CA209915: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab Combined with Ipilimumab versus Nivolumab Monotherapy after Complete Resection of Stage IIIb/c/d or Stage IV Melanoma

Study CA209915 was designed to investigate whether nivolumab and ipilimumab combination treatment will improve RFS compared to nivolumab monotherapy (primary outcome) as adjuvant treatment in patients with completely resected Stage IIIb/c/d or Stage IV no evidence of disease (NED) melanoma. A total of 1844 adults and adolescents between 12 to <18 years of age were randomized to nivolumab + ipilimumab or nivolumab monotherapy. Of these, 3 adolescent subjects were randomized and treated; 2 adolescents were treated with nivolumab monotherapy and 1 adolescent was treated with nivolumab + ipilimumab combination therapy. This study was assessed within procedure EMEA/H/C/003985/P46/043.

Of the 1844 subjects randomized to nivolumab + ipilimumab or nivolumab, 1833 (99.4%) were treated (916 with nivolumab + ipilimumab, 917 with nivolumab).

For the 3 included adolescents between 12 to <18 years of age, the dosing of nivolumab was based on body weight as follows: Q2W dosing - 3 mg/kg IV Q2W up to a maximum of 240 mg; Q4W dosing - 6 mg/kg Q4W up to a maximum of 480 mg.

Table 49 ***Baseline Disease Characteristics in Adolescent Subjects - CA209915***

Age/Sex/Race	Time from Surgical Resection to Randomization (Weeks)	Completion Lymph Node Dissection	Equivocal Lymph Nodes Present	Tumor Origin	Location of Primary Tumor	Melanoma Subtype
Nivolumab						
15/M/C	6.4	YES	NO	RECURRENT	SKIN	CUTANEOUS
16/F/C	10.1	YES	NO	PRIMARY	SKIN	CUTANEOUS
Nivo+ipi						
16/M/C	8.1	YES	NO	PRIMARY	LYMPH NODE	OTHER

Age/Sex/Race	Disease Stage at Study Entry According to: IRT	Disease Stage at Study Entry According to: CRF (M-Status)	Tumor Thickness (mm)	Tumor Ulceration Status	Lymph Node Involvement	Total Number of Tumor-Involved Regional Lymph Nodes	Number of Clinically Occult Nodes/ Clinically Detected Nodes	Presence of In-Transit Satellite and/or Microsatellite Metastases
Nivolumab								
15/M/C	STAGE IIIB	STAGE IIIC*	NO EVIDENCE OF PRIMARY MELANOMA	UNKNOWN	NOT REPORTED	2 - 3	NOT REPORTED/ 2 - 3	NOT APPLICABLE
16/F/C	STAGE IIIC/IIID	STAGE IIIC	>2.0-4.0	PRESENT	CLINICALLY DETECTED ONLY	1	0/ 1	NOT APPLICABLE
Nivo+ipi								
16/M/C	STAGE IIIC/IIID	STAGE IIIC	>2.0-4.0	ABSENT	CLINICALLY DETECTED AND CLINICALLY OCCULT	>= 4	>= 4/ 1	NOT APPLICABLE

*discrepancy from IRT.
Source: refer to Appendix 3.4 and Appendix 3.5 of the CA209915 Primary CSR[10]

Study CA209915 did not meet the primary endpoint demonstrating statistically significant improvement in RFS with nivo+ipi vs nivo in all randomized subjects or all randomized subjects with tumour PD L1 < 1%. All randomized HR 0.92 [97.295% CI: 0.77, 1.09]; stratified log-rank p = 0.26861; all randomized with PD-L1 < 1%: 0.91 [95% CI: 0.73, 1.14].

Overall, RFS in adolescent subjects treated with nivo (n = 2) was 11.2 months (1 subject) and 30.4 months (1 subject), and with nivo+ipi (n = 1) was 16.9 months. Due to the small sample size (n = 3), no definitive conclusion could be drawn about efficacy of nivo+ipi vs nivolumab in adolescents with completely resected Stage IIIb/c/d or Stage IV no evidence of disease melanoma.

Table 50 ***Recurrence-free survival in adolescent subjects in study CA209915***

Unique Subject ID (Age/Sex/Race)	Randomization Date	First/Last Dose Date	Event/Censored Date	Event Occurred	Event/Censoring Status	RFS (Months)	Subsequent Therapy Date
[redacted] (15/M/C)	23OCT2017	24OCT2017/ 25SEP2018	05MAY2020	NO	IN FOLLOW-UP	30.4	
[redacted] (16/M/C)	05MAR2018	06MAR2018/ 11DEC2018	01AUG2019	YES	DISTANT METASTASIS	16.9	07AUG2019
[redacted] (16/F/C)	02MAR2018	05MAR2018/ 11FEB2019	06FEB2019	YES	REGIONAL RECURRENCE	11.2	13MAR2019

Table 51 ***All PD-L1 IHC data in adolescent subjects in study CA209915***

			Primary Definition			Secondary Definition		
Unique Subject ID (Age/Sex/Race)	Randomization Date	First/Last Dose Date	PFS (Months)	Event or Censored/ Date	Event or Censoring Status	PFS (Months)	Event or Censored/ Date	Event or Censoring Status
[redacted] (15/M/C)	23OCT2017	24OCT2017/ 25SEP2018	30.4	CENSORED/ 05MAY2020	NO NEXT-LINE SYSTEMIC THERAPY AND NO DEATH	30.4	CENSORED/ 05MAY2020	NO NEXT-LINE SYSTEMIC THERAPY AND NO DEATH
[redacted] (16/M/C)	05MAR2018	06MAR2018/ 11DEC2018	17.2	EVENT/ 11AUG2019	END OF NEXT-LINE SYSTEMIC THERAPY	17.2	EVENT/ 11AUG2019	END OF NEXT-LINE SYSTEMIC THERAPY
[redacted] (16/F/C)	02MAR2018	05MAR2018/ 11FEB2019	27.2	EVENT/ 05JUN2020	END OF NEXT-LINE SYSTEMIC THERAPY	27.2	EVENT/ 05JUN2020	END OF NEXT-LINE SYSTEMIC THERAPY

Table 52 ***Subsequent Systemic Cancer Therapy in Adolescent Subjects – CA209915***

Age/Sex/Race	First/Last Dose	Visit	Regimen Number Regimen Setting Line of Therapy	Start/Stop FU Therapy	FU Therapy Specification	Best Response Progression (Y/N) - Date Reason for Discontinuation
Nivolumab 16/F/C	05MAR2018/ 11FEB2019	FOLLOW-UP 1	1 ADJUVANT NOT APPLICABLE	29APR2019/ 05JUN2020	ANTINEOPLASTIC & IMMUNOMODULATING AGENT ANTINEOPLASTIC AGENTS DABRAFENIB DABRAFENIB	COMPLETE RESPONSE COMPLETED TREATMENT
	05MAR2018/ 11FEB2019		1 ADJUVANT NOT APPLICABLE	29APR2019/ 05JUN2020	ANTINEOPLASTIC & IMMUNOMODULATING AGENT ANTINEOPLASTIC AGENTS TRAMETINIB TRAMETINIB	COMPLETE RESPONSE COMPLETED TREATMENT
Nivo+ipi 16/M/C	06MAR2018/ 11DEC2018	OFF-TREATMENT	1 METASTATIC FIRST LINE	07AUG2019/ 11AUG2019	ANTINEOPLASTIC & IMMUNOMODULATING AGENT ANTINEOPLASTIC AGENTS TEMOZOLOMIDE TEMOZOLOMIDE	UNABLE TO DETERMINE DEATH

Source: refer to Appendix 5.6 of the CA209915 Primary CSR[10]

Study CA209238: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c/d or Stage IV Melanoma in Subjects who are at High Risk for Recurrence

Study CA209238 provides data for nivolumab monotherapy in subjects ≥ 18 years in the approved adjuvant melanoma indication in adult patients.

Table 53 ***Key Demographic and Baseline Characteristics - All Randomized Subjects - CA209238***

	Nivo N = 453	**Ipi N =453**	**Total N =906**
Age, median (range), yrs	56.0 (19, 83)	54.0 (18, 86)	55.0 (18, 86)
Male (n, %)	258 (57.0)	269 (59.4)	527 (58.2)
White (n, %)	425 (93.8)	434 (95.8)	859 (94.8)
ECOG PS, n (%)			
0	413 (91.2)	405 (89.4)	818 (90.3)
1	40 (8.8)	48 (10.6)	88 (9.7)
Median time from surgical resection to randomization (range), wks	9.0 (0, 15)	9.7 (0, 35)	9.3 (0, 35)

	Nivo N = 453	Ipi N =453	Total N =906
CRF disease stage at study entry (n, %)			
stage IIIB	163 (36.0)	148 (32.7)	311 (34.3)
stage IIIC	204 (45.0)	218 (48.1)	422 (46.6)
stage IV	82 (18.1)	87 (19.2)	169 (18.7)
Other[a]	2 (0.4)	0	2 (0.2)
not reported	2 (0.4)	0	2 (0.2)
CRF PD-L1 status, (n, %)			
< 1%	140 (30.9)	133 (29.4)	273 (30.1)
>= 1%	287 (63.4)	307 (67.8)	594 (65.6)
indeterminate	25 (5.5)	13 (2.9)	38 (4.2)
unevaluable/ not reported	1 (0.2)	0	1 (0.1)
BRAF mutation status			
mutant	187 (41.3)	194 (42.8)	381 (42.1)
wildtype	197 (43.5)	214 (47.2)	411 (45.4)
not reported	69 (15.2)	45 (9.9)	114 (12.6)

[a] Subjects with Disease Stage IIIa

Source: refer to Table 5.3.1-1 and Table 5.3.1-2 of the CA209238 Interim CSR

At the pre-specified interim RFS analysis (minimum follow-up 18 months, SmPC), a statistically significant improvement in RFS with nivolumab vs ipilimumab was demonstrated. A statistically significant improvement in DMFS was also observed with nivolumab vs ipilimumab. Higher tumour PD-L1 expression (≥ 5%) was associated with a lower risk of recurrence for nivolumab relative to ipilimumab, with nivolumab showing benefit over ipilimumab regardless of tumour PD-L1 expression status (EMEA/H/C/003985/II/0041).

Table 54 **Efficacy Summary- All Randomized Subjects - CA209238**

Efficacy Parameter	**Minimum follow-up: 18 months DBL: 12-Jun-2017**	
	Nivolumab N = 453	**Ipilimumab N = 453**
• ***Primary endpoint***	•	
• **RFS**	•	
Events, n (%)	• 154 (34.0)	206 (45.5)
Median RFS (95% CI)[a], months	• N.A.	N.A. (16.56, N.A.)
hazard ratio (HR) (97.56% CI)[b]	0.65 (0.51, 0.83)	
Stratified log rank p-value[c]	<0.0001	
Rate at 12 months, % (95% CI)[a]	• 70.5 (66.1, 74.5)	60.8 (56.0, 65.2)
Rate at 18 months, % (95% CI)[a]	• 66.4 (61.8, 70.6)	52.7 (47.9, 57.4)
• ***Secondary endpoints***	•	

Table 54 **Efficacy Summary- All Randomized Subjects - CA209238**

Efficacy Parameter	Minimum follow-up: 18 months DBL: 12-Jun-2017	
	Nivolumab N = 453	**Ipilimumab N = 453**
• **RFS by Baseline PD-L1 Expression (5% tumour cell membrane expression)**	•	
Subjects with ≥ 5% PD-L1 Expression, n (%)	• 152 (33.6)	154 (34.0)
Unstratified HR (95% CI)[d]	0.50 (0.32, 0.78)	
Median (95% CI)[a], months	• N.A.	N.A.
Subjects with < 5% PD-L1 Expression, n (%)	• 275 (60.7)	286 (63.1)
Unstratified HR (95% CI)[d]	0.71 (0.56, 0.91)	
Median (95% CI)[a], months	• N.A.	15.90 (10.38, N.A.)
Subjects with Non-quantifiable PD-L1 Expression, n (%)	• 26 (5.7)	13 (2.9)
Unstratified HR (95% CI)[d]	0.78 (0.28, 2.19)	
Median (95% CI)[a], months	• N.A. (6.70, N.A.)	N.A. (4.76, N.A.)
• ***Exploratory endpoints***	•	
• **DMFS** in subjects with Stage III disease at study entry	•	
Events/no. of subjects, n/N (%)	• 93/369 (25.2%)	115/366 (31.4%)
Median DMFS (95% CI)[a], months	• N.A.	N.A.
HR (95% CI)[b]	0.73 (0.55, 0.95)	
Stratified log rank p-value[e]	0.0204	
Rate at 12 months, % (95% CI)[a]	• 80.2 (75.6, 83.9)	73.4 (68.4, 77.7)
Rate at 18 months, % (95% CI)[a]	• 75.1 (70.3, 79.3)	66.6 (61.2, 71.3)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. HR is nivolumab over ipilimumab.

[c] Log-rank test stratified by baseline tumour PD-L1 status and disease stage at study entry as entered into the IVRS.

[d] Unstratified Cox proportional hazards model. HR is nivolumab over ipilimumab.

[e] Log-rank test stratified by PD-L1 status as entered into the IVRS

Source: Table 7.1-1 of the CA209238 Interim CSR

At a minimum follow-up of 48 months and for final OS and updated RFS analyses (final CSR, SmPC), CA209238 continued to demonstrate improvement in RFS with nivolumab vs ipilimumab. Median OS was not reached in either arm. RFS benefit was consistently demonstrated across all subgroups, including tumour PD-L1 expression, BRAF status, and stage of disease (EMEA/H/C/003985/II/0098).

Table 55 **Efficacy Summary - Long-Term Follow-up (All Randomized Subjects - CA209238)**

Efficacy Parameter	Minimum follow-up: 48 months DBL: 30-Jan-2020	
	Nivolumab N = 453	**Ipilimumab N = 453**
Primary endpoint		
RFS		
Events, n (%)	212 (46.8)	253 (55.8)
Median RFS (95% CI)[a], months	52.37 (42.51, N.A.)	24.08 (16.56, 35.09)
HR (95% CI)[b]	0.71 (0.60, 0.86)	
Stratified log rank p-value[c]	0.0003	
Rate at 36 months, % (95% CI)[a]	57.6 (52.8, 62.1)	44.4 (39.6, 49.1)
Rate at 42 months, % (95% CI)[a]	54.8 (50.0, 59.4)	42.8 (38.1, 47.5)
Rate at 48 months, % (95% CI)[a]	51.7 (46.8, 56.3)	41.2 (36.4, 45.9)
Secondary endpoints		
OS		
Events, n (%)	100 (22.1)	111 (24.5)
Median OS (95% CI)[a], months	N.A	N.A
HR (95.03% CI)[b]	0.87 (0.66, 1.14)	
Stratified log rank p-value[c]	0.3148	
Rate at 36 months, % (95% CI)[a]	81.7 (77.8, 85.1)	81.6 (77.6, 85.0)
Rate at 42 months, % (95% CI)[a]	80.3 (76.3, 83.8)	78.3 (74.0, 81.9)
Rate at 48 months, % (95% CI)[a]	77.9 (73.7, 81.5)	76.6 (72.2, 80.3)
RFS by Baseline Tumor PD-L1 Expression (5% tumour cell membrane expression)		
Tumor PD-L1 ≥ 5%, n/N	55/153	71/154
Unstratified HR (95% CI)[d]	0.67 (0.47, 0.96)	
Median (95% CI)[a], months	N.A. (50.17, N.A.)	52.86 (24.15, N.A.)
Tumor PD-L1 < 5%, n (%)	146/275	173/286
Unstratified HR (95% CI)[d]	0.75 (0.60, 0.93)	
Median (95% CI)[a], months	36.30 (19.84, N.A.)	16.56 (10.87, 25.79)
Tumor PD-L1 Non-quantifiable, n (%)	11/25	9/13
Unstratified HR (95% CI)[d]	0.60 (0.25, 1.45)	
Median (95% CI)[a], months	N.A. (6.70, N.A.)	28.25 (4.76, N.A.)
Exploratory endpoint		
DMFS in subjects with Stage III disease at study entry		
Events/number of subjects, n/N (%)	142/370 (38.4)	160/366 (43.7)
Median DMFS (95% CI)[a], months	N.A. (52.37, N.A.)	52.86 (42.41, N.A.)

Table 55 **Efficacy Summary - Long-Term Follow-up (All Randomized Subjects - CA209238)**

Efficacy Parameter	Minimum follow-up: 48 months DBL: 30-Jan-2020	
	Nivolumab N = 453	Ipilimumab N = 453
HR (95% CI)[b]	0.79 (0.63, 0.99)	
Stratified log rank p-value[e]	0.0447	
Rate at 36 months, % (95% CI)[a]	65.2 (59.9, 70.0)	57.2 (51.7, 62.3)
Rate at 42 months, % (95% CI)[a]	62.0 (56.7, 66.9)	55.8 (50.3, 60.9)
Rate at 48 months, % (95% CI)[a]	59.2 (53.7, 64.2)	53.3 (47.7, 58.5)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. HR is nivolumab over ipilimumab.

[c] Log-rank test stratified by baseline tumour PD-L1 status and disease stage at study entry as entered into the IVRS.

[d] Unstratified Cox proportional hazards model. HR is nivolumab over ipilimumab.

[e] Log-rank test stratified by baseline tumour PD-L1 status as entered into the IVRS

Source: refer to Table 7.1-1 of the CA209238 Final CSR

2.4.2. Discussion on clinical efficacy

This is an application for the extension of the approved indications for Opdivo (nivolumab) monotherapy, and in combination with ipilimumab, for the treatment of advanced or metastatic melanoma, and as monotherapy for the adjuvant treatment of complete resected advanced melanoma, to include adolescent patients (12 years and older).

This application is based on the results from study CA209070 (ADVL1412), included as one of the measures in the two approved Paediatric Investigation Plans (PIP) for nivolumab (procedures ref. EMEA-001407-PIP01-12-M03 and EMEA-001407-PIP02-15-M05). Supportive efficacy data are provided by study CA209067 (CheckMate 067), the pivotal trial on which the nivolumab and ipilimumab approvals (EMEA/H/C/003985/II/0003 and EMEA/H/C/002213/II/0055) for the treatment of advanced melanoma were based. This study only enrolled adult patients. The similarity of melanoma, in terms of course of the disease and expected response to treatment, between adults and adolescents, is discussed below.

Design and conduct of clinical studies

Study CA209070 is a phase 1/2 open-label trial of nivolumab and nivolumab in combination with ipilimumab in children, adolescents, and young adults with recurrent or refractory solid tumours. The study was initially planned with 3 parts (part A, B and C) with the aim to establish the RP2D for both nivolumab monotherapy (part A) and the combination of nivolumab+ipilimumab (part C) and to evaluate toxicity of the nivolumab monotherapy RP2D in some disease specific cohorts (part B). The study protocol was later amended to include parts D and E. Part D allowed inclusion of patients from select cohorts in part B who had not progressed on nivolumab monotherapy to be further treated with the combination of nivolumab+ipilimumab (nivo+ipi). Part E used an alternative dosing of nivolumab 1 mg/kg + ipilimumab 3 mg/kg in comparison with the RP2D from part C (nivo 3mg/kg + ipi 1 mg/kg) in patients with rhabdomyosarcoma or Ewing sarcoma/peripheral PNET. The study was designed to

evaluate the safety and tolerability, assess antitumor effects, to determine whether the systemic nivolumab exposure in children is similar to the systemic exposure in adults and to evaluate the PK of nivolumab alone and in combination with ipilimumab.

The study enrolled patients from 12 months to 18 years with recurrent or refractory solid tumours without CNS tumours or CNS metastases in parts A, C and B7 (melanoma), and from 12 months to 30 years of age in parts B and D. The disease specific cohorts in parts B and D enrolled patients with neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma or peripheral PNET, NHL, HL or melanoma (these two last diagnoses were available only in part B of the study). All included patients must not have any curative or proven to prolong survival therapy available at enrolment.

Subjects included in parts A and B received nivolumab at a dose of 3 mg/kg Q2W. There was a first dose level for part C consisting in nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3W for cycles 1 to 4, followed by nivolumab 3 mg/kg Q2W until progression. If no DLTs were reported, the dose was escalated to nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for cycles 1 to 4, followed by nivolumab 3 mg/kg Q2W until progression, and this was the dosing used for part D of the study. Nivolumab was administered over a 60 min infusion and ipilimumab during 90 minutes.

There were maximum 375 subjects planned to be included in the whole study, based on a Simon's optimal two-stage design, depending on the number of patients evaluable for response in each stage or cohort and the appearance or not of any DLT that would prevent or allow a cohort expansion. Additionally, within protocol Amendment 2A, in light of the observed activity for nivolumab in adult patients with melanoma, a cohort with non-statistical design was opened (part B7) to enrolment of patients with unresectable, metastatic, relapsed, or refractory melanoma.

Analyses were performed on all treated subjects per treatment group and cohort, also by pooling patients treated with nivolumab monotherapy or the combination, separating solid tumours and hematologic malignancies. Additional analyses by disease diagnosis and age category were included.

The original protocol version, dated 16-Jan-2015, was provided. According to the MAH, up to the latest DBL, 12 global amendments were issued that resulted in new versions of the study protocol and these have been submitted but, apparently, other region-specific amendments were also performed, without relevant changes; as the first included version (after the original) is Amendment 1A and the next version is Amendment 2C, where, in fact, a reference to the melanoma cohort (part B7) having been added in Amendment 2A/2B has been found. Part D was included by Amendment 4, in order to assess the activity of the combination of nivo+ipi for select disease cohorts which had not progressed beyond initial part B due to the lack of responses to monotherapy. The rationale behind this change was based on recently published new data that reported that pembrolizumab (anti-PD1) had shown little activity in osteosarcoma and Ewing's sarcoma combined with the fact that, in melanoma, response rates were higher with the combination compared to nivolumab monotherapy in adults. However, a melanoma cohort in Part D was never planned. Of note, the protocol of study CA209067 (supportive) only allowed the inclusion of subjects ≥18 years old. Amendment 6 (24-Feb-2017) included assessment of cardiac function based on the occurrence of myocarditis in patients using ipilimumab + nivolumab in other studies. By Amendment 10 (31-Jul-2019), infusion time for nivolumab was reduced from 60 to 30 min.

Although there were 91 important protocol deviations reported in this study with 21 of them categorised as major protocol deviations, these deviations were not considered relevant based on the reports from internal audits of the study provided by the sponsor.

Efficacy data and additional analyses

A total of 132 subjects were enrolled and 126 were treated. Baseline demographics in all treated subjects were balanced between the nivo and nivo+ipi treatment groups. Ninety-seven subjects were <18 years old and, among them, 53 subjects ≥12 to <18 years old. A minimum follow-up of 14 months has been reported for all patients treated with nivolumab monotherapy (n=80) and 28 months for patients treated with the combination (n=46). The median follow-up for all patients treated in the study was 44 months. At the DBL (30-Sep-2019 for nivolumab patients and 30-Jun-2020 for nivo+ipi subjects), only one patient with HL in part B5 was still on treatment. The most common reason for treatment discontinuation was disease progression. A high percentage of patients (67.2% of the subjects treated with nivolumab and 93.9% from the subjects treated with the combination) were not continuing in the study at the time of the DBL, most of them due to death but there were also some patients who withdrew consent, enrolled in other studies or were lost to follow-up. By treatment, 64 patients <18 years old received nivolumab monotherapy in parts A and B while 33 patients <18 years old received the combination in parts C and D. Focusing on adolescents (≥12 to <18 years old), 33 subjects received nivolumab and 20 subjects received nivolumab + ipilimumab. Regarding baseline PD-L1 expression per validated Dako PD-L1 IHC assay, there were 63 (78.8%) evaluable patients from those who were treated with nivolumab and 39 (84.8%) evaluable patients treated with the combination. Among those PD-L1 evaluable subjects, 34.9% of the subjects treated with nivo monotherapy and 17.9% of the patients treated with nivo+ipi presented a baseline PD-L1 expression ≥1%. Baseline PD-L1 expression for the only melanoma patient enrolled was missing. From the 80 patients who were treated with nivolumab monotherapy, there were 20 neuroblastoma, 13 osteosarcoma, 11 rhabdomyosarcoma, 11 Ewing sarcoma/peripheral PNET, 10 Hodgkin lymphoma and another 10 non-Hodgkin lymphoma, 1 melanoma and 4 subjects diagnosed with other solid tumours. Among the 46 patients treated with nivolumab + ipilimumab, there were one neuroblastoma, 13 osteosarcoma, 10 rhabdomyosarcoma, another 10 with Ewing sarcoma/peripheral PNET and 12 patients diagnosed with other solid tumours.

Efficacy endpoints included ORR, TTR, DOR and OS, and all analyses were descriptive. For nivolumab monotherapy, no objective response was observed for the solid tumours cohorts (from 58 response evaluable subjects including melanoma) while ORR was 23.5% (95% CI: 6.8, 49.9) for the haematological tumours cohort (N=17 response evaluable subjects). For nivo+ipi treatment (solid tumour only, based on 43 response evaluable subjects), the ORR was 4.7% (95% CI: 0.6, 15.8). Considering that there were only four responders, the longest reported DOR was 2.8 months, in addition to one patient whose DOR was reported as 2.7 months but was censored on the date of their last evaluable tumour assessment. There were 21 (28%) patients who reported stable disease from those treated with nivolumab and 7 (16.3%) subjects treated with nivo+ipi with stable disease. The only advanced melanoma patient included (female, Asian 15-year-old) reported a BOR of PD, discontinued treatment due to progression and died 137 days after the last nivolumab dose.

OS was also reported with a 47.5% of events in the nivo monotherapy group and 58.7% of events in the combination pooled group. Overall, the median OS was 11.07 (95% CI: 6.37, 27.63) months for nivo monotherapy and 8.87 (95% CI: 5.75, 18.50) months for subjects treated with nivo + ipi. Among those patients treated with nivolumab, median OS was 7.00 (95% CI: 5.98, 14.06) months for solid tumours (N=60 treated subjects), and not reached for haematological tumours (N=20 treated subjects). No further information about subsequent therapies received by enrolled patients is available.

Response by PD-L1 tumour expression was evaluated as a secondary endpoint. From the 80 subjects treated with nivo monotherapy, 22 (27.5%) presented a baseline PD-L1 tumour expression ≥1%. Of these 22 patients, no CR were observed and 3 PR were reported. Eight (36.4%) patients presented with SD and 9 (40.9%) reported PD. From the 41 (51.3%) subjects treated with nivo who reported a

PD-L1 expression <1%, no responses were observed while 9 (22%) subjects reported SD and 25 (61%) presented PD. Of the 46 subjects treated with nivo + ipi treatment, 7 (15.2%) subjects had baseline PD-L1 expression ≥1% and 32 (69.6%) subjects had PD-L1 expression <1%. There was only one PR in the PD-L1 ≥1% group while there were three SD and PD, respectively. For the PD-L1 <1% group treated with the combination, there was also one PR but 4 (12.5%) SD and 24 (75%) PD reported.

The main efficacy endpoints (ORR and OS) were analysed by age subgroups (≥12 to <18 years, <18 years, and ≥18 years) and no relevant differences were observed although these subgroups had a small size which precludes definitive conclusions.

Supportive Study CA209067

This phase 3 randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma provides data for nivolumab monotherapy and nivo+ipi in subjects ≥18 years in the approved advanced melanoma indication in adult patients.

Study CA209067 has been assessed in multiple procedures, from the extension of the indication variation procedure (EMEA/H/C/003985/II/0003) to the latest update, up to 7.5 years of follow-up (EMEA/H/C/WS2289). This study did not allow the inclusion of patients <18 years old. A total of 945 patients were randomized either to receive nivolumab monotherapy (n=316), nivo+ipi (n=314) or ipilimumab monotherapy, which was the comparator arm (n=315). The extension of the indication was granted based on the final and interim analysis for the co-primary endpoints of PFS and OS, respectively, (DBL 17-Feb-2015) and an updated exploratory analysis (DBL 13-Nov-2015). The final OS analysis was performed based on a DBL of 13-Sep-2016. In this analysis, an OS HR of 0.63 (98% CI: 0.48, 0.81) was estimated for the comparison of nivolumab vs. ipilimumab monotherapy an HR 0.55 (98% CI: 0.42, 0.72) for the comparison of nivo+ipi vs. ipilimumab. Median OS was NA for the experimental arms and 19.98 (95% CI: 17.08, 24.61) for the ipilimumab monotherapy arm. The HR point estimates for PFS were 0.54 (95% CI: 0.45, 0.66) for the comparison of nivolumab vs. ipilimumab monotherapy and 0.42 (95% CI: 0.34, 0.51) for nivo+ipi vs. ipilimumab. For the latest update (12-Nov-2021 DBL), OS estimated HR was 0.63 (95% CI: 0.52, 0.77) for the comparison between nivolumab and ipilimumab monotherapy and 0.53 (95% CI: 0.44, 0.65) for nivo+ipi vs. ipilimumab. Estimated median OS were 36.93 (95% CI: 28.25, 58.71) months for the nivolumab arm, 72.08 (95% CI: 38.18, NA) months for nivo+ipi and 19.94 (95% CI: 16.85, 24.61) months for the ipilimumab arm.

Efficacy of both nivolumab monotherapy and the combination of nivolumab + ipilimumab have been widely established for adult patients.

Supportive Study CA209915

This study was designed to investigate whether nivolumab and ipilimumab combination treatment will improve RFS compared to nivolumab monotherapy (primary outcome) as adjuvant treatment in patients with completely resected Stage IIIb/c/d or Stage IV no evidence of disease (NED) melanoma. A total of 1844 subjects were randomized and, among them, three adolescents: two of them were treated with nivolumab monotherapy and one patient received nivolumab + ipilimumab. This study was assessed within procedure EMEA/H/C/003985/P46/043. Study CA209915 did not meet the primary endpoint of demonstrating statistically significant improvement in RFS with nivo+ipi vs nivo in all randomized subjects or all randomized subjects with tumour PD L1 < 1%. RFS in adolescent subjects treated with nivo (n = 2) was 11.2 months (1 subject) and 30.4 months (1 subject), and with nivo+ipi (n = 1) was 16.9 months.

Supportive Study CA209238

The extension of the nivolumab indication for the adjuvant treatment of melanoma in adults was granted based on the assessment of this study (EMEA/H/C/003985/II/0041). In this study, 906 adult patients were randomized to receive nivolumab 3 mg/kg (n=453) or ipilimumab 10 mg/kg (n=453) for a maximum of one year.

At the pre-specified interim RFS analysis (minimum follow-up 18 months, SmPC), a statistically significant improvement in RFS with nivolumab vs ipilimumab was demonstrated. At a minimum follow-up of 48 months and for final OS and updated RFS analyses (final CSR, SmPC), CA209238 continued to demonstrate improvement in RFS with nivolumab vs ipilimumab. Median OS was not reached in either arm (EMEA/H/C/003985/II/0098).

Data from this study which included only adult patients are proposed to be applicable to the requested indication expansion for adolescent patients based on disease similarity. As in the advanced setting, similarities between melanoma in adults and adolescents are acknowledged but less information is available for early stage disease, where the better clinical conditions may play a role in the response to treatment.

Assessment of paediatric data on clinical efficacy

The totality of the paediatric data generated according to the agreed PIP01 for nivolumab (EMEA-C-001407-PIP01-12-M03, adopted by PDCO on 21 January 2022) are provided as part of this application, in order to fulfil regulatory requirements. The updates proposed to the SmPC are therefore intended to reflect the clinical safety and efficacy data for the entire paediatric population included in Parts A to D of study CA209070 (N = 97 patients aged $\geq$ 1 year to < 18 years), Study 2 of PIP01 and pivotal clinical trial for this application, covering all the paediatric tumour types (solid and haematological tumours) and treatment regimens (nivo and nivo+ipi) studied and not limited to melanoma.

Efficacy data for the combination of nivolumab and ipilimumab in the treatment of adolescent patients with advanced melanoma are not available. The efficacy of nivolumab+ipilimumab in adolescents with melanoma could not be assessed in study CA209070 as only one melanoma patient was enrolled, and she was treated with nivolumab monotherapy. In addition, other adolescents enrolled in study CA209070 treated with this combination, all diagnosed with solid tumours, received the RP2D nivolumab 3 mg/kg + ipilimumab 1 mg/kg instead of the approved dose for this combination for the treatment of advanced melanoma in adults: nivolumab 1 mg/kg + ipilimumab 3 mg/kg. It is then necessary to extrapolate results from the adult population included in study CA209067 to support the efficacy of this combination in adolescent patients with advanced melanoma. On the basis of similarity of the disease in adult and adolescent patients with melanoma, and the expected similarity in the exposure-response to nivolumab and nivo+ipi treatment, the efficacy of nivolumab-based regimens in adolescents is expected to be similar to that of adults. Literature references were also provided in support of this extrapolation plan (data not shown).

It is acknowledged that a similar approach has been used in relevant precedents, highlighting that the biological similarity of the disease between adults and adolescents is recognised. However, emerging data could indicate that this is not the case for all paediatric cancers tested. In several trials with anti PD-1/PD-L1 agents limited responses to monotherapy have been reported in most common paediatric (solid) tumours included. Indeed, the overall positive results in such trials appear to be (mainly) driven by HL enrolled patients, a fact that could be related to an overexpression of PD-L1/PD-L2 in these haematological cancers. Very limited data have been found for these agents used in combination, apart

from study CA209070. There are some publications suggesting that most paediatric solid tumours show low TMB, which is not unexpected as these cancers are not usually the result of exposure to carcinogens like tobacco or UV light. The lack of tumour infiltrating lymphocytes (TILs) has also been mentioned as a possible explanation for the lack of response in paediatric tumours. In addition, paediatric solid tumours seem to present a less-inflamed microenvironment than tumours in adult patients, for the same reasons exposed above. However, melanoma in adolescents is supposed to share most biological characteristics with adult melanoma (constituting the basis for this extrapolation approach), related to UV exposure in many cases, which should leave it out from these expected low responses to ICIs reported in other paediatric tumours.

The MAH has provided a brief discussion on the disease similarity between melanoma in adult and adolescent patients to allow the proposed extrapolation approach and a review of evidence on this topic. Some studies have shown that the presence of somatic mutations in BRAF and PTEN were higher in the group of adolescents and young adults (15-30 years old) in comparison with older adults, suggesting that these young patients contained a higher proportion of mutation signatures unrelated to UV radiation, which is to be expected since exposure to radiation is shorter for them. This was also observed in a study using data from the Dutch Melanoma Treatment Registry (DMTR), where adolescents and young adults received more targeted therapy for 1L treatment. Although the incidence of BRAF mutated melanomas in adolescents may be higher, there seems to be no data suggesting that the behaviour and prognosis of these patients might be different. A meta-analysis has also been provided where no significant differences in TMB were found between adolescents and young adults and older patients (40-94 years). The available data on the use of immune-checkpoint inhibitors for the treatment of melanoma in adolescent patients is very limited but the provided information seems to confirm that the differences in the reported responses are not due to differential characteristics between melanoma in adolescents and older adults.

Based on the similarity of the tumour biology in adolescents vs. adults and the expected similarity of response to treatment, data in adults from Study CA209067 are considered to be applicable to the requested indication expansion for adolescent patients.

2.4.3. Conclusions on the clinical efficacy

Only one melanoma adolescent patient was enrolled in study CA209070 who received nivolumab monotherapy and showed PD as BOR. No clinical data are available for the combination in adolescents with melanoma. Therefore, this application basically relies on the extrapolation of efficacy data from adult patients in the same disease setting. Nivolumab, as monotherapy and in combination with ipilimumab, was approved for the treatment of advanced melanoma based on the results from the phase 3 study CA902067, which is considered supportive to this application. For the adjuvant setting, study CA209238, which included only adult patients, provides the data for the extrapolation exercise. Considering the drug behaves similarly and a comparable exposure-response to treatment can be expected between adults and adolescents, and that the disease biology can be considered similar in the two populations, the proposed extrapolation approach is considered acceptable.

2.5. Clinical safety

Introduction

Safety data in support of the applied extension of the approved adult melanoma indications to include adolescents (≥12 to <18 years) is based on the results from study CA209070. This is a multicentre,

open-label, single arm, phase 1/2 trial of nivolumab +/- ipilimumab in children, adolescents and young adults with recurrent or refractory solid tumours or lymphomas.

The primary objectives of this study included: to determine the tolerability and define and describe the toxicities of nivolumab administered as a single agent in children with relapsed or refractory solid tumours at the adult recommended dose of 3 mg/kg, and to determine the MTD and/or RP2D and to define and describe the toxicities of nivolumab plus ipilimumab administered to children.

In addition, data from the 3 pivotal Phase 3 studies conducted in adult melanoma patients were included:

- CA209067: supportive safety data from nivolumab monotherapy arm and nivo + ipi arm for advanced melanoma.
- CA209915: supportive safety data from nivolumab monotherapy arm for the adjuvant treatment of melanoma.
- CA209238: supportive safety data from nivolumab monotherapy arm for the adjuvant treatment of melanoma.

Patient exposure

A total of 132 subjects were enrolled (85 enrolled to nivolumab and 47 to nivo + ipi), and 126 subjects were treated (80 treated with nivolumab and 46 with nivo + ipi).

As of the DBLs (30-Sep-2019 for Parts A and B and 30-Jun-2020 for Parts C and D), only 1 subject receiving nivolumab was still on treatment. No subjects receiving nivo + ipi were still on treatment.

There was an overall minimum follow-up for survival of 14.0 months for subjects treated with nivolumab, and 28.3 months for subjects treated with nivo + ipi. The median follow-up time for all subjects treated with nivolumab or nivo + ipi was 44.0 months.

The percentage of subjects who discontinued treatment in both the nivolumab and nivo + ipi arms was similar, with clinical or radiographic evidence of progressive disease of >40% increase in target lesions being the most common reason (tables 56 and 57 for subjects <18 years of age).

Table 56 ***End of Treatment Period Subject Status Summary- Pooled Analysis: Solid vs. Hematology vs. Total for Each Treatment - All Treated Subjects in CA209070***

Status (%)	Nivo			Nivo + Ipi
	Solid N = 60	Hemato N = 20	Total N = 80	Solid N = 46
ONGOING TREATMENT	0	1 (5.0)	1 (1.3)	0
COMPLETED TREATMENT	0	0	0	0
DISCONTINUED TREATMENT	60 (100.0)	19 (95.0)	79 (98.8)	46 (100.0)
REASON FOR DISCONTINUED TREATMENT				
REFUSAL OF FURTHER PROTOCOL THERAPY BY PATIENT/PARENT/GUARDIAN	5 (8.3)	2 (10.0)	7 (8.8)	1 (2.2)
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE OF GREATER THAN 40% INCREASE FROM BASELINE TARGET LESIONS SELECTED ACCORDING TO RECIST CRITERIA	32 (53.3)	3 (15.0)	35 (43.8)	30 (65.2)
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE GREATER THAN 12 WEEKS AFTER START OF PROTOCOL THERAPY	7 (11.7)	4 (20.0)	11 (13.8)	8 (17.4)
PHYSICIAN DETERMINES IT IS NOT IN THE PATIENT'S BEST INTEREST	10 (16.7)	5 (25.0)	15 (18.8)	3 (6.5)
ADVERSE EVENTS REQUIRING REMOVAL FROM PROTOCOL THERAPY	3 (5.0)	4 (20.0)	7 (8.8)	3 (6.5)
DEATH	3 (5.0)	1 (5.0)	4 (5.0)	1 (2.2)
CONTINUING IN THE STUDY	12 (20.0)	14 (70.0)	26 (32.5)	5 (10.9)
NOT CONTINUING IN THE STUDY	48 (80.0)	6 (30.0)	54 (67.5)	41 (89.1)
REASON FOR NOT CONTINUING IN THE STUDY				
WITHDRAWAL OF CONSENT FOR ANY FURTHER REQUIRED OBSERVATIONS OR DATA SUBMISSION	4 (6.7)	2 (10.0)	6 (7.5)	2 (4.3)
LOST TO FOLLOW-UP	2 (3.3)	0	2 (2.5)	4 (8.7)
ENROLLMENT ONTO ANOTHER COG THERAPEUTIC (ANTI-CANCER) STUDY	8 (13.3)	0	8 (10.0)	8 (17.4)
DEATH	34 (56.7)	4 (20.0)	38 (47.5)	27 (58.7)

Source: CA209070 Interim CSR Table 5.1-1

Table 57 ***End of Treatment Period Subject Status Summary Pooled Analysis: Solid vs. Hemato vs. Total for Each Treatment - All Treated Subjects Aged Less than 18 Years in CA209070***

Status (%)	Nivo			Nivo + Ipi
	Solid N = 49	Hemato N = 15	Total N = 64	Solid N = 33
ONGOING TREATMENT	0	0	0	0
COMPLETED TREATMENT	0	0	0	0
DISCONTINUED TREATMENT	49 (100.0)	15 (100.0)	64 (100.0)	33 (100.0)
REASON FOR DISCONTINUED TREATMENT				
REFUSAL OF FURTHER PROTOCOL THERAPY BY PATIENT/PARENT/GUARDIAN	4 (8.2)	2 (13.3)	6 (9.4)	0
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE OF GREATER THAN 40% INCREASE FROM BASELINE TARGET LESIONS SELECTED ACCORDING TO RECIST CRITERIA	26 (53.1)	2 (13.3)	28 (43.8)	23 (69.7)
CLINICAL OR RADIOGRAPHIC EVIDENCE OF PROGRESSIVE DISEASE GREATER THAN 12 WEEKS AFTER START OF PROTOCOL THERAPY	6 (12.2)	3 (20.0)	9 (14.1)	6 (18.2)
PHYSICIAN DETERMINES IT IS NOT IN THE PATIENT'S BEST INTEREST	8 (16.3)	4 (26.7)	12 (18.8)	3 (9.1)
ADVERSE EVENTS REQUIRING REMOVAL FROM PROTOCOL THERAPY	3 (6.1)	3 (20.0)	6 (9.4)	0
DEATH	2 (4.1)	1 (6.7)	3 (4.7)	1 (3.0)
CONTINUING IN THE STUDY	11 (22.4)	10 (66.7)	21 (32.8)	2 (6.1)
NOT CONTINUING IN THE STUDY	38 (77.6)	5 (33.3)	43 (67.2)	31 (93.9)
REASON FOR NOT CONTINUING IN THE STUDY				
WITHDRAWAL OF CONSENT FOR ANY FURTHER REQUIRED OBSERVATIONS OR DATA SUBMISSION	4 (8.2)	1 (6.7)	5 (7.8)	2 (6.1)
LOST TO FOLLOW-UP	2 (4.1)	0	2 (3.1)	4 (12.1)
ENROLLMENT ONTO ANOTHER COG THERAPEUTIC (ANTI-CANCER) STUDY	6 (12.2)	0	6 (9.4)	6 (18.2)
DEATH	26 (53.1)	4 (26.7)	30 (46.9)	19 (57.6)

Percentages based on subjects entering period.
Source: CA209070 Interim CSR Table S.2.7P.1

Nivolumab monotherapy

Among subjects in Parts A and B, the median number of nivolumab doses received was 2 (range: 1 - 89), see Table 56. The median duration of nivolumab treatment was 0.84 months (0.53 months for solid tumours and 1.23 months for hematology tumours).

Nivolumab + Ipilimumab

Among subjects in Parts C and D, the median number of doses received was 2.0 (range: 1 - 24) for nivolumab and 2.0 (range: 1 - 4) for ipilimumab, see Table 58). The median duration of nivo + ipi treatment for solid tumours was 0.72 months.

Table 58 ***Cumulative Dose Summary By Treatment and Dose Level - All Treated Subjects in CA209070***

		Nivo + Ipi					
	Nivo 3 mg/kg N = 80	Total N = 46		Nivo 1 mg/kg + Ipi 1 mg/kg N = 6		Nivo 3 mg/kg + Ipi 1 mg/kg N = 40	
	Nivolumab N = 80	Nivolumab N = 46	Ipilimumab N = 46	Nivolumab N = 6	Ipilimumab N = 6	Nivolumab N = 40	Ipilimumab N = 40
NUMBER OF CYCLES RECEIVED							
MEAN (SD)	3.7 (6.8)	2.8 (2.5)	2.3 (1.1)	2.2 (1.8)	2.0 (1.5)	3.0 (2.6)	2.4 (1.0)
MEDIAN	1.5	2.0	2.0	1.0	1.0	2.0	2.0
(MIN - MAX)	(1 - 45)	(1 - 14)	(1 - 4)	(1 - 5)	(1 - 4)	(1 - 14)	(1 - 4)
NUMBER OF DOSES RECEIVED							
MEAN (SD)	6.9 (13.4)	3.4 (4.2)	2.3 (1.1)	2.3 (2.2)	2.0 (1.5)	3.6 (4.5)	2.4 (1.0)
MEDIAN	2.0	2.0	2.0	1.0	1.0	2.0	2.0
(MIN - MAX)	(1 - 89)	(1 - 24)	(1 - 4)	(1 - 6)	(1 - 4)	(1 - 24)	(1 - 4)
CUMULATIVE DOSE (MG/KG)							
MEAN (SD)	20.73 (40.31)	9.66 (12.78)	2.31 (1.09)	3.01 (3.63)	2.00 (1.54)	10.66 (13.38)	2.35 (1.03)
MEDIAN	6.08	6.00	2.00	1.02	1.02	6.00	2.00
(MIN - MAX)	(3.0 - 266.7)	(1.0 - 72.1)	(1.0 - 4.0)	(1.0 - 10.0)	(1.0 - 4.0)	(3.0 - 72.1)	(1.0 - 4.0)

For Parts A and B, the planned dosing schedule for Nivolumab was Q2W with a cycle length of 28 days.
For Parts C and D, the planned dosing schedule for Nivolumab and Ipilimumab during the first 4 cycles was Q3W with a cycle length of 21 days, followed by Nivolumab alone Q2W with a 28-day cycle.
Source: CA209070 Interim CSR Table S.4.1.2.3

Adverse events

Table 59 ***Overall Safety Summary- Pooled Analysis: Solid vs. Hematology vs. Total for Nivolumab Monotherapy and Nivolumab + Ipilimumab - All Treated Subjects in CA209070***

	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)	
Preferred Term	**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)
≥ 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
Decreased appetite	13 (21.7)	0	2 (10.0)	0	15 (18.8)	0	6 (13.0)	1 (2.2)
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

	Number of Subjects (%)							
	Nivo						Nivo + Ipi	
	Solid N = 60		Hemato N = 20		Total N = 80		Solid N = 46	
Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
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 (B)								
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
(B) For Select AE definition, refer to CA209070 Interim CSR Section 3.6.3.2
Source: CA20970 Interim CSR Table 8.1-1

Dose limiting toxicities (DLT)

DLT was defined as any of the investigator and recorded on the case report form (CRF). DLT was defined as any of the non-hematological and hematological DLTs that were possibly, probably, or definitely attributable to protocol therapy. The DLT observation period was Cycle 1 (the first 28 days for Part A and 21 days for Part C). Toxicities with subsequent cycles were also monitored.

Per the study design, Part A defined RP2D for Part B. Similarly, Part C defined RP2D for Part D. The dose determination in Part A and Part C was done by COG at the time of study conduct and Part A results were published.

Nivolumab monotherapy

In Part A, the DLT observation period was the first cycle of treatment (28 days). A total of 12 subjects were treated with nivo 3 mg/kg Q2W. No DLTs were observed, therefore the dose was not de-escalated and the RP2D for Part B was determined as nivo 3 mg/kg Q2W (Table 58). In Part B, Cycle 1 DLT rate was below 33% (pre-specified rate) in all cohorts tested, showing that nivo 3 mg/kg Q2W did not exceed the MTD in any of the cohorts tested.

In addition, DLT equivalents were evaluated beyond Cycle 1 in Part A and regardless of cycle in Part B for all treated subjects in Parts A and B. Among the 80 subjects evaluated for DLT equivalents, 12 (15.0%) had a total of 18 DLT equivalents (Table 59).

Nivolumab + Ipilimumab

In Part C, the DLT observation period was the first cycle of treatment (21 days). A total of 6 subjects were treated with nivo 1 + ipi 1 Q3W (dose level 1), and no DLTs were observed. Therefore, the dose was escalated to nivo 3 + ipi 1 Q3W (dose level 2). Among the 12 subjects treated with nivo 3 + ipi 1 Q3W for DLT evaluation, 1 DLT was observed on Day 14 (blood creatinine increased), which was within the predefined occurrence of <2 DLTs to be considered 'safe.' Therefore, the RP2D for Part D was determined as nivo 3 + ipi 1 Q3W (Table 58). In Part D, Cycle 1 DLT rate was below 33% (pre-specified rate) in all disease cohorts tested, showing that nivo 3 + ipi 1 Q3W did not exceed the MTD in any of these disease cohorts.

In addition, DLT equivalents were evaluated beyond Cycle 1 in Part C and regardless of cycle in Part D for all treated subjects in Parts C and D. Among the 46 subjects evaluated for DLT equivalents, 6 (13.0%) had a total of 21 DLT equivalents; 1 DLT equivalent for nivo 1 + ipi 1 Q3W and 20 DLT equivalents in 5 subjects for nivo 3 + ipi 1 Q3W (Table 61).

Table 60 ***Dose Limiting Toxicities Summary - Treated Subjects in Part A and Part C in CA209070***

	Part A	Part C		
	Nivo 3 mg/kg N = 12	Nivo 1 mg/kg + Ipi 1 mg/kg N = 6	Nivo 3 mg/kg + Ipi 1 mg/kg N = 12	Total N = 18
NUMBER OF SUBJECTS HAVING AT LEAST 1 DLT (A)	0	0	1 (8.3)	1 (5.6)
Cycle 1	0	0	1 (8.3)	1 (5.6)
NUMBER OF DLT (B)	0	0	1 (100.0)	1 (100.0)
Cycle 1	0	0	1 (100.0)	1 (100.0)

(A) Percent of subjects having at least 1 DLT.

(B) Percent of DLT out of the total number of DLT.

The DLT observation period for the purposes of dose-escalation in Part C or dose de-escalation in Part A is the first cycle of therapy.

Source: CA209070 Interim CSR Table 8.2-1

Table 61 ***Dose Limiting Toxicities Equivalents Summary by Treatment and Dose Level - All Treated Subjects in CA209070***

		Nivo + Ipi		
	Nivo 3 mg/kg N = 80	Total N = 46	Nivo 1 mg/kg + Ipi 1 mg/kg N = 6	Nivo 3 mg/kg + Ipi 1 mg/kg N = 40
NUMBER OF SUBJECTS HAVING AT LEAST 1 DLT (A)	12 (15.0)	6 (13.0)	1 (16.7)	5 (12.5)
Cycle 1	5 (6.3)	1 (2.2)	0	1 (2.5)
Cycle 2	4 (5.0)	1 (2.2)	0	1 (2.5)
Cycle 3	0	1 (2.2)	0	1 (2.5)
Cycle 4	1 (1.3)	1 (2.2)	0	1 (2.5)
Cycle 5	0	1 (2.2)	1 (16.7)	0
Cycle 14	0	1 (2.2)	0	1 (2.5)
Follow-Up 1	3 (3.8)	1 (2.2)	0	1 (2.5)
NUMBER OF DLT (B)	18 (100.0)	21 (100.0)	1 (100.0)	20 (100.0)
Cycle 1	6 (33.3)	1 (4.8)	0	1 (5.0)
Cycle 2	6 (33.3)	1 (4.8)	0	1 (5.0)
Cycle 3	0	2 (9.5)	0	2 (10.0)
Cycle 4	1 (5.6)	6 (28.6)	0	6 (30.0)
Cycle 5	0	1 (4.8)	1 (100.0)	0
Cycle 14	0	2 (9.5)	0	2 (10.0)
Follow-Up 1	5 (27.8)	8 (38.1)	0	8 (40.0)

(A) Percent of subjects having at least 1 DLT.

(B) Percent of DLT out of the total number of DLT.

Dose Limiting Toxicities Equivalents are DLTs that occurred beyond Cycle 1 for Part A and C.

For parts B and D, DLT equivalents are regardless of Cycle.

Source: CA209070 Interim CSR Table 8.2-2

Common Adverse Events

Results presented here are based on all treated subjects (N=126) in the nivolumab (N=80) and nivo+ipi (N=46) arms in CA209070 study.

Nivolumab monotherapy

All-causality any-grade AEs were reported in 80 (100.0%) subjects treated with nivolumab. All causality Grade 3-4 AEs were reported in 55 (68.8%) subjects treated with nivolumab. Grade 5 AEs were reported in 18 (22.5%) subjects (17 disease progression and 1 cardiac arrest); 1 subject with disease progression also had hematoma.

- The most frequently reported all-causality any-grade AEs (≥ 50%) were anemia (78.8%), lymphocyte count decreased (62.5%), fatigue (61.3%), white blood cell count decreased (61.3%), platelet count decreased (60.0%), hyponatremia (55.0%), neutrophil count decreased (55.0%), hypoalbuminemia (52.5%), and hypocalcemia (50.0%).
- The most frequently reported all-causality Grade 3-4 AEs (≥ 10%) were lymphocyte count decreased (40.0%), neutrophil count decreased (35.0%), anemia (30.0%), platelet count decreased (28.8%), white blood cell count decreased (25.0%), tumour pain (13.8%), febrile neutropenia (12.5%), and hypokalemia (11.3%).

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 AEs (≥20%) were 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

All-causality any-grade AEs were reported in 46 (100.0%) subjects treated with nivo + ipi. All causality Grade 3-4 AEs were reported in 23 (50.0%) subjects treated with nivo + ipi. Grade 5 AEs were reported in 8 (17.4%) subjects (6 disease progression and 2 respiratory failure).

- The most frequently reported all-causality any-grade AEs (≥ 50%) were anemia (71.7%), lymphocyte count decreased (60.9%), hyponatremia (52.2%), and fatigue (50.0%).
- The most frequently reported all-causality Grade 3-4 AEs (≥ 10%) were lymphocyte count decreased (28.3%), anemia (21.7%), hyponatremia (15.2%), AST increased, dyspnea, lipase increased, dehydration, pleural effusion, hypoxia, and platelet count decreased (10.9% each).

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%).

Table 62 ***Any Adverse Events Summary by Worst CTC Grade (≥ 20% of Total Subjects in Either Treatment group) - 100 Days Safety Window - Pooled Analysis: Solid vs. Hematology vs. Total for Each Treatment - All Treated Subjects in CA209070***

System Organ Class (%) Preferred Term (%)	Nivo Solid N = 60 Any Grade	Nivo Solid N = 60 Grade 3-4	Nivo Hemato N = 20 Any Grade	Nivo Hemato N = 20 Grade 3-4	Nivo Total N = 80 Any Grade	Nivo Total N = 80 Grade 3-4	Nivo + Ipi Solid N = 46 Any Grade	Nivo + Ipi Solid N = 46 Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	60 (100.0)	40 (66.7)	20 (100.0)	15 (75.0)	80 (100.0)	55 (68.8)	46 (100.0)	23 (50.0)
Metabolism and nutrition disorders	59 (98.3)	15 (25.0)	20 (100.0)	7 (35.0)	79 (98.8)	22 (27.5)	43 (93.5)	15 (32.6)
Hyponatraemia	33 (55.0)	5 (8.3)	11 (55.0)	2 (10.0)	44 (55.0)	7 (8.8)	24 (52.2)	7 (15.2)
Hypoalbuminaemia	28 (46.7)	3 (5.0)	14 (70.0)	1 (5.0)	42 (52.5)	4 (5.0)	19 (41.3)	1 (2.2)
Hypocalcaemia	27 (45.0)	0	13 (65.0)	0	40 (50.0)	0	15 (32.6)	1 (2.2)
Decreased appetite	26 (43.3)	3 (5.0)	3 (15.0)	1 (5.0)	29 (36.3)	4 (5.0)	17 (37.0)	2 (4.3)
Hyperglycaemia	25 (41.7)	2 (3.3)	7 (35.0)	0	32 (40.0)	2 (2.5)	17 (37.0)	1 (2.2)
Hypokalaemia	21 (35.0)	6 (10.0)	12 (60.0)	3 (15.0)	33 (41.3)	9 (11.3)	16 (34.8)	4 (8.7)
Hypophosphataemia	21 (35.0)	4 (6.7)	10 (50.0)	1 (5.0)	31 (38.8)	5 (6.3)	14 (30.4)	3 (6.5)
Hypomagnesaemia	13 (21.7)	0	9 (45.0)	0	22 (27.5)	0	7 (15.2)	0
Hyperkalaemia	12 (20.0)	1 (1.7)	4 (20.0)	2 (10.0)	16 (20.0)	3 (3.8)	4 (8.7)	0
Dehydration	8 (13.3)	5 (8.3)	3 (15.0)	1 (5.0)	11 (13.8)	6 (7.5)	11 (23.9)	5 (10.9)
General disorders and administration site conditions	55 (91.7)	4 (6.7)	15 (75.0)	2 (10.0)	70 (87.5)	6 (7.5)	34 (73.9)	4 (8.7)
Fatigue	36 (60.0)	1 (1.7)	13 (65.0)	0	49 (61.3)	1 (1.3)	23 (50.0)	2 (4.3)
Pyrexia	31 (51.7)	2 (3.3)	7 (35.0)	2 (10.0)	38 (47.5)	4 (5.0)	20 (43.5)	1 (2.2)
Pain	18 (30.0)	4 (6.7)	3 (15.0)	0	21 (26.3)	4 (5.0)	6 (13.0)	1 (2.2)
Disease progression	15 (25.0)	0	2 (10.0)	0	17 (21.3)	0	6 (13.0)	0
Non-cardiac chest pain	8 (13.3)	0	2 (10.0)	0	10 (12.5)	0	10 (21.7)	1 (2.2)
Investigations	55 (91.7)	36 (60.0)	20 (100.0)	16 (80.0)	75 (93.8)	52 (65.0)	45 (97.8)	21 (45.7)
Lymphocyte count decreased	36 (60.0)	23 (38.3)	14 (70.0)	9 (45.0)	50 (62.5)	32 (40.0)	28 (60.9)	13 (28.3)
Platelet count decreased	36 (60.0)	16 (26.7)	12 (60.0)	7 (35.0)	48 (60.0)	23 (28.8)	17 (37.0)	5 (10.9)
White blood cell count decreased	35 (58.3)	14 (23.3)	14 (70.0)	6 (30.0)	49 (61.3)	20 (25.0)	14 (30.4)	4 (8.7)
Neutrophil count decreased	32 (53.3)	18 (30.0)	12 (60.0)	10 (50.0)	44 (55.0)	28 (35.0)	11 (23.9)	4 (8.7)
Aspartate aminotransferase increased	24 (40.0)	2 (3.3)	12 (60.0)	2 (10.0)	36 (45.0)	4 (5.0)	15 (32.6)	5 (10.9)
Alanine aminotransferase increased	21 (35.0)	4 (6.7)	13 (65.0)	1 (5.0)	34 (42.5)	5 (6.3)	18 (39.1)	3 (6.5)
Blood creatinine increased	18 (30.0)	3 (5.0)	5 (25.0)	0	23 (28.8)	3 (3.8)	15 (32.6)	0
Weight decreased	15 (25.0)	0	4 (20.0)	1 (5.0)	19 (23.8)	1 (1.3)	17 (37.0)	2 (4.3)
C-reactive protein increased	14 (23.3)	0	5 (25.0)	0	19 (23.8)	0	11 (23.9)	0
Blood alkaline phosphatase increased	13 (21.7)	3 (5.0)	4 (20.0)	1 (5.0)	17 (21.3)	4 (5.0)	11 (23.9)	1 (2.2)
Lipase increased	5 (8.3)	2 (3.3)	2 (10.0)	1 (5.0)	7 (8.8)	3 (3.8)	10 (21.7)	5 (10.9)
Blood and lymphatic system disorders	49 (81.7)	21 (35.0)	15 (75.0)	8 (40.0)	64 (80.0)	29 (36.3)	34 (73.9)	11 (23.9)
Anaemia	49 (81.7)	18 (30.0)	14 (70.0)	6 (30.0)	63 (78.8)	24 (30.0)	33 (71.7)	10 (21.7)
Gastrointestinal disorders	49 (81.7)	13 (21.7)	14 (70.0)	7 (35.0)	63 (78.8)	20 (25.0)	28 (60.9)	5 (10.9)
Nausea	31 (51.7)	3 (5.0)	7 (35.0)	0	38 (47.5)	3 (3.8)	16 (34.8)	2 (4.3)
Vomiting	29 (48.3)	4 (6.7)	7 (35.0)	2 (10.0)	36 (45.0)	6 (7.5)	20 (43.5)	1 (2.2)
Constipation	25 (41.7)	0	5 (25.0)	0	30 (37.5)	0	11 (23.9)	0
Abdominal pain	21 (35.0)	2 (3.3)	5 (25.0)	2 (10.0)	26 (32.5)	4 (5.0)	13 (28.3)	3 (6.5)
Diarrhoea	16 (26.7)	1 (1.7)	5 (25.0)	1 (5.0)	21 (26.3)	2 (2.5)	11 (23.9)	1 (2.2)
Respiratory, thoracic and mediastinal disorders	46 (76.7)	16 (26.7)	14 (70.0)	2 (10.0)	60 (75.0)	18 (22.5)	32 (69.6)	9 (19.6)
Cough	26 (43.3)	0	9 (45.0)	0	35 (43.8)	0	21 (45.7)	1 (2.2)
Dyspnoea	17 (28.3)	5 (8.3)	3 (15.0)	1 (5.0)	20 (25.0)	6 (7.5)	10 (21.7)	5 (10.9)
Nasal congestion	15 (25.0)	0	3 (15.0)	0	18 (22.5)	0	8 (17.4)	0
Pleural Effusion	10 (16.7)	5 (8.3)	1 (5.0)	0	11 (13.8)	5 (6.3)	12 (26.1)	5 (10.9)

System Organ Class (%) Preferred Term (%)	Nivo Solid N = 60 Any Grade	Nivo Solid N = 60 Grade 3-4	Nivo Hemato N = 20 Any Grade	Nivo Hemato N = 20 Grade 3-4	Nivo Total N = 80 Any Grade	Nivo Total N = 80 Grade 3-4	Nivo + Ipi Solid N = 46 Any Grade	Nivo + Ipi Solid N = 46 Grade 3-4
Musculoskeletal and connective tissue disorders	37 (61.7)	11 (18.3)	10 (50.0)	1 (5.0)	47 (58.8)	12 (15.0)	29 (63.0)	4 (8.7)
Pain in extremity	18 (30.0)	3 (5.0)	6 (30.0)	0	24 (30.0)	3 (3.8)	13 (28.3)	3 (6.5)
Back pain	14 (23.3)	4 (6.7)	4 (20.0)	1 (5.0)	18 (22.5)	5 (6.3)	12 (26.1)	1 (2.2)
Nervous system disorders	33 (55.0)	7 (11.7)	10 (50.0)	4 (20.0)	43 (53.8)	11 (13.8)	25 (54.3)	2 (4.3)
Headache	20 (33.3)	0	6 (30.0)	0	26 (32.5)	0	18 (39.1)	0
Skin and subcutaneous tissue disorders	32 (53.3)	3 (5.0)	11 (55.0)	1 (5.0)	43 (53.8)	4 (5.0)	22 (47.8)	2 (4.3)
Pruritus	13 (21.7)	0	4 (20.0)	0	17 (21.3)	0	4 (8.7)	0
Rash maculo-papular	11 (18.3)	2 (3.3)	5 (25.0)	0	16 (20.0)	2 (2.5)	9 (19.6)	1 (2.2)
Cardiac disorders	29 (48.3)	0	5 (25.0)	0	34 (42.5)	0	24 (52.2)	1 (2.2)
Sinus tachycardia	29 (48.3)	0	3 (15.0)	0	32 (40.0)	0	22 (47.8)	0
Vascular disorders	27 (45.0)	4 (6.7)	7 (35.0)	2 (10.0)	34 (42.5)	6 (7.5)	20 (43.5)	4 (8.7)
Hypertension	16 (26.7)	0	3 (15.0)	2 (10.0)	19 (23.8)	2 (2.5)	15 (32.6)	4 (8.7)
Psychiatric disorders	24 (40.0)	2 (3.3)	6 (30.0)	0	30 (37.5)	2 (2.5)	21 (45.7)	1 (2.2)
Anxiety	13 (21.7)	1 (1.7)	4 (20.0)	0	17 (21.3)	1 (1.3)	13 (28.3)	1 (2.2)
Renal and urinary disorders	23 (38.3)	7 (11.7)	8 (40.0)	1 (5.0)	31 (38.8)	8 (10.0)	19 (41.3)	2 (4.3)
Haematuria	14 (23.3)	3 (5.0)	4 (20.0)	0	18 (22.5)	3 (3.8)	4 (8.7)	0
Proteinuria	11 (18.3)	0	4 (20.0)	0	15 (18.8)	0	13 (28.3)	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.

In the nivo group, 15 subjects with solid tumour had Grade 5 events of disease progression. 3 subjects with hematology tumour had 4 Grade 5 events: 1 subject had 2 Grade 5 events (disease progression and hematoma) and 1 subject each had disease progression and cardiac arrest. In the nivo + ipi group, 8 subjects were reported as having a Grade 5 event (disease progression in 6 subjects and respiratory failure in 2 subjects).
Source: CA209070 Interim CSR Table 8.6-1

Table 63 ***Any Possibly Drug-Related Adverse Events Summary by Worst CTC Grade (≥ 5% of Total Subjects in Either Treatment Group) - 100 Days Safety Window - Pooled Analysis: Solid vs. Hematology vs. Total for Each Treatment - All Treated Subjects in CA209070***

System Organ Class (%) Preferred Term (%)	Nivo Solid N = 60 Any Grade	Nivo Solid N = 60 Grade 3-4	Nivo Hemato N = 20 Any Grade	Nivo Hemato N = 20 Grade 3-4	Nivo Total N = 80 Any Grade	Nivo Total N = 80 Grade 3-4	Nivo + Ipi Solid N = 46 Any Grade	Nivo + Ipi Solid N = 46 Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	53 (88.3)	15 (25.0)	19 (95.0)	12 (60.0)	72 (90.0)	27 (33.8)	46 (100.0)	16 (34.8)
Investigations	42 (70.0)	9 (15.0)	19 (95.0)	10 (50.0)	61 (76.3)	19 (23.8)	40 (87.0)	10 (21.7)
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)
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)
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)
C-reactive protein increased	12 (20.0)	0	2 (10.0)	0	14 (17.5)	0	9 (19.6)	0
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)
Blood alkaline phosphatase increased	5 (8.3)	0	0	0	5 (6.3)	0	2 (4.3)	0
Lipase increased	5 (8.3)	2 (3.3)	1 (5.0)	1 (5.0)	6 (7.5)	3 (3.8)	7 (15.2)	4 (8.7)
Weight decreased	5 (8.3)	0	0	0	5 (6.3)	0	5 (10.9)	1 (2.2)
Blood creatinine increased	4 (6.7)	0	3 (15.0)	0	7 (8.8)	0	7 (15.2)	0
C-reactive protein	4 (6.7)	0	1 (5.0)	0	5 (6.3)	0	1 (2.2)	0
Amylase increased	3 (5.0)	0	0	0	3 (3.8)	0	7 (15.2)	1 (2.2)
Blood bilirubin increased	2 (3.3)	0	0	0	2 (2.5)	0	3 (6.5)	0
General disorders and administration site conditions	32 (53.3)	0	8 (40.0)	0	40 (50.0)	0	20 (43.5)	0
Fatigue	23 (38.3)	0	7 (35.0)	0	30 (37.5)	0	16 (34.8)	0
Pyrexia	9 (15.0)	0	2 (10.0)	0	11 (13.8)	0	7 (15.2)	0
Pain	4 (6.7)	0	1 (5.0)	0	5 (6.3)	0	0	0
Non-cardiac chest pain	2 (3.3)	0	0	0	2 (2.5)	0	3 (6.5)	0
Metabolism and nutrition disorders	30 (50.0)	0	11 (55.0)	1 (5.0)	41 (51.3)	1 (1.3)	27 (58.7)	4 (8.7)
Decreased appetite	13 (21.7)	0	2 (10.0)	0	15 (18.8)	0	6 (13.0)	1 (2.2)
Hyponatraemia	8 (13.3)	0	2 (10.0)	0	10 (12.5)	0	7 (15.2)	3 (6.5)
Hypocalcaemia	6 (10.0)	0	5 (25.0)	0	11 (13.8)	0	1 (2.2)	0

System Organ Class (%) Preferred Term (%)	Nivo Solid N = 60 Any Grade	Nivo Solid N = 60 Grade 3-4	Nivo Hemato N = 20 Any Grade	Nivo Hemato N = 20 Grade 3-4	Nivo Total N = 80 Any Grade	Nivo Total N = 80 Grade 3-4	Nivo + Ipi Solid N = 46 Any Grade	Nivo + Ipi Solid N = 46 Grade 3-4
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
Hyperglycaemia	2 (3.3)	0	2 (10.0)	0	4 (5.0)	0	8 (17.4)	0
Hypoglycaemia	2 (3.3)	0	2 (10.0)	0	4 (5.0)	0	0	0
Blood and lymphatic system disorders	25 (41.7)	2 (3.3)	11 (55.0)	4 (20.0)	36 (45.0)	6 (7.5)	19 (41.3)	2 (4.3)
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)
Gastrointestinal disorders	25 (41.7)	2 (3.3)	5 (25.0)	2 (10.0)	30 (37.5)	4 (5.0)	17 (37.0)	1 (2.2)
Nausea	12 (20.0)	0	2 (10.0)	0	14 (17.5)	0	10 (21.7)	1 (2.2)
Vomiting	7 (11.7)	0	2 (10.0)	0	9 (11.3)	0	6 (13.0)	0
Abdominal pain	5 (8.3)	0	3 (15.0)	1 (5.0)	8 (10.0)	1 (1.3)	5 (10.9)	1 (2.2)
Diarrhoea	5 (8.3)	0	1 (5.0)	0	6 (7.5)	0	3 (6.5)	0
Constipation	4 (6.7)	0	1 (5.0)	0	5 (6.3)	0	0	0
Abdominal pain upper	1 (1.7)	0	1 (5.0)	0	2 (2.5)	0	3 (6.5)	0
Dry mouth	1 (1.7)	0	0	0	1 (1.3)	0	3 (6.5)	0
Respiratory, thoracic and mediastinal disorders	14 (23.3)	2 (3.3)	4 (20.0)	0	18 (22.5)	2 (2.5)	11 (23.9)	2 (4.3)
Cough	6 (10.0)	0	3 (15.0)	0	9 (11.3)	0	7 (15.2)	0
Dyspnoea	6 (10.0)	1 (1.7)	0	0	6 (7.5)	1 (1.3)	2 (4.3)	1 (2.2)
Pleural effusion	4 (6.7)	2 (3.3)	0	0	4 (5.0)	2 (2.5)	6 (13.0)	2 (4.3)
Skin and subcutaneous tissue disorders	14 (23.3)	1 (1.7)	3 (15.0)	0	17 (21.3)	1 (1.3)	14 (30.4)	1 (2.2)
Pruritus	7 (11.7)	0	0	0	7 (8.8)	0	1 (2.2)	0
Rash maculo-papular	5 (8.3)	0	3 (15.0)	0	8 (10.0)	0	8 (17.4)	1 (2.2)
Dry skin	1 (1.7)	0	0	0	1 (1.3)	0	3 (6.5)	0

System Organ Class (%) Preferred Term (%)	Nivo Solid N = 60 Any Grade	Nivo Solid N = 60 Grade 3-4	Nivo Hemato N = 20 Any Grade	Nivo Hemato N = 20 Grade 3-4	Nivo Total N = 80 Any Grade	Nivo Total N = 80 Grade 3-4	Nivo + Ipi Solid N = 46 Any Grade	Nivo + Ipi Solid N = 46 Grade 3-4
Nervous system disorders	13 (21.7)	0	4 (20.0)	1 (5.0)	17 (21.3)	1 (1.3)	7 (15.2)	0
Headache	7 (11.7)	0	4 (20.0)	0	11 (13.8)	0	4 (8.7)	0
Peripheral sensory neuropathy	4 (6.7)	0	0	0	4 (5.0)	0	0	0
Endocrine disorders	10 (16.7)	0	5 (25.0)	0	15 (18.8)	0	9 (19.6)	0
Hypothyroidism	7 (11.7)	0	3 (15.0)	0	10 (12.5)	0	7 (15.2)	0
Hyperthyroidism	4 (6.7)	0	2 (10.0)	0	6 (7.5)	0	2 (4.3)	0
Vascular disorders	8 (13.3)	0	1 (5.0)	0	9 (11.3)	0	4 (8.7)	1 (2.2)
Hypertension	4 (6.7)	0	0	0	4 (5.0)	0	3 (6.5)	1 (2.2)
Hypotension	4 (6.7)	0	0	0	4 (5.0)	0	2 (4.3)	0
Cardiac disorders	7 (11.7)	0	2 (10.0)	0	9 (11.3)	0	6 (13.0)	1 (2.2)
Sinus tachycardia	6 (10.0)	0	1 (5.0)	0	7 (8.8)	0	4 (8.7)	0
Musculoskeletal and connective tissue disorders	6 (10.0)	1 (1.7)	1 (5.0)	0	7 (8.8)	1 (1.3)	9 (19.6)	0
Myalgia	0	0	0	0	0	0	4 (8.7)	0
Renal and urinary disorders	5 (8.3)	0	1 (5.0)	0	6 (7.5)	0	8 (17.4)	0
Haematuria	2 (3.3)	0	1 (5.0)	0	3 (3.8)	0	3 (6.5)	0
Proteinuria	2 (3.3)	0	1 (5.0)	0	3 (3.8)	0	7 (15.2)	0
Injury, poisoning and procedural complications	2 (3.3)	0	2 (10.0)	0	4 (5.0)	0	3 (6.5)	0
Infusion related reaction	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.

There were no Grade 5 events reported

Source: CA209070 Interim CSR Table 8.6-2

Serious adverse event/deaths/other significant events

Deaths

Nivolumab

Among the 80 subjects treated with nivolumab, 38 (47.5%) subjects had died; 34/60 (56.7%) subjects in solid tumour group and 4/20 (20.0%) subjects in hematology tumour group (Table 62). For subjects with solid and hematology tumours, disease progression was the most common cause of death, including within 30 days and 100 days of the last dose. One subject with relapsed or refractory non-Hodgkin tumour died due to intraparenchymal hematoma, 57 days after the last dose. There were no deaths due to study drug toxicity.

Nivolumab + Ipilimumab

Among the 46 subjects with solid tumours treated with nivo + ipi, 27 (58.7%) had died (Table 62). 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 assessed as related to study drug toxicity.

Table 64 ***Death Summary by Treatment, All Treated Subjects in CA209070***

	Nivo N = 80			Nivo + Ipi N = 46
	Solid N = 60	Hemato N = 20	Total N = 80	Solid N = 46
NUMBER OF SUBJECTS WHO DIED (%)	34 (56.7)	4 (20.0)	38 (47.5)	27 (58.7)
PRIMARY REASON 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)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	4 (6.7)	1 (5.0)	5 (6.3)	2 (4.3)
PRIMARY REASON FOR DEATH (%)				
DUE TO THIS DISEASE	4 (6.7)	1 (5.0)	5 (6.3)	2 (4.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	15 (25.0)	3 (15.0)	18 (22.5)	8 (17.4)
PRIMARY REASON FOR DEATH (%)				
DUE TO THIS DISEASE	15 (25.0)	2 (10.0)	17 (21.3)	8 (17.4)
DUE TO OTHER CAUSE	0	1 (5.0)	1 (1.3)	0

(A) Intraparenchymal hematoma with intracranial pressure secondary to disease progression in 1 subject with NHL

Source: CA209070 Interim CSR Table 8.3-1

Serious Adverse Events

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) (Table 63).

- The most frequently reported all-causality any-grade SAEs (≥ 5%) were pyrexia (16.3%), disease progression and tumour 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 tumour 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 (Table 63).

- The 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).

Table 65 ***Any Serious Adverse Events Summary by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) (≥ 5% in any treatment group) 100 Days Safety Window Pooled Analysis: Solid vs. Hematologic vs. Total for Each Treatment - All Treated Subjects in CA20907***

	Nivo									Nivo + Ipi		
	Solid N=60			Hemato N=20			Total N=80			Solid N=46		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total subjects with an event	32 (53.3)	22 (36.7)	8 (13.3)	11 (55.0)	10 (50.0)	1 (5.0)	43 (53.8)	32 (40.0)	9 (11.3)	20 (43.5)	12 (26.1)	4 (8.7)
General disorders and administration site conditions	19 (31.7)	1 (1.7)	8 (13.3)	2 (10.0)	1 (5.0)	0	21 (26.3)	2 (2.5)	8 (10.0)	5 (10.9)	0	2 (4.3)
Pyrexia	11 (18.3)	1 (1.7)	0	2 (10.0)	1 (5.0)	0	13 (16.3)	2 (2.5)	0	2 (4.3)	0	0
Disease progression	8 (13.3)	0	8 (13.3)	0	0	0	8 (10.0)	0	8 (10.0)	2 4.3)	0	2 (4.3)
Respiratory, thoracic and mediastinal disorders	11 (18.3)	8 (13.3)	0	2 (10.0)	1 (5.0)	0	13 (16.3)	9 (11.3)	0	6 (13.0)	4 (8.7)	2 (4.3)
Pleural effusion	6 (10.0)	4 (6.7)	0	1 (5.0)	0	0	7 (8.8)	4 (5.0)	0	5 (10.9)	3 (6.5)	0
Dyspnoea	4 (6.7)	3 (5.0)	0	1 (5.0)	1 (5.0)	0	5 (6.3)	4 (5.0)	0	2 (4.3)	1 (2.2)	0
Hypoxia	1 (1.7)	0	0	0	0	0	1 (1.3)	0	0	3 (6.5)	3 (6.5)	0
Cough	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	1 (2.2)	0	0
Tachypnea	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Gastrointestinal disorders	7 (11.7)	5 (8.3)	0	3 (15.0)	3 (15.0)	0	10 (12.5)	8 (10.0)	0	5 (10.9)	5 (10.9)	0
Abdominal pain	1 (1.7)	1 (1.7)	0	2 (10.0)	2 (10.0)	0	3 (3.8)	3 (3.8)	0	2 (4.3)	2 (4.3)	0
Stomatitis	1 (1.7)	0	0	1 (5.0)	1 (5.0)	0	2 (2.5)	1 (1.3)	0	0	0	0
Large intestinal obstruction	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Musculoskeletal and connective tissue disorders	5 (8.3)	4 (6.7)	0	0	0	0	5 (6.3)	4 (5.0)	0	3 (6.5)	2 (4.3)	0
Pain in extremity	2 (3.3)	2 (3.3)	0	0	0	0	2 (2.5)	2 (2.5)	0	3 (6.5)	2 (4.3)	0

	Nivo									Nivo + Ipi		
	Solid N=60			Hemato N=20			Total N=80			Solid N=46		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (8.3)	5 (8.3)	0	3 (15.0)	3 (15.0)	0	8 (10.0)	8 (10.0)	0	1 (2.2)	1 (2.2)	0
Tumour pain	5 (8.3)	5 (8.3)	0	3 (15.0)	3 (15.0)	0	8 (10.0)	8 (10.0)	0	1 (2.2)	1 (2.2)	0
Renal and urinary disorders	5 (8.3)	4 (6.7)	0	0	0	0	5 (6.3)	4 (5.0)	0	1 (2.2)	1 (2.2)	0
Blood and lymphatic system disorders	4 (6.7)	4 (6.7)	0	3 (15.0)	3 (15.0)	0	7 (8.8)	7 (8.8)	0	1 (2.2)	1 (2.2)	0
Anemia	2 (3.3)	2 (3.3)	0	1 (5.0)	1 (5.0)	0	3 (3.8)	3 (3.8)	0	1 (2.2)	1 (2.2)	0
Febrile neutropenia	2 (3.3)	2 (3.3)	0	3 (15.0)	3 (15.0)	0	5 (6.3)	5 (6.3)	0	0	0	0
Vascular disorders	4 (6.7)	3 (5.0)	0	0	0	0	4 (5.0)	3 (3.8)	0	3 (6.5)	2 (4.3)	0
Hypotension	3 (5.0)	2 (3.3)	0	0	0	0	3 (3.8)	2 (2.5)	0	0	0	0
Infections and infestations	3 (5.0)	3 (5.0)	0	1 (5.0)	0	0	4 (5.0)	3 (3.8)	0	4 (8.7)	3 (6.5)	0
Metabolism and nutrition disorders	3 (5.0)	3 (5.0)	0	1 (5.0)	1 (5.0)	0	4 (5.0)	4 (5.0)	0	6 (13.0)	6 (13.0)	0
Dehydration	2 (3.3)	2 (3.3)	0	0	0	0	2 (2.5)	2 (2.5)	0	3 (6.5)	2 (4.3)	0
Hypercalcemia	0	0	0	1 (5.0)	1 (5.0)	0	1 1.3)	1 (1.3)	0	0	0	0
Hyperuricemia	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Hypokalemia	0	0	0	1 (5.0)	1 (5.0)	0	0	0	0	1 (2.2)	1 (2.2)	0
Nervous system disorders	2 (3.3)	2 (3.3)	0	2 (10.0)	2 (10.0)	0	4 (5.0)	4 (5.0)	0	1 (2.2)	1 (2.2)	0
Headache	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Nervous system disorder	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Presyncope	0	0	0	1 (5.0)	1 (5.0)	0	1 1.3)	1 (1.3)	0	0	0	0
Syncope	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0

	Nivo									Nivo + Ipi		
	Solid N=60			Hemato N=20			Total N=80			Solid N=46		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Cardiac disorders	1 (1.7)	0	0	1 (5.0)	0	1 (5.0)	2 (2.5)	0	1 (1.3)	1 (2.2)	1 (2.2)	0
Cardiac arrest	0	0	0	1 (5.0)	0	1 (5.0)	1 (1.3)	0	1 (1.3)	0	0	0
Injury, poisoning and procedural complications	1 (1.7)	1 (1.7)	0	1 (5.0)	1 (5.0)	0	2 (2.5)	2 (2.5)	0	0	0	0
Fracture	1 (1.7)	1 (1.7)	0	1 (5.0)	1 (5.0)	0	2 (2.5)	2 (2.5)	0	0	0	0
Investigations	1 (1.7)	1 (1.7)	0	4 (20.0)	4 (20.0)	0	5 (6.3)	5 (6.3)	0	4 (8.7)	4 (8.7)	0
Lipase increased	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	1 (2.2)	1 (2.2)	0
Lymphocyte count decreased	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Neutrophil count decreased	0	0	0	2 (10.0)	2 (10.0)	0	2 (2.5)	2 (2.5)	0	0	0	0
Platelet count decreased	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	1 (2.2)	1 (2.2)	0
White blood cell count decreased	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Aspartate aminotransferase increased	1 (1.7)	1 (1.7)	0	0	0	0	1 (1.3)	1 (1.3)	0	3 (6.5)	3 (6.5)	0
Immune system disorders	0	0	0	2 (10.0)	1 (5.0)	0	2 (2.5)	1 (1.3)	0	0	0	0
Autoimmune disorder	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Cytokine release syndrome	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	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.
Source: CA209070 Interim CSR Table 8.6.1.32.3

Table 66 ***Any Possibly Drug-related Serious Adverse Events Summary by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) (≥ 5% in any treatment group) 100 Days Safety Window Pooled Analysis: Solid vs. Hematologic vs. Total For Each Treatment - All Treated Subjects in CA209070***

	Nivo									Nivo + Ipi		
	Solid N=60			Hemato N=20			Total N=80			Solid N=46		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total subjects with an event	13 (21.7)	8 (13.3)	0	4 (20.0)	4 (20.0)	0	17 (21.3)	12 (15.0)	0	9 (19.6)	7 (15.2)	0
General disorders and administration site conditions	4 (6.7)	0	0	1 (5.0)	0	0	5 (6.3)	0	0	1 (2.2)	0	0
Pyrexia	4 (6.7)	0	0	1 (5.0)	0	0	5 (6.3)	0	0	1 (2.2)	0	0
Respiratory, thoracic and mediastinal disorders	4 (6.7)	2 (3.3)	0	1 (5.0)	0	0	5 (6.3)	2 (2.5)	0	4 (8.7)	2 (4.3)	0
Pleural effusion	3 (5.0)	2 (3.3)	0	0	0	0	3 (3.8)	2 (2.5)	0	4 (8.7)	2 (4.3)	0
Cough	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	1 (2.2)	0	0
Tachypnoea	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Gastrointestinal disorders	3 (5.0)	1 (1.7)	0	2 (10.0)	2 (10.0)	0	5 (6.3)	3 (3.8)	0	1 (2.2)	1 (2.2)	0
Abdominal pain	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Stomatitis	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Blood and lymphatic system disorders	1 (1.7)	1 (1.7)	0	2 (10.0)	2 (10.0)	0	3 (3.8)	3 (3.8)	0	0	0	0
Febrile neutropenia	0	0	0	2 (10.0)	2 (10.0)	0	2 (2.5)	2 (2.5)	0	0	0	0
Investigations	1 (1.7)	1 (1.7)	0	2 (10.0)	2 10.0)	0	3 (3.8)	3 (3.8)	0	2 (4.3)	2 (4.3)	0
Lipase increased	0	0	0	1 5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	1 (2.2)	1 (2.2)	0
Neutrophil count decreased	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Immune system disorders	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Autoimmune disorder	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Infections and infestations	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Enterocolitis infectious	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	0	0	0	3 (6.5)	3 (6.5)	0
Nervous system disorders	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	0
Headache	0	0	0	1 (5.0)	0	0	1 (1.3)	0	0	0	0	0
Nervous system disorder	0	0	0	1 (5.0)	1 (5.0)	0	1 (1.3)	1 (1.3)	0	0	0	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.
Source: CA209070 Interim CSR Table S.6.1.32.4

Select AEs

Select AEs included the following categories: endocrine, gastrointestinal, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reactions. AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs.

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 59.

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 maculo papular (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 and AST increased (4.3% each), and gamma-glutamyl transferase increased and rash maculo papular (2.2% each).

Immune mediated adverse event (**IMAEs)**

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 and regardless of investigator attribution.

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 mellitus, or hypophysitis events were reported in subjects treated with nivolumab.

Nivolumab + ipilimumab

Among the 46 subjects treated with nivolumab 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 mellitus, or hypophysitis events were reported in subjects treated with nivolumab.

Other events of special interest (OESIs)

OESIs 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).

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.

Laboratory findings

Haematology

Nivolumab

Among the 79 subjects with on-treatment hematology test results, hematologic abnormalities were primarily Grade 1 or 2. The only adolescent subject with melanoma in CA209070 did not report any hematologic abnormalities.

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).

Clinical Chemistry

Liver tests

Nivolumab

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.

Nivolumab + Ipilimumab

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 x ULN with total bilirubin > 2 x ULN within 1 day and within 30 days.

Table 67 ***Laboratory Test Results Summary of Laboratory Abnormalities in Specific Liver Tests (SI Units) - Pooled Analysis: Solid vs Hematology vs Total for Each Treatment - All Treated Subjects with at Least One On-Treatment Measurement in CA209070***

	Nivo			Nivo + Ipi
Abnormality (%)	Solid N = 59	Hemato N = 20	Total N = 79	Solid N = 46
	N = 59	N = 20	N = 79	N = 46
ALT OR AST > 3XULN	2 (3.4)	1 (5.0)	3 (3.8)	2 (4.3)
ALT OR AST > 5XULN	0	0	0	0
ALT OR AST > 10XULN	0	0	0	0
ALT OR AST > 20XULN	0	0	0	0
	N = 59	N = 20	N = 79	N = 46
TOTAL BILIRUBIN > 2XULN	0	0	0	0
	N = 59	N = 20	N = 79	N = 46
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	0	0	0	0
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	0	0	0	0
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	0	0	0	0
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	0	0	0	0

Includes laboratory results reported after the first dose and within 100 days of last dose of study therapy.

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.

Source: CA209070 Interim CSR Table 8.11.2.1-1

Thyroid Function Tests

Nivolumab

TSH increases (> ULN) from baseline (≤ ULN) were reported in 9 (26.5%) subjects in the nivolumab arm, and there were no decreases (< lower limit of normal (LLN)) from baseline (≥ LLN) reported.

Nivolumab + Ipilimumab

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.

Table 68 ***Laboratory Test Results - Summary of Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - Pooled Analysis: Solid vs Hematology vs Total for Each Treatment - All Treated Subjects with at Least One On-Treatment TSH Measurement in CA209070***

	Nivo			Nivo + Ipi
Abnormality (%)	Solid N = 22	Hemato N = 12	Total N = 34	Solid N = 31
TSH > ULN	8 (36.4)	5 (41.7)	13 (38.2)	6 (19.4)
TSH > ULN				
WITH TSH <= ULN AT BASELINE	5 (22.7)	4 (33.3)	9 (26.5)	5 (16.1)
TSH > ULN				
WITH AT LEAST ONE FT4 TEST VALUE < LLN (A)	2 (9.1)	0	2 (5.9)	0
WITH ALL OTHER FT4 TEST VALUES >= LLN (A)	5 (22.7)	5 (41.7)	10 (29.4)	4 (12.9)
WITH FT4 TEST MISSING (A) (B)	1 (4.5)	0	1 (2.9)	2 (6.5)
TSH < LLN	0	1 (8.3)	1 (2.9)	1 (3.2)
TSH < LLN				
WITH TSH >= LLN AT BASELINE	0	0	0	1 (3.2)
TSH < LLN				
WITH AT LEAST ONE FT4 TEST VALUE > ULN (A)	0	0	0	1 (3.2)
WITH ALL OTHER FT4 TEST VALUES <= ULN (A)	0	1 (8.3)	1 (2.9)	0
WITH FT4 TEST MISSING (A) (B)	0	0	0	0

Includes laboratory results reported after the first dose and within 100 days of last dose of study therapy.

(A) Within a 2-week window after the abnormal TSH test date.

(B) Includes subjects with TSH abnormality and with no FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Source: CA209070 Interim CSR Table 8.11.2.2-1

Kidney Function Tests

Nivolumab

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.

Nivolumab + Ipilimumab

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

Nivolumab

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.

Nivolumab + Ipilimumab

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

Nivolumab

Among the 79 subjects in the nivolumab arm with on-treatment results for blood sodium, potassium, calcium and magnesium, abnormalities were infrequent and 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, none had hyperglycemia and 2 (2.8%) subjects had Grade 1 hypoglycemia.

Nivolumab + Ipilimumab

Among the 46 subjects in the nivo + ipi arm with on-treatment results for blood sodium, potassium, calcium and magnesium, abnormalities were infrequent and 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, none had hyperglycemia and 1 (2.4%) subject had Grade 1 hypoglycemia.

Safety in special populations

Intrinsic and Extrinsic Factors (CA209070)

Age

Age subgroups were divided based on 3 sets of categorizations:

Categorization 1: ≥ 1 to < 6 years (N=3), ≥ 6 to < 12 years (N=10), ≥ 12 to < 18 years (N=20), and ≥ 18 years (N=13)

Categorization 2: < 12 years (N=13), and ≥ 12 years (N=33)

Categorization 3: < 18 years (N=33), and ≥ 18 years (N=13) (Table 67)

Table 69 ***Any Adverse Events Summary (in ≥ 25% Subjects in Age < 18 Subgroup) by Worst CTC Grade by Age with 100 Days Safety Window - All Treated Subjects***

	Age < 18 years								Age ≥ 18 years							
	Nivo						Nivo+Ipi		Nivo						Nivo+Ipi	
SOC (%)	Solid (N=49)		Hemato (N=15)		Total (N=64)		Solid (N=33)		Solid (N=11)		Hema (N=5)		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	Any	G3-4	Any	G3-4
Total subjects with an event	**49 (100)**	**31 (63.3)**	**15 (100)**	**11 (73.3)**	**64 (100)**	**42 (65.6)**	**33 (100)**	**15 (45.5)**	**11 (100)**	**9 (81.8)**	**5 (100)**	**4 (80.0)**	**16 (100)**	**13 (81.3)**	**13 (100)**	**8 (61.5)**
Metabolism and nutrition disorders	**48 (98.0)**	**13 (26.5)**	**15 (100)**	**7 (46.7)**	**63 (98.4)**	**20 (31.3)**	**31 (93.9)**	**12 (36.4)**	**11 (100)**	**2 (18.2)**	**5 (100)**	**0**	**16 (100)**	**2 (12.5)**	**12 (92.3)**	**3 (23.1)**
Hyponatraemia	27 (55.1)	4 (8.2)	9 (60.0)	2 (13.3)	36 (56.3)	6 (9.4)	19 (57.6)	6 (18.2)	6 (54.5)	1 (9.1)	2 (40.0)	0	8 (50.0)	1 (6.3)	5 (38.5)	1 (7.7)
Hypocalcaemia	23 (46.9)	0	11 (73.3)	0	34 (53.1)	0	13 (39.4)	1 (3.0)	4 (36.4)	0	2 (40.0)	0	6 (37.5)	0	2 (15.4)	0
Hypoalbuminaemia	22 (44.9)	2 (4.1)	12 (80.0)	1 (6.7)	34 (53.1)	3 (4.7)	15 (45.5)	1 (3.0)	6 (54.5)	1 (9.1)	2 (40.0)	0	8 (50.0)	1 (6.3)	4 (30.8)	0
Hyperglycaemia	21 (42.9)	2 (4.1)	7 (46.7)	0	28 (43.8)	2 (3.1)	11 (33.3)	1 (3.0)	4 (36.4)	0	0	0	4 (25.0)	0	6 (46.2)	0
Decreased appetite	20 (40.8)	2 (4.1)	3 (20.0)	1 (6.7)	23 (35.9)	3 (4.7)	9 (27.3)	0	6 (54.5)	1 (9.1)	0	0	6 (37.5)	1 (6.3)	8 (61.5)	2 (15.4)
Hypokalaemia	19 (38.8)	5 (10.2)	8 (53.3)	3 (20.0)	27 (42.2)	8 (12.5)	12 (36.4)	4 (12.1)	2 (18.2)	1 (9.1)	4 (80.0)	0	6 (37.5)	1 (6.3)	4 (30.8)	0
Hypophosphataemia	17 (34.7)	4 (8.2)	9 (60.0)	1 (6.7)	26 (40.6)	5 (7.8)	11 (33.3)	2 (6.1)	4 (36.4)	0	1 (20.0)	0	5 (31.3)	0	3 (23.1)	1 (7.7)
Hyperkalaemia	10 (20.4)	1 (2.0)	4 (26.7)	2 (13.3)	14 (21.9)	3 (4.7)	2 (6.1)	0	2 (18.2)	0	0	0	2 (12.5)	0	2 (15.4)	0
Hypomagnesaemia	10 (20.4)	0	8 (53.3)	0	18 (28.1)	0	6 (18.2)	0	3 (27.3)	0	1 (20.0)	0	4 (25.0)	0	1 (7.7)	0
Hypercalcaemia	5 (10.2)	0	4 (26.7)	1 (6.7)	9 (14.1)	1 (1.6)	1 (3.0)	0	0	0	0	0	0	0	2 (15.4)	0
General disorders and administration site conditiona	**45 (91.8)**	**4 (8.2)**	**11 (73.3)**	**2 (13.3)**	**56 (87.5)**	**6 (9.4)**	**22 (66.7)**	**2 (6.1)**	**10 (90.9)**	**0**	**4 (80.0)**	**0**	**14 (87.5)**	**0**	**12 (92.3)**	**2 (15.4)**
Fatigue	28 (57.1)	1 (2.0)	10 (66.7)	0	38 (59.4)	1 (1.6)	14 (42.4)	1 (3.0)	8 (72.7)	0	3 (60.0)	0	11 (68.8)	0	9 (69.2)	1 (7.7)
Pyrexia	27 (55.1)	2 (4.1)	5 (33.3)	2 (13.3)	32 (50.0)	4 (6.3)	14 (42.4)	1 (3.0)	4 (36.4)	0	2 (40.0)	0	6 (37.5)	0	6 (46.2)	0
Pain	17 (34.7)	4 (8.2)	2 (13.3)	0	19 (29.7)	4 (6.3)	4 (12.1)	0	1 (9.1)	0	1 (20.0)	0	2 (12.5)	0	2 (15.4)	1 (7.7)
Disease progression	13 (26.5)	0	2 (13.3)	0	15 (23.4)	0	5 (15.2)	0	2 (18.2)	0	0	0	2 (12.5)	0	1 (7.7)	0
Investigation	**45 (91.8)**	**28 (57.1)**	**15 (100)**	**12 (80.0)**	**60 (93.8)**	**40 (62.5)**	**32 (97.0)**	**14 (42.4)**	**10 (90.9)**	**8 (72.7)**	**5 (100)**	**4 (80.0)**	**15 (93.8)**	**12 (75.0)**	**13 (100)**	**7 (53.8)**
Platelet count decreased	29 (59.2)	12 (24.5)	10 (66.7)	6 (40.0)	39 (60.9)	18 (28.1)	14 (42.4)	4 (12.1)	7 (63.6)	4 (36.4)	2 (40.0)	1 (20.0)	9 (56.3)	5 (31.3)	3 (23.1)	1 (7.7)
White blood cell count decreased	28 (57.1)	9 (18.4)	11 (73.3)	5 (33.3)	39 (60.9)	14 (21.9)	10 (30.3)	3 (9.1)	7 (63.6)	5 (45.5)	3 (60.0)	1 (20.0)	10 (62.5)	6 (37.5)	4 (30.8)	1 (7.7)
Lymphocyte count decreased	26 (53.1)	16 (32.7)	9 (60.0)	6 (40.0)	35 (54.7)	22 (34.4)	18 (54.5)	7 (21.2)	10 (90.9)	7 (63.6)	5 (100)	3 (60.0)	15 (93.8)	10 (62.5)	10 (76.9)	6 (46.2)
Neutrophil count decreased	26 (53.1)	12 (24.5)	9 (60.0)	7 (46.7)	35 (54.7)	19 (29.7)	7 (21.2)	3 (9.1)	6 (54.5)	6 (54.5)	3 (60.0)	3 (60.0)	9 (56.3)	9 (56.3)	4 (30.8)	1 (7.7)

	Age < 18 years								Age ≥ 18 years							
	Nivo						Nivo+Ipi		Nivo						Nivo+Ipi	
SOC (%)	Solid (N=49)		Hemato (N=15)		Total (N=64)		Solid (N=33)		Solid (N=11)		Hema (N=5)		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	Any	G3-4	Any	G3-4
AST increased	19 (38.8)	2 (4.1)	9 (60.0)	2 (13.3)	28 (43.8)	4 (6.3)	11 (33.3)	3 (9.1)	5 (45.5)	0	3 (60.0)	0	8 (50.0)	0	4 (30.8)	2 (15.4)
ALT increased	17 (34.7)	4 (8.2)	11 (73.3)	1 (6.7)	28 (43.8)	5 (7.8)	13 (39.4)	1 (3.0)	4 (36.4)	0	2 (40.0)	0	6 (37.5)	0	5 (38.5)	2 (15.4)
Blood creatinine increased	12 (24.5)	3 (6.1)	4 (26.7)	0	16 (25.0)	3 (4.7)	12 (36.4)	0	6 (54.5)	0	1 (20.0)	0	7 (43.8)	0	3 (23.1)	0
C-reactive protein increased	11 (22.4)	0	4 (26.7)	0	15 (23.4)	0	6 (18.2)	0	3 (27.3)	0	1 (20.0)	0	4 (25.0)	0	5 (38.5)	0
Weight decreased	11 (22.4)	0	2 (13.3)	1 (6.7)	13 (20.3)	1 (1.6)	10 (30.3)	1 (3.0)	4 (36.4)	0	2 (40.0)	0	6 (37.5)	0	7 (53.8)	1 (7.7)
Blood alkaline phosphatase increased	6 (12.2)	2 (4.1)	4 (26.7)	1 (6.7)	10 (15.6)	3 (4.7)	8 (24.2)	1 (3.0)	7 (63.6)	1 (9.1)	0	0	7 (43.8)	1 (6.3)	3 (23.1)	0
Gastrointestinal disorders	**41 (83.7)**	**11 (22.4)**	**10 (66.7)**	**4 (26.7)**	**51 (79.7)**	**15 (23.4)**	**17 (51.5)**	**4 (12.1)**	**8 (72.7)**	**2 (18.2)**	**4 (80.0)**	**3 (60.0)**	**12 (75.0)**	**5 (31.3)**	**11 (84.6)**	**1 (7.7)**
Nausea	26 (53.1)	2 (4.1)	6 (40.0)	0	32 (50.0)	2 (3.1)	9 (27.3)	1 (3.0)	5 (45.5)	1 (9.1)	1 (20.0)	0	6 (37.5)	1 (6.3)	7 (53.8)	1 (7.7)
Vomiting	25 (51.0)	4 (8.2)	5 (33.3)	2 (13.3)	30 (46.9)	6 (9.4)	12 (36.4)	1 (3.0)	4 (36.4)	0	2 (40.0)	0	6 (37.5)	0	8 (61.5)	0
Constipation	20 (40.8)	0	4 (26.7)	0	24 (37.5)	0	8 (24.2)	0	5 (45.5)	0	1 (20.0)	0	6 (37.5)	0	3 (23.1)	0
Abdominal pain	18 (36.7)	1 (2.0)	5 (33.3)	2 (13.3)	23 (35.9)	3 (4.7)	8 (24.2)	2 (6.1)	3 (27.3)	1 (9.1)	0	0	3 (18.8)	1 (6.3)	5 (38.5)	1 (7.7)
Diarrhoea	15 (30.6)	1 (2.0)	3 (20.0)	0	18 (28.1)	1 (1.6)	7 (21.2)	1 (3.0)	1 (9.1)	0	2 (40.0)	1 (20.0)	3 (18.8)	1 (6.3)	4 (30.8)	0
Blood and lymphatic system disorder	**40 (81.6)**	**18 (36.7)**	**12 (80.0)**	**6 (40.0)**	**52 (81.3)**	**24 (37.5)**	**27 (81.8)**	**10 (30.3)**	**9 (81.8)**	**3 (27.3)**	**3 (60.0)**	**2 (40.0)**	**12 (75.0)**	**5 (31.3)**	**7 (53.8)**	**1 (7.7)**
Anaemia	40 (81.6)	16 (32.7)	11 (73.3)	5 (33.3)	51 (79.7)	21 (32.8)	27 (81.8)	10 (30.3)	9 (81.8)	2 (18.2)	3 (60.0)	1 (20.0)	12 (75.0)	3 (18.8)	6 (46.2)	0
Febrile neutropenia	3 (6.1)	3 (6.1)	5 (33.3)	5 (33.3)	8 (12.5)	8 (12.5)	1 (3.0)	1 (3.0)	1 (9.1)	1 (9.1)	1 (20.0)	1 (20.0)	2 (12.5)	2 (12.5)	1 (7.7)	1 (7.7)
Respiratory, thoracic and mediastinal disorders	**39 (79.6)**	**13 (26.5)**	**10 (66.7)**	**2 (13.3)**	**49 (76.6)**	**15 (23.4)**	**21 (63.6)**	**7 (21.2)**	**7 (63.6)**	**3 (27.3)**	**4 (80.0)**	**0**	**11 (68.8)**	**3 (18.8)**	**11 (84.6)**	**2 (15.4)**
Cough	23 (46.9)	0	5 (33.3)	0	28 (43.8)	0	14 (42.4)	0	3 (27.3)	0	4 (80.0)	0	7 (43.8)	0	7 (53.8)	1 (7.7)
Dyspnoea	14 (28.6)	4 (8.2)	2 (13.3)	1 (6.7)	16 (25.0)	5 (7.8)	7 (21.2)	4 (12.1)	3 (27.3)	1 (9.1)	1 (20.0)	0	4 (25.0)	1 (6.3)	3 (23.1)	1 (7.7)
Musculoskeletal and connective tissue disorders	**29 (59.2)**	**7 (14.3)**	**7 (46.7)**	**1 (6.7)**	**36 (56.3)**	**8 (12.5)**	**20 (60.6)**	**3 (9.1)**	**8 (72.7)**	**4 (36.4)**	**3 (60.0)**	**0**	**11 (68.8)**	**4 (25.0)**	**9 (69.2)**	**1 (7.7)**
Pain in extremity	15 (30.6)	2 (4.1)	5 (33.3)	0	20 (31.3)	2 (3.1)	9 (27.3)	3 (9.1)	3 (27.3)	1 (9.1)	1 (20.0)	0	4 (25.0)	1 (6.3)	4 (30.8)	0

	Age < 18 years								Age ≥ 18 years							
	Nivo						Nivo+Ipi		Nivo						Nivo+Ipi	
SOC (%)	Solid (N=49)		Hemato (N=15)		Total (N=64)		Solid (N=33)		Solid (N=11)		Hema (N=5)		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	Any	G3-4	Any	G3-4
Nervous system disorders	**27 (55.1)**	**6 (12.2)**	**7 (46.7)**	**3 (20.0)**	**34 (53.1)**	**9 (14.1)**	**18 (54.5)**	**2 (6.1)**	**6 (54.5)**	**1 (9.1)**	**3 (60.0)**	**1 (20.0)**	**9 (56.3)**	**2 (12.5)**	**7 (53.8)**	**0**
Headache	16 (32.7)	0	4 (26.7)	0	20 (31.3)	0	12 (36.4)	0	4 (36.4)	0	2 (40.0)	0	6 (37.5)	0	6 (46.2)	0
Skin and subcutaneous tissue disorders	**26 (53.1)**	**3 (6.1)**	**7 (46.7)**	**1 (6.7)**	**33 (51.6)**	**4 (6.3)**	**17 (51.5)**	**2 (6.1)**	**6 (54.5)**	**0**	**4 (80.0)**	**0**	**10 (62.5)**	**0**	**5 (38.5)**	**0**
Pruritis	9 (18.4)	0	4 (26.7)	0	13 (20.3)	0	2 (6.1)	0	4 (36.4)	0	0	0	4 (25.0)	0	2 (15.4)	0
Cardiac disorders	**24 (49.0)**	**0**	**4 (26.7)**	**0**	**28 (43.8)**	**0**	**17 (51.5)**	**1 (3.0)**	**5 (45.5)**	**0**	**1 (20.0)**	**0**	**6 (37.5)**	**0**	**7 (53.8)**	**0**
Sinus tachycardia	24 (49.0)	0	3 (20.0)	0	27 (42.2)	0	15 (45.5)	0	5 (45.5)	0	0	0	5 (31.3)	0	7 (53.8)	0
Vascular disorders	**23 (46.9)**	**3 (6.1)**	**5 (33.3)**	**1 (6.7)**	**28 (43.8)**	**4 (6.3)**	**12 (36.4)**	**2 (6.1)**	**4 (36.4)**	**1 (9.1)**	**2 (40.0)**	**1 (20.0)**	**6 (37.5)**	**2 (12.5)**	**8 (61.5)**	**2 (15.4)**
Hypertension	14 (28.6)	0	1 (6.7)	1 (6.7)	15 (23.4)	1 (1.6)	9 (27.3)	2 (6.1)	2 (18.2)	0	2 (40.0)	1 (20.0)	4 (25.0)	1 (6.3)	6 (46.2)	2 (15.4)
Psychiatric disorders	**19 (38.8)**	**1 (2.0)**	**5 (33.3)**	**0**	**24 (37.5)**	**1 (1.6)**	**13 (39.4)**	**1 (3.0)**	**5 (45.5)**	**1 (9.1)**	**1 (20.0)**	**0**	**6 (37.5)**	**1 (6.3)**	**8 (61.5)**	**0**
Anxiety	11 (22.4)	1 (2.0)	4 (26.7)	0	15 (23.4)	1 (1.6)	8 (24.2)	1 (3.0)	2 (18.2)	0	0	0	2 (12.5)	0	5 (38.5)	0
Renal and urinary disorders	**17 (34.7)**	**6 (12.2)**	**8 (53.3)**	**1 (6.7)**	**25 (39.1)**	**7 (10.9)**	**11 (33.3)**	**1 (3.0)**	**6 (54.5)**	**1 (9.1)**	**0**	**0**	**6 (37.5)**	**1 (6.3)**	**8 (61.5)**	**1 (7.7)**
Haematuria	11 (22.4)	3 (6.1)	4 (26.7)	0	15 (23.4)	3 (4.7)	2 (6.1)	0	3 (27.3)	0	0	0	3 (18.8)	0	2 (15.4)	0
Proteinuria	7 (14.3)	0	4 (26.7)	0	11 (17.2)	0	8 (24.2)	0	4 (36.4)	0	0	0	4 (25.0)	0	5 (38.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (12.2)**	**4 (8.2)**	**4 (26.7)**	**3 (20.0)**	**10 (15.6)**	**7 (10.9)**	**2 (6.1)**	**0**	**4 (36.4)**	**3 (27.3)**	**1 (20.0)**	**1 (20.0)**	**5 (31.3)**	**4 (25.0)**	**3 (23.1)**	**1 (7.7)**
Tumour pain	5 (10.2)	4 (8.2)	4 (26.7)	3 (20.0)	9 (14.1)	7 (10.9)	2 (6.1)	0	3 (27.3)	3 (27.3)	1 (20.0)	1 (20.0)	4 (25.0)	4 (25.0)	3 (23.1)	1 (7.7)

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 ≥ 25% subjects in any of the treatment groups for the age < 18 years subgroup.
Source: Table S.6.1.5.4

Gender

All subjects treated with both nivolumab and nivo + ipi had at least 1 all-causality any grade AE. All-causality Grade 3-4 AEs were reported in 65.3% of male subjects and 74.2% of female subjects treated with nivolumab, and in 50.0% in both male and female subjects treated with nivo+ ipi.

Race

Most subjects were clustered in a single category (White). Low sample sizes in the other categories of race limit the interpretability of potential differences.

Ethnicity

The overall safety profile of nivolumab and nivo + ipi was comparable across ethnicities. Most subjects were not Hispanic or Latino.

Discontinuation due to adverse events

Nivolumab

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. 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 tumour 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.

Table 70 ***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***

	Nivo						Nivo + Ipi	
	Solid N = 60		Hemato N = 20		Total N = 80		Solid N = 46	
System Organ Class (%) Preferred Term (%)	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 disorders	1 (1.7)	0	0	0	1 (1.3)	0	0	0
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 Interim CSR Table 8.5-1

Supportive study CA209067 (advanced melanoma)

An overview of safety data for nivo+ipi and/or nivolumab treatment groups for CA209070 (all treated subjects ≥ 1 to ≤ 30 years and paediatric subjects ≥ 1 to < 18 years) and CA209067 (adult subjects with advanced melanoma) studies is provided side-by-side in Table 69. To facilitate comparisons, the overview includes AEs in subjects with extended follow-up (100 days). Of note, different combination regimens were used in CA209070 (nivolumab 1 or 3 mg/kg + ipilimumab 1 mg/kg) and CA209067 (nivolumab 1 mg/kg + ipilimumab 3 mg/kg). No pooled analyses were performed due to the different disease stages in the studies.

Table 71 ***Overall Safety Summary for CA209070 and CA209067 Studies (100 Days after Last Dose of Study Therapy)***

	Multiple Tumor Types				Advanced Melanoma	
	CA209070 Parts A to D[a] (≥ 1 to ≤ 30 years)		CA209070 Parts A to D[a] (≥ 1 to < 18 years)		CA209067[b] (≥ 18 years)	
	Nivo Mono (N = 80)	Ipi+nivo (N = 46)	Nivo Mono (N = 64)	Ipi+nivo (N = 33)	Nivo Mono (N = 313)	Ipi+nivo (N = 313)
Treatment	3 mg/kg Q2W	Nivo 1 or 3 mg/kg + ipi 1 mg/kg Q3W x 4 then nivo mono	3 mg/kg Q2W	Nivo 1 or 3 mg/kg + ipi 1 mg/kg Q3W x 4, then nivo mono	3 mg/kg Q2W	Nivo 1 mg/kg + ipi 3 mg/kg Q3W x 4, then nivo mono
All causality all-grade SAEs	43 (53.8)	20 (43.5)	34 (53.1)	14 (42.4)	176 (56.2)	243 (77.6)
All causality Grade 3-4 SAEs	32 (40.0)	12 (26.1)	25 (39.1)	8 (24.2)	119 (38.0)	175 (55.9)
Drug-related all-grade SAEs	17 (21.3)	9 (19.6)	14 (21.9)	6 (18.2)	35 (11.2)	162 (51.8)
Drug-related Grade 3-4 SAEs	12 (15.0)	7 (15.2)	10 (15.6)	5 (15.2)	26 (8.3)	124 (39.6)
All causality all-grade AEs leading to discontinuation	15 (18.8)	6 (13.0)	11 (17.2)	2 (6.1)	63 (20.1)	159 (50.8)
All causality Grade 3-4 AEs leading to discontinuation	10 (12.5)	3 (6.5)	7 (10.9)	0	42 (13.4)	121 (38.7)
All causality all-grade AEs	80 (100.0)	46 (100.0)	64 (100)	33 (100)	313 (100.0)	313 (100.0)
All causality Grade 3-4 AEs	55 (68.8)	23 (50.0)	42 (65.6)	15 (45.5)	167 (53.4)	226 (72.2)
Drug-related all-grade AEs	72 (90.0)	46 (100.0)	58 (90.6)	33 (100.0)	271 (86.6)	300 (95.8)
Drug-related Grade 3-4 AEs	27 (33.8)	16 (34.8)	21 (32.8)	10 (30.3)	68 (21.7)	193 (61.7)
Drug-related all-grade Select AEs by category						
Skin	16 (20.0)	11 (23.9)	12 (18.8)	9 (27.3)	147 (47.0)	193 (61.7)
Gastrointestinal	6 (7.5)	3 (6.5)	6 (9.4)	1 (3.0)	70 (22.4)	153 (48.9)
Endocrine	19 (23.8)	11 (23.9)	18 (28.1)	8 (24.2)	NR	NR
Hepatic	32 (40.0)	13 (28.3)	27 (42.2)	9 (27.3)	24 (7.7)	103 (32.9)
Pulmonary	0	1 (2.2)	0	0	6 (1.9)	24 (7.7)
Renal	7 (8.8)	7 (15.2)	6 (9.4)	5 (15.2)	3 (1.0)	22 (7.0)
Hypersensitivity/infusion reactions	4 (5.0)	2 (4.3)	1 (1.6)	1 (3.0)	14 (4.5)	13 (4.2)
Drug-related Select Grade 3-4 AEs by category						
Skin	1 (1.3)	1 (2.2)	1 (1.6)	1 (3.0)	7 (2.2)	20 (6.4)

	Multiple Tumor Types				Advanced Melanoma	
	CA209070 Parts A to D[a] (≥ 1 to ≤ 30 years)		CA209070 Parts A to D[a] (≥ 1 to < 18 years)		CA209067[b] (≥ 18 years)	
	Nivo Mono (N = 80)	Ipi+nivo (N = 46)	Nivo Mono (N = 64)	Ipi+nivo (N = 33)	Nivo Mono (N = 313)	Ipi+nivo (N = 313)
Gastrointestinal	0	0	0	0	12 (3.8)	53 (16.9)
Endocrine	0	0	0	0	NR	NR
Hepatic	1 (1.3)	2 (4.3)	1 (1.6)	0	8 (2.6)	65 (20.8)
Pulmonary	0	0	0	0	1 (0.3)	5 (1.6)
Renal	0	0	0	0	1 (0.3)	8 (2.6)
Hypersensitivity/infusion reactions	0	0	0	0	1 (0.3)	0
All causality all-grade immune-mediated AEs treated with immune-modulating medication within 100 days of last dose[c]						
Diarrhea/colitis	21 (26.3)	11 (23.9)	18 (28.1)	7 (21.2)	21 (6.7)	79 (25.2)
Hepatitis	49 (61.3)	23 (50.0)	39 (60.9)	17 (51.5)	11 (3.5)	45 (14.4)
Pneumonitis	0	2 (4.3)	0	1 (3.0)	5 (1.6)	20 (6.4)
Nephritis and renal dysfunction	24 (30.0)	15 (32.6)	17 (26.6)	12 (36.4)	3 (1.0)	8 (2.6)
Rash	23 (28.8)	12 (26.1)	19 (29.7)	11 (33.3)	46 (14.7)	72 (23.0)
Hypersensitivity/infusion reactions	6 (7.5)	2 (4.3)	3 (4.7)	1 (3.0)	3 (1.0)	2 (0.6)
All causality Grade 3-4 immune-mediated AEs treated with immune-modulating medication within 100 days of last dose[c]						
Diarrhea/colitis	2 (2.5)	1 (2.2)	1 (1.6)	1 (3.0)	13 (4.2)	47 (15.0)
Hepatitis	7 (8.8)	6 (13.0)	7 (10.9)	4 (12.1)	9 (2.9)	38 (12.1)
Pneumonitis	0	0	0	0	1 (0.3)	4 (1.3)
Nephritis and renal dysfunction	4 (5.0)	0	4 (6.3)	0	2 (0.6)	6 (1.9)
Rash	3 (3.8)	2 (4.3)	3 (4.7)	2 (6.1)	7 (2.2)	10 (3.2)
Hypersensitivity/infusion reactions	0	0	0	0	0	0
All causality all-grade immune-mediated endocrine AEs treated with or without immune-modulating medication within 100 days of last dose[c]						
Adrenal insufficiency	0	0	0	0	5 (1.6)	19 (6.1)
Hypophysitis	0	0	0	0	5 (1.6)	28 (8.9)
Hypothyroidism/thyroiditis	12 (15.0)	9 (19.6)	11 (17.2)	7 (21.2)	39 (12.5)	79 (25.2)
Hyperthyroidism	7 (8.8)	2 (4.3)	7 (10.9)	0	19 (6.1)	35 (11.2)

	Multiple Tumor Types				Advanced Melanoma	
	CA209070 Parts A to D[a] (≥ 1 to ≤ 30 years)		CA209070 Parts A to D[a] (≥ 1 to < 18 years)		CA209067[b] (≥ 18 years)	
	Nivo Mono (N = 80)	Ipi+nivo (N = 46)	Nivo Mono (N = 64)	Ipi+nivo (N = 33)	Nivo Mono (N = 313)	Ipi+nivo (N = 313)
Diabetes mellitus	0	0	0	0	5 (1.6)	7 (2.2)
All causality Grade 3-4 immune -mediated endocrine AEs treated with or without immune-modulating medication within 100 days of last dose[c]						
Adrenal insufficiency	0	0	0	0	1 (0.3)	7 (2.2)
Hypophysitis	0	0	0	0	3 (1.0)	9 (2.9)
Hypothyroidism/thyroiditis	0	0	0	0	0	4 (1.3)
Hyperthyroidism	0	0	0	0	0	4 (1.3)
Diabetes mellitus	0	0	0	0	2 (0.6)	3 (1.0)

Sources: CA209070: Interim CSR Table 8.1-1, Table S.6.1.5.4; SCS Appendix 1 Table S.7.7, Table S.7.8, Table S.12.2, Table S.12.4, Table S.12.6, Table S.12.8, Table S.12.10, Table S.12.12, Table S.13.2. CA209067: Final CSR Table 8-1, Table S.6.2b, Table S.6.3b, Table S.6.17.b, Table S.6.19b, Table S.6.21.b, Table S.6.100b, Table S.6.102b.

[a] CA209070: DBL 30-Sep-2019 (Parts A and B) and 30-Jun-2020 (Parts C and D); include events reported between first dose and 100 days after last dose of study therapy.

[b] CA209067: DBL 13-Sep-2016; include events reported between first dose and 100 days after last dose of study therapy.

[c] For CA209070, IMAEs could not be derived per CRF design. Modified IMAEs were used. (CA209070 CSR Section 8.9). For CA209067 and CA209238 studies, IMAEs include diarrhea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, and endocrine (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus)

Supportive Study CA209915 (adjuvant setting)

Supportive data from both the nivolumab (480 mg Q4W) and nivo + ipi (nivo 240 mg Q2W + ipi 1 mg/kg Q6W) arms with a comparable median follow-up between arms (28.06 [range 0.0, 37.5] and 27.96 [0.0, 38.4], respectively) have been provided focusing on adolescents.

The median duration of therapy was higher in the nivolumab arm (11.07 months), compared to the nivo + ipi arm (7.61 months). Overall, the safety profiles of nivolumab and nivo + ipi in all treated subjects were consistent with those in other tumour types, and no new safety signals were identified.

Adolescent subjects in Study CA209915

Three adolescents (≥12 to <18 years of age) were randomized and treated: 2 in the nivolumab arm and 1 in the nivo + ipi arm.

- Nivolumab:
    - A 15-year-old White male with tumour cell PD-L1 status ≥ 5%, was randomized to nivolumab at a site in Australia. The subject had been treated with wide local extension, resective surgery, and complete lymph node dissection prior to the study. The subject completed the treatment period.
    - A 16-year-old White female with PD-L1 status < 1% was randomized to nivolumab at a site in the UK. The subject had been treated with resective surgery and complete lymph node dissection prior to the study. The subject completed the treatment period.
- Nivo + Ipi:
    - A 16-year-old White male with tumour cell PD-L1 status < 1% was randomized to nivo + ipi at a site in Italy. The subject had been treated with resective surgery and complete lymph node dissection prior to the study. The subject received 16 doses of nivolumab and 6 doses of ipilimumab. The subject died of disease progression.

Table 72 ***Serious Adverse Events in Adolescent Subjects in Study CA209915***

Unique Subject ID (Age/Sex/Race)	Current Trt Period Visit	Onset D/T Resolution D/T Study Day	Dur TRD Type	System Organ Class Preferred Term Reported Term	REL CTC	TRT ACT
16/M/C	ENDED TREATMENT 30-100 DAYS FOLLOW-UP ON TREATMENT WEEK 31	04MAR2019/16:00 07MAR2019 364	3D 83D SAE	Blood and lymphatic system disorders Thrombocytopenia THROMBOCYTOPENIA	5 3	1 1
	ENDED TREATMENT POST 100 DAYS FOLLOW-UP ON TREATMENT WEEK 31	26APR2019 02MAY2019 417	7D 136D SAE	Infections and infestations Pneumocystis jirovecii pneumonia PNEUMOCISTIS JIROVECII PNEUMONIA	5 2	1 1

REL (RELATIONSHIP): 5 = NOT RELATED 6 = RELATED; TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
CTC (COMMON TERMINOLOGY CRITERIA): 1 = GRADE 1 2 = GRADE 2 3 = GRADE 3 4 = GRADE 4 5 = GRADE 5
ACT (ACTION): 1 = DOSE NOT CHANGED 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DOSE DELAYED 5= DRUG INTERRUPTED 6 = DRUG WITHDRAWN
DUR (DURATION OF EVENT)/ TRD (TIME RELATIVE TO MOST RECENT DOSE): D = DAYS H = HOURS M = MINUTES S = SECONDS
MedDRA Version: 23.0 ; CTC Version 4.0
Source: Table S.6.3.1.1 of the CA209915 CSR[6]

Supportive Study CA209238 (adjuvant setting)

Study CA209238 provides data for nivolumab monotherapy (3 mg/kg Q2W) in subjects ≥18 years in the approved adjuvant melanoma indication in adult patients. This study was initially assessed within the Opdivo extension of the indication procedure for adjuvant therapy (EMEA/H/C/003985/II/0041) and later updated within procedure EMEA/H/C/003985/II/0098.

While subjects aged 15 years and older were eligible in CA209238, no adolescent (< 18 years of age) subjects were enrolled.

Minimum follow-up (last subject's randomization date to clinical cut-off date) for all randomized subjects was approximately 18 months. The majority of subjects in both treatment arms received ≥90% of the intended dose intensity of nivolumab with a median duration of therapy of 11.50 months (range: 11.47 - 11.53).

Table 73 **Key Demographic and Baseline Characteristics - All Randomized Subjects (CA209238)**

	Nivo N = 453	**Ipi N =453**	**Total N =906**
Age, median (range), yrs	56.0 (19, 83)	54.0 (18, 86)	55.0 (18, 86)
Male (n, %)	258 (57.0)	269 (59.4)	527 (58.2)
White (n, %)	425 (93.8)	434 (95.8)	859 (94.8)

Table 73 **Key Demographic and Baseline Characteristics - All Randomized Subjects (CA209238)**

	Nivo N = 453	Ipi N =453	Total N =906
ECOG PS, n (%)			
0	413 (91.2)	405 (89.4)	818 (90.3)
1	40 (8.8)	48 (10.6)	88 (9.7)
Median time from surgical resection to randomization (range), wks	9.0 (0, 15)	9.7 (0, 35)	9.3 (0, 35)
CRF disease stage at study entry (n, %)			
stage IIIB	163 (36.0)	148 (32.7)	311 (34.3)
stage IIIC	204 (45.0)	218 (48.1)	422 (46.6)
stage IV	82 (18.1)	87 (19.2)	169 (18.7)
Other[a]	2 (0.4)	0	2 (0.2)
not reported	2 (0.4)	0	2 (0.2)
CRF PD-L1 status, (n, %)			
< 1%	140 (30.9)	133 (29.4)	273 (30.1)
>= 1%	287 (63.4)	307 (67.8)	594 (65.6)
indeterminate	25 (5.5)	13 (2.9)	38 (4.2)
unevaluable/ not reported	1 (0.2)	0	1 (0.1)
BRAF mutation status			
mutant	187 (41.3)	194 (42.8)	381 (42.1)
wildtype	197 (43.5)	214 (47.2)	411 (45.4)
not reported	69 (15.2)	45 (9.9)	114 (12.6)

[a] Subjects with Disease Stage IIIa

Source: refer to Table 5.3.1-1 and Table 5.3.1-2 of the CA209238 Interim CSR

Table 74 ***Summary of Safety Results - All Treated Subjects in CA209238 (18 months minimum follow-up)***

	Number (%) Subjects	
	Nivolumab 3 mg/kg (N=452)	Ipilimumab 10 mg/kg (N=453)
DEATHS	44 (9.7)	45 (9.9)
WITHIN 30 DAYS OF LAST DOSE	0	0
WITHIN 100 DAYS OF LAST DOSE	3 (0.7)	2 (0.4)
DUE TO STUDY DRUG TOXICITY	0	2 (0.4)

	Number (%) Subjects			
	Nivolumab 3 mg/kg (N=452)		Ipilimumab 10 mg/kg (N=453)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	79 (17.5)	48 (10.6)	183 (40.4)	144 (31.8)
DRUG-RELATED SAEs	24 (5.3)	15 (3.3)	141 (31.1)	111 (24.5)
ALL CAUSALITY AEs LEADING TO DC	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)

DRUG-RELATED AEs LEADING TO DC	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)
ALL-CAUSALITY AEs	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
FATIGUE	193 (42.7)	3 (0.7)	185 (40.8)	4 (0.9)
DIARRHOEA	167 (36.9)	11 (2.4)	247 (54.5)	48 (10.6)
PRURITUS	127 (28.1)	0	167 (36.9)	5 (1.1)
RASH	115 (25.4)	5 (1.1)	150 (33.1)	16 (3.5)
HEADACHE	106 (23.5)	2 (0.4)	142 (31.3)	9 (2.0)
NAUSEA	104 (23.0)	1 (0.2)	127 (28.0)	0
PYREXIA	32 (7.1)	0	96 (21.2)	5 (1.1)
DRUG-RELATED AEs	385 (85.2)	65 (14.4)	434 (95.8)	208 (45.9)
Most Frequent Drug-related AEs (≥15% of Any Grade in either treatment group)				
FATIGUE	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
DIARRHOEA	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
PRURITUS	105 (23.2)	0	152 (33.6)	5 (1.1)
RASH	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
NAUSEA	68 (15.0)	1 (0.2)	91 (20.1)	0
HEADACHE	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
ALL-CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY				
Immune-mediated AEs Treated with Immune-modulating medication				
RASH	73 (16.2)	3 (0.7)	105 (23.2)	22 (4.9)
DIARRHEA/COLITIS	29 (6.4)	9 (2.0)	144 (31.8)	78 (17.2)
HEPATITIS	15 (3.3)	9 (2.0)	43 (9.5)	34 (7.5)
PNEUMONITIS	8 (1.8)	0	12 (2.6)	4 (0.9)
NEPHRITIS AND RENAL DYSFUNCTION	3 (0.7)	1 (0.2)	1 (0.2)	0
HYPERSENSITIVITY/INFUSION REACTIONS	1 (0.2)	0	2 (0.4)	0
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications				
HYPOTHYROIDISM/THYROIDITIS	63 (13.9)	1 (0.2)	41 (9.1)	3 (0.7)
HYPERTHYROIDISM	39 (8.6)	1 (0.2)	22 (4.9)	2 (0.4)
HYPOPHYSITIS	9 (2.0)	2 (0.4)	64 (14.1)	19 (4.2)
ADRENAL INSUFFICIENCY	7 (1.5)	2 (0.4)	19 (4.2)	6 (1.3)
DIABETES MELLITUS	4 (0.9)	2 (0.4)	8 (1.8)	1 (0.2)

MedDRA version 20.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.
Source: CA209238 Interim CSR Table 8.1-1

2.5.1. Discussion on clinical safety

The assessment of the safety profile of nivolumab, as monotherapy or in combination with ipilimumab, for the treatment of advanced melanoma and as monotherapy for the adjuvant treatment of melanoma after complete resection, in adolescents, is based on the safety results from study CA209070. Supportive data come from studies CA209067 and CA209238, which are the pivotal trials for the approved indications in adults, and study CA209915 which included adolescent subjects treated in the adjuvant setting.

A total of 126 subjects received, at least, one treatment dose in study CA209070 and constitute the Safety Population. Among these patients, 80 were treated with nivolumab monotherapy and 46 with nivolumab + ipilimumab. A total of 97 paediatric patients aged ≥ 1 year to < 18 years, 53 patients 12 to < 18 years, were treated in study CA209070. As of the DBLs (30-Sep-2019 for Parts A and B and 30-Jun-2020 for Parts C and D), only 1 subject receiving nivolumab was still on treatment. No subjects receiving nivo + ipi were still on treatment. There was an overall minimum follow-up for survival of 14.0 months for subjects treated with nivolumab, and 28.3 months for subjects treated with nivo + ipi. Among subjects who received nivolumab monotherapy (parts A and B), the median number of nivolumab doses received was 2 (range: 1 - 89) and, for nivolumab + ipilimumab, the median number of doses was 2.0 (range: 1 - 24) for nivolumab and 2.0 (range: 1 - 4) for ipilimumab, as only 4 ipilimumab doses were recommended as RP2D by the study protocol, also in line with other studies and the approved indication for adult patients with melanoma.

The overall safety profile of nivolumab and nivo + ipi in study CA209070, as assessed by the incidence of SAEs, AEs leading to discontinuation, AEs, and select AEs, seems consistent with that seen in the

adult studies for nivolumab and nivo + ipi across tumour types. There were no new safety signals identified. There were no toxicities noted that were specific to a given disease cohort.

A nivolumab dose of 3 mg/kg Q2W was recommended for Part B as none of the 12 subjects treated in Part A of the study reported any DLT. The nivolumab + ipilimumab dosing regimen for this study (nivo 3 mg/kg + ipi 1 mg/kg x 4 doses) was selected based on the fact that none of the 6 patients treated with the starting dose of nivo 1 mg/kg + ipi 1 mg/kg reported any DLT and, among the 12 subjects treated with nivo 3 mg/kg + ipi 1 mg/kg (dose level 2), only one DLT was observed which was within the predefined occurrence of <2 DLTs to establish the RP2D. This mentioned DLT was observed on Day 14 of the first treatment cycle and reported as blood creatinine increased.

All-causality any-grade AEs were reported in 80 (100.0%) subjects treated with nivolumab while all causality Grade 3-4 AEs were reported in 55 (68.8%) subjects treated with nivolumab. Drug-related any-grade AEs were reported in 72 (90.0%) subjects being the most commonly observed: anaemia (43.8%), fatigue (37.5%) and white blood cell count decreased (30.0%). Similarly, all-causality any-grade AEs were reported in 46 (100.0%) subjects treated with nivo + ipi, while all causality Grade 3-4 AEs were reported in 23 from the 46 (50.0%) subjects treated with nivo + ipi. Drug-related any-grade AEs were reported in all 46 treated subjects, being the most commonly observed: lymphocyte count decrease (43.5%), anaemia (41.3) and fatigue (34.8%). ALT increase, platelet count decrease, white cell count decrease and nausea were also commonly reported.

There were no deaths assessed as related to study drug toxicity in study CA209070. Most deaths were due to disease progression but there was one subject treated with nivolumab (NHL) who died due to intraparenchymal hematoma secondary to disease progression 57 days after the last treatment dose and another patient treated with the combination who died due to unknown causes. Other deaths were reported as due to respiratory failure and one case of cardiac arrest, all in the context of disease progression.

Regarding SAEs, all-causality any-grade SAEs (within 100 days of last dose) were reported in 43 (53.8%) subjects treated with nivo and Grade 3-4 SAEs were reported in 32 (40.0%) subjects. Drug-related SAEs were reported in 17 (21.3%) subjects treated with nivo while drug-related Grade 3-4 SAEs were reported in 12 (15.0%) patients. The drug-related Grade 3-4 SAEs reported in ≥2 subjects were febrile neutropenia and pleural effusion (2.5% subjects each). All-causality SAEs were reported in 20 (43.5%) subjects treated with nivo + ipi and all-causality Grade 3-4 SAEs were reported in 12 (26.1%) subjects. Drug-related any-grade SAEs were reported in 9 (19.6%) subjects treated with nivolumab + ipilimumab while drug-related Grade 3-4 SAEs were reported by 7 (15.2%) subjects. Drug-related Grade 3-4 SAEs reported in ≥2 subjects were: ALT increase, AST increase, hyponatremia and pleural effusion (4.3%) each.

Select AEs included the usual categories along nivolumab and ipilimumab clinical development: endocrine, gastrointestinal, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reactions. As expected, most common select AEs fall into the categories of hepatic, endocrine and skin for both nivolumab monotherapy and nivolumab + ipilimumab. Drug-related serious select AEs included hepatic enzymes elevations as the most commonly reported.

In Study CA209070, IMAEs data could not be directly obtained due to the design of the case report form, so a list of IMAEs was generated from AEs (up to 100 days after the last treatment dose) observed as PTs included in an "IMAE PTs" list, regardless of whether or not the subject received immune-modulating medication and regardless of investigator attribution. In both subjects treated with either nivolumab monotherapy or the combination, any grade IMAEs were reported by ≥20% of subjects. The most common Grade 3-4 IMAEs in patients treated with nivolumab were hepatitis events (8.8%) and nephritis and renal dysfunction events (5%). In patients treated with the nivolumab +

ipilimumab combination, the most frequently reported Grade 3-4 IMAEs were hepatitis events (13%). Similarly to other nivolumab and ipilimumab studies performed in a wide variety of disease settings, for both the monotherapy and the combination, the most common any-grade IMAEs were hepatitis, nephritis and renal dysfunction, rash and diarrhoea/colitis; all of them reported in more of the 25% of treated subjects. The MAH provided a tabular summary of IMAEs separated by age groups of adolescents (≥12 to < 18) and young adults (≥18 years) from study CA209070. Considering the limited sample sizes, it is difficult to reach any conclusion based on the available data so, in the clinical practice, adolescent patients should be closely monitored for an early detection of these events, similarly to adults.

Focusing on events defined as OESIs, among the 80 patients treated with nivolumab, 2 patients reported drug-related pancreatitis and one patient a Grade 3 event of GVHD in the context of allogeneic transplant. For the 46 subjects treated with the combination, one patient reported an event of uveitis and another one a drug-related Grade 3 event of pancreatitis.

Data on safety in special populations have been analysed by age, gender, race and ethnicity. The safety profile of both nivolumab monotherapy and the combination seems comparable between age subgroups (< 12 years, ≥ 12 years to <18 years, and ≥18 years of age). Unfortunately, subgroups are too small to draw any conclusion from these analyses. However, by reviewing tabular summaries for patients <18 and ≥18 years, there seems to be a slight trend for a worse toxicity in terms of higher incidences of reported SOC and PTs events for patients <18 years old. Considering that only the adolescent (≥12 years to < 18 years) subgroup is the target population of this extension of the indication, a tabular comparison between safety data for the treated adolescents and adults in study CA209070 was provided. Some differences in the reported SOC and PT incidences are observed, as expected considering the small number of subjects included, but they are not considered relevant in the clinical scenario where this study was performed.

Assessment of paediatric data on clinical safety

The totality of the paediatric data generated according to the agreed PIP01 for nivolumab (EMEA-C-001407-PIP01-12-M03, adopted by PDCO on 21 January 2022) are provided as part of this application, in order to fulfil regulatory requirements. The updates proposed to the SmPC are therefore intended to reflect the clinical safety for the entire paediatric population included in Parts A to D of study CA209070 (N = 97 patients aged ≥ 1 year to < 18 years), Study 2 of PIP01 and pivotal clinical trial for this application, covering all the paediatric tumour types (solid and haematological tumours) and treatment regimens (nivo and nivo+ipi) studied and not limited to melanoma.

Despite the results reported above, from a safety perspective, the proposed extension of the indications to adolescents relies on extrapolation of (safety) data from adult patients in the same disease settings, due to the limited clinical data available in adolescents with melanoma. In this context, supportive data from studies CA209067 for the advanced setting, and studies CA209915 and CA209238 for the adjuvant setting, have been presented within the current application.

Study CA209067 has been thoroughly assessed since the initial melanoma indication application and multiple later updates. A tabular comparison of incidences for the main AEs items between data from study CA209067 (DBL 16-Sept-2016) and results from study CA209070 for both the all-treated population and patients <18 years old has been submitted but comparisons are not possible since different nivolumab+ipilimumab doses were administered in both studies.

Patients in study CA209070 received nivo 3 mg/kg + ipi 1 mg/kg but patients randomized to the combination in study CA209067 received nivo 1 mg/kg + ipi 3 mg/kg, which is the approved dosing for adults in the advanced melanoma setting and also the recommended dose for the extension of the

indication application to treat adolescents. This is the main reason why study CA209070 is not adequate to support the safety assessment of nivo+ipi for the treatment of advanced melanoma in adolescent patients. Nivolumab monotherapy was administered at the same dose (3 mg/kg Q2W) in both studies.

The approved dose of nivo+ipi for the treatment of advanced melanoma in adults presents a remarkable toxicity, higher than the observed toxicity with other combination indications where the administered doses for nivolumab and ipilimumab are the same as used in study CA209070. This difference, which is expected to be observed in adolescents too, added to the initial concerns regarding the performed model-based simulations that do not seem to capture the expected higher incidence of AEs in adolescents (based on expected higher exposure), gave rise to concern in relation to the acceptability of the full extrapolation approach proposed (see section 2.3.4). Of note, data on the use of ipilimumab, at different doses (3 mg/kg, 5 mg/kg and 10 mg/kg), in paediatric population is available from studies CA184070 and CA184078, where patients with advanced melanoma were treated, although with a very small sample size (data not shown). Although there is no available clinical data of the use of nivo+ipi in adolescent patients with advanced melanoma, the acceptability of the proposed indication relies on a full extrapolation approach that is agreeable also from a safety point of view. As for long-term safety data, the MAH proposed to extend the ongoing post-authorization long-term follow-up safety study CA184557 to include paediatric patients treated with nivolumab monotherapy and nivolumab in combination with ipilimumab in the DMTR, as an additional pharmacovigilance activity (see RMP).

In the adjuvant setting, study CA209915 included 3 adolescent patients. Two of these patients received nivolumab monotherapy (480 mg Q4W) and both of them completed the treatment period. Reported safety data do not raise any concern. The adjuvant indication approval for adults was based on study CA209238. While subjects aged 15 years and older were eligible in CA209238, no adolescent (<18 years of age) subjects were enrolled and therefore, the safety assessment for nivolumab in the melanoma adjuvant setting for adolescents also relies on extrapolation. This study was considered adequate to characterize the safety profile of nivolumab in adults although the comparator was ipilimumab at a 10 mg/kg dose which is known for carrying a remarkable toxicity and is not approved in this disease setting.

2.5.2. Conclusions on clinical safety

Key safety results are summarized in Sections 4.8 of the SmPC. The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab monotherapy were fatigue (35.9%) and decreased appetite (21.9%). The majority of adverse reactions reported for nivolumab monotherapy were Grade 1 or 2 in severity. Twenty-one patients (33%) had one or more Grades 3 to 4 adverse reactions. The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab in combination with ipilimumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for nivolumab in combination with ipilimumab were Grade 1 or 2 in severity. Ten patients (30%) had one or more Grades 3 to 4 adverse reactions.

The safety of nivolumab as monotherapy (3 mg/kg every 2 weeks) and in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in 97 paediatric patients aged ≥ 1 year to < 18 years (including 53 patients 12 to < 18 years) with recurrent or refractory solid or haematological tumours, including advanced melanoma, in clinical study CA209070. The safety profile in paediatric patients was generally similar to that seen in adults treated with nivolumab as monotherapy or in combination with ipilimumab. No new safety signals were observed.

Study CA209070 did not enrol any melanoma patient to be treated with the combination and the dosing used is not the same as that approved for melanoma adult patients, which is also the one proposed for the extension of the indication to treat adolescents. For these reasons, the safety assessment of this application relies mainly in a full extrapolation approach based on clinical data in adults from the already assessed studies CA209067 and CA209238, in addition to study CA209915, which was conducted in the adjuvant setting and included two adolescents treated with nivolumab monotherapy. As previously concluded, based on an acceptable extrapolation approach, the well characterised safety profile can be considered extrapolated to adolescents. However, as long-term safety in adolescent patients is missing this has been reflected in the RMP as missing information and expected to be further characterized in DMTR (study CA184557).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 30.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Long-term safety in adolescent patients ≥ 12 years of age has been added to the section of missing information. This has been reflected in the pharmacovigilance plan and the risk minimization measures.

Table 75 **Summary of Safety Concerns**

Important identified risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis and renal dysfunction
	Immune-related endocrinopathies
	Immune-related skin ARs
	Other immune-related ARs
	Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity

Table 75 **Summary of Safety Concerns**

	Complications of allogeneic HSCT following nivolumab therapy in cHL
	Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab
	Long-term safety in adolescent patients ≥ 12 years of age

Pharmacovigilance plan

Table 76 ***Summary Table of Additional Pharmacovigilance Activities***

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)
Category 3 - Required additional pharmacovigilance activities			
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557)[a] Voluntary PASS	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients > 12 years of age	1. Submission of protocol[a] 2. Interim Study Report 3. Final report of study results
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission

[a] The protocol, CA184557, which includes patients treated with ipilimumab monotherapy, will be amended to include patients who received nivolumab monotherapy or nivolumab in combination with ipilimumab (including those receiving therapy prior to the start of data collection). The study milestones presented are specific to the protocol extension for nivolumab or nivolumab in combination with ipilimumab treated patients.

Risk minimisation measures

Table 77 **Summary of Risk Minimization Measures**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Immune-related nephritis and renal dysfunction	Additional risk minimization measures:	Additional pharmacovigilance activities:
Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs	Patient Alert Card	Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

Table 77 **Summary of Risk Minimization Measures**

Safety Concern	**Risk Minimization Measures**	**Pharmacovigilance Activities**
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

Table 77 **Summary of Risk Minimization Measures**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Long-term safety in adolescent patients ≥ 12 years of age	Routine risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: MAH to sponsor the extension of the DMTR to include paediatric subjects treated with nivolumab monotherapy and nivolumab + ipilimumab to collect their safety data (CA184557).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. It is considered that the submitted type II variation to extend the currently approved indications for Opdivo (nivolumab) in the treatment of adults with melanoma, both in the advanced (nivolumab monotherapy and nivolumab in combination with ipilimumab) and the adjuvant settings (nivolumab monotherapy), to include adolescents 12 years of age and older, does not have a relevant impact on the PIL text. Therefore, the MAH's justification to not undertake further consultation with target patient groups is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is an extension of the indication to adolescents 12 years of age and older for nivolumab, as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma and, as monotherapy, in the adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

3.1.2. Available therapies and unmet medical need

Although melanoma is rare in paediatric patients, the risk of developing melanoma grows significantly in adolescents and young adults, and represents the second most common type of cancer in this age group. Most melanomas occurring in adolescents are conventional or adult subtypes of melanoma. Because of its rarity in the paediatric population, the approach to diagnosis and treatment in paediatric melanoma has been adopted from adult guidelines. The mainstay of treatment for melanoma in children is surgical. As in adults, immune checkpoint inhibitors (nivolumab, ipilimumab, pembrolizumab) and BRAF-targeted therapy (vemurafenib, dabrafenib/trametinib) are effective options for adjuvant treatment of high-risk resected melanoma and are recommended by the NCCN and the ESMO. Same treatment options are recommended for first-line therapy of unresectable or distant metastatic disease. For second-line or subsequent systemic therapy, the NCCN recommends to consider therapies whose mechanism of action differs from prior lines of therapy that resulted in poor response or disease progression. For the ESMO, standard-of-care second-line selection depends on the strategy used for the first-line and the mutational status of the disease. Clinical trials should always be considered when available. For subsequent lines of therapy clinical trials or rechallenge, either with targeted or immunotherapies, can be an option.

Ipilimumab as monotherapy was approved in 2018 (Yervoy, EMEA/H/C/002213/II/0044) for the treatment of patients ≥12 years in this same setting based on a partial extrapolation approach. An extension of indication for pembrolizumab was granted in June 2022 (Keytruda, EMEA/H/C/003820/II/0111) to include adolescents in the treatment of advanced melanoma therapeutic indication.

3.1.3. Main clinical studies

The evidence in support of the claimed extension of the indication is based on data from study CA209070, an investigator-sponsored phase 1/2 open-label trial of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumours as a single agent and in combination with ipilimumab. A total of 132 subjects were enrolled and 126 were treated. Ninety-seven subjects were <18 years old and, among them, 53 subjects ≥12 to <18 years old. Overall, 80 patients were treated with nivolumab monotherapy and 46 nivolumab in combination with ipilimumab.

To support the proposed extrapolation approach results from study CA209067, which was the basis for the authorization of nivolumab monotherapy and nivolumab in combination with ipilimumab in the advanced melanoma setting in adults, have been provided. In the same way, results from studies CA209915 and CA209238 were included to support the use of nivolumab in the adjuvant setting for adolescents.

3.2. Favourable effects

In study CA209070, for nivolumab monotherapy, no objective response was observed in the solid tumour cohorts (from 58 response evaluable subjects including melanoma) while the ORR was 23.5% (95% CI: 6.8, 49.9) in the haematological tumour cohort (N=17 response evaluable subjects). For nivo+ipi treatment (solid tumour only, based on 43 response evaluable subjects), the ORR was 4.7% (95% CI: 0.6, 15.8).

In the population of adolescent subjects (≥12 to < 18 years) specifically, ORR in patients with haematological tumours was 6.5% (95% CI: 0.8, 21.4) (1 CR in HL and 1 PR in NHL) in subjects treated with nivolumab (N = 31), and there were no objective responses in subjects treated with ipi+nivo (N = 19).

OS was reported in the overall population of study CA209070 with 47.5% of events in the nivo monotherapy group and 58.7% of events in the combination pooled group having occurred. Overall, the median OS was 11.07 (95% CI: 6.37, 27.63) months for nivo monotherapy and 8.87 (95% CI: 5.75, 18.50) months for subjects treated with nivo + ipi.

3.3. Uncertainties and limitations about favourable effects

The administered doses of nivolumab and ipilimumab in study CA209070 are not the same as approved for adult patients (study CA209067) nor the recommended doses for adolescents within this procedure which are based upon extrapolation of data from adult patients and modelling and simulation studies.

OS data reported in study CA209070 are difficult to interpret in a single-arm design.

Limited clinical efficacy data are available in adolescent subjects with melanoma, i.e. in study CA209070 only one adolescent with advanced melanoma was treated with nivolumab as monotherapy and reported PD as BOR. No definitive conclusions can therefore be drawn regarding efficacy of nivolumab (alone or in combination) in adolescent subjects with melanoma based on experimental data.

However, this application relies on extrapolation of data obtained in adult patients based on the principles that disease biology is similar in both the adult and adolescent population, and on the assumption that the drugs behave similarly and comparable exposure-response to treatment can be expected between adults and adolescents.

3.4. Unfavourable effects

All-causality any-grade AEs were reported in 80 (100%) subjects treated with nivolumab and in 46 (100%) of patients treated with nivo+ipi, while causality Grade 3-4 AEs were reported in 55 (69%) subjects treated with nivolumab and 23 (50%) treated with nivo+ ipi. Drug-related any-grade AEs were reported in 72 (90.0%) subjects treated with nivolumab and in all 46 subjects who received nivo+ipi. The most commonly observed drug-related any-grade AEs were anaemia (43.8%), fatigue (37.5%) and white blood cell count decreased (30.0%), for nivolumab monotherapy, and lymphocyte count decreased (43.5%), anaemia (41.3) and fatigue (34.8%), for nivo+ipi.

Regarding SAEs, all-causality (within 100 days of last dose) were reported in 43 (54%) subjects treated with nivolumab and in 20 (43.5%) subjects treated with nivo + ipi. All-causality Grade 3-4 SAEs were reported in 15% and 26% subjects treated with nivo or nivo+ipi, respectively (12 patients in both cases).

Any grade IMAEs were reported by ≥20% of subjects treated either with nivolumab as monotherapy or in combination. The most commonly observed for both populations (all reported in more of the 25% of treated subjects) were hepatitis, nephritis and renal dysfunction, rash and diarrhoea/colitis.

3.5. Uncertainties and limitations about unfavourable effects

A comparison between data from study CA209067, CA209238 and results from study CA209070 for both the all-treated population and patients <18 years old has been submitted. However, a direct comparison is not possible due to the different disease settings and the fact that different doses for nivolumab + ipilimumab were administered in the studies.

The approved dose of nivo + ipi for the treatment of advanced melanoma in adults (nivo 1 mg/kg + ipi 3 mg/kg) presents a remarkable toxicity, higher than that observed in other combination indications where the administered doses for nivolumab and ipilimumab are the same used in study CA209070 (nivo 3 mg/kg + ipi 1 mg/kg). This difference is expected to be observed in adolescents too (relevant aspects are reflected in SmPC 4.2 and 4.8).

Long-term safety in adolescent patients is missing this has been reflected in the RMP as missing information and expected to be further characterized in DMTR (study CA184557).

3.6. Effects Table

Table 78 ***Effects Table for nivolumab in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adolescent patients 12 years and older (data cut-off: 30-Sep-2019 nivolumab monotherapy, 30-Jun-2020 nivolumab + ipilimumab, Study CA209070)***

Effect	Short description	Unit	Nivolumab	Nivo+Ipi	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR		% (95% CI)	5.3 (1.5, 13.1)	4.7 (0.6, 15.8)	Descriptive	CSR study CA209070
OS	median	months (95% CI)	11.07 (6.37, 27.63)	8.87 (5.75, 18.50)	Descriptive and of difficult interpretation in the context of a SAT.	
Unfavourable Effects						
Any-grade AEs	incidence	%	100	100	Different disease settings Different doses for nivolumab + ipilimumab	CSR study CA209070
Grade 3-4 AEs	incidence	%	68.8	50		
SAEs	incidence	%	53.8	43.5		

Abbreviations: ORR: objective response rate, OS: overall survival, AE: Adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from study CA209070 that included paediatric patients (12 months to <18 years) and young adults (≤30 years) with recurrent or refractory solid (including melanoma) and haematology (only lymphoma) tumours, have been submitted within this application. However, considering the limited clinical data available with the use of nivolumab, both alone and in combination with ipilimumab, in adolescents with melanoma (only a single patient), the assessment relies mainly in extrapolation of data from adult patients in both the adjuvant and advanced settings (results come from studies CA209238 and CA209067, respectively). The extrapolation approach proposed is based on two main principles: that the drug behaves similarly and a comparable exposure-response to treatment can be expected between adults and adolescents; and that the disease biology can be considered similar between the two populations. This is considered acceptable, and the relevance and importance of the favourable and unfavourable effects can be extrapolated from adults to adolescents.

3.7.2. Balance of benefits and risks

As the extrapolation approach is considered acceptable, a positive benefit-risk balance can also be concluded for the relevant treatment of adolescents 12 years of age and older.

3.7.3. Additional considerations on the benefit-risk balance

The agreed changes to SmPC are intended to reflect the clinical safety and efficacy data for the entire paediatric population included in Parts A to D of study CA209070 (N = 97) and pivotal clinical trial for this application, covering all the paediatric tumour types (solid and haematological tumours) and not limited to melanoma. The extension of indication and posology proposed for adolescents 12 years of age and older in sections 4.1 and 4.2 of the SmPC are mostly based upon extrapolation of data from adult patients and modelling and simulation studies, respectively, which is acceptable. Key efficacy results are summarized in Sections 4.8 and 5.1, respectively, of the proposed SmPC.

3.8. Conclusions

The overall B/R of Opdivo is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include adolescent patients aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) for Opdivo, based on results from a nonclinical biomarker study (Expression of PD-L1 (CD274), and characterization of tumor infiltrating immune cells in tumors of pediatric origin), also based on results from a Phase 1/2 clinical study (CA209070, A Phase 1/2 Study of Nivolumab (Ind# 124729) In Children, Adolescents, And Young Adults With Recurrent Or Refractory Solid Tumors As A Single Agent And In Combination With Ipilimumab) and a modelling and simulation study. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated.
The Package Leaflet is updated in accordance.

Version 30.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0432/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Opdivo-H-C-3985-II-0125’